Vascular and Endovascular Consensus Update

CONSENSUS UPDATE

Roger M Greenhalgh

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Limit of Liability/Disclaimer Warranty

Acute stroke consensus

Thoracic aortic consensus

Abdominal aortic consensus

Peripheral arterial consensus

Venous consensus

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INTRODUCTION

Today, 17 March 2020, is a unique moment—five weeks before the Charing Cross meeting. In short, the virus is at work! Not just the Charing Cross Symposium will be disrupted and unable to meet, but also many aspects of life in the whole world will be disrupted. We know at this stage that it is highly unlikely that 4,000 people would be allowed to meet in Olympia at the end of April. Allowed or not, it would be irresponsible for such a gathering because it is unlikely that the virus would be under control by that time.

At the time of writing, we are being warned that there will be vast numbers of members of the population all over the world infected with the virus. As it is new and unknown largely, its management is also largely unknown and experimental. It is not known if once the virus has attacked someone, whether antibodies are generated in the patient to make it very unlikely that the patient gets the virus again. There is a suspicion that the virus does not strike twice but the mechanism is not known. It does not seem to attack children and fit people to the same extent as older people and/or those with underlying conditions.

All of the Schengen area of the European Union has suddenly and overnight disappeared. Only a few weeks ago, we (in the UK) were talking about Brexit. Now there is no talk about Brexit, if anything there is pleasure that we are a separate island. Instead the focus of all the countries of Europe is to close their own borders to be able to stop infection from the neighbouring country. This really is a disruptive virus!

My wife Karin, who remembers well the ending of the Second World War, describes this as World War Three. In World War One and World War Two, the men went off to war. In World War Three, as described by Karin, everyone stays at home! The problems are going to be different but very challenging.

What do we do about the Book this year? Frankly, it is a small question against the huge backdrop of matters that are affecting all of us. It seems logical that the content of the Book being ready that it should be made available. Therefore, we are planning to have it made available online. The original Programme is completely available and as well as the Book being available in electronic form, the Programme itself needs to be heard. Why is that? There are some topics so important for health, they must be heard. There are a number of Podium 1st presentations and we need to have those open and that information made available to those who would otherwise have attended Charing Cross. So a form of the Charing Cross Symposium will take place, but it will not be in the same live format.

At the time of writing, we are hoping that we shall use what we are calling "Plan B". Plan B would have the presentations pre-recorded but the speakers perform live and moderators and chairmen to be live and for discussions to take place with the presenter livestreamed. This will then run for three and a half days. Of course the whole event would be videoed and available online.

But will even this be possible? Will the doctors involved be so consumed with managing patients struck by the virus that they cannot attend, even from home or their office? In this event, we shall have to move to "Plan C"; this is the third option that somehow the wonderful learning that we have prepared needs to be

communicated in one format or another. At the very least it will appear as a whole programme on the internet to be viewed by those who would otherwise come to Charing Cross as and when they are able to view it. The Book may also be accessible to those who wish to see it.

These are very different times that the 42nd Charing Cross will not be the highlight of the year; that that prime place will be for the virus. There are those who are talking in philosophical terms. This is nature striking back! Is this the case? Have the human race been unwise, flying too much, gobbling up the resources, is this the way that nature culls the species on earth? This is deep philosophy and not the purpose of this introduction, but to say that these are the comments which are being discussed right now, the time of writing this introduction.

May I wish that those who read these words are safe and their families around them are safe and they are able to attend a large Charing Cross Symposium in a year's time.

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Standard carotid endarterectomy is superseded by eversion endarterectomy

F Qayyum and R Clement Darling III

Introduction

ACAS (Asymptomatic carotid atherosclerosis study) and ACST (Asymptomatic carotid surgery trial) determined that carotid endarterectomy was effective in reducing stroke risk in patients with asymptomatic carotid stenosis >60%. Patients with symptomatic carotid stenosis of >50% were shown to benefit from endarterectomy in NASCET (North American symptomatic carotid endarterectomy trial) and ECST (European carotid surgery trial).[1-4] Carotid endarterectomy can be performed in the conventional longitudinal manner (with or without patch closure) and the eversion technique.

The technique of eversion carotid endarterectomy was first reported by Debakey *et al.* However, this technique involved transection of the common carotid artery and atheroma removal.[5] This technique limited plaque exposure and visualisation of the distal endpoint, thereby limiting its wider acceptance. The technique was later revised by Kasparzak and Raithel, who transected the internal carotid artery at the carotid bulb, improving distal endpoint visualisation and complete plaque removal.[6]

Despite data proving good outcomes with eversion carotid endarterectomy, most surgeons still prefer the conventional method. According to the Vascular Quality Initiative database, only 12.6% of endarterectomies performed nationally between 2003 and 2018 were eversion. Patients undergoing conventional endarterectomy had more postoperative haemodynamic instability, longer operative times, and a hospital stay longer than one day. No difference was noted in perioperative stroke, one-year stroke, death and restenosis rates.[7]

Surgeons debate the use of patch for closure of arteriotomy in conventional carotid endarterectomy. A consensus was reached in favour of patch angioplasty because of a higher rate of stroke and restenosis with primary closure.[7,8] Use of patch, however, has consequences. Patch infection, pseudoaneurysms and even ruptures have been reported.[9,10] The eversion technique eliminates the need for any prosthetic material. The common carotid and internal carotid arteries are used to patch each other, reducing the risk of substantial narrowing or restenosis. Women are more likely to have a higher rate of restenosis due to the smaller calibre of the internal carotid artery.[11] However, data demonstrate a <1% risk of recurrent stenosis in female patients with the eversion technique.[12]

Eversion endarterectomy should not be employed cautiously in early recurrent stenosis. It may result in neointimal hyperplasia as well as radiation-related carotid stenosis, as it may not be possible to separate the intima from the outer layer.
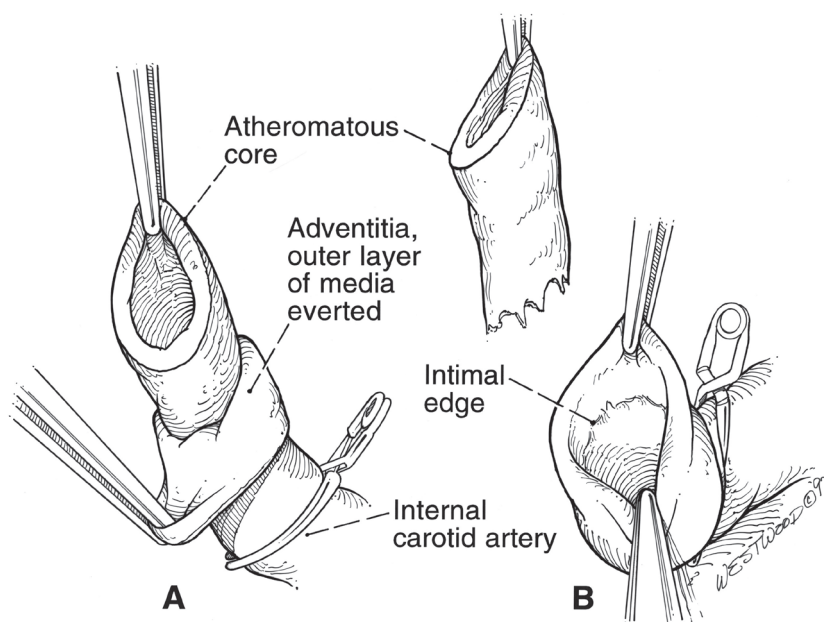
Figure 1: Eversion endarterectomy with removal of atheromatous core of the internal carotid artery. *Copyright 1997 William B Westwood.*

Additionally, the eversion technique should not be used for re-exploration of early occlusion after a patch closure, due to the longitudinal suture line. However, eversion carotid endarterectomy is an acceptable technique for reoperation in select patients, especially without prosthetic patch closures after the healing of the longitudinal suture lines.[13]

Indications for treatment

Carotid endarterectomy continues to be the gold-standard treatment for severe asymptomatic carotid stenosis as well as symptomatic carotid stenosis of at least 50%, despite less invasive treatment modalities such as transcarotid artery revascularisation (TCAR) and transfemoral carotid stenting. Conventional and eversion carotid endarterectomy are generally equivalent.

Traditionally accepted indications for eversion endarterectomy are a carotid artery with extensive tortuosity or short lesions confined to carotid bifurcation.[14] It has also been used for patients with a narrow internal artery in order to avoid narrowing of the distal artery. These patients tend to be women. Eversion endarterectomy is proven safe and results in a low incidence of restenosis.[15] This is achieved because the anastomosis in eversion carotid endarterectomy is in the widest portion of the internal artery.

More recently, as we analysed our results of early carotid endarterectomy (less than two weeks) for stroke, we discovered, much to our surprise, that eversion carotid endarterectomy was a positive predictor for good outcome.[16] This has made us more aggressive in using this technique in this challenging patient population.

Preoperative preparation

All patients should get a preoperative carotid duplex. Computed tomography (CT) angiography can be considered to confirm the degree of stenosis. Magnetic resonance (MR) angiography, or conventional contrast angiography are rarely indicated. Patients should obtain preoperative cardiac clearance. All patients should be on an antiplatelet agent.

Anaesthesia choice for standard carotid endarterectomy and eversion endarterectomy is per surgeon preference. Both can be performed under general anaesthesia with cerebral monitoring. Our preference is to perform the eversion carotid endarterectomy under cervical block. We use selective shunting only in patients who develop neurological deterioration during cross-clamp or who are undergoing carotid endarterectomy for acute stroke.[6,7]

Technique

There are few differences in the exposure of the carotid artery for eversion and conventional endarterectomy. In the eversion technique, circumferential mobilisation of the distal internal artery well beyond the extent of plaque is essential. This allows adequate examination of endarterectomy endpoint. Periadventitial tissue must be completely cleared off the artery to allow for its adequate eversion. Most of this can be achieved after the internal artery has been transected and lifted away from the operative field. This manoeuvre minimises the risk of cranial nerve injury.

Internal carotid artery
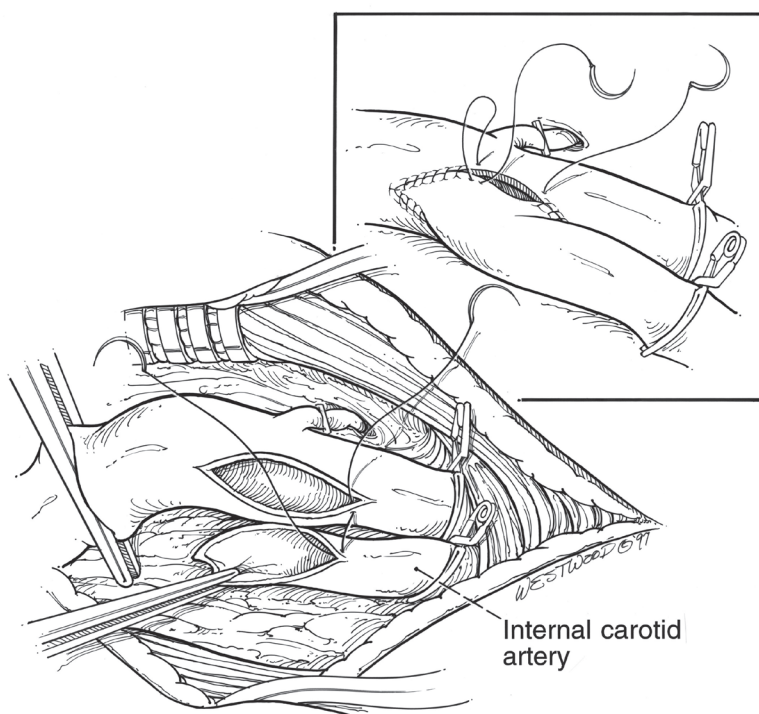
Figure 2: Anastomosis of the internal carotid artery to the carotid bulb. *Copyright 1997 William B Westwood.*

Then 30 units/kg of heparin are administered, followed by clamping of the internal carotid artery using a Yasargil neurosurgical clip or Kartchner clamp. This is followed by clamping of the external and common carotid arteries. Using an 11 blade, an oblique arteriotomy is made at the origin of the internal artery that is then completely transected in an oblique direction at its origin using scissors. The arteriotomy is extended along the medial side of the internal artery for 1–2cm. The arteriotomy in the common carotid artery is also extended for the same distance. Eversion of the internal artery is performed by identifying the dissection plane in the proximal internal carotid artery. The adventitia is peeled off the plaque until it begins to "feather out" before separating off the adventitia. If there is a residual rim of plaque, it should be removed as a spiral to avoid dissection of the distal intima. Heparinised saline irrigation allows for clearance of residual debris. A clear view of the endpoint is essential. If this is not achieved, the clamp should be moved further cephalad on the internal artery.

If the plaque does not "feather out," it may become continuous with the distal intima. The endarterectomy must be stopped before the internal carotid artery enters the skull base and becomes out of reach. We have used 7–0 or 8–0 prolene in a U stitch fashion in order to tack the plaque to the endarterectomised area. If this is not possible, a common carotid artery to internal carotid artery bypass may also be performed. The internal artery may be transected and a distal anastomosis performed thus tacking down the distal intima with a 7–0 or 6–0 polypropylene suture.

Common carotid artery endarterectomy is then performed by identifying a plane between the adventitia and the plaque. The plaque is transected proximally, just beyond the origin of the external artery. Failure to endarterectomise the common artery leads to a higher incidence of restenosis. If there is extensive plaque in the common artery, the arteriotomy may be extended proximally on that artery and an extensive endarterectomy performed. This arteriotomy may be closed primarily due to the large calibre of the common carotid artery. Eversion endarterectomy of the external artery can be performed in the same manner as the internal.

After adequate endarterectomy, the internal artery is anastomosed to the common artery with a continuous 6-0 polypropylene suture with parachute technique. The clamps are released and the artery is irrigated with heparinised saline before completion of the anastomosis. Once flow is re-established, it is confirmed via Doppler. Duplex imaging of the internal and external carotid arteries may also be used. There may be no flow in the external artery if there is a dissection there, or if there is an issue with the endpoint. This may be corrected with external carotid re-exploration, or left alone in a difficult case. If left occluded, it may result in jaw claudication or masseter muscle claudication.

No flow in the internal carotid artery at the end of the anastomosis mandates exploration. This is the case even if the patient is asymptomatic. If there is thrombosis of the artery, an emergent exploration must be carried out. The endpoint must be evaluated and revised as needed. Retrograde flow from the internal artery is generally sufficient to wash out the thrombus. Additionally, in highly select cases, a No.2 embolectomy catheter may be inserted for a short, pre-measured distance to retrieve thrombus. If "white" thrombus is retrieved at the endarterectomy site, heparin-induced thrombocytopenia should be considered along with a technical issue resulting in injury leading to platelet aggregation.

An endarterectomised internal carotid artery may be replaced with an interposition graft, vein, or prosthetic.[17] A potent antiplatelet agent should also be considered.

If shunting is required during eversion carotid endarterectomy, any conventional shunt may be used. The internal artery is transected and eversion endarterectomy is performed quickly. The distal shunt of choice is then inserted and secured with a balloon or shunt clamp. This may be performed prior to endarterectomy of the internal artery in select cases where the plaque is short. The proximal end of the shunt is then inserted in the common artery and secured. The flow though the shunt is confirmed by Doppler in the distal internal artery. The common carotid artery endarterectomy can then be performed. The anastomosis is then carried out in the manner described above with removal of shunt before flushing and completion of the anastomosis.

The use of a shunt raises frequent objections to eversion carotid endarterectomy. Shunt use is perceived to be more difficult than conventional endarterectomy. However, shunt insertion can be performed safely and expeditiously with use of good technique. There are two options—one can incise the plaque medially on the internal carotid and then insert the shunt; or our preference is to complete the eversion of the internal carotid artery and then insert the small end of a Burbank, Brener or Javid shunt under direct vision past the endpoint and then insert the proximal end of the shunt. This potentially minimises the chance of "snow ploughing" the atheromatous debris distally and confirms back flow in the internal carotid artery.[7]

Although many surgeons choose to stent patients presenting with recurrent carotid stenosis, eversion endarterectomy can be safely performed in more than 95% of patients.[18,19]

Conclusion

The eversion technique is safe and effective in the treatment of carotid stenosis. Its results are comparable to conventional endarterectomy and may be used routinely for treatment of symptomatic or severe asymptomatic carotid stenosis. Eversion technique is especially well suited in cases of redundant and tortuous internal carotid arteries and in patients with early acute stroke and significant carotid artery disease. It does not require implantation of foreign patch material or vein patch which can lead to complications such as infection and rupture. Regardless of the vascular surgeon's choice of routine procedure, every vascular surgeon should be familiar with the eversion carotid endarterectomy technique.

Summary

Benefits of eversion carotid endarterectomy over conventional approach:

- Shorter operative time, smaller incision, and less carotid cross clamp time.

- Better for smaller arteries.

- All autogenous reconstruction.

- Shortens redundant internal carotid artery and restores haemodynamic shape of carotid bifurcation.

- Potentially less restenosis and cranial nerve injury, and better results in acute stroke patients.

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Carotid patch type impacts outcomes following carotid endarterectomy

L Edenfield, BW Nolan and J Eldrup-Jorgensen

Introduction

The purpose of carotid endarterectomy is to reduce the risk of stroke from atherosclerotic narrowing of the carotid bifurcation. Given that the aim of the procedure is prevention, ensuring that the risk of complication is kept to an absolute minimum is critically important. Furthermore, in the context of endarterectomy, most perioperative strokes are thought to be a result of technical issues; thus, surgeons put great emphasis on the details and execution of the operation. The goal of this chapter is to provide a broad overview of operative techniques for carotid endarterectomy while focusing on outcomes with respect to patch type used for closure.

History of endarterectomy

Carotid endarterectomy has been the gold-standard treatment for symptomatic carotid stenosis for the past six decades. Eastcott *et al* reported the first successful carotid revascularisation procedure in 1954.[1] Initially, carotid endarterectomy was performed with a longitudinal arteriotomy and primary closure.[2] After the lumen has been cleared by endarterectomy of the diseased intima and media, the adventitia is sutured directly together. Primary closure is associated with a higher incidence of long-term restenosis—probably because of narrowing of the lumen with the closure.[3]

In an effort to minimise the potential for restenosis, patch angioplasty—closing the endarterectomised vessel with a patch—is frequently performed. Currently, closure of the arteriotomy with patch angioplasty is generally preferred as it has been shown to have lower complication rates compared with primary repair.[4,5] The most common patch materials are Dacron, PTFE, autogenous vein, and bovine pericardium. An alternative technique for carotid revascularisation is eversion endarterectomy, whereby the internal carotid artery is transected at the carotid bulb, the vessel is everted to remove the diseased intima, and the internal carotid artery is re-implanted onto the bulb by circumferential primary closure.[6] Eversion endarterectomy is advantageous for redundant or tortuous carotid arteries by avoiding the kinking of the artery that may occur with closure of a longitudinal arteriotomy.[7] Eversion endarterectomy has been shown to be a safe and viable technique for carotid repair with results comparable to patch closure.[8]

Carotid endarterectomy is usually performed with patch angioplasty (Figure 1), though it has long been debated which patch material is superior. Multiple studies, including several Cochrane reviews, have attempted to determine which, if any,

patch type has superior outcomes. The most recent Cochrane review (published in 2010) examined the results of 2,083 procedures in 13 different trials and compared PTFE, Dacron, autologous vein, and bovine pericardium. The study found that Dacron had inferior outcomes with higher rates of restenosis and postoperative neurologic events. Use of a vein patch demonstrated higher rates of pseudoaneurysm and aneurysmal degeneration. However, the primary conclusion of the study was that the number of cases studied in the analysis was too small to draw a reliable conclusion.[9]

In a more recent meta-analysis, published in the *Journal of Vascular Surgery* in 2018, Texakalidis *et al* evaluated patch types from more than 3,000 carotid endarterectomy procedures in 18 different studies to compare the rates of postoperative restenosis, perioperative myocardial infarction, postoperative stroke or transient ischaemic attack (TIA), and postoperative wound complications.[10] They concluded that there was no significant difference in postoperative outcomes based on patch type, likely due to lack of sufficient power for the study. Despite the paucity of data to support any material, many surgeons have a strong preference for a particular patch type.

Results of carotid patch type analysis
The Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) is a voluntary, prospectively maintained database containing patient- and procedure-specific data.[11] The VQI collects over 250 variables in-hospital, and, at an average of one year (range 9–21 months) follow-up, from more than 280 centres and 4,000 physicians in the USA and Canada on carotid endarterectomy. Using data from the VQI registry, a retrospective analysis was performed examining the outcomes of over 70,000 carotid endarterectomy procedures from 2012 to 2018 in order to evaluate the safety and efficacy of primary closure and the different patch materials.[12] The analysis was limited to patients undergoing initial carotid endarterectomy and excluded patients who underwent eversion endarterectomy, reoperative carotid endarterectomy, and combined carotid endarterectomy with coronary artery bypass
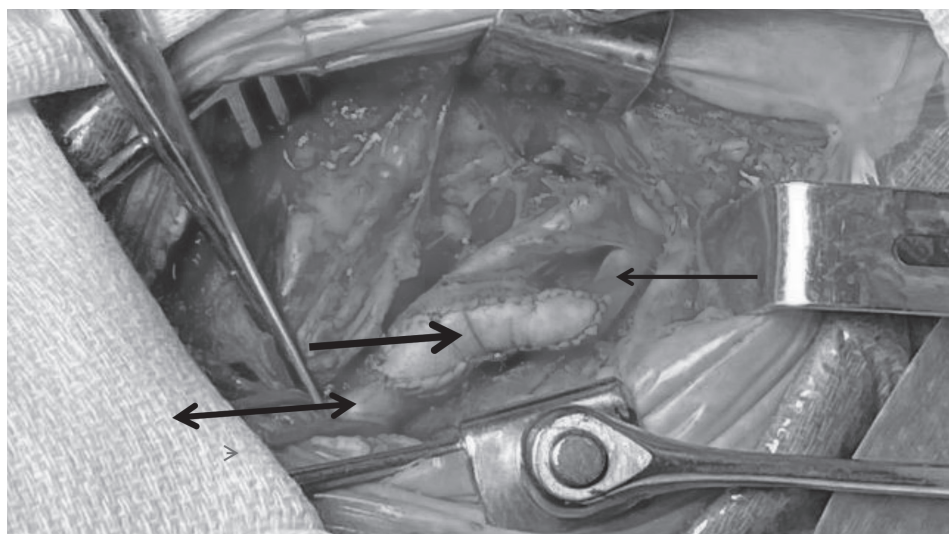
Figure 1: Thick arrow = carotid patch; thin arrow = internal carotid artery; double headed arrow = common carotid artery.

grafting. The primary outcomes studied included rates of postoperative neurologic event (stroke or TIA), return to operating room for bleeding, neurologic event or wound complication, and restenosis at one-year post procedure determined by surveillance duplex imaging. The patch materials studied were bovine pericardium, Dacron, PTFE, and autogenous vein.

Univariate analysis (Table 1) revealed similar rates of returns to the operating room during the index hospitalisation between bovine pericardium, Dacron, and vein (1.8%, 2% and 1.8%, respectively). PTFE was associated with a significantly higher rate, 2.8% (p=0.05). Postoperative neurologic events were also more common in patients undergoing PTFE patch closure, 2.8% (p=0.002) than bovine, Dacron or vein patch closure (1.5%, 1.5%, 1.9%). Restenosis ≥80% at one year was significantly higher in patients patched with vein, 2.6% (p=0.03) and PTFE, 2.5% (p=0.001), compared with bovine, 1.3% and Dacron, 1.4% and was not different from carotids repaired primarily, 2.7%. Rates of moderate restenosis (≥50%) were lowest for bovine pericardium, 13% (p=0.001) compared to all other groups (Dacron 16%; vein 16%, PTFE 19%, no patch 20%).

A multivariate analysis was used to adjust for potential confounders such as surgeon outcomes, medication use, smoking status, symptom status, patient age and gender, comorbidities, and procedure characteristics. By multivariate analysis bovine pericardium was associated with reduced rates of return to operating room compared to all other patch types (Table 2). Other factors associated with return to operating room were urgent or emergent surgery, symptom status, history of congestive heart failure. However, protamine use was found to be protective.

Bovine pericardium and Dacron patches were associated with reduced postoperative neurologic events compared with PTFE and vein (which both had similar rates of postoperative neurologic events to primary repair). Urgent or emergent surgery and symptom status were also associated with these types of events. Bovine pericardium, Dacron and vein were associated with reduced rates of restenosis ≥50% at one year. Patients who had never smoked had a lower rate of restenosis while female gender was associated with a higher incidence of restenosis.

	Return to OR[1]	Stroke or TIA[2]	Re-stenosis >50%[3]	Re-stenosis >80%[3]
Bovine Pericardium	1.8%	1.5%	13.0%	1.3%
Dacron	2.0%	1.5%	15.2%	1.4%
Vein	1.8%	1.9%	16.3%	2.6%
PTFE	2.8%	2.8%	18.9%	2.5%
Primary closure	2.6%	2.8%	20.0%	2.7%
p-value[4]	<0.01	<0.01	<0.01	<00.01

1. Return to operating room (OR) for neuro event or bleeding during index hospitalisation.
2. Any post op ipsilateral neuro event (TIA or stroke) occurring during index hospitalisation.
3. Restenosis on one-year follow-up imaging.
4. p-value for chi-square analysis across all patch types. Individual patch type results compared by Bonferroni analysis (referenced in results section of text).

Table 1: Unadjusted outcomes by patch type.

	Return to OR OR (95% CI)	Stroke or TIA OR (95% CI)	Re-stenosis >50% OR (95% CI)
Bovine Pericardium	0.70 (0.56-0.89)	0.59 (0.48-0.72)	0.57 (0.44-0.75)
Dacron	0.81 (0.62-1.05)	0.56 (0.43-0.74)	0.70 (0.50-0.98)
Vein	0.69 (0.44-1.08)	0.72 (0.49-1.06)	0.72 (0.53-0.98)
PTFE	0.95 (0.65-1.40)	1.10 (0.74-1.65)	0.90 (0.48-1.68)
Reference – primary closure			

OR = Operating room
CI = Confidence interval

Table 2: Outcomes of multivariable analysis.

The SVS VQI registry has a large number of patients with robust clinical data for analysis. The large numbers in the database makes it possible to detect small differences in outcomes that have not been previously identified. Though prior studies, systematic reviews and meta-analyses have been unable to demonstrate any difference, the ≥70,000 carotid procedures in the VQI registry provided a large enough sample size to detect differences in performance in different patch types.

Overall, bovine pericardium is associated with slightly, but significantly, better outcomes in terms of postoperative neurologic events, return to the operating room, and ≥50% restenosis at one year compared to all other patch types or primary closure.

About 150,000 carotid endarterectomy operations are performed annually in the USA and UK, and approximately 25% are done with primary closure or materials other than bovine pericardium. Assuming that the incidence of return to the operating room is 2.5% for all other closures and can be reduced by 30% (odds ratio [OR] 0.7), that is 281 fewer patients who require an emergent reoperation simply by altering type of closure. If the postoperative neurologic event rate is 2.6% and can be reduced by 41% (OR 0.59) by using bovine pericardium patch closure, that is 400 TIAs and strokes that could be avoided annually. If 2.5% of patients develop a ≥80% stenosis and it can be reduced by 43% (OR 0.57), that is another 403 patients. Using conservative estimates, there are potentially more than 900 patients annually who would benefit from a simple modification of the operation—using bovine pericardium for carotid patch angioplasty.

Conclusion

The VQI registry provides a large sample size that allows meaningful analysis that can detect small differences. Using bovine pericardium for carotid endarterectomy patch closure is associated with reduced postoperative neurologic events, return to the operating room, and restenosis at one year. Based on these results, bovine pericardium is the preferred material for carotid endarterectomy patch closure.

Summary

- Patch closure of carotid endarterectomy reduces postoperative neurologic events and restenosis.

- Use of bovine pericardium patch material is associated with reduced postoperative neurologic events, return to the operating room and restenosis at one year compared to Dacron, PTFE and vein.

- Patch closure of carotid endarterectomy with bovine pericardium is recommended to reduce postoperative complications.

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Diagnosis and management of internal carotid artery "String sign": When to Intervene

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Introduction

Advances in contemporary ultrasound imaging has allowed duplex scanning to become the best initial, and, frequently, the most accurate diagnostic modality in the assessment of carotid disease. Numerous published reports describe various ultrasound technical features and manoeuvres that allow the detection and confirmation of patency of internal carotid arteries (ICAs) with very low flow velocities in the presence of high grade/critical stenoses (95–99% diameter reduction) or "string sign".[1–5]

In some studies, colour flow duplex scanning has been shown to pick up a patent ICA believed to be completely occluded by contrast arteriography.[6] While in other investigations, "pseudo-occlusions" of the ICA with rapid sequence CAT-scans and magnetic resonance (MR) angiography, have been identified.[7,8] Unquestionably, duplex scanning has the combined advantage of precisely identifying arterial wall characteristics and indicating the operability of them. Unfortunately, a high percentage pre-occlusive carotid arteries with very low flow state may go undetected when recommended standard "arterial" duplex protocols are used.

Over the years several synonyms have been introduced and "pseudo-occlusions" of the ICA have been also named "string sign", "poststenotic carotid slim sign", "hypoplasia" and "nearly occluded".[9–12] While the exact incidence of pseudo-occlusions of the ICA remains unclear, they account for about 0.5% to 10% of all carotid endarterectomy surgeries.[4,5,13] Additionally, it is reasonable to suggest that many patients with neurologic symptoms in the presence of presumed carotid occlusion diagnosed with the so-called "carotid stump syndrome", in reality, are cases of near total occlusion of the ICA or "pseudo-occlusion".[14] These symptoms may have been caused either by an embolic atherosclerotic lesion or acute partial thrombosis. Indeed, some of these symptomatic patients would have benefited from carotid endarterectomy surgery if they were not misdiagnosed by less sensitive imaging modalities. On the other hand, some cases of ICA pseudo-occlusions are not technically feasible for surgical repair because of very small, often recanalised lumen, and thickened wall throughout its extracranial course and represent high surgical risk candidates.

Some earlier studies have suggested routine exploration for all patients diagnosed with near total occlusion or string sign of the ICA.[13–16] However, simple identification of possible flow presence by a trace-like wisp of colour in the extracranial ICA was not adequate to verify operability as many of the reported cases ultimately required arterial ligation. This belief is based on the fact that arteriography could not differentiate an operable collapsed ICA with thin walls from an inoperable thickened

and recanalised one. Therefore, it is reasonable to assume that the use of duplex imaging may help identify accurate criteria for operability by measuring residual arterial lumen and wall thickness. In this respect, some authors have suggested operability criteria that included an ICA peak systolic velocity >120cm/sec and a distal ICA calibre of >3mm.[5] Unfortunately, the outer diameter of the ICA often does not always represent its residual lumen, particularly in cases of very small atretic arteries or string sign. As described in this series, we have identified 30 cases of ICA pseudo-occlusions that were assessed and diagnosed by our modified duplex scan protocol. Based on our experience, use of this protocol allows to increase detection of patent ICAs previously believed to be occluded as well as accurately identify the ones that can be successfully operated on.

Materials and methods

Thirty patients were referred to the Vascular Institute of New York for a second opinion regarding their diagnosis of occluded ICA by standard duplex scan protocol (15 cases) or MR angiography plus duplex scan (15 cases). There were 20 males and 10 females whose age ranged from 53 years to 80 years (mean 72.7–6.8 years). Seven of these patients (23%) presented with mild strokes, six (20%) with transient ischaemic attacks, and the remaining 17 patients (57%) were neurologically asymptomatic. Associated risk factors included hypertension (80%), diabetes (47%), smoking (37%) and coronary artery disease (27%). Twenty-four patients (81%) were taking antiplatelet medications (aspirin, 11; clopidogrel, eight) or warfarin (five). All 30 patients had bilateral carotid duplex scans at our Intersocietal Accreditation Commission-accredited vascular laboratory, and these tests were performed by registered vascular technologists with extensive experience in cerebrovascular studies using an ATL HDI 5000 or IU-22 scanner (both Philips).

Modified carotid duplex protocol

Recommended "standard" pre-sets for Doppler and colour modes assessment during extracranial carotid duplex examinations usually include the following values: about 5000Hz pulse repetition frequency (PRF), and medium levels of wall filter, persistence and sensitivity. If patency of the ICA cannot be confirmed (occlusion suggested by lack of colour and Doppler flow) with these settings, then technologists are advised to select "standard" venous pre-set (2000HzPRF; low wall filter for Doppler and colour modes) with the aim of detecting lower flow velocities. As we discovered, whenever colour flow is still not detectable in the ICA with the "venous" settings described above, then the following manoeuvres may be helpful:

1. Use of colour power angiogram (CPA)
2. Use of the lowest PRF for Doppler (1250 Hz), colour (150-350 Hz) and CPA (500 Hz) to demonstrate the slowest detectable flow
3. Increase of colour persistence and sensitivity settings to the maximum available for any particular scanner
4. Increase of CPA persistence and sensitivity to the maximum
5. Use of the lowest wall filter setting for colour, Doppler and CPA modes
6. Careful insonation of the common and external carotid arteries to exclude branches (usually differentiated by higher resistive index) that could mimic a small ICA and
7. Exclusion of an aberrant ICA branch by colour and spectral analysis.

When the ICA still appears occluded after completing the scan with all settings described before, we usually recommend to assess the most distal extracranial segment of the ICA (behind and under the jawline) with a curved configuration 4 to 9 MHz probe. This approach usually extends the field of view and helps visualise a patent ICA segment beyond the area of presumed arterial occlusion.

If above manoeuvres result in identification of colour presence in the ICA, the addition of high definition zooming/magnification allows for more detailed and accurate measurements of the wall thickness and lumen diameter of the stenotic and post-stenotic arterial segments (Figure 1). This assessment and measurements are typically performed using colour and CT angiogram for better lumen definition. Moreover, Doppler spectral waveform analysis is routinely performed in the distal ICA to assure that detected colour actually represents intraluminal ICA flow and not mere motion of a thrombosed ICA caused by CCA pulsatility (Figure 2).

Results

Thirty cases were found to have patent ICAs when subjected to our described modified duplex protocol. The ICA PSV ranged from 5cm/sec to 30cm/sec (mean 16.2±9.4cm/sec) and end diastolic velocity ranged from 0cm/sec to 11cm/sec (mean 3.3±2.8cm/sec) in the poststenotic ICA segment. Resistive index (RI) in the ICA varied from 0.33cm/sec to 1.0cm/sec (mean 0.75±0.2). The outer diameter of the distal ICA varied from 3mm to 4.9mm (mean 3.8±0.55mm) while the luminal diameter varied from 0.5mm to 3.6mm (mean 1.6±1mm). The distal ICA wall thickness ranged from 0.6mm to 1.9mm (mean 1.1±0.4mm) in all cases.
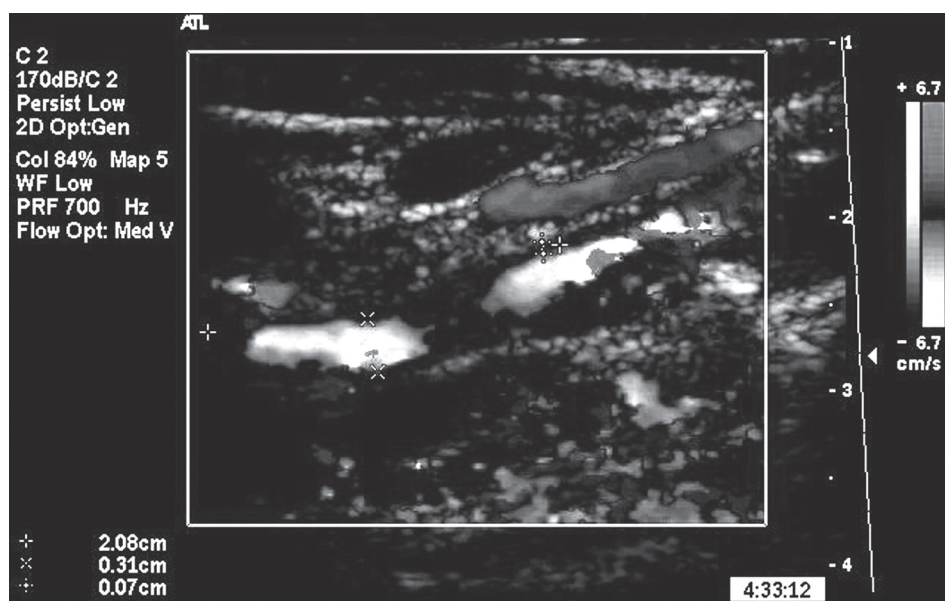
Figure 1: Duplex image of the ICA shown occluded by MR angiogram. Distal post-stenotic ICA assessed with modified protocol showed patent ICA for 2.08cm, with lumen 3.1mm, thin wall 0.7mm, considered operable by our criteria, patient underwent successful carotid endarterectomy.
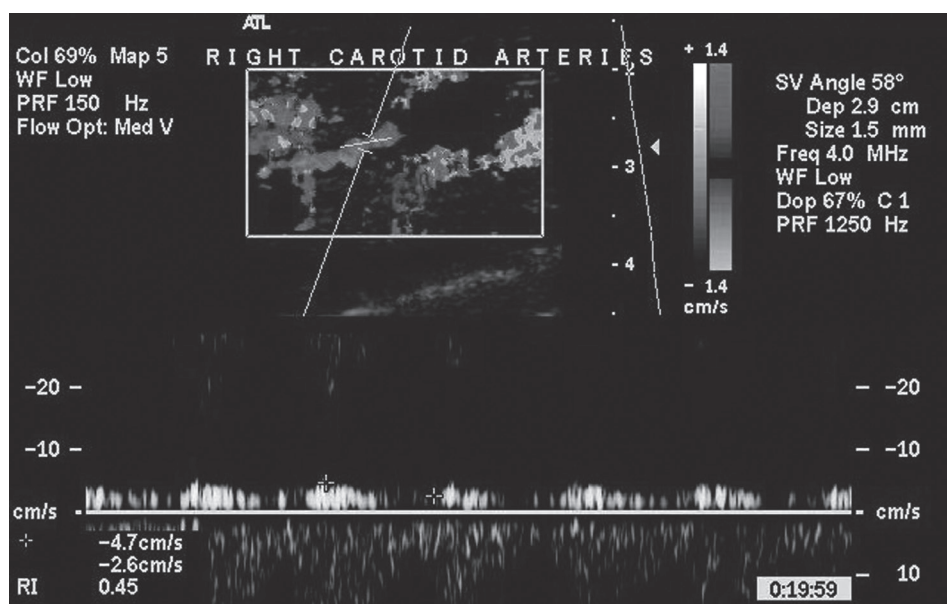
Figure 2: Spectral waveform analysis of the distal ICA depicted in Figure 1. Very low velocities noted; PSV=4.6 cm/sec, EDV=2.6cm/sec.

Surgical treatment

Seventeen of these 30 patients (57%) underwent surgical explorations with the intent of an ICA endarterectomy being performed. Successful ICA endarterectomy with patch angioplasty was possible in 11 of these patients (group one). The ICAs were found to be too small with thickened walls in the remaining six patients (group two). In two of these patients, attempts at endarterectomy were unsuccessful and both ICAs were ligated intraoperatively. In the remaining four symptomatic patients, the ICA was simply ligated primarily. The values of the outer diameter, lumen and wall thickness of the ICA for the 11 patients with successful endarterectomies were compared to the six patients in whom the ICA was ligated. Although the mean outer diameters of operated ICAs (4.16±0.52mm) were significantly larger as compared to ligated ones (3.45±0.24mm; p<0.01 for difference), there were three cases of values overlap. On the other hand, the ICA luminal diameter and wall thickness in all 11 patients who underwent successful endarterectomy surgeries were ≥2mm and ≤1mm, respectively, while they were <2mm and >1mm, respectively in the remaining six patients (p<0.01 for the difference).

Intraoperative findings

All operated patients had general anaesthesia (endarterectomy or ICA exploration with ligation). Critical almost occlusive plaques were present in all 11 cases in group, and superimposed floating clots were also found to extend beyond the stenotic segment in two of these patients. All endarterectomised ICAs were patched (eight synthetic; three vein) and only one patient was shunted. Pulsatile back bleeding from the distal ICA was observed in the remaining 10 patients that were not shunted. The adequacy of the reconstructions was assessed by intraoperative duplex scan performed immediately after cross-clamp release. B-mode imaging, colour flow, CPA and Doppler spectral analysis of operated ICAs did not reveal any

significant residual disease or technical defects. Intraoperative mean ICA volume flows ranged from 55cc/min to 242cc/min (mean 116±49cc/min).

Postoperative ICA duplex scan

Follow-up duplex scans were performed two weeks after endarterectomies and showed mean ICA volume flows ranging from 114cc/min to 251cc/min (mean 174 cc/min±49cc/min). In these patients, the luminal diameter of the ICA increased from a mean of 2.8mm±0.5mm preoperatively to a mean of 4.3mm±0.4mm postoperatively (p<0.001). Absolute mean increase of the ICA lumen was 155±19%. The outer diameter of the ICA increased from a mean of 4.2mm±0.5mm to a mean of 5.6mm±0.5 (p<0.001). The wall thickness of the ICA remained unchanged (0.7mm±0.1mm).

Non-operative treatment

Thirteen patients with ICA lesions considered unreconstructable (wall thickness >1mm and lumen diameter <2mm) are being observed and treated medically (Figure 3). The range and mean values of the outer diameter, lumen and wall thickness of the ICA for all 13 patients were 3mm to 4.6mm (3.7mm±0.5mm), 0.4mm to 1.8mm (0.9mm±0.3mm) and 1.1mm to 1.9mm (1.4mm±0.3mm).

Patient survival and neurologic outcome

One patient who did not undergo surgical exploration died of chronic renal failure and congestive heart failure within the first follow-up month. The remaining 29 patients remain alive and were neurologically asymptomatic from three months to 48 months (mean 28±14).
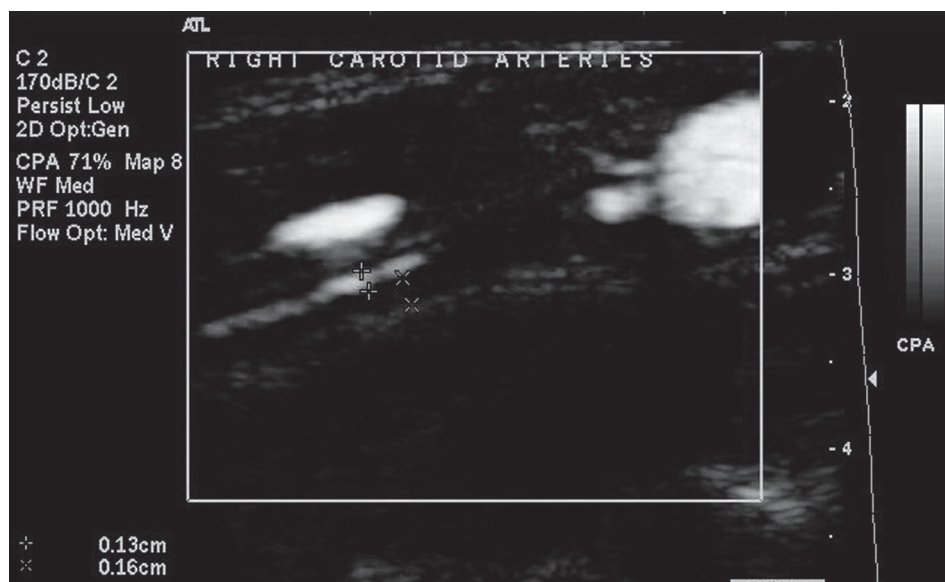
Figure 3: Image of non-operable ICA with long critical stenosis; distal ICA has small lumen (1.3mm) and thickened wall (1.6mm).

Discussion

Duplex scan imaging had significantly advanced and improved over the years and became drastically more accurate and reliable in diagnosis of vascular diseases. These developments allowed physicians and technologists to expand imaging to more complex pathology detection as well as guidance of treatment. In our practice, we have successfully used duplex arterial mapping to replace invasive contrast arteriography for infrainguinal reconstructions in the majority of our patients over last 20 years.[17] In this chapter, we have shown that a modified duplex protocol can help identification of patent ICAs previously thought to be completely occluded by MR angiography studies or standard arterial duplex protocols.

The accuracy of colour flow duplex for the detection of pseudo-occlusions has varied from 83% to 93% when compared to standard contrast arteriography.[4,18]

These results were much better than the 28% accuracy for angiographically-confirmed string sign diagnosed by B-mode and Doppler spectral analysis.[3] In this cohort, none of the patients were subjected to carotid arteriography as we did not believe it would provide additional information to the one obtained by modified duplex study. To expand on assessment of entire ipsilateral carotid system, adequate visualisation of the entire cervical ipsilateral common carotid artery was possible with ultrasound. However, the intracranial portion of the ICA is impossible to evaluate appropriately by duplex; therefore, significant stenoses can at times be missed. Thus, we recommend that an intraoperative completion duplex or arteriographic study be performed to ensure not only the adequacy of the endarterectomy but also the status of the runoff in these high risk cases. Acceptable ICA volume flows (>100cc/min) and low resistive index by intraoperative duplex should corroborate an unimpeded runoff.

Once the diagnosis of pseudo-occlusion is established, the surgeons are presented with a clinical challenge on how to optimally manage this condition. This is mainly caused by the fact that its natural history is not well studied. There are no large series published on this subject and the evidence is limited to a handful of articles describing few patients with relatively short follow-up. For patients presenting with transitory ischaemic attacks or strokes, the surgeon's choices are to perform an endarterectomy or to ligate the ICA to prevent further embolisation. Mehigan has suggested that ligation is a safe alternative for these patients since four of his patients with string sign underwent uneventful ICA ligations.[19] So far, the decision between ligating the ICA vs. performing an endarterectomy appears to be made on the basis of intraoperative findings with the former being applied only when an endarterectomy is deemed technically unfeasible or dangerous. Archie suggests that unless the outer diameter of the ICA is >4mm, one should not expect good results following endarterectomy.[13] Our data, as outlined in this chapter, disagree with his findings and highlight the importance of measuring the lumen diameter and the wall thickness prior to manipulation of vessel. It is a known phenomenon that arterial spasm can develop during dissection and exposure of the ICA and this can certainly interfere with the accurate measurement of both the outer and inner lumen diameter. Indeed, the ICA may enlarge significantly in the subsequent two postoperative weeks. We noticed a 150% increase in lumen diameter of the ICA in this period.

For neurologically asymptomatic patients, the decision to operate is not as obvious, particularly if the surgeon does not know whether the ICA may end

up being ligated. The duplex criteria described in this article may assist in the decision-making process by selecting candidates for endarterectomy. Consequently, it may be used to avoid unnecessary surgery for inoperable arteries.

Although hyperperfusion syndrome is a real threat in patients with critical and chronic ICA stenoses, particularly in presence of contralateral disease, none of our 11 endarterectomy patients had severe headaches, seizures or stroke. It is possible that an increased experience with such cases will show this entity to occur in a small percentage of patients—not high enough to forgo carotid endarterectomy as have been reported by others.[4] Careful attention was given to control of postoperative hypertension in our patients, and this may have contributed to the observed good results despite the presence of severe contralateral carotid disease in two of these patients.

Conclusion

The data presented in this chapter reflect enhanced and expanded capabilities of the contemporary duplex scanners when used by experienced vascular technologist under the supervision of interested vascular surgeons. We feel confident that a thoroughly performed duplex exam can detect a patent ICA previously believed to be occluded by other imaging techniques. Our modified duplex scanning protocol can provide accurate and reliable information regarding patency of the ICA with pre-occlusive lesion even when an MR angiogram, CT angiography or contrast arteriogram demonstrated total occlusion. Furthermore, the wall thickness ≤1mm and lumen diameter ≥2mm have shown to be acceptable predictors of ICA operability. On the other hand, an atretic ICA with lumen diameter <2mm and a thickened wall (>1mm) probably should be ligated for symptomatic patients or observed in the patients with no ipsilateral haemispheric neurologic symptoms.

Summary

- A modified duplex protocol can help identify a patent ICA that was previously thought to be completely occluded on MR angiography, CT angiography and, at times, carotid angiography.

- Contemporary duplex scanners appear to be more sensitive to low flow in the ICA than other imaging modalities.

- Duplex-measured wall thickness ≤1mm and lumen diameter ≥2mm have shown to be acceptable predictors of ICA operability.

- Atretic or recanalised ICAs with lumen diameter <2mm and a thickened wall (>1mm) probably should be ligated for symptomatic patients or observed in the patients with no ipsilateral haemispheric neurologic symptoms.

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Risk of cardiovascular events and death in patients with symptomatic bilateral carotid artery: A population-based cohort study

IU Builyte and DPJ Howard

Introduction

Atherosclerosis is a systemic disease, caused by multiple risk factors, and is the number one cause of death and disability across the globe.[1–3] Numerous studies have shown that multiple arterial beds are often affected and even extensive multi-territory disease can remain silent until a significant, potentially life- or limb-threatening, event occurs (such as myocardial infarction, critical limb ischaemia or stroke.[4] Identifying individuals with extensive disease prior to a major complication is challenging, and the cost-effectiveness of aggressive primary prevention is currently unclear.[5] Medical therapy for the prevention of cardiovascular disease has evolved rapidly over the last two decades with pinnacle studies, such as the Heart Protection Study in 2002, changing practice worldwide.[6] However, despite advances, there are still many high-risk individuals who are dying from cardiovascular events and who are suboptimally treated prior to becoming symptomatic.[2–4]

As the prevalence of diabetes and obesity is rising, together with the ageing population, new and more proactive strategies for cardiovascular risk prevention have to be considered.[7,8] Recently, in patients with stable atherosclerotic cardiovascular disease, the COMPASS trial reported a 30% relative reduction in the risk of cardiovascular events in patients receiving rivaroxaban plus aspirin vs. aspirin alone, albeit with an increased risk of major bleeding.[9] Evidence is also emerging that tighter control of cholesterol levels than the current guideline target (low density lipoprotein [LDL] <2.6mmol/L) may be necessary, with a recent multicentre randomised controlled trial revealing the benefits of LDL reduction to <1.8mmol/L.[10,11] Trials of new cholesterol lowering therapies—proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors—have also focused on populations with stable cardiovascular disease; they report significant reductions in LDL-cholesterol and subsequent cardiovascular events (as compared with placebo) in patients on high-dose statins with LDL levels >1.8mmol/l.[12–14] Although PCSK-9 inhibitors reduce the relative risk of major cardiovascular events by up 25%, they are expensive and may only be cost-effective in selected high-risk subgroups.[15]

Traditional risk factors alone cannot accurately identify higher-risk individuals in need of intensive prevention strategies, and there is ongoing controversy regarding

population screening for cardiovascular disease; the archetypal debate of targeted "high risk" vs. "population-wide" preventive interventions that was first articulated by Geoffrey Rose.[16–18]

Patients with asymptomatic carotid stenosis are a potential high-risk subgroup who are at risk of events in other vascular territories and premature cardiovascular death.[19] The degree of risk in relation to the extent of carotid artery disease has not been quantified, and rates of events are unknown in patients on contemporary best medical therapy. Post-hoc subgroup analysis of patients from ECST (European carotid surgery trial) has shown that patients with bilateral asymptomatic carotid disease are at high risk of future vascular events.[20] However, these data are extrapolated from selected trial patients in the pre-statin era and so, may not be valid to inform current practice.
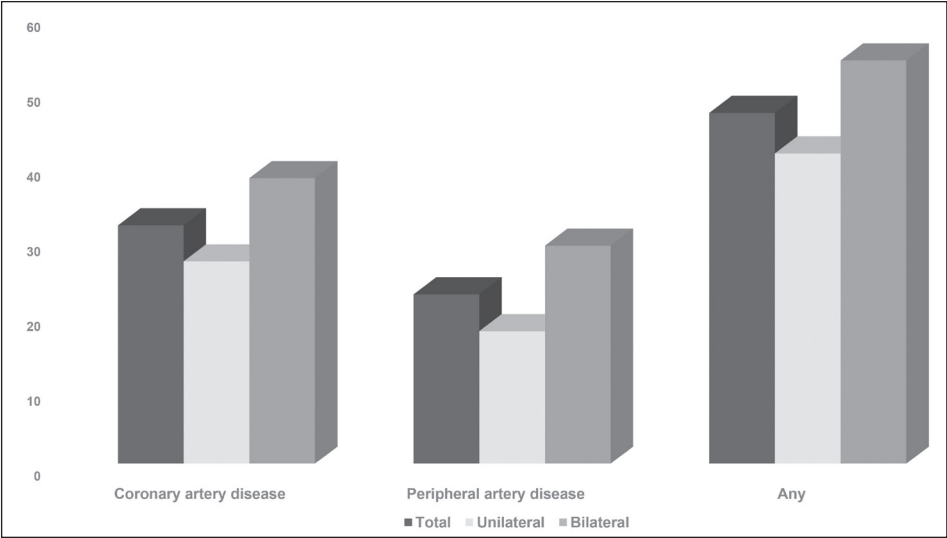
Figure 1: Prior vascular disease.
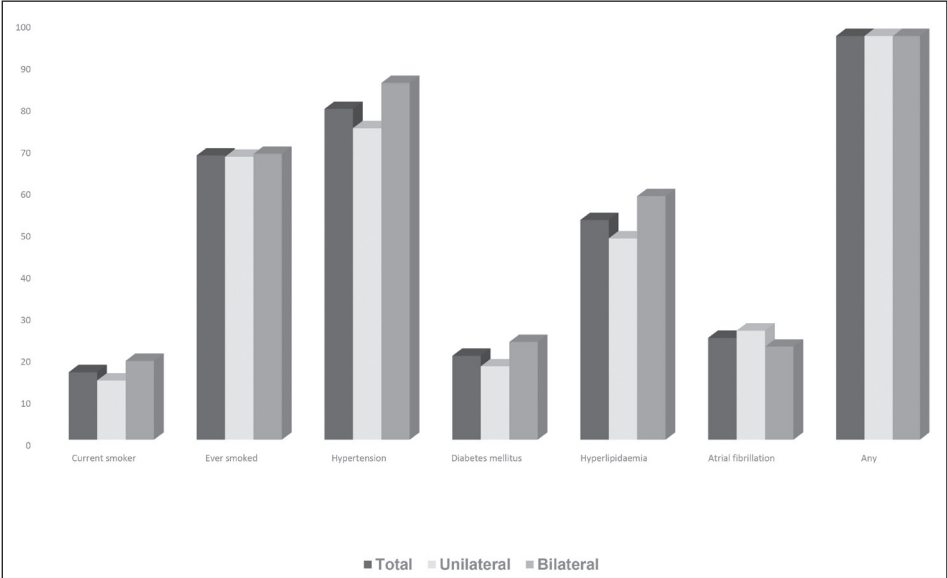
Figure 2: Cardiovascular risk factors.
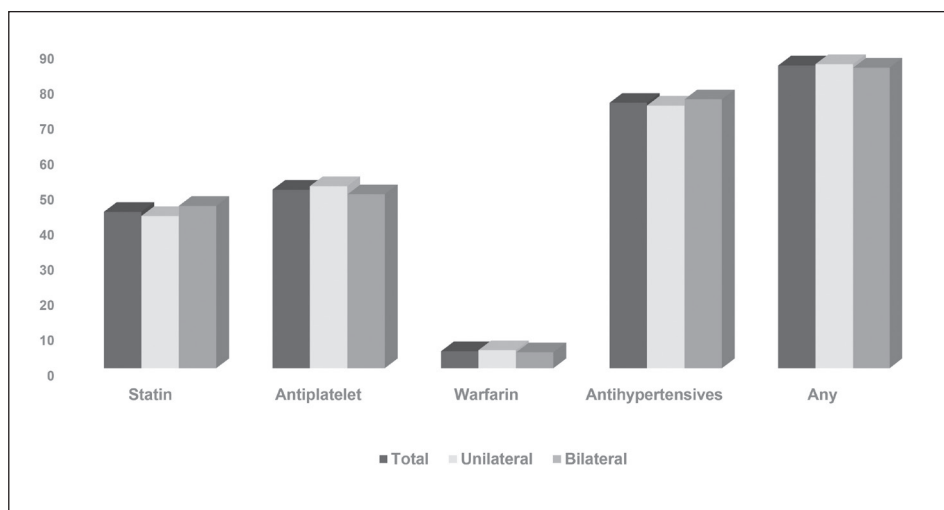
Figure 3: Baseline medical therapy.

Our group has performed the first contemporary analysis of the risk of cardiovascular events and associated death in patients with asymptomatic carotid stenosis participating in OXVASC (Oxford Vascular Study), a prospective population-based cohort study of vascular disease.

Baseline demographic results
OXVASC is a prospective population based study of all acute vascular events in a population, irrespective of age, of 92,728 in Oxfordshire, UK, from 2002 onwards. It connects more than 100 general practitioners. The incidence, outcome, risk factors, and long-term prognosis of all cardiovascular events are determined. For the purposes of this project, all patients detected to have asymptomatic carotid disease from 1 April 2002 to 1 April 2017 were ascertained and followed-up annually. During the 15-year period, 2,178 patients underwent a form of carotid artery imaging with 207 found to have ≥50% asymptomatic carotid stenosis, which resulted in 1,316 patient-years of follow-up (mean 6.4 years). Mean (SD) age in years was 77.4 (10.3) with 57.5% male predominance.

For the 207 identified individuals with asymptomatic carotid disease, cardiovascular comorbidity was significant with coronary artery disease found in 31.9% of patients. Additionally, 11.6% patients had cardiac failure and 22.7% had peripheral arterial disease. Overall, 46.9% had a prior history of any vascular disease (Figure 1). Almost all patients—200 (96.6%)—had at least one cardiovascular risk factor, which included smoking history, hypertension, diabetes mellitus, hyperlipidaemia and atrial fibrillation (Figure 2). Even though almost half of the patients already had vascular disease, and virtually all of them had cardiovascular risk factors, the baseline levels of medical therapy were poor; only 92 (44.4%) patients were on a statin and only 105 (50.7%) were taking an antiplatelet (Figure 3). Following ascertainment, best medical therapy was commenced immediately, resulting in 94% patients being on an antiplatelet and 89% being a statin at one-year follow-up.

The extent and severity of asymptomatic carotid disease

Unilateral stenosis was detected in 118 (57%) patients, and 89 patients (43%) had bilateral disease. Severe stenosis (70–99%) was found in 53 (25.6%), and moderate stenosis (50–69%) was found in 154 patients (74.4%). Prevalence of risk factors, prior medication, and prior vascular disease were similar in patients with unilateral vs. bilateral disease, except for peripheral arterial disease which was found more often in the bilateral stenosis group; 26 (29.2%) vs. 21 (17.8%), p=0.05.

Annual risk of major cardiovascular events and mortality

The overall annual risks of major cardiovascular events and mortality were substantial, but significantly greater in those with bilateral carotid disease vs. those with unilateral disease. For cardiovascular events, the annual risk was 11.6 (8.04–16.22) vs. 6.79 (4.83–9.29); p=0.04 for the difference). And for mortality, risk was 11.39 (8.31–15.24) vs. 8.22 (6.19–10.7); p=0.03 for the difference). Taking into account that intensive medical treatment started after ascertainment, even higher rates of cardiovascular events and deaths could be expected in the general (not treated) population. However, the degree of unilateral carotid stenosis (moderate vs. severe) did not significantly influence the risk for death (p=0.46) or other cardiovascular events (p=0.41) (Figure 6).
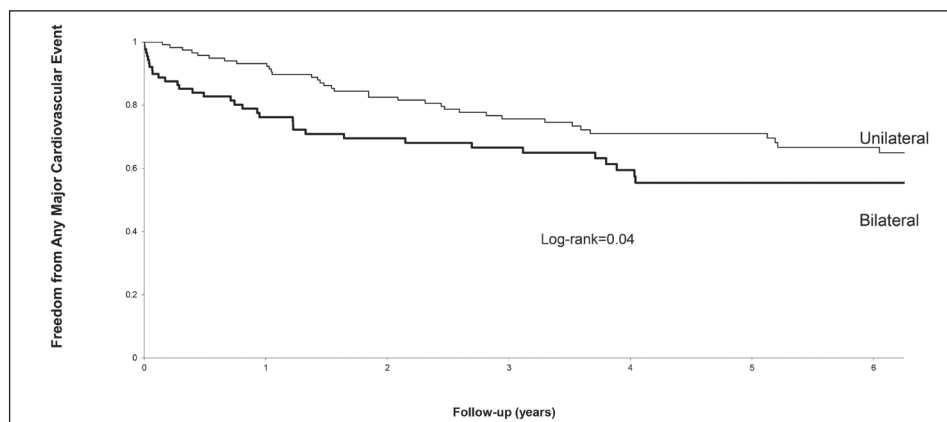
Figure 4: Freedom from any major cardiovascular event by extent of carotid disease (unilateral vs. bilateral).
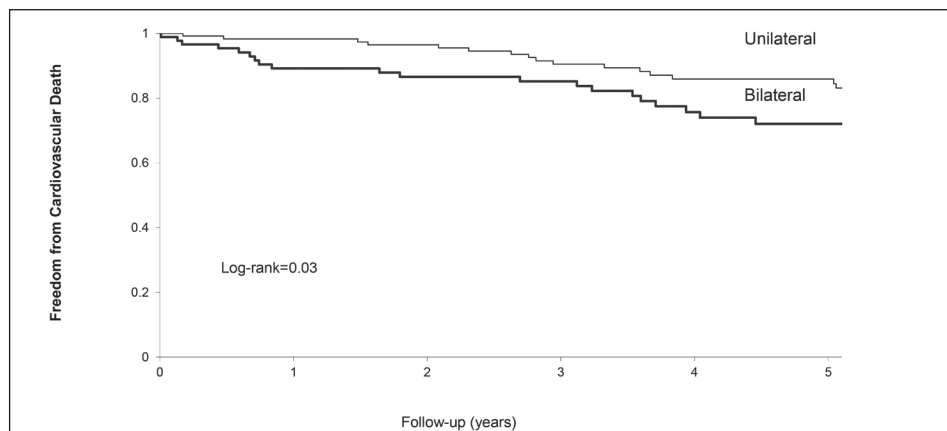
Figure 5: Freedom from cardiovascular death by extent of carotid disease.
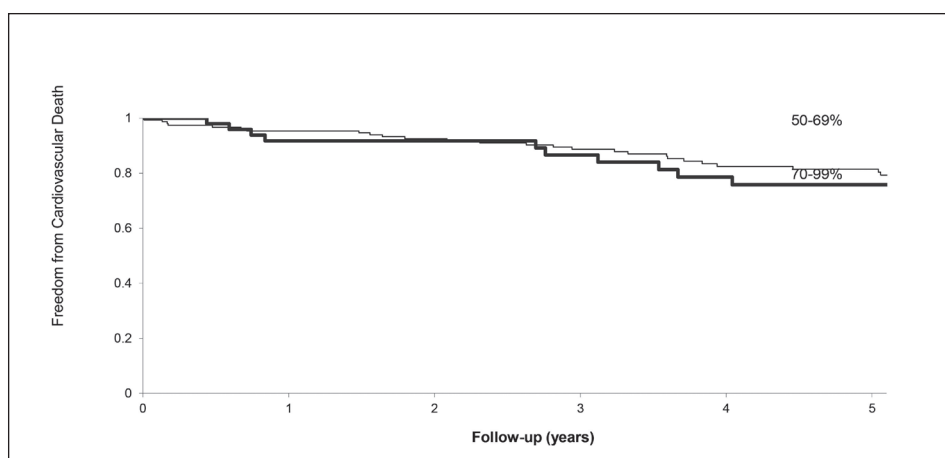
Figure 6: Freedom from cardiovascular death by degree of stenosis.

Conclusion

Identifying and treating individuals at high risk of cardiovascular events and death is an important healthcare strategy. Furthermore, such a strategy is essential if the death and disability from atherosclerotic disease is to be tackled effectively in the next two decades. In our study, we have demonstrated high rates of cardiovascular events and related mortality in patients with asymptomatic carotid disease. Best medical therapy was commenced after ascertainment but prior to this, many of these high risk patients were suboptimally treated—with only 50% receiving effective medical therapy despite the vast majority of them having multiple cardiovascular risk factors or prior cardiovascular disease.

The extent of carotid disease, particularly bilateral moderate-to-severe carotid stenosis, was significantly associated with future cardiovascular morbidity. This finding provides support for intensive medical therapy to be commenced and monitored in all patients found to have asymptomatic carotid disease, whether or not surgical intervention is being considered. Patients with bilateral carotid artery disease are a particularly vulnerable high-risk cohort who may warrant novel agents such as PCSK-9 inhibitor therapy, and combined anticoagulant/antiplatelet therapy. They are also a potential target cohort for future cardiovascular preventive trials.

These findings are highly relevant for clinical practice as, firstly, patients in the OXVASC study received contemporary best medical therapy with high rates of compliance confirmed during follow-up. Secondly, these patients are representative of those diagnosed with asymptomatic carotid stenosis in normal clinical practice, diagnosed following routine carotid artery imaging in the absence of any widespread carotid screening programme. Thirdly, as a population-based prospective study of vascular events with no age limit and near complete ascertainment of all events, our estimate of risk of vascular events is reliable. Finally, OXVASC provides an appropriate population for describing the natural history of asymptomatic carotid stenosis because of the policy of no immediate surgical intervention. Over the last 15 years, this policy has worked extremely well; only 4.8% of patients received carotid endarterectomy for asymptomatic carotid stenosis that remained asymptomatic.

Summary

- Patients with significant (>50% stenosis) asymptomatic carotid disease are at high risk of future cardiovascular events and associated death.

- The extent of carotid artery disease (bilateral vs. unilateral) is associated with significantly increased risk of cardiovascular events and death.

- All patients identified with asymptomatic carotid disease require contemporary intensive medical therapy, whether or not surgical intervention is being considered.

- Patients with bilateral carotid artery disease are a particularly vulnerable high-risk cohort who may warrant novel agents such as PCSK-9 inhibitor therapy and combined anticoagulant/antiplatelet therapy. They are also a potential target cohort for future cardiovascular preventive trials.

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Debate: Outcomes of carotid artery stenting in selected patients are now as good or better than endarterectomy— for the motion

C Huynh and PA Schneider

Introduction

More than 795,000 strokes occur annually in the USA, with more than 80% classified as ischaemic, and approximately 10–20% of these can be attributed to atherosclerotic carotid artery disease.[1–4] Surgical management of carotid artery stenosis is a key component to reduce the incidence of both stroke and death in patients with symptomatic disease.[5,6] Studies have shown that carotid endarterectomy is superior to medical management for symptomatic and high-grade asymptomatic carotid artery disease (in appropriately selected patients).[6,7] While endarterectomy is the most frequently performed surgical procedure to prevent stroke, as interventions have evolved, the use of stenting has continued to develop.

However, stenting (via the transfemoral approach) has been associated with a higher periprocedural stroke risk compared with endarterectomy—especially in patients who have symptomatic disease or who are elderly. On the other hand, the risk of myocardial infarction is higher with endarterectomy.[8–12] When intervention is needed, the decision between endarterectomy and stenting has often been based on individual patient risk factors. A number of randomised controlled trials have compared endarterectomy with stenting, but their results have been conflicting.

Stenting trials

The SAPPHIRE (Stenting and angioplasty with protection in patients at high risk for endarterectomy) trial compared stenting, with an embolic protection device, to endarterectomy in patients who were at increased surgical risk (because of comorbidities) and who had a symptomatic stenosis of ≥50% or asymptomatic stenosis of ≥80%. The trial found no difference in the one-year rate of death, stroke, or myocardial infarction in symptomatic patients (the primary endpoint)—12.2% stenting vs. 20.1% endarterectomy (p=0.004 for non-inferiority and p=0.053 for superiority)—suggesting that stenting is non-inferior to endarterectomy. Also, stenting was associated with a lower cumulative incidence of the primary endpoint in asymptomatic patients (9.9% vs. 21.5%; p=0.02) compared with endarterectomy.[13] After one year, significantly more endarterectomy patients required repeat revascularisation (4.3% vs. 0.6%; p=0.04) than stenting patients.

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Debate: Outcomes of carotid artery stenting in selected patients are now as good or better than endarterectomy —for the motion

At three years, there was no difference in the rate of major adverse cardiac events, death, or stroke between groups.[14]

The EVA-3S (Endarterectomy vs. angioplasty in patients with symptomatic severe carotid stenosis) trial compared stenting vs. endarterectomy in patients with >60% symptomatic stenosis, and it initially reported that the rate of any stroke or death within 30 days after the procedure was higher with stenting than with endarterectomy; however, outcomes were worse in patients with stenting without an embolic protection device—with the rate of stroke/death being 7.9% in patients with embolic protection and 25% in patient without embolic protection (p=0.03).[10] However, after the periprocedural period, the risk of ipsilateral stroke was low and similar in both treatment groups after four years.[15] Similarly, initial results from the SPACE (Stent protected angioplasty vs. carotid endarterectomy) trial, which compared stenting vs. endarterectomy in patients with ≥70% symptomatic carotid stenosis on duplex ultrasound, did not prove non-inferiority of stenting compared with endarterectomy for the 30-day complication rate. However, the rate of recurrent ipsilateral ischaemic strokes reported was not significantly different between the treatment groups after two years of follow-up. The incidence of recurrent carotid stenosis at two years, as defined by ultrasound, was significantly higher with stenting.[16]

The ICSS (International Carotid Stenting Study) was a large multicentre, international randomised controlled trial involving 1,710 patients with >50% symptomatic carotid artery stenosis, who were randomly assigned to treatment with stenting or endarterectomy. The primary endpoint, the cumulative five-year risk of fatal or disabling strokes, was similar between stenting and endarterectomy (6.4% vs. 6.5%; p=0.77).[17] Any stroke was more frequent in the stenting group than in the endarterectomy group, but they were mainly non-disabling strokes. The distribution of modified Rankin scale scores at one year, five years, or final follow-up did not differ significantly between treatment groups, and the long-term risk of disabling stroke was similar for stenting and endarterectomy in symptomatic carotid stenosis.

CREST (Carotid revascularization endarterectomy vs. stenting trial), which included both symptomatic and asymptomatic patients, demonstrated no significant difference between carotid endarterectomy and stenting with embolic protection for severe carotid stenosis in the composite endpoint of stroke, death, or myocardial infarction. Periprocedural rates differed between stenting and endarterectomy groups, with death (0.7% for stenting vs. 0.3% for endarterectomy; p=0.18), increased rate of stroke in stenting (4.1% vs. 2.3% for endarterectomy; p=0.01), and increased rate of myocardial infarction in endarterectomy (1.1% for stenting vs. 2.3% for endarterectomy; p=0.03). Beyond the perioperative period, the incidences of ipsilateral stroke were low for both stenting and endarterectomy (2.0% and 2.4%, p=0.85).[11] At 10 years, postprocedural ipsilateral stroke rates were not significantly different between the stenting and endarterectomy groups (6.9% vs. 5.6% respectively). The incidence of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke did not differ between groups.[18]

ACT (Asymptomatic carotid trial) I compared stenting with embolic protection and endarterectomy in patients 79 years of age or younger who had severe stenosis >80% and were asymptomatic and were not considered to be at high risk for surgical complications. Patients were followed for up to five years, with a primary

composite endpoint of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within one year. Stenting was non-inferior to endarterectomy with regard to death, stroke, or myocardial infarction within 30 days after the procedure (3.8% stenting and 3.4% endarterectomy; p=0.01 for non-inferiority). The rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the endarterectomy group (p=0.33). The cumulative five-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group (p=0.44); thus, the authors concluded stenting was not inferior to endarterectomy with regards to death, stroke, or myocardial infarction within 30 days after the procedure in this patient cohort. They also noted that were no significant differences between the study groups in the rates of non–procedure-related stroke, all stroke, and survival.[19]

Development and results of transcarotid artery revascularisation

Currently, stenting is considered in selected patients, such as those patients with high risk factors for endarterectomy because of comorbidities, previous endarterectomy with recurrent stenosis, and patients with a history of radiation treatment to the neck. The potential for a higher rate of perioperative stroke in stenting compared to endarterectomy is probably from emboli shed during the procedure, during aortic arch manipulation, and insufficient cerebral protection when first crossing the diseased lesion with a wire with no distal protection.[11,20] Additionally, even with an embolic protection filter in place, there may also be microembolic events because of the fit of the embolic filter within the artery, porosity of the filter, or thrombus formation on the surface of the filter, with a higher frequency of new ischaemic lesions seen on diffusion-weighted magnetic resonance imaging (DWI MR) after stenting compared to endarterectomy.[21–23]

Cerebral protection via reversal of carotid arterial flow was developed to address concerns regarding increased periprocedural stroke rate in patients undergoing stenting. Transcarotid artery revascularisation (TCAR) involves the Enroute transcarotid neuroprotection and stent system (Silk Road Medical) and proximal clamping and flow reversal from the common carotid artery to the contralateral femoral vein prior to any manipulation of the carotid bifurcation lesion. A short incision and exposure of the common carotid artery is performed at the base of the neck. A sheath is placed into the common carotid artery with a 2.5cm tip. An arteriovenous circuit is established between the common carotid artery and the femoral vein. The proximal common carotid artery is clamped. The carotid stent is placed via transcarotid route, thus avoiding aortic arch manipulation. Reversing cerebral blood flow during lesion manipulation and stent placement, and for a few minutes afterward, reduces the possibility of embolic events and debris traveling to the brain. This approach has been demonstrated to minimise the risk of cerebral embolisation and has comparable rates, on DWI MRI imaging, to those demonstrated with endarterectomy.[24]

TCAR is indicated in patients who are have high risk factors for endarterectomy because of anatomic or medical comorbidities. ROADSTER (Safety and efficacy study for reverse flow used during carotid artery stenting procedure) was a prospective, single-arm, multicentre trial to evaluate the use of the Enroute transcarotid neuroprotection system during stenting procedures in patients

considered to be at high risk for complications from carotid endarterectomy. Symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥70% stenosis were enrolled. The study compared outcomes of TCAR in high surgical risk patients with standard surgical risk patients for endarterectomy in CREST, showing a difference in rate of 30-day perioperative stroke (1.4% TCAR vs. 2.3% endarterectomy), a 30-day rate of combined perioperative stroke and death of 2.8% for TCAR and 2.6% for endarterectomy, and 0% unresolved cranial nerve injury vs. 2% for endarterectomy. The risk of myocardial infarction was 1.4% for TCAR vs. 2.3% in patients undergoing endarterectomy.[25]

Subsequently, the ROADSTER 2 trial included expanded use of the TCAR device to include 70% of new sites for real-world usage of Enroute transcarotid stent with the Enroute transcarotid neuroprotection system, with endpoints including procedural success at 30 days after TCAR and the rates of cranial injury, death, stroke, and myocardial infarction. The ROADSTER 2 trial included 21% of patients who were over the age of 80, 26.1% who are symptomatic, and 10% who have a contralateral carotid artery occlusion. Additionally, 19.3% of patients had prior endarterectomy. Results from the ROADSTER 2 trial have a reported stroke rate of 0.6%, and combined stroke and death rate of 0.8% among per protocol patients. Overall, the ROADSTER data has demonstrated that TCAR is a safe and effective option in the treatment of extracranial carotid stenosis, with excellent outcomes in high-risk patients, and those with symptomatic disease.

Recent studies to further assess the safety of TCAR in patients have used data from Society for Vascular Surgery Vascular Quality Initiative TCAR Surveillance Project (SVS VQI TSP) to analyse outcomes in a real-world setting comparing patients undergoing endarterectomy, stenting, and TCAR. Schermerhorn *et al* examined the in-hospital outcomes of patients undergoing TCAR and endarterectomy from January 2016 to March 2018 by using the SVS VQI TSP and SVS VQI endarterectomy database, with examined primary outcomes of in-hospital stroke and death. Comparable stroke and death rates were demonstrated between TCAR and

	CEA (n=62032)	TCAR (n=3435)	P-value
In-Hospital Outcomes			
Death	163 (0.3)	15 (0.4)	0.06
Ipsilateral Stroke	587 (0.95)	37 (1.1)	0.44
Stroke	784 (1.3)	42 (1.2)	0.83
Stroke/Death	884 (1.4)	52 (1.5)	0.67
Stroke/Death/MI	1278 (2.1)	69 (2.0)	0.84
Cranial Nerve Injury	1661 (2.7)	11 (0.4)	<0.001
Post-procedural Hypotension	6049 (9.8)	462 (13.5)	<0.001
Post-procedural Hypertension	11863 (19.2)	457 (13.4)	<0.001
Bleeding with intervention	639 (1.0)	51 (1.5)	0.01
LOS more than 1 day	19,540 (31.5)	1000 (29.1)	<0.01

Table 1: Transcarotid artery revascularisation compared to carotid endarterectomy in-hospital outcomes on univariable analysis.[27]

endarterectomy. Also, TCAR patients were more likely to be older, symptomatic, and with more medical comorbidities such as chronic obstructive pulmonary disease, coronary artery disease, chronic heart failure, and chronic kidney disease. On adjusted analysis, there was no difference in terms of stroke/death, stroke/death/myocardial infarction, or individual outcomes, with the in-hospital stroke rate for TCAR reported to be 1.4%, compared to 1.2% for endarterectomy, and no statistically significant different in re-do carotid intervention stroke rate 1.9% for TCAR compared to 1.6% for endarterectomy. TCAR patients were also reported to be less likely to have cranial nerve injuries (Table 1).[26,27]

Malas *et al* compared the outcomes between TCAR and stenting using the SVS VQI TSP database and reported that TCAR was safer than stenting with lower odds of in-hospital adverse neurological events, TIA, stroke, or death compared to TCAR.[28] Outcomes of TCAR and stenting were also compared using the SVS VQI TSP and Carotid Stent Registry of asymptomatic and symptomatic patients in the USA and Canada undergoing transcarotid artery revascularisation and transfemoral carotid artery stenting for carotid artery stenosis, from September 2016 to April 2019. TCAR was associated with a lower risk of in-hospital stroke or death (1.6% vs. 3.1%; p<0.001), stroke (1.3% vs. 2.4%; p=0.001), and death (0.4% vs 1.0%; p=0.008). There was no statistically significant difference in the risk of perioperative myocardial infarction between the two groups (0.2% for TCAR vs. 0.3% for stenting). At one year, TCAR was associated with lower risk of ipsilateral stroke or death (5.1% for TCAR vs 9.6% stenting; p<0.001); however, TCAR was associated with a higher risk of access site complications needing intervention, but lower fluoroscopy time and less contrast administration compared with stenting. This study demonstrated that TCAR, compared with transfemoral carotid artery stenting, had a significantly lower risk of stroke or death.[29]

Patient selection strategy

Anatomic requirements for the selection of patients for TCAR include a non-diseased common carotid artery access site, a length of 5cm minimum from access site to bifurcation lesion, and a common carotid artery diameter of 6mm or larger. This is assessed preoperatively using CT angiography. Appropriate carotid lesions for stent placement must also be selected, which include those without the following; circumferential calcification, non-circumferential calcium of >3mm thickness, severe tortuosity or fresh luminal thrombus.

Conclusion

The decision between endarterectomy and TCAR in patients who need repair of atherosclerotic carotid artery bifurcation disease must be individualised based on comorbid conditions and anatomic characteristics of the patient. Multiple studies have shown that the results of carotid stent placement using TCAR are as good or better than stenting.

Summary

- Prospective neurologically controlled studies have demonstrated low stroke and death rates with TCAR in high-risk patients that are consistent with carotid endarterectomy in standard risk patients.

- The VQI database demonstrates low stroke and death rates for TCAR in real world practice that compares favourably with endarterectomy.

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Debate: Outcomes of carotid artery stenting in selected patients are now as good or better than endarterectomy—against the motion

M Machin, S Onida and AH Davies

Introduction

Carotid artery stenosis causes significant morbidity and mortality, accounting for approximately 8% of all ischaemic strokes.[1] The National Institute for Health and Care Excellence (NICE) guidelines, updated in 2019, recommend that patients suffering from transient ischaemic attacks or non-disabling strokes who have ipsilateral carotid stenosis of 50–99% undergo urgent assessment for carotid endarterectomy.[2] NICE recommends that if the carotid stenosis is <50%, despite presence of symptoms, patients should be managed with best medical therapy alone.[2] The benefits of carotid endarterectomy in symptomatic patients with >70% carotid stenosis for stroke prevention has been clearly demonstrated previously by pooling results from ECST (European carotid surgery trial), NASCET (North American symptomatic carotid endarterectomy trial), and the Veterans affairs trial.[3]

Carotid artery stenting offers an endovascular alternative to carotid endarterectomy, suggested as a viable option in those deemed high-risk for open carotid endarterectomy due to medical comorbidities or operative technical factors. NICE guidelines on carotid artery stenting, last updated in 2011, currently recommend this as a viable option after discussion at a neuroradiology multidisciplinary team meeting when carotid endarterectomy would not be suitable.[4]

However, rates of carotid artery stenting in the UK are still low. Numbers taken from the Hospital Episode Statistics suggest that as few as 265 carotid artery stenting procedures were undertaken in 2017.[5] There are far more carotid artery stenting procedures undertaken in the USA even when considering the population size, with as many as 10,208 procedures undertaken in 2014 based on Medicare claimants.[6] This is likely to reflect, in the UK, the impact of the more restrictive NICE guidelines. There is current debate as to whether carotid artery stenting has a larger role to play in those patients that are at "high-risk" of undergoing open carotid endarterectomy.

Carotid artery stenting or carotid endarterectomy?

Carotid artery stenting was first performed using a bare metal stent in 1989.[7] Subsequent use of neuroprotection devices was introduced in 1990 to reduce

the risk of embolic events from the stent site and risk of periprocedural stroke.[8] Newer devices include self-expanding, coated and drug-eluting stents. There is current debate over whether the less invasive endovascular approach renders carotid artery stenting a more attractive procedure in patients deemed high-risk for carotid endarterectomy.

The Society of Vascular Surgery (SVS) guidelines for management of extracranial carotid disease state that carotid artery stenting is preferred to carotid endarterectomy in symptomatic patients with ≥50% stenosis and the following technical factors:[9]

- Prior ipsilateral carotid endarterectomy
- Tracheal stoma
- External beam irradiation resulting in fibrosis of the tissues of the ipsilateral neck
- Prior cranial nerve injury
- Lesions that extend proximal to the clavicle or distal to the C2 vertebral body.

Furthermore, the SVS guidelines also recommend carotid artery stenting when the patient has any of the following medical factors:

- Non-correctable coronary artery disease
- Heart failure
- Chronic obstructive pulmonary disease.

These recommendations are also mirrored in the 2019 clinical guideline for peripheral vascular disease produced by the European Society of Cardiology (ESC) and the European Society for Vascular Surgery (ESVS), which recommend that carotid artery stenting should be offered in both symptomatic and asymptomatic patients in the presence of a patient or technical factors that makes carotid endarterectomy "high-risk".[10]

However, it is argued that the evidence that underpins these recommendations is generally inconclusive and of low quality. Hence, the matter is up for debate as to whether carotid artery stenting should be used in place of carotid endarterectomy in selected patients.

Carotid artery stenting in selected patients is now as good as or better than carotid endarterectomy in selected patients

Carotid artery stenting demonstrated promise in patients deemed to be high-risk for carotid endarterectomy in the SAPPHIRE (Stenting and angioplasty with protection in patients at high risk for endarterectomy) trial.[11] This trial deemed that carotid artery stenting was non-inferior to carotid endarterectomy in patients that have at least one variable that would render carotid endarterectomy high risk.[11] Briefly, 334 patients who met criteria to be suitable for either carotid artery stenting or carotid endarterectomy intervention but had at least one factor rendering them high-risk for carotid endarterectomy were randomised. Composite outcome of death, stroke or myocardial infarction at 30 days was lower in patients receiving carotid artery stenting compared with carotid endarterectomy (12.2% vs. 20.1%), resulting in an absolute risk reduction of 7.9% and reaching significance for non-inferiority (p=0.004). However, the SAPPHIRE trial was criticised for a variety

of reasons including being industry-supported and having a high periprocedural stroke risk.

Carotid artery stenting can be undertaken with minimal disruption to cerebral blood flow. A recent systematic review deemed that the stroke risk was the same for patients with contralateral carotid occlusion undergoing carotid artery stenting or carotid endarterectomy.[12] However, we would highlight that these are all observational studies and are subject to confounding by indication. It is likely patients undergoing carotid artery stenting had more challenging anatomy or a hostile neck. The increase in mortality rate, but not stroke rate, with carotid artery stenting also suggests that the patients were confounded by more severe medical comorbidities. Hence, in an interventional study a more favourable effect may be demonstrated.

Furthermore, the difficult dissection encountered in patients that have undergone neck radiotherapy may result in carotid artery stenting being superior. A meta-analysis was performed pooling 533 patients whom had undergone radiation therapy to the neck, 361 of whom underwent carotid artery stenting and 172 underwent carotid endarterectomy. This identified a non-significant difference in 30-day risk of stroke in patients receiving carotid artery stenting in comparison to carotid endarterectomy (3.9 vs. 3.5%, p=0.77). However, the risk of cranial nerve injury was significantly higher in the carotid endarterectomy group, with a pooled risk of 9.2% suggesting the open dissection was difficult and resulted in nerve injury. This is of particular importance if contralateral intervention is planned in the future.

It has been clearly demonstrated that carotid artery stenting confers a lower perioperative risk of myocardial infarction compared to carotid endarterectomy.[13] Therefore, in patients with known coronary artery disease who are at risk of myocardial infarction, carotid artery stenting offers a lower risk intervention.

Furthermore, developments in carotid artery stenting technique may be able to reduce the perioperative stroke risk associated with the classical femoral access technique for carotid artery stenting. Transcarotid artery revascularisation is a novel technique in which the common carotid artery is cannulated and the blood flow is reversed away from the brain towards the device itself and returned into the femoral vein (see Figure 1).[14] Such that, in theory, any debris caused by stenting of the plaque is collected in the reverse flow device.

There is currently no high-quality evidence from randomised controlled trials to support the use of transcarotid artery revascularisation; however, data from registries presented at international conferences suggest an in-hospital perioperative stroke risk as low as 1.4%.[15] If this technique can successfully lower perioperative stroke risk, then transcarotid artery revascularisation could be ideally suited for patients with ischaemic heart disease who would be at risk of myocardial infarction during carotid endarterectomy. Furthermore, if the perioperative stroke rate to be lowered to that of contemporary carotid endarterectomy, then a non-inferior trial of transcarotid artery revascularisation vs. carotid endarterectomy would be required for unselected patients.
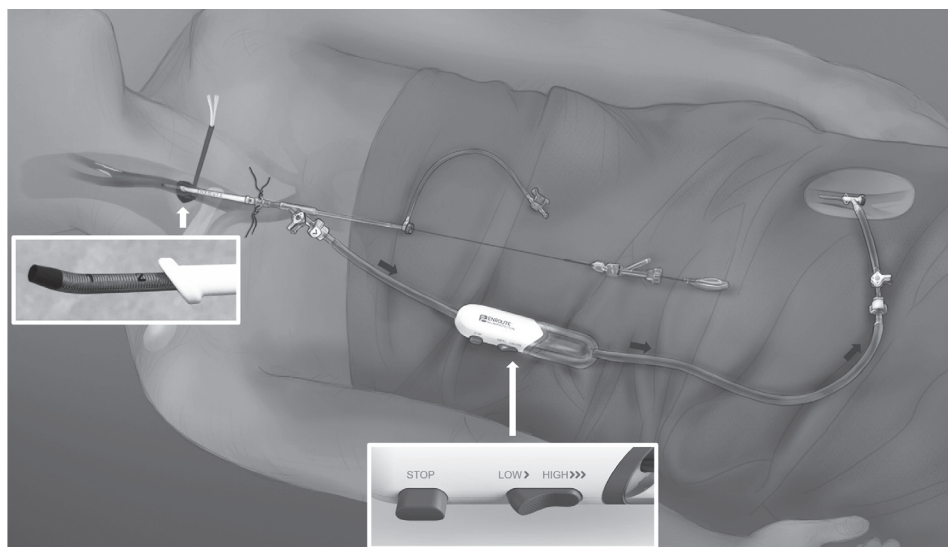
Table 1: Transcarotid artery revascularisation in which the common carotid artery is cannulated and the blood flow is reversed away from the brain towards the device itself and returned into the femoral vein.

Carotid artery stenting is never as good as carotid endarterectomy

The initial benefits reported in the SAPPHIRE trial can be easily criticised. As highlighted in the ESVS 2017 guidelines, at least 70% were asymptomatic patients, 6% of whom subsequently had a stroke or died after intervention and hence received no benefit regarding stroke prevention.[16] Therefore, the analysis on non-inferiority is relatively futile as the selected population received no benefit from either intervention. The only use for this evidence is to suggest avoiding either intervention.

Furthermore, more pragmatic data have suggested the opposite effect. A retrospective analysis was performed of 51,492 patients in the Vascular Quality Initiative database who underwent carotid artery stenting or carotid endarterectomy for symptomatic or asymptomatic carotid stenosis.[17] Carotid endarterectomy was performed in 44,912 cases and carotid artery stenting was performed in the remaining 7,030 cases. Patients were classified as high risk or normal risk of undergoing carotid endarterectomy based on the Centers for Medicare and Medicaid Services policy— one that mirrors the inclusion criteria of the SAPPHIRE trial. Analysis based on 2,920 matched pairs, matched on preoperative variables, was performed comparing stroke risk in carotid artery stenting vs. carotid endarterectomy in patients who were at high risk of undergoing carotid endarterectomy. The analysis revealed a higher risk of 30-day and two-year stroke risk in patients in the carotid artery stenting in comparison to the carotid endarterectomy, despite them all being at high risk of undergoing open carotid endarterectomy (two-year risk: HR: 1.65, p=0.03).

Regarding high-risk criteria, it is interesting that patients >80 years of age were deemed to be at high risk for carotid endarterectomy as the evidence suggests that older patients are best treated with open surgery in comparison to carotid artery stenting.

Meta-analysis pooling 4,754 patients who were randomly assigned to carotid endarterectomy or carotid artery stenting for treatment of symptomatic carotid stenosis from four randomised-controlled trials in the Carotid Stenosis Trialists' Collaboration stratifying for age was undertaken.[18] Periprocedural stroke (<120 days) and stroke within median follow-up time of 2.7 years was used as the primary outcome. In patients undergoing carotid artery stenting, periprocedural risk of stroke and death in patients aged 65–69 years was higher vs. patients aged 70–74 years (HR 4·01, CI 2.19–7·32). There was no relationship between age and poor outcome in patients undergoing carotid endarterectomy. Comparison of the two interventions in patients aged 70−74 years revealed that carotid artery stenting had a higher risk of stroke and death in comparison to carotid endarterectomy (HR 2.09, CI 1·32–3·32).

Additionally, regarding patients with cardiovascular and respiratory disease, we are not aware of a randomised controlled trial that compares carotid artery stenting to carotid endarterectomy under local anaesthesia alone with patients sat upright to minimise cardiopulmonary complications. Hence, it could be argued that carefully planned carotid endarterectomy under local anaesthetic is the procedure of choice given the lower periprocedural stroke risk.

It appears logical that carotid artery stenting offers benefit in certain scenarios which would render carotid endarterectomy technically challenging. Theoretically, the disruption of blood flow during artery stenting is minimal, which would be advantageous in contralateral carotid occlusion.

However, a retrospective analysis of data from the American College of Surgeons National Surgical Quality Initiative Project, including 11,948 patients who underwent carotid endarterectomy and 422 who underwent carotid artery stenting, demonstrated that contralateral carotid occlusion was indeed associated with increased risk of stroke, but the risk was the same across both carotid artery stenting and carotid endarterectomy groups.[19] Therefore, contralateral carotid occlusion is simply a marker of risk rather than an indication for carotid artery stenting.

Lastly, cerebral hyperperfusion syndrome is likely responsible for a significant proportion of perioperative death and stroke risk. This occurs in ~1% of patient undergoing carotid endarterectomy if the postoperative blood pressure is poorly controlled.[16] However, the act of placing a stent in the carotid artery reduces its ability to modulate cerebral blood flow, decreasing transit time and increasing cerebral blood flow.[20] An analysis pooling 8,731 carotid artery stenting procedures revealed an estimated risk of developing hyperperfusion syndrome to be 4.6%, a value much higher than experienced in carotid endarterectomy.[21] Despite the use of reverse flow devices and the theoretical unproven reduction in cerebral emboli, this problem will remain and contribute to the increased risk associated with the procedure.

Conclusion
Carotid artery stenting is associated with an increased risk of perioperative stroke in compared to carotid endarterectomy. Based on current evidence, carotid artery stenting is still inferior to carotid endarterectomy in patients deemed high risk for carotid endarterectomy.

Carotid artery stenting is associated with a lower risk of biochemical perioperative myocardial infarction; however, it is unclear if those with cardiopulmonary disease would be better served with carotid artery stenting in comparison to carotid endarterectomy under local anaesthesia.

Novel techniques aim to reduce the cerebral emboli and subsequent perioperative stroke risk that appear promising, but there is currently a lack of evidence to support these procedures.

Summary

- Carotid artery stenosis causes significant morbidity and mortality.

- Current guidelines recommend assessment for carotid endarterectomy in the treatment of symptomatic carotid stenosis with 50–99% occlusion.

- There is current debate as to whether carotid artery stenting has a larger role to play in those patients that are at "high-risk" of undergoing open carotid endarterectomy.

- Carotid artery stenting is considered in patients with the following technical factors: prior ipsilateral carotid endarterectomy, tracheal stoma, previous neck radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body.

- Carotid artery stenting is considered in patients with the following medical factors: non-correctable coronary artery disease, heart failure and chronic obstructive pulmonary disease.

- Based on current evidence, carotid artery stenting is still inferior to carotid endarterectomy in patients deemed "high-risk" for carotid endarterectomy.

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Intervention in extracranial carotid aneurysms: Indications and techniques

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Introduction

The extracranial carotid artery aneurysm (ECAA) is a rare vascular pathology that accounts for less than 1% of all peripheral artery aneurysms.[1–7] The extracranial carotid artery includes the common carotid artery arising from the aortic arch and brachiocephalic artery, external carotid artery, and the internal carotid artery till the skull base. ECAAs are mostly located at the carotid bifurcation or the distal part of the internal carotid artery.[5,8] Morphologically, the aneurysms are usually considered either fusiform or saccular (Figure 1). In general, a dilatation of 1.5 times the non-affected contralateral artery is defined as aneurysm, but for saccular shaped extracranial aneurysms, any distension is accepted.[1–8] In case of bilateral dilatation, the diameter of the non-affected ipsilateral artery is used as reference. Non-affected mean diameters of the common carotid artery range from 6.0mm in women to 6.5mm in men and for the internal carotid artery from 4.5mm and 6.0mm respectively.[9]

The first literature reporting extracranial aneurysms was by Sir Astley Cooper (1768–1841), being one of the first surgeons to operate on an aneurysm of the common carotid artery in 1805.[10] Despite having knowledge of ECAAs back then, our current insight into natural history or optimised care for carotid aneurysms is still minimal in comparison with our knowledge of the much more prevalent carotid occlusive or stenotic disease. As a starting point to gain knowledge, the international carotid aneurysm registry (CAR) was initiated in 2014 based in the University Medical Center Utrecht, to register data of this seldom seen disease in a prospective manner.[11] The registry currently includes 417 patients from more than 30 centres worldwide (dated December 2019).

Aetiology and pathogenesis

Vascular physiology

In general, the cellular composition of the blood vessels are the same throughout the entire cardiovascular system. Every blood vessel wall contains the following basic components: endothelial cells, smooth muscle cells and the extracellular matrix including elastin, collagen and glycosaminoglycans.[12] The vessel wall comprises three separated layers:
- The luminal intima, consisting of one layer of endothelial cells with minimal underlying subendothelial connective tissue and supported by the internal elastic lamina
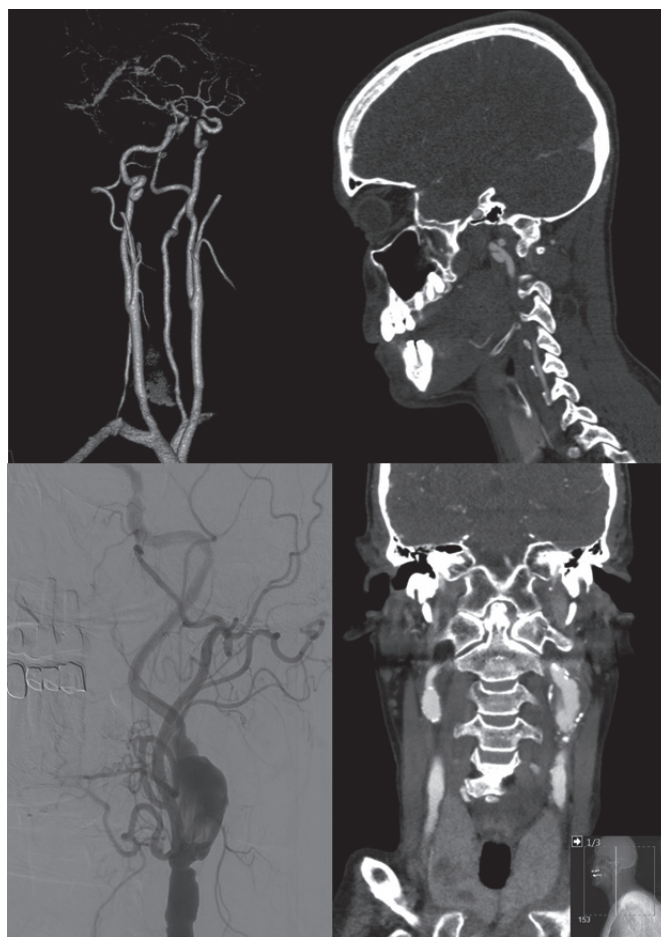
Figure 1: CT angiogram and digital subtraction angiography reconstruction of ECAA patients. (Top) Saccular aneurysm of the right internal carotid artery. (Bottom) fusiform aneurysm of the left internal carotid artery.

- The media, formed by smooth muscle cells that can constrict or dilate the vessel and lined by the external elastic lamina
- The adventitia, the outermost layer that contains mostly connective tissue with nerve fibres and the vasa vasorum (Figure 2).

All the basic cellular components of the vessel wall and their integrated functions are key to the homeostasis of the vasculature subject to haemodynamic and biochemical stimuli. Based on anatomic site and dynamic environmental factors, the phenotype of separate vascular layers differs, though a similar cascade is observed in case of vascular injury. Normally, vascular remodelling stops when the endothelial cell layer is intact or the chronic stimulation comes to a hold. However, an exaggerated healing response at lesion-prone areas may lead to cellular changes initiating stenosis, occlusion or wall weakening in aneurysmal disease.[13–17]

Development of aneurysms

Since cellular dysfunction or imbalance can occur in the entire vasculature, wall weakening can occur in any blood vessel.[12,13] Most aneurysms are considered a focal manifestation of a underlying systemic condition. Predisposing genetic and environmental factors may determine which individual develops an aneurysm; regional factors are presumably determinants of the vascular site.[12] Literature indicates aneurysms are most prone to develop in locations where the vasculature bifurcates (e.g. circle of Willis), or where impingement is prone to extensively test compliance and elasticity of the vessel wall (e.g. the infrarenal aorta), or a combination of both by ectatic vessels with less tone and sharpened (branched) angles.[12–14,17] This could partly contribute to the prone location of ECAAs around the carotid bifurcation.[5,8]

Presumed aetiologies of ECAA

In fusiform or true aneurysms, every layer of the vessel wall is affected and most reported causes for true ECAAs are atherosclerotic changes, mycotic (such as Behcet's disease or human immunodeficiency virus) and connective tissue diseases (for example fibromuscular dysplasia, Ehlers-Danlos or Marfan syndrome). For
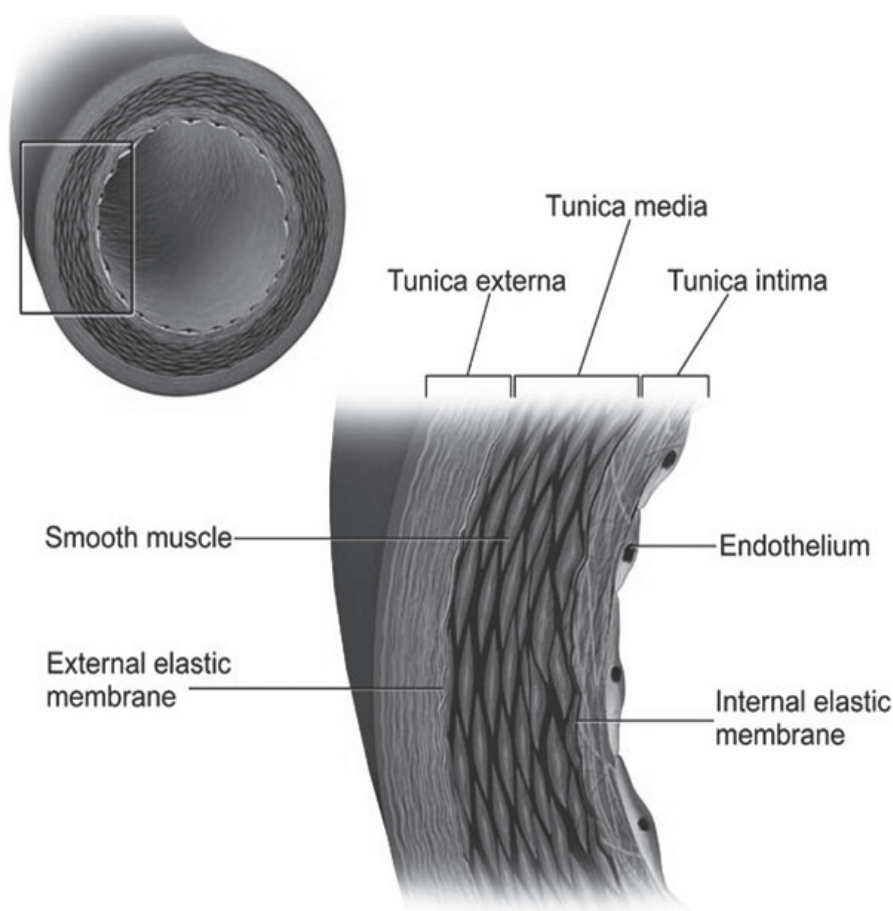
Figure 2: Schematic overview of the vascular arterial wall.

saccular or pseudo-aneurysms, only the luminal intima layer is affected, mostly by dissection that can occur either spontaneous or traumatic.[1–8, 18,19] In observations of the carotid aneurysm registry, these post-dissection ECAAs are mostly located in the distal part of the extracranial internal carotid artery. One study histopathologically examined 13 ECAA patients treated surgically, indicating two distinct aneurysms: degenerative and post-dissection.[20] Since inflammatory cell infiltration and medial loss of elastin was observed in both aneurysms, the authors pointed out that the distinctive categories could be different stages of the same disease.

Dissection of the carotid artery seems to play a larger role in ECAA development than previously thought, and will be explored further by the carotid aneurysm registry research team in a recent collaboration with an international consortium of cervical artery dissection centres. Another observation in the registry research is the possible association with tortuosity (or kinking or coiling) and ECAAs, or aneurysm formation in general.[21–23] This has been mostly investigated in intracranial arteries where tortuosity induces haemodynamic disturbances with increased wall shear stress and predisposes aneurysm formation.[21,22] The same increased wall shear stress as caused by tortuous arteries have been associated with cervical dissection.[24,25] The question remains if tortuosity without carotid dissection also predisposes ECAA formation, and the results of a case-controlled study of extranical aneurysm and healthy patients is expected in 2020.[26]

Genetics

For rare vascular diseases like Marfan or Ehlers-Danlos syndrome, genetic clinical utility has been proven and applied, but for more common complex diseases like aneurysmal disease, the interpretation and translation of large-scale genetic studies is challenging at best.[27,28] Since abdominal, thoracic aortic and intracranial aneurysms are most prevalent, genetic derived association studies were mainly investigated in these patient groups. Despite differences in vascular structure and clinical risk factors of aortic and intracranial aneurysms, utility of genetic developments in one arterial bed may be translated beneficially to another. Abundant retrospective research indicates co-prevalence of different aneurysms in the same patient, and shared genetic risk factors of solitary aneurysms have been identified.[29–30] Although obtaining a sufficient sample size of ECAA patients is challenging, the University Medical Center Utrecht as tertiary referral centre initiated an ECAA biobank in 2018 to collect blood samples of every ECAA patient visiting the outpatient clinic. In time, a separate genetic analysis of carotid aneurysm patients could elucidate genetic determinants for this rare vascular pathology.

Clinical features

The majority of ECAA patients are asymptomatic, and the carotid aneurysm is often found by coincidence. The presentation is highly dependent of aetiology, location and size of the carotid aneurysm. If symptomatic, most observed symptoms are cervical complaints like pain, mass or thrill, and nerve palsies (e.g. Horner's syndrome) due to local compression by the dilated carotid artery. A smaller proportion of patients presents with cerebral ischaemia, i.e. transient ischaemic attack or stroke.[1–8] The risk of rupture, a feared complication by affected patients, seems to be negligible in ECAAs. In general, ECAA patients are relatively young with an average age of 55 years at time of diagnosis, and the male to female ratio

in the CAR is approximately 60%:40%. In comparison with e.g. abdominal aortic aneurysm and carotid occlusive disease, ECAA patients seem to be younger and more often female.[2]

Diagnostic evaluation

The proposed gold standard to diagnose carotid aneurysms is by angiography, performed by either thin slice computed tomography (CT) angiography or at least 3.0 Tesla magnetic resonance (MR) angiography.[1] The purpose of imaging in ECAA patients is to confirm the diagnosis, potentially classify in true or false aneurysm, and assess its extent and anatomy to explore follow-up scheme and potential treatment options. The only histopathological study of ECAAs showed that post-dissection carotid aneurysms are observed, even if the radiological examination showed no intimal tear.[20] Developments in vascular wall imaging could non-invasively predict aneurysm aetiology. A recent pilot study was conducted by the CAR research group, using MR angiography with gadolinium contrast as imaging modality in 15 ECAA patients. It is believed that Gd-enhancement reflects both density of the vasa vasorum and endothelial permeability, and can indicate local inflammation of the vessel wall.[31] Up to 70% of aneurysms exhibited gadolinium enhancement, and as only a minority (3/11) of patients with ipsilateral enhancement also had contralateral enhancement; gadolinium enhancement seems to reflect disease activity of the vessel wall (Figure 3). [Paper submitted November 2019].

At present, ECAA size is mostly defined by determination of maximum diameter, though a standardised method to measure the aneurysm size or growth is currently not available. Diameters are usually assessed by measuring the bi-directional maximum aneurysm diameter from outer to outer vessel wall, extracted from the well-established approach for abdominal aortic aneurysms.[28] However, ECAAs may present in a large variety of shapes and sizes. The dilatation of the aneurysm may be focal and saccular, or extensive and fusiform, or a combination of both, and

Figure 3: (Left) MRA reconstruction of an ECAA of the right internal carotid artery. (Right) Axial plane of the aneurysm before and after gadolinium administration with enhancement by the aneurysm wall, indicated by white arrows.

Figure 4: Volumetric 3D reconstruction of an ECAA, white segmentations replicate the aneurysm sac, grey segmentation the non-affected internal carotid artery.

maximum aneurysm diameters between 4mm and 60mm have been reported.[5,9,32] Furthermore, it is imaginable that aneurysm growth might occur in other directions than just obliquely. In this light, a protocol for volumetric assessment for ECAAs was recently reported, which was designed as a step-up towards (semi)automatic volumetric measurements to monitor these patients (Figure 4).[33] A robust and feasible tool to monitor the aneurysm sac, by measuring growth and geometrical alterations, is crucial in any clinical decision making. In time, the (semi)automatic volume tool will aid in selection of patients who should undergo intervention to prevent future adverse events.

Management
Due to the rarity of ECAAs, the natural clinical course and risk factors for adverse outcome are largely unknown.[2,34] As a consequence, currently no evidence-based guidelines on their treatment exist. The goal of ECAA treatment is to reduce the risk of future (sub)clinical neurological sequalae or possible pharyngeal compression. The treatment choices, either conservative or invasive, depend on
- The clinical presentation of the ECAA
- The presumed aetiology
- The condition of the patient
- The location of the ECAA
- The well-being of the cerebrovascular tree.[34]

Ideally, therapy decision-making should be performed in a neurovascular radiological meeting to address all territories.

Invasive treatment includes both open surgery and/or endovascular techniques. Traditional surgical treatment of ECAA consists of open resection of the complete aneurysm with or without replacement with an interposition graft. The hybrid

approach with concomitant stenting of the aneurysm combines open with endovascular techniques. Invasive exclusion of the aneurysm has been considered the treatment of choice where it is symptomatic or growing.[2,32,34]

The conservative approach (antihypertensive medication, statin therapy, antiplatelet therapy and regular follow-up) may be appropriate in asymptomatic non-growing aneurysms, inoperable cases and patients with life-limiting comorbidities. In a recent publication from a small single-centre series with midterm follow-up, a conservative approach has been suggested to be acceptable in asymptomatic patients with non-growing ECAAs.[32]

The majority of the published data on treatment of ECAAs report surgical treatment and short-term outcome of symptomatic aneurysms.[2–8] More insight in endovascular therapies, long-term outcome, and the natural history is essential to learn about the risk/benefit ratio of ECAA exclusion. The benefit of such exclusion in asymptomatic patients is largely unexplored, and it remains unclear whether asymptomatic patients should be exposed to the risks of invasive treatments.

Conclusion

In the future, data analysis from the CAR will give insight of natural history and long-term follow-up of both conservative and invasively treated ECAA patients.[11] The inclusions for the registry are ongoing and independent of treatment strategy. If you have eligible patients, please contact info@carotisaneurysma.nl or visit the website carotidaneurysmregistry.com/en/home.

Summary

- ECAAs are rare, and often found by coincidence.

- Preventing (sub)clinical ischaemic events is the main goal with treatment.

- Conservative therapy is probably optimal for asymptomatic non-growing aneurysms.

- Both surgical and endovascular approaches have been developed for symptomatic and growing aneurysms, yet no clinical treatment guidelines exist.

- The ongoing international Carotid Aneurysm Registry (carotidaneurysmregistry.com/en/home) will provide future guidance in pathogenesis, natural history, and optimal care of primary ECAAs.

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Thoracic aortic consensus

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Homemade fenestrated stent graft for complete endovascular treatment of aortic arch lesions

L Canaud, P Alric and T Gandet

Introduction

Surgical treatments to address aortic arch pathology traditionally have involved open techniques of total arch replacement with circulatory arrest and reimplantation of the supra-aortic trunks. Even in a high-risk patient population, excellent results can be achieved and many centres continue to advocate this open surgical approach as the standard criterion.[1] However, in other centres, despite advances in surgical techniques and postoperative management, this open procedure is still associated with significant in-hospital mortality, a greater incidence of cerebral injury, and other end-organ injury compared with surgery on the more proximal ascending aorta and root.[2] Thoracic endovascular aortic repair (TEVAR) offers a less-invasive surgical procedure but typically requires hybrid open surgical procedures, such as debranching of cervical branches, to provide an adequate landing zone.[3,4]

Branched stent grafts have been proposed that permit completely percutaneous aortic arch repair.[5] The disadvantages of this modular approach include the time required to manufacture and deliver custom-made stent grafts for urgent cases and the high costs. Most notably, there is a high rate of embolisation associated with this approach—probably related to the complexity of deploying a multibranched unibody stent graft.[6]

An alternative option is a physician-modified thoracic stent graft. This involves deployment of a conventional stent graft device, fashioning of custom fenestrations, and reconstraining the device back into the delivery system.

Methods and techniques

Protocol and informed consent were approved by the Institutional Review Boards. All patients gave written consent and the local authorities approved the study. Patients who received single or double homemade fenestrated stent grafts for the treatment of aortic arch lesions at a tertiary referential centre (A de Villeneuve Hospital, Montpellier, France) were included. All patients were at high surgical risk owing to serious comorbidities (American Society of Anesthesiologists score ≥III or emergent repair). Furthermore, vascular and cardiothoracic surgeons—all of whom were routinely involved in endovascular procedures—discussed the management of all aortic lesions. This experience with homemade fenestrated stent graft, as outlined in this chapter, started in July 2014.

Zone 2 aortic arch lesions were treated with a single fenestrated stent graft, which involves the fenestration being secured by placement of a balloon-expandable covered stent. A double fenestrated stent graft was used to treat Zone 0 and 1 lesions; this procedure consisted of one proximal large fenestration for both the brachiocephalic trunk and the left common carotid artery. The size of the fenestration is 2mm larger laterally than that of the brachiocephalic trunk and left common carotid artery orifices. The distal fenestration for the left subclavian artery matches the diameter of the vessel. The distance between the two fenestrations equals that between the left common carotid artery and the left subclavian artery as measured on the preoperative high resolution computed tomography (CT) angiography.

Demographic, anatomic, intraoperative, and postoperative data were recorded by means of a prospectively maintained database. Follow-up CT angiography was performed at one week, three and six months and annually thereafter.

Planning, sizing and device preparation

A vascular imaging workstation (EndoSize Workstation, Therenva) with centreline luminal reconstructions was used.

Centreline luminal reconstruction was used to determine aortic diameter at both the proximal and distal landing zone. Stent grafts of sufficient length were selected to enable proximal and distal landing zones in healthy aorta of at least 20mm. The stent graft oversizing was <5% for acute dissections and between 5% and 10% for other aortic arch lesions.

Modification of the stent graft was performed on a back table, commencing before the start of anaesthesia.

Single fenestrated stent graft

A portion of the device was unsheathed. Our preference was to unsheathe the area to be modified plus one additional stent. The fenestration is premarked in the main stent graft according to the measurements obtained from centreline analysis.

A single fenestration for the supra-aortic trunk target vessel of appropriate size and location was made between the stent graft stent struts. Fenestrations were circular, did not have stent struts going across them, and were of comparable size to the target vessel. A cautery device was used to carefully burn the Dacron fabric to create the fenestration. Thereafter, to enforce sealing power around the fenestration, a radiopaque nitinol wire was sewn onto the edge of the fenestration.

Heparin (5000 IU) was administered as the thoracic stent graft was introduced over an ultra-stiff guidewire. Angiographic runs were performed through a pigtail catheter, introduced percutaneously through the contralateral common femoral artery. Mean blood pressure at deployment was lowered to approximately 80mmHg to optimise accuracy.

As the branch vessels originate from the arch's superior aspect, it was necessary to position the delivery system such that the stent graft fenestration was oriented superiorly on entering the arch. The stent graft fenestration markers were positioned on the outer curve of the thoracic aorta. We had to ascertain that the fenestration was oriented toward the left subclavian artery by aligning the radiopaque marker with the artery. If not aligned, the stent graft was pulled back in the descending thoracic aorta. We rotated the stent graft to adjust the position of fenestration. Thereafter, the stent graft was reintroduced into the aortic arch. A 7F sheath

was placed through retrograde left brachial artery access at the ostium of the left subclavian artery.

The stent graft was partially unsheathed. The optimal position of the C arm was determined preoperatively on 3D reconstruction. An angiogram "opening" the aortic arch was used to align the radiopaque marker with the target vessel. A perpendicular angiogram was also obtained to aid clock face alignment. After ascertaining that the fenestration was oriented toward the supra-aortic trunk target vessel, the stent graft was partially deployed. Minor adjustments were possible to rotate the stent graft to adjust the position of fenestrations once the first stents are deployed. A 0.035inch guidewire from the brachial access was advanced through the fenestration into the stent graft lumen. The 7F brachial sheath was then advanced through the fenestration into the stent graft lumen. Then, the thoracic stent graft was fully deployed. A 8- to 10-mm balloon-expandable iCAST covered stent (Atrium) was deployed. The stent was deployed approximately one quarter into the stent graft lumen and three quarters into the branch vessel. The intra stent graft portion of the covered stent was flared using a 14–20mm balloon introduced from the brachial access.

Double fenestrated stent graft

The proximal large fenestration for the brachiocephalic trunk and left common carotid artery was made without removing the stent graft stent struts. The site of the left subclavian artery fenestration was chosen such that it was not crossed by stent struts. Clock position was used to determine the position of the left subclavian artery relative to the position of the brachiocephalic trunk and left common carotid artery island using the reconstructed images.

For the proximal large fenestration, to avoid damage to the fabric, the fenestration was created using a size 11 blade. At least 5mm of fabric seemed to be required between the proximal fenestration, and the proximal edge of the stent graft to avoid compromise of the integrity and stability of the graft. A cautery device was used to carefully burn the Dacron fabric to create the left subclavian artery fenestration. Thereafter, to reinforce seal around the fenestration (in conjunction with a covered stent) and to mark the position of the left subclavian artery fenestration, a radiopaque nitinol wire (Amplatz Goose Neck Snare, Medtronic) was sewn onto the edge of the left subclavian artery fenestration.

Placement of a double fenestrated stent graft is based on the fact that accurate placement of the left subclavian artery fenestration, secured by covered stent placement, should align the position of the proximal fenestration for the brachiocephalic trunk and the left common carotid artery (the appropriate position of which has been determined as described).

Mean blood pressure at deployment is lowered to approximately 80mmHg to optimise accuracy. As we required a variable amount of time to cannulate the left subclavian artery fenestration, we did not use rapid pacing during stent graft deployment

The optimal position of the C arm was determined preoperatively on 3D CT reconstruction. An angiogram strictly perpendicular to the left subclavian artery was obtained to achieve clock face alignment. As the branch vessels originate from the arch's superior aspect, it is necessary to position the delivery system such that the stent graft fenestrations are oriented superiorly on entering the arch. The stent graft fenestration markers of the left subclavian artery are positioned on the

Figure 1: (A) Single homemade fenestrated stent graft. (B) 3D volume rendering reconstruction showed the single homemade fenestrated stent graft and patency of the supra-aortic trunks.

outer curve of the thoracic aorta and are aligned with the left subclavian artery. If misaligned, the stent graft is pulled back in the descending thoracic aorta, rotated to adjust the position of fenestration and reintroduced into the aortic arch. Large axial adjustments in the arch are ill advised because of the risk of embolisation and indeed because of the poor torquability of the stent graft in this location. Thereafter, the stent graft is reintroduced into the aortic arch. A 7F sheath is placed through retrograde left brachial artery access to the ostium of the left subclavian artery. After ascertaining that the fenestration is oriented toward the supra-aortic trunk target vessel, the stent graft is partially deployed. Only very minor adjustments are possible to rotate the stent graft to adjust the position of fenestrations once the first stents are deployed. A 0.035inch guidewire from the brachial access was advanced through the fenestration into the stent graft lumen. The 7F brachial sheath is then advanced through the fenestration into the stent graft lumen. Then, the thoracic stent graft is fully deployed. A 8–10mm balloon-expandable iCAST covered stent is deployed (38mm or 59 mm in length) protruding approximately 5mm into the aortic stent graft lumen, with the remaining length in the branch vessel. Completion angiography was performed.

Follow-up
Follow-up surveillance was performed with serial CT scans at one week, then at three, six, and 12 months, and annually thereafter. A duplex scan was additionally performed in case of clinical or CT abnormality

Single homemade fenestrated stent graft
From July 2014 through September 2018, 54 consecutive patients who received a single homemade fenestrated stent graft between November 2013 and May 2019 were included. Indications for aortic repair were: acute complicated type B aortic dissection (31%), degenerative aneurysm (24%), acute traumatic rupture of the aortic isthmus (16%), post chronic dissection aneurysmal evolution (15%),

penetrating aortic ulcer (6%), intramural haematoma (4%), and aortic floating thrombus (4%). Emergent cases accounted for 59% of the sample.

Mean follow-up was 26±16 months. Technical success was 94% (Figure 1). Postoperative minor stroke with full neurological recovery with medical treatment was observed in three patients (6%). Unintentional coverage of the left subclavian artery occurred in 6% of patients. In 4%, type 2 endoleaks were identified and successfully treated leading to a 4% reintervention rate. No other endoleaks were identified. The rate of both 30-day and long-term all-cause mortality rate was 7%. The aortic mortality rate was 2% (one patient). Fifteen patients (28%) had at least three years of follow-up. In this subgroup of patients, all the left subclavian artery remained clinically and radiologically patent. There were no conversions to open repair, ruptures, retrograde dissection, stent fracture, migrations or other aortic complication

Double homemade fenestrated stent graft

From January 2018 through December 2018, 30 patients underwent double homemade fenestrated TEVAR for repair of aortic arch dissections while preserving the patency of the supra-aortic trunk. Emergent cases accounted for 26.2% (n=8) of the sample.

Indications included degenerative aortic arch aneurysm (43%), acute complicated type B aortic dissection (7%), chronic complicated type B aortic dissection (27%), and dissecting aortic arch aneurysms subsequent to surgical treatment of acute type A dissections (23%).

Median duration for stent graft modification was 18 minutes (range 16–20 minutes). Endovascular exclusion of the aortic arch was achieved in all the cases but one: 96.6%. One failed fenestrated stent graft deployment was treated using a double chimney. Two cases of left subclavian artery catheterisation failed and surgical revascularisation and coverage of the fenestration by additional stent graft placement was required.

One patient had a stroke without permanent sequelae (2.8%). No type 1 endoleak was observed, but there was one type 2 endoleak and one patient died during the postoperative course of multiorgan failure.

During follow-up, two additional patients died of a non-aortic cause. Overall mortality was 10%. Aortic related mortality was 3.3%. All left supra-aortic trunks were patent. The stoke rate was 0%. During a mean follow up of 12.6±5 months, there were no conversions to open surgical repair, aortic rupture, paraplegia and all supra-aortic trunks were patent.

Discussion

This retrospective analysis reports our experience of homemade fenestrated stent grafts for endovascular aortic arch repair of aortic arch. With a 2.3% aortic related mortality, and patency of all the revascularised arteries in this difficult subgroup of patients (emergent cases accounted for 47.6%), we can conclude that this approach is feasible and provides encouraging results in the short term.

A complete repair of the aortic arch with or without the frozen elephant trunk procedure is a complex process with a relevant risk of postoperative morbidity and mortality.[7,8] The surgical outcome has been improving lately. However, Sundt *et al* reported that the 30-day mortality after aortic arch surgery in the standard risk
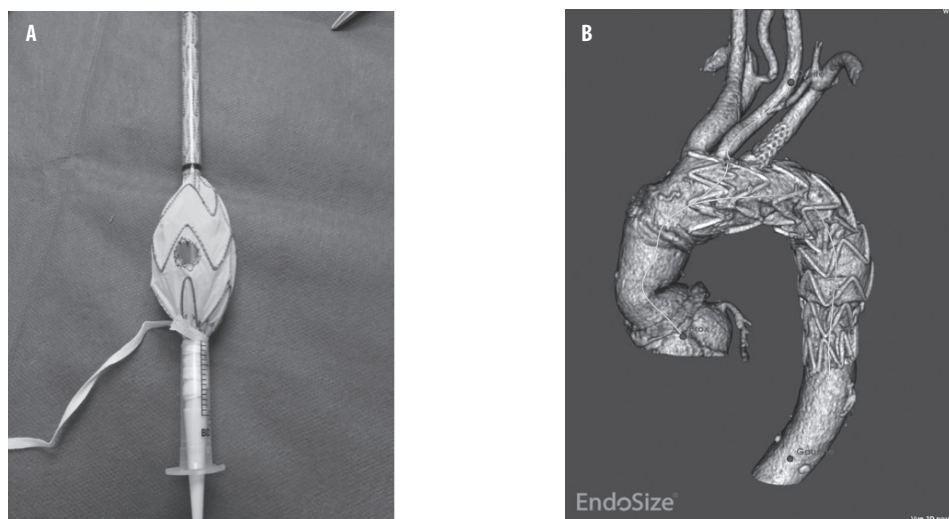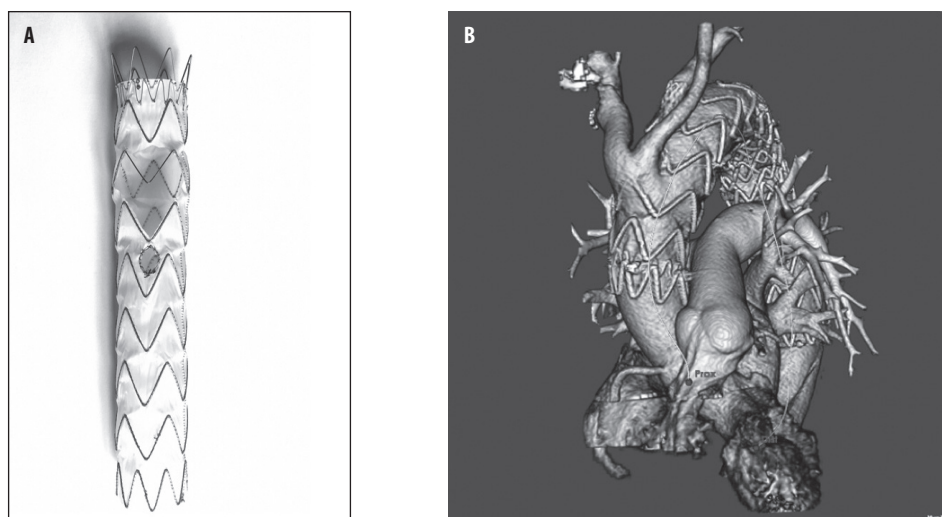
Figure 2: (A) Double homemade fenestrated stent graft. (B) 3D volume rendering reconstruction showed the double homemade fenestrated stent graft and patency of the supra-aortic trunks.

population (renal failure 5%; diabetes mellitus 7%; prior cerebrovascular accident 9%; and prior myocardial infarction 7%) ranges from 4% to 28.6%, varying with the adjunctive measure for cerebral protection used (profound hypothermia and antegrade or retrograde cerebral perfusion) and mode of presentation (elective or emergency).[9] Furthermore, many patients are deemed unsuitable owing to serious comorbidities. As a consequence, a less invasive approach is favourable for a significant number of patients.

As all cases reported here used customised systems, accurate preoperative planning is essential. Intraoperatively ascertaining that the fenestration is well oriented toward the supra-aortic trunk target vessel is crucial. As a consequence of the homemade nature of these devices, graft rotation and misalignment of the fenestration/vessel ostium interface can nevertheless occur. Additionally, the aorta may change configuration after insertion of the semi-rigid stent graft. It may be necessary to manipulate a semi-constrained or partially deployed arch stent graft to orient fenestrations correctly, which increases the risk of cerebral embolisation. One case of stroke without permanent sequelae was observed in our series.

The specific feature of the double fenestrated device is its simple handling during operation with the proximal fenestrations being directed to the orifices of the brachiocephalic trunk and left common carotid artery automatically when left subclavian artery fenestration is catheterised and secured by covered stent placement. Furthermore, because the proximal fenestration is large enough to accommodate the branches with low risk of branch occlusion, neither bare metal nor covered stents necessarily need to be placed into the branches. The deployment algorithm actively steers the operator away from superfluous manipulations of the device within the arch and avoids guidewire manipulation in the brachiocephalic trunk and in the left common carotid artery. We believe that is likely to be the reason, compared to other endovascular techniques, that the double homemade fenestrated stent graft led to fewer neurological complications. This can be explained by several factors. Firstly, with careful preoperative planning, the simple handling of the device during operation decreases manipulations in the aortic arch. Namely, the

proximal fenestration is appropriately directed to the orifices of the brachiocephalic trunk and left common carotid artery automatically when the left subclavian artery fenestration is catheterised. Secondly, no manipulation, clamping, catheterisation or stenting of the brachiocephalic trunk and left common carotid artery are required. This approach is an off-label use of the Valiant stent graft (Medtronic). Our group has a large experience with complex thoracic endovascular repairs (over 800 TEVAR procedures were performed). The risk of technical failure with the double fenestrated approach may be increased if performed by unexperienced teams.

The fragility of homemade stent grafts is a crucial problem. The question of fabric durability still needs to be evaluated. Metal fatigue and material deterioration are known complications of stent grafting. These alterations might have an impact on general ring stability of the graft. In our series, no stent fractures were detected by routine radiologic follow-up examinations. The long-term interactions between the stent graft and the covered stent will need to be monitored closely over time because of the potential for stent collapse or stent breakage and the development of a late type 3 endoleak between the two components. Careful long-term monitoring of patients is required to avoid major complications resulting from inadequate durability of these devices

There are several different alternatives that allow for attaining an adequate proximal seal for thoracic stent grafting. The debranching technique and the chimney technique have been proposed for proximal extension of the stent graft with preservation of supra-aortic branch blood flow. However, debranching requires an adjunctive invasive procedure. Whilethe chimney technique can be performed in a less invasive manner, there are concerns about the type 1 gutter endoleaks. Furthermore, most chimney grafts reported to date have been applied to only one branch; therefore, cases requiring two or three supra-aortic branch preservation are supplemented by additional extra-anatomic bypasses.

Custom-made branched devices are currently available. The world experience with 38 branched arch devices was first reported as a multicentre experience in 2014 by Haulon *et al.*[7] They reported a 13% mortality rate, a 16% stroke rate, a technical failure rate of 15.8%, and a secondary procedure rate of 19.6%. Factors such as the delay in device planning and manufacturing, anatomical, technical limitations and expense limit the widespread uptake of this technology which is additionally unsuitable for emergent cases. Above all, the technical difficulty of side branch catheterisation results in an inherently high risk of cerebral embolism. The results of inner branched endograft repair of the aortic arch in contemporary series demonstrates an improvement in patient outcome when compared with the early experience of the approach published in 2014.[8,10]

Until an "off-the-shelf" device is available, patients with rapidly expanding, symptomatic, or ruptured arch aneurysms, who are poor candidates for open surgical repair, have limited options other than immediate physician modification. More data are required to confirm the general applicability of this approach and to establish durability. In the long-term, strict surveillance of these stent grafts and modifications will be necessary to monitor and ensure durability of repair because of the potential for stent collapse or stent breakage.

Conclusion

The use of homemade fenestrated stent grafts for endovascular repair of aortic arch lesions is both feasible and effective for maintaining the patency of the supra-aortic

trunks and allows total endovascular aortic arch repair. Durability concerns will need to be assessed in additional studies with long-term follow up.

Summary

- Double fenestrated stent graft for thoracic endovascular aortic repair of zone 0 and 1 dissecting aortic arch aneurysm; the proximal large fenestration for the brachiocephalic trunk and the left common carotid artery.

- Accurate preoperative planning is essential.

- Homemade fenestrated stent grafts for endovascular repair of aortic arch lesions is both feasible and effective.

- Homemade fenestrated stent grafts allow treatment of emergent and elective cases.

- Durability concerns will need to be assessed in additional studies with long-term follow up.

- The deployment algorithm actively steers the operator away from superfluous manipulations of the device within the arch and avoids guidewire manipultion in the brachiocephalic trunk and the left common carotid artery.

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Endovascular options for left subclavian branch incorporation

GS Oderich and ER Tenorio

Introduction

Revascularisation of the left subclavian artery (LSA) has been widely recommended as a means to minimise the risk of arm ischaemia, stroke and spinal cord injury during thoracic endovascular aortic repair (TEVAR). Although routine use of LSA revascularisation remains controversial, according to a systematic review, subclavian artery coverage without revascularisation is associated with a three-fold increase in paraplegia, a 2.5-fold increase in anterior circulation strokes, a 48-fold increase in arm ischaemia, and a 11-fold increase in vertebrobasilar ischaemia.

Carotid-subclavian revascularisation is associated with a low risk of mortality, but it does carry a risk of nerve injury (including risk of phrenic nerve palsy in up to 25% of patients).[1,2] The Society for Vascular Surgery (SVS) and European Society for Vascular Surgery (ESVS), in joint guidelines, recommend that subclavian revascularisation is performed whenever possible in patients undergoing elective TEVAR with extensive coverage; they also recommend it for patients with a patent left internal mammary to coronary artery graft, termination of the left vertebral artery into the posterior inferior cerebellar artery, absent or atretic right vertebral artery, patent left arm arteriovenous fistula or graft, prior infrarenal aortic repair, planned extensive coverage (>20cm) of the descending thoracic aorta, and occlusion of the internal iliac arteries.[3,4] Most recently, interest in endovascular LSA incorporation has led to development of fenestrated and branched stent grafts.

Endovascular fenestrated and branched stent graft designs

There are currently several investigational LSA branched stent grafts using either "off-the-shelf" or patient-specific platforms (Figure 1). Two of these are being investigated in the USA and Europe for zone 2 aortic arch indications: TAG Thoracic Branch Endoprosthesis (Gore) and the Valiant Mona LSA (Medtronic). Additionally, the Cook LSA branch stent graft offers a patient-specific design that is available in selected centres.

Thoracic branch endoprosthesis

The TAG Thoracic Branch Endoprosthesis is an off-the-shelf stent graft designed with an inner portal to incorporate a single arch vessel, either the innominate artery (zone 0) or the LSA (zone 2). The left common carotid artery is less frequently suitable because of its proximity to the innominate artery (zone 1). The aortic component is based on the Gore C-TAG platform (expanded polytetrafluoroethylene supported
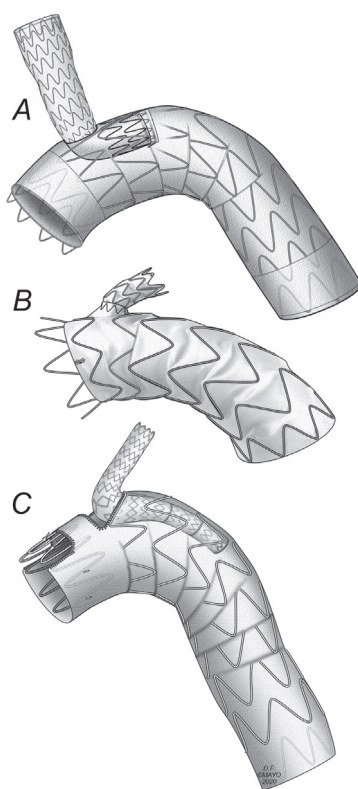
Figure 1: (A) Gore Thoracic Branch Endoprosthesis; (B) Medtronic Mona left subclavian artery (LSA); (C) Cook Medical arch-branch thoracic device (single branch for LSA). *By permission of Mayo Foundation for Medical Education and Research. All rights reserved.*

with self-expanding nitinol stents), with diameters ranging from 21mm to 53mm. It is built with a precannulated internal retrograde branch, which is either 8mm (zone 2) or 12mm (zone 0). There are sealing cuffs on both ends with a partially uncovered stent proximally for wall apposition. The separate side branch is available in 8–20mm diameters and is heparin bonded to improve patency. The overlapping segment of the side branch has retrograde anchors to prevent migration with a tapered more flexible segment in the middle to accommodate arch movement. The distal segment has reinforced sealing cuffs for durable distal seal. The main device is delivered over two wires, one in the aorta and the other in the arch branch to be incorporated. The wire for the side branch can be snared for a through-and-through brachial femoral access to help with alignment in hostile anatomy (Figure 2). The US feasibility multicentre clinical trial evaluated 22 patients undergoing TEVAR with the TAG Thoracic Branch Endoprosthesis in Ishimaru zone 2. The primary endpoint—device delivery and branch vessel patency—was achieved in 100% of patients, without any death, stroke, or permanent paraplegia being observed at 30 days. Type 1 endoleaks at completion angiography were observed in four patients, and all resolved by one month.[5] The pivotal trial is ongoing and has already enrolled 285 patients.

Labels in illustration:

A — Basilic vein, Brachial artery, Brachial fascia, Median nerve

B —

C — Kumpe, Indy snare

D —

E — 8 Fr Brite tip

F —

G — .035 Lunderquist wire, .035 Nitrex brachial wire

H, I, J, K —
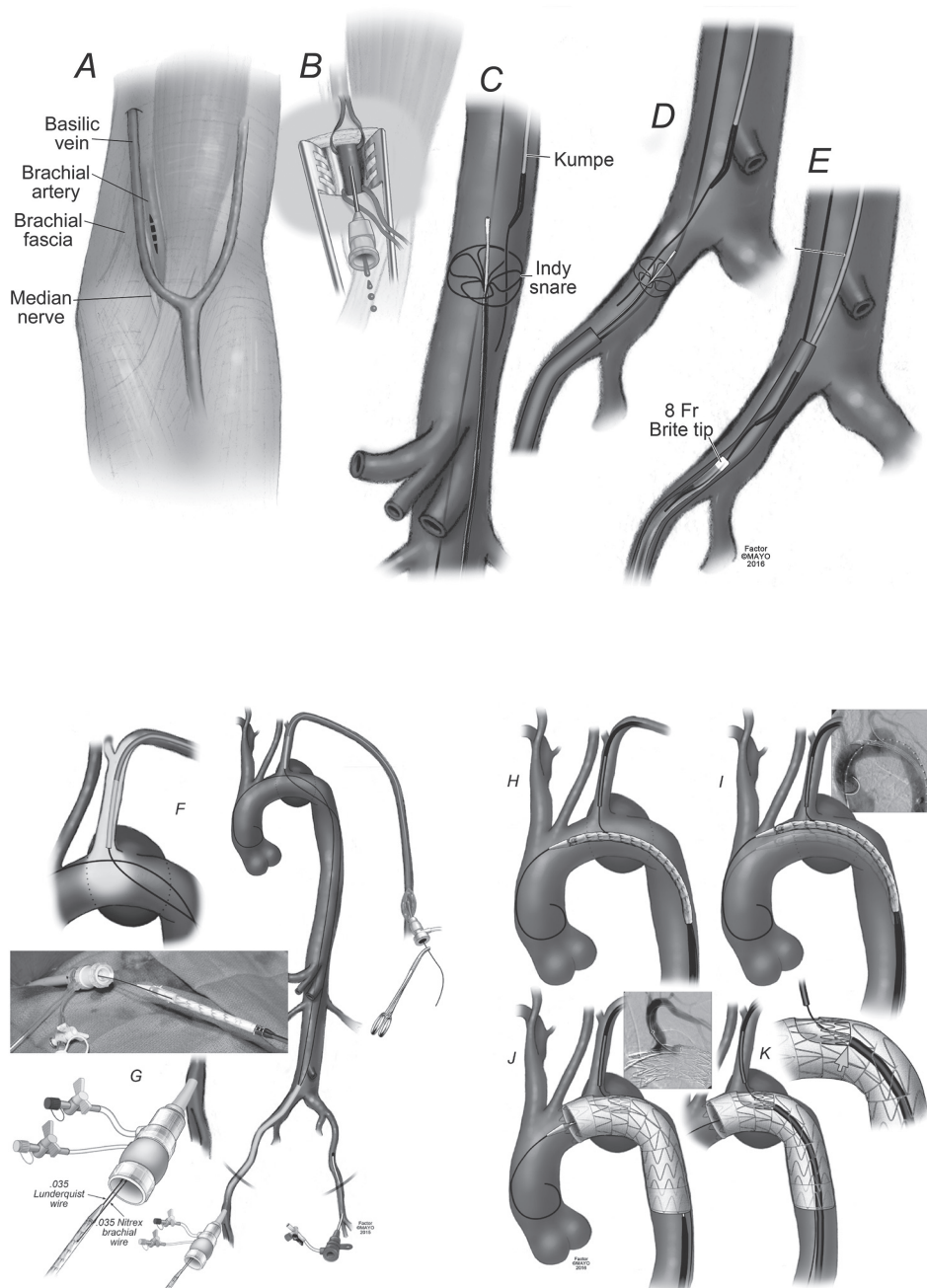
Figure 2A-K: (A−E) Establishment of bilateral femoral access and left brachial access for delivery of the thoracic branch endoprosthesis. (F−G) The device is loaded and advanced into position; (H−K) followed by deployment.
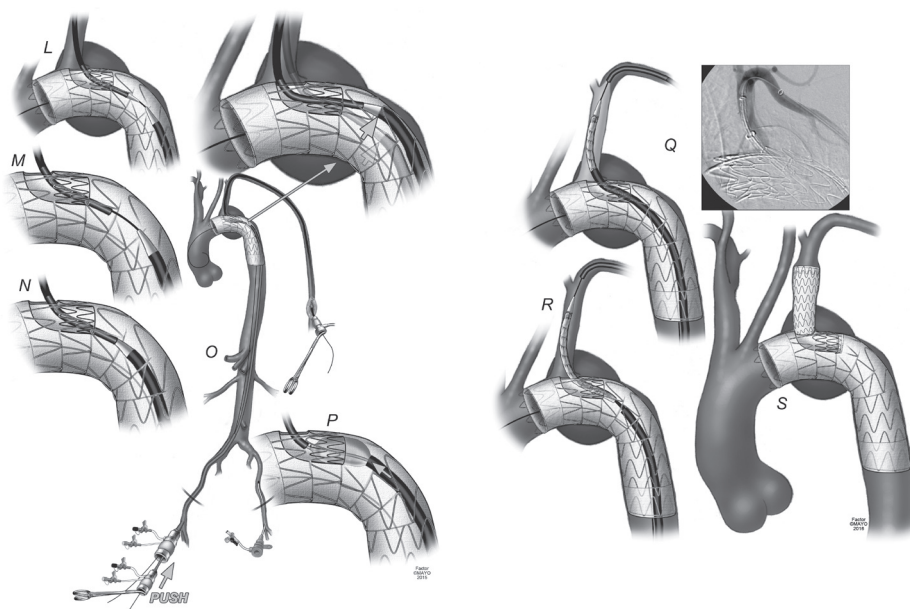
Figure 2L-S: (L–P) advancement of the left subclavian sheath; and (Q–S) placement of the bridging stent. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved.*

Valiant Mona LSA

The Mona LSA stent graft is a modular system that has been modified from the Valiant Captivia (Medtronic). It is currently being evaluated in an ongoing second-phase multicentre investigational feasibility study in the USA. The aortic component has low-profile polyester sewn to nitinol exoskeleton with a proximal bare stent. The device has a single "volcano" shaped opening with a precannulated flexible externally oriented cuff. The cuff itself is composed of high-density polyester fabric with a mobile external connector stent and two platinum iridium markers. It is a pivot design that allows 20–30 degrees of misalignment. The separate side-branch component is conformed to a proximal flare with an intended 1cm overlap to enhance proximal seal. The aortic component diameter ranges from 30mm to 46mm, and the branch stent has available diameters of 10mm, 12mm, and 14mm. The instruction for use (IFU) for the investigational Mona LSA device mandates through-and-through brachial femoral access. The device is delivered over the aortic wire. Prior to deployment, a separate wire is advanced via the precannulated branch lumen and is snared via brachial access. The device is then aligned and deployed with simultaneous traction on the brachial-femoral wire to position the branch at the subclavian orifice. The branch graft is then advanced and deployed over the subclavian wire.

An early prospective, non-randomised, single-arm premarket study was conducted in three centres (two US sites and one UK site). Nine patients were enrolled (seven US patients and two UK patients). Inclusion criteria required patients with a descending thoracic aneurysm having a distance of at least 10mm between the left common carotid artery and the LSA. The device was successfully implanted into nine patients and remained functional as intended. No stent graft occlusion,

kinking, twisting, component separation, fracture, or migration was reported. Four endoleaks developed before discharge in four of eight evaluable patients. Two were identified as type 2, and two were of undetermined type. No endoleak resulted in a secondary intervention.[6]

Multibranch devices

The multibranch option incorporates axially oriented, covered stent graft cuffs to accommodate the great vessels. These stent graft configurations are custom-made, adding at least six to eight weeks between evaluation and treatment. Although they are novel solutions, these techniques clearly add a new level of complexity to endovascular aortic repair. Multibranch configuration devices currently in early investigation include the Bolton Medical Relay NBS Plus (both single and dual branch configurations available) and the Cook Medical arch-branch thoracic device (single, dual and triple branch configurations available). The branch for the LSA in the Cook arch-branch platform is designed to be accessed from below using a preloaded catheter system. There is no literature available specifically with a single arch branch to LSA using these devices.

Scalloped and fenestrated endografts

Cook and Terumo Aortic offer patient-specific scalloped and fenestrated endografts that can be used to extend a seal zone from the descending thoracic aorta into the aortic arch. These devices are ideally suited to aneurysms involving the descending thoracic aorta, which arise close to the LSA. The use of a scallop or fenestration proximally allows for a single supra-aortic trunk (e.g. LSA) to continue to be perfused while extending the seal zone more proximally.[7] Concerns remain over the use of scallops in a seal zone, given that a large portion of the proximal sealing stent remains uncovered. Proximal seal can be improved by implanting a covered balloon-expandable bridging stent through a fenestration.

In situ retrograde fenestration

In contrast to the abdominal aorta, fenestrated constructs are less attractive in the arch portion of the aorta because of anatomic issues of longer distance to the target vessels, greater tortuosity, less torque control and alignment precision, and lower cerebral tolerance to transient ischaemia and embolic complications.

Alternatively, to resolve these limitations, *in situ* retrograde fenestration of the LSA, after stent graft insertion, have been described, with a variety of methods to create the fenestration *in situ* (Figure 3). These have included thin-wire cutting needle (e.g., trans-septal or transjugular intrahepatic portosystemic shunt type) or laser perforation with serial dilatation of the fabric material.

Energy-based fenestration (laser or radiofrequency) in woven Dacron grafts has been shown to cause less fabric fraying during *in vitro* benchtop evaluation with pulsatile fatigue testing compared with needle-based techniques, and we prefer use of laser technique at our institution.[8] In a recent systematic review of 46 aortic branch vessels (72% LSA), in 44 patients, reported outcomes using *in situ* fenestration for the treatment of degenerative aneurysms, chronic type B dissections, intra-mural haematomas, and acute type B dissections. Technical success of the 46 attempted

aortic branch fenestrations was 95.6%, with two reported technical failures related to two overlapping thoracic stent grafts at the site of attempted fenestration and a tortuous subclavian artery that made orthogonal access to the thoracic stent graft difficult. At a mean follow-up of 11 months, no cases of branch vessel occlusion were reported. The most common reported technique related complication was a type 1c endoleak (9.1%), which occurred in four patients and all were treated successfully with coil embolisation. Potential issues surrounding these techniques include tear propagation of the fenestration leading to a type 3 endoleak, which would be difficult to treat. How fast the fenestration can be created is another challenge given time-critical end-organ ischaemia can occur.[9]

Parallel stent graft techniques

Endovascular options that do not involve branched endografts *per se* have been developed in the last two decades to overcome unmet technological needs in this segment of aortic therapy and regional unavailability of the devices due to regulatory and/or commercial issues. These options include parallel stents (e.g. "chimney," "snorkel," or "periscope") with placement of a stent alongside (parallel to) the main aortic endograft, starting from just proximal or distal to the endograft margin and continuing into the target arch vessel (Figure 4).

A recent review of the chimney technique for the preservation of aortic branch vessels, including "triple-barrel" grafts for landing in zone 0, has yielded satisfactory mid-term results for high-risk patients with postoperative mortality and stroke rates of 3.2–4.8% and 4–5.3%, respectively. It is worth noting that strokes associated with the chimney technique appear to have a relatively high mortality rate of approximately 40%. Additionally, the most common complication of the chimney technique is a type 1a endoleak, because of flow within the "gutters" between the
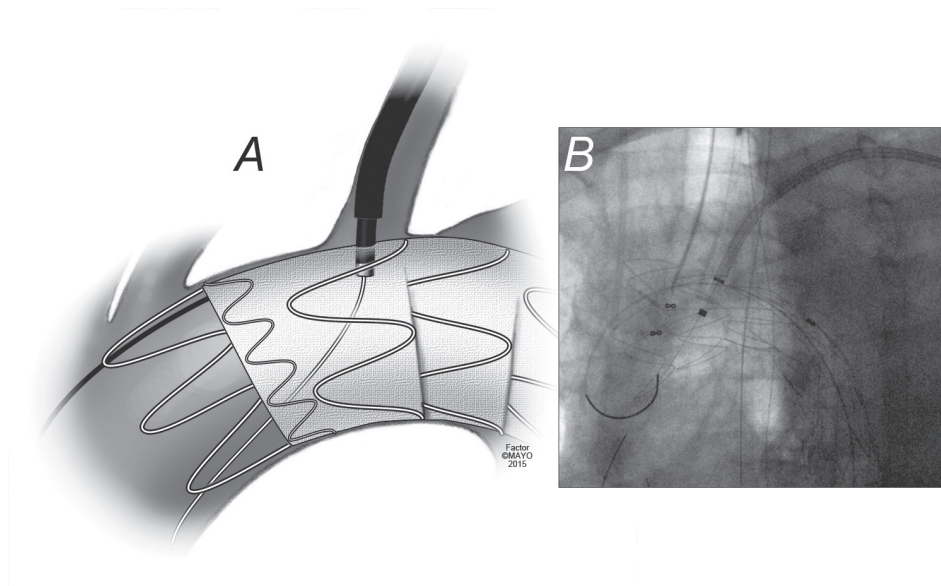
Figure 3: (A) Laser fenestration created with gentle forward pressure and application of laser energy. (B) A 0.018-inch wire passed through the fenestration. Fluoroscopic view post laser fenestration and wire passage. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved.*
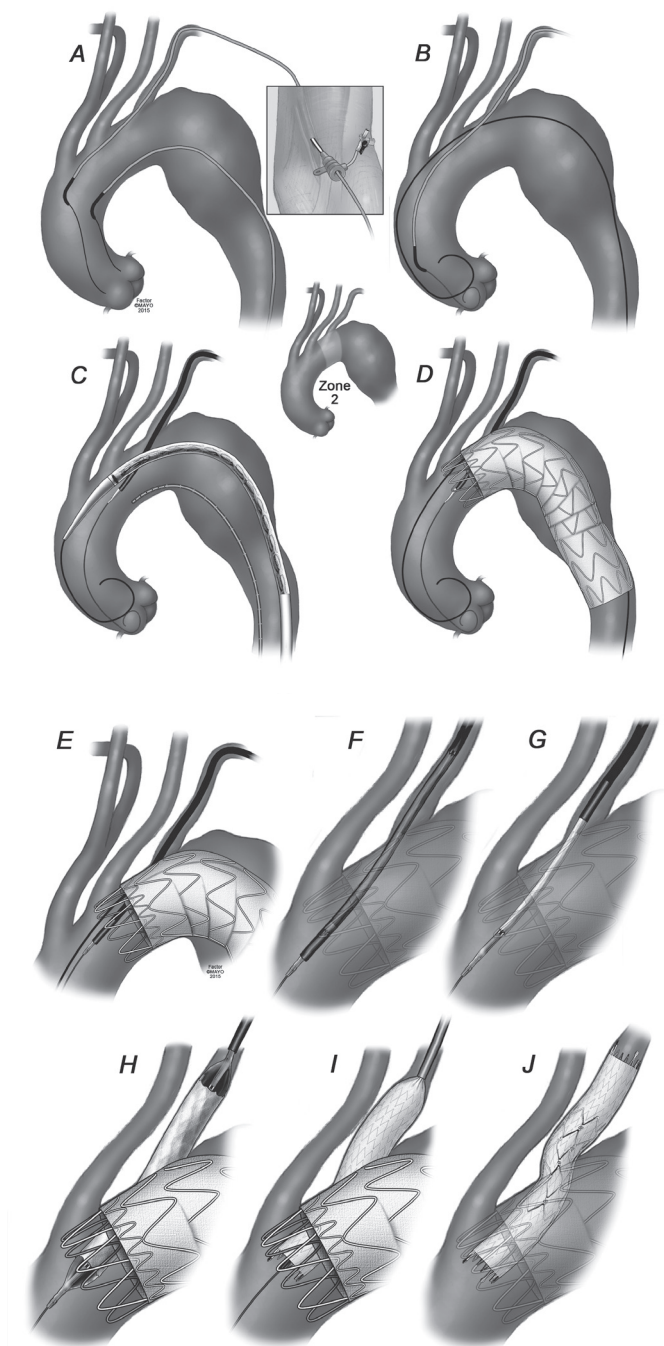
Figure 4: (A) Technique of parallel stent graft for zone 2 thoracic endovascular aortic repair. Access is established using trans-brachial percutaneous (inset) or surgical cut-down exposure. (B) Guidewire is exchanged for a 0.035-inch stiff wire for advancement of a thoracic stent graft. (C) The thoracic endograft and LSA chimney stent have been delivered to the target position, and (D) the thoracic device has been deployed. (E–H) Deployment of LSA chimney-covered stent. (I) Self-expanding stent is used for larger vessels and should be reinforced with (J) balloon expandable bare metal stent. *By permission of Mayo Foundation for Medical Education and Research. All rights reserved.*

chimney graft and the thoracic endograft, with an associated endoleak rate of 18–18.5%. However, most type 1a endoleaks resolve spontaneously on follow-up imaging. Another concern with use of the chimney technique is compression of the chimney graft, although this appears to be a relatively uncommon occurrence with one recent report demonstrating a two-year freedom from branch occlusion of 96%.[10] The periscope technique is less commonly used with limited available literature, but when performed is most commonly used to preserve the LSA. Based on one small study of 14 patients, the two-year patency of periscope grafts for preserving the LSA during TEVAR was 93%.[11]

Conclusion

LSA revascularisation is feasible and can be performed with high technical success. It should be recommended for TEVAR with the need to extend the repair to zone 2 or beyond that.

Summary

- LSA revascularisation is safe and can be performed with low mortality and morbidity.

- Branched stent grafts represent a promising therapeutic option for pathologies of the aortic arch with insufficient proximal landing zone.

- *In situ* fenestration and parallel techniques are good options for urgent/emergent cases or as "bailout" manoeuvres in the effort to preserve or revascularised branches that were inadvertently covered by the endograft.

- Endovascular LSA revascularisation may be recommend over open surgery.

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Open thoracoabdominal aortic repair following aortic arch repair with frozen elephant trunk

A Gombert, MJ Jacobs and D Kotelis

Introduction

Disease of the aortic arch and the descending aorta, regardless if degenerative or post-dissection, remains an extraordinary challenge. It remains a challenge even if endovascular techniques are gaining ground, and the indication for total endovascular aortic repair is receiving more and more attention (Figure 1).[1,2]

Since the early 1980s, when Borst and colleagues reported their results for the staged elephant trunk principle to treat the combined disease of aortic arch and the descending aorta, it has become a standard procedure in cardiothoracic surgery.[3] In the first step, a prosthetic replacement of the ascending aorta and aortic arch with an elephant trunk extension of the arch graft inserted into the descending aorta during the first stage operation was performed through a median sternotomy. The elephant trunk is floating freely in the aortic lumen, which leads to a hampered thrombus formation between graft and the aneurysmal wall.

Based on this pioneer work, Karck *et al* described the concept of the frozen elephant trunk in 2003.[4] This approach allows a definitive treatment
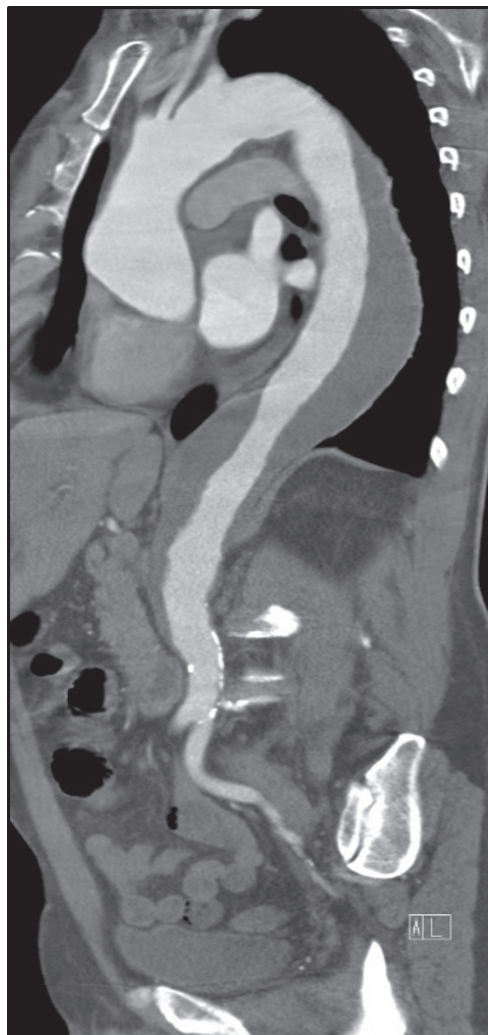
Figure 1: Preoperative CT scan showing the aneurysm involving the thoracic and abdominal aorta.
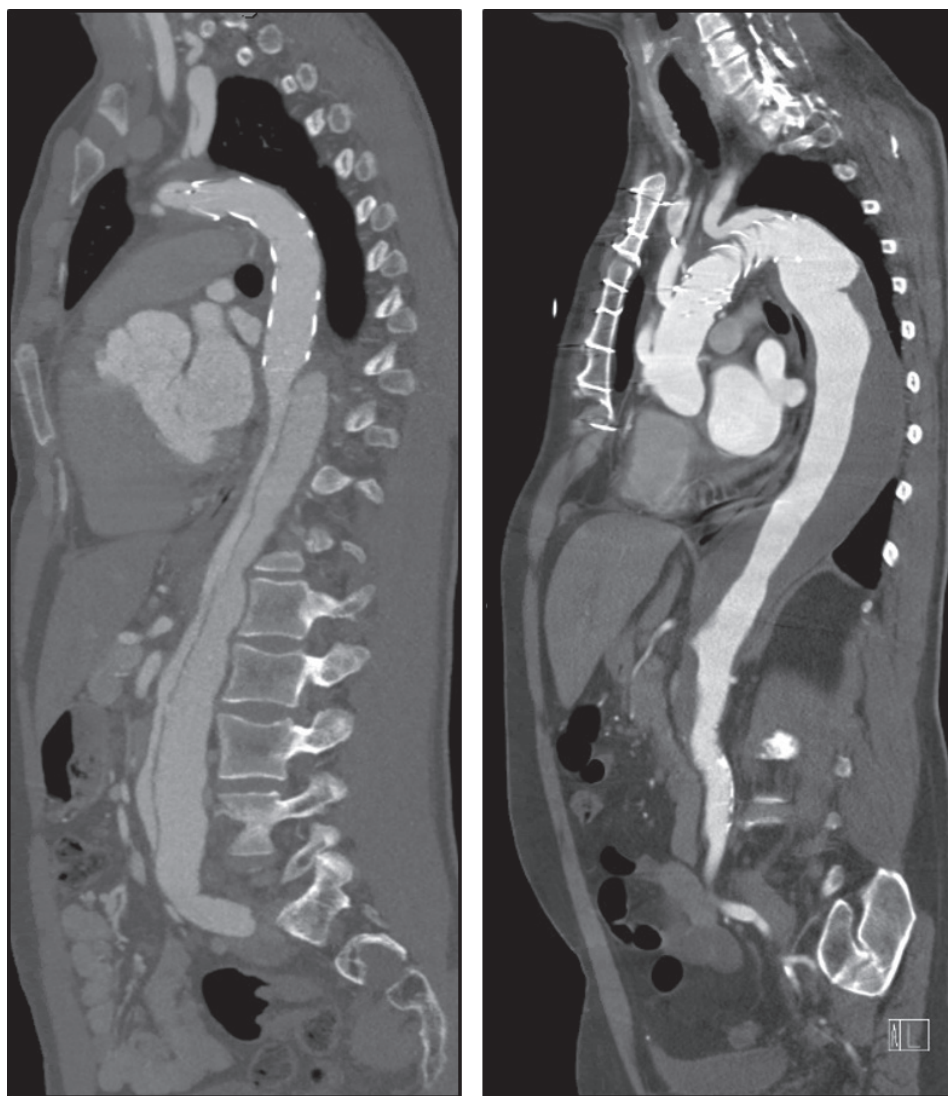
Figure 2: CT scan after open ascending aorta repair including frozen elephant trunk.

of combined aortic lesions in a one-stage procedure, which amalgamates the elephant trunk principle and an antegrade endovascular stenting of the descending aorta. As existent comorbidities, in the acute as well as in an elective setting, are relevant and may be one major factor influencing postoperative outcome, less invasive and, therefore, less traumatic surgery seems favourable.

If compared with the elephant trunk technique, the definite placement of the frozen elephant trunk and its anchorage in an aspired landing zone are advantageous. If occlusive, the placed frozen elephant trunk enables thrombus formation in the aneurysmal sac, which has been excluded from the blood flow. Even if the frozen elephant trunk procedure for the treatment of combined, complex thoracic aortic aneurysms is related to a relevant mortality and neurological complication rate, the results seem favourable if compared with a clamshell approach as alternative approach for this extensive aortic disease.[5,6] Furthermore, new devices including an extra-anatomic bypass to the distal left subclavian artery may lead to an improved

early postoperative outcome.[7] As the thrombotic occlusion is mandatory for the wall stress reduction in the landing zone of the frozen elephant trunk in the diseased segment of the aorta to avoid further growing of the aneurysm, an appropriate, non-affected landing zone is required. Alternatively, with now appropriate sealing of the stent or in case of a subsequent thoracoabdominal aortic aneurysm, a second surgical repair through a left thoracolaparotomy or an endovascular repair may be required.[8,9] In this chapter, we will describe our approach for the open repair of subsequent thoracoabdominal aortic aneurysm after previous frozen elephant trunk that has been implanted to treat an acute type A dissection or as first step in case of extensive degenerative aortic aneurysm involving the complete thoracoabdominal aorta (Figure 2).

Surgical repair

The presented protocol is the standard approach for all patients undergoing open thoracoabdominal aortic aneurysm repair in our department. Intubation is performed with a double-lumen endotracheal tube or a selective left main bronchus blocker, enabling collapse of the left lung.

An appropriate anaesthetic technique using sufentanil and ketamine is crucial for obtaining motor evoked potentials (MEPs). As complete neuromuscular blockade is not preferable while applying MEP monitoring, the level of neuromuscular blockade is assessed with a relaxograph neuromuscular transmission monitor.[10] Mean arterial pressure was maintained between 60mg and 100mg/Hg.

Transcranial stimulation and the technique of MEP recording has been described before.[10] A series of five stimuli with an interstimulus interval of two ms and a stimulus intensity of 500V is applied to the scalp through four electroencephalographic disc electrodes placed in the vertex position with three inactive electrodes over the forehead. The MEPs are recorded with skin electrodes over the right and left anterior tibialis and rectus femoris muscles as well as over the abductor pollicis brevis muscles on both sides, which servers as control for confounders that might influence the MEP amplitudes other than spinal cord injury. A reduction of MEP amplitude to <50% of baseline is considered as an indication of ischaemic spinal cord dysfunction.

If MEPs remain normal, intercostal arteries are reattached if the aortic wall allowed a safe anastomosis. If MEPs decrease to critical levels, patent intercostal or lumbar arteries are revascularised. In any case, attempts to revascularise the spinal cord are carried out until the MEPs restored.

Patients are placed in a left helical position on a vacuum beanbag. A thoracolaparotomy through the sixth intercostal space is followed by limited incision of the anterior diaphragm and opening of the crus. A loop around the diaphragm enables movement of the diaphragm and exposes the aorta without the necessity of completely transecting the muscle. After limited heparinisation (0.5mg/kg; anticoagulation therapy approximately 200 seconds), distal aortic perfusion is established with cannulation of the left femoral vein and the femoral artery using a centrifugal pump. An arterial line is inserted in the contralateral femoral artery. In general, the aortic reconstruction is performed from proximal to distal. However, in extensive (chronic) type B aortic dissection involving the iliac arteries, we prefer to reverse the surgical direction because of the unpredictable changes in organ perfusion with retrograde flow through dissected iliac arteries and aorta.

Figure 3: Intraoperative situs of an open type 2 thoracoabdominal repair.

This is feasible if the infrarenal aorta can be cross clamped temporarily. The aorto-bi-iliac prosthesis is anastomosed distally first and subsequently the main body is crossclamped and cannulated as arterial inflow site. After starting extracorporeal circulation, the aortic reconstruction is commenced with the abdominal phase, followed by the thoracic segment. The patient is allowed to cool to 32–33 degrees Centigrade and actively rewarmed at the end of the procedure. A four-branched tubing system is connected to the heart-lung machine, and four catheters with balloon-inflatable tips are used for perfusion of the coeliac axis, superior mesenteric artery, and both renal arteries. These perfusion catheters are equipped with pressure channels, enabling pressure-controlled selective perfusion. The aorta is completely freed from the oesophagus after transection of the ductus arteriosus. The frozen elephant trunk is prepared for cross-clamping. While performing the proximal anastomosis, which involves the frozen elephant trunk and the aneurysm sac in the area, a Teflon felt-supported suture line is used (Figure 3). In the abdomen, the aorta is approached via the left retrocolic and retrorenal access. After the left kidney is tilted, the left renal artery is dissected and secured with a vessel loop. After proximal cross-clamping, transection of the aorta, and performance of the anastomosis, distal aortic perfusion is maintained at a mean pressure of 60mmHg or higher. Based on urine output (<15ml per 15 minutes) and the amplitude of MEPs, this
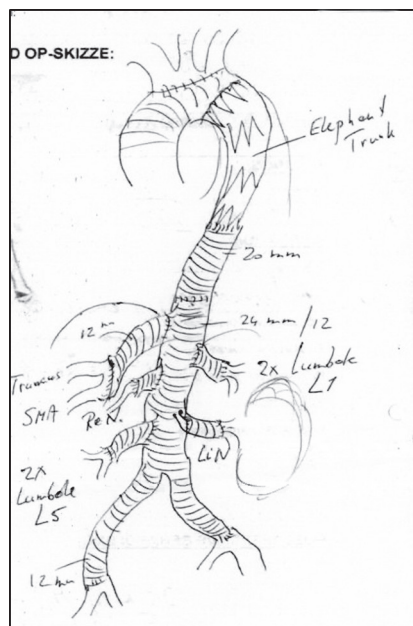
Figure 4: Schematic drawing of open type 2 thoracoabdominal repair including the replacement of the infrarenal aorta and the iliac arteries after frozen elephant trunk.

arterial pressure is increased if necessary. After completion of the surgical repair, the patient will stay for at least 72 hours on the intensive care unit, until the cerebrospinal fluid drain will be removed (Figure 4).

Selective literature review and own experience

Regarding outcomes during early and long-term follow-up, data are scarce for open and endovascular thoracoabdominal aortic repair following ascending aorta/arch repair including frozen elephant trunk. However, the articles of Roselli *et al* and Czerny *et al* have to be mentioned.[8,9] While Czerny *et al* observed no case of in-hospital mortality in their cohort of nine patients undergoing open thoracoabdominal aortic repair after frozen elephant trunk, several major complications have been reported elsewhere:

- Acute renal failure requiring dialysis
- Severe gastrointestinal bleeding
- Prolonged stay on ICU.

Yet, no stroke or spinal cord ischaemia was assessed. The surgical procedure including the organ-protective measures were comparable as described by our group before. Roselli *et al,* while comparing open and endovascular completion of thoracoabdominal aortic aneurysm, observed 133 patients undergoing open thoracoabdominal aortic repair. A 30-day mortality rate of 6% was reported; major bleeding occurred in 8.9% of all patients. Neurological complications, namely stroke and paraparesis, were observed in 4.9% and 3.8% respectively. Acute respiratory failure with or without tracheotomy were assessable in 12% and 9% respectively and forms the most common severe complication after open repair following frozen elephant trunk procedures. With regard to follow-up, 85 patients were available, of whom 13 required further open surgical procedures. Within the first year of follow-up, five patients after open thoracoabdominal repair following frozen elephant trunk died in a skilled nursing facility due their severe perioperative complications.

With regard to our own experience, we oversaw 24 cases of extensive thoracoabdominal aortic repair after frozen elephant trunk, mostly performed as type 2 repair. Of these, 50% required aorto-bi-iliac repair for concomitant iliac artery aneurysm. Of these patients, 25% had pneumonia and/or prolonged weaning. Acute kidney injury classified according to Kidney Disease Improving Global Outcomes (KDIGO) was observed as grade 1 in 30% and as grade 2 or 3 requiring intermittent haemofiltration in 5%.[10] One case of paraparesis and no strokes occurred. During the follow-up (mean time 24±12 months), including the hospital stay, a mortality of 15% was assessed. At the time of writing, no surgical reintervention has been required.

Conclusion

Open thoracoabdominal aortic repair following frozen elephant trunk procedures is related to a relevant mortality rate during the short and mid-term follow-up; furthermore, major complication including the kidneys and the lung are common. According to the existent literature, favourable outcome with a low surgical reintervention rate may be possible if these extensive repairs are performed in

specialised aortic centres. According to our results, favourable low spinal cord ischaemia rates may be achieved if a dedicated neurological monitoring protocol can be used.

Summary

- The frozen elephant trunk technique allows a definitive treatment of combined aortic lesions in a one-stage procedure, which amalgamates the elephant trunk principle and an antegrade endovascular stenting of the descending aorta.

- Furthermore, the frozen elephant trunk may form a first step during treatment of complex thoracoabdominal aortic aneurysm involving the ascending aorta or the aortic arch followed by a second surgical repair through a left thoracolaparotomy or an endovascular repair.

- Literature regarding outcome after open and endovascular thoracoabdminal aortic aneurysm repair following ascending aorta/arch repair including frozen elephant trunk during early and long-term follow up is scarce.

- A relevant mortality and complication rate has been described in two retrospective studies focusing on outcomes after open and endovascular thoracoabdminal aortic aneurysm repair after frozen elephant trunk.

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Incidence and predictors of early and mid-term neurological complications following TEVAR

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Introduction

Neurologic adverse events after thoracic endovascular aortic repair (TEVAR) include stroke and spinal cord injuries. Most complications have an immediate onset, within 24 hours from the procedure, but they can also be of delayed onset (between 24 hours and 30 days) and of late onset (after 30 days from the index procedure). The mechanisms of immediate-onset complications lie in the manipulation with guidewires and catheters in the aortic arch for acute stroke, and coverage of intercostal arteries for spinal cord ischaemia, but the pathophysiology of delayed and late events is poorly understood.[1,2]

There is also a high variability in the reported incidence of early (30-days) neurological complications, ranging from 4% to 7% for cerebrovascular accidents and from 1% to 10% for spinal cord injuries, probably as a result of high heterogeneity in treated aortic pathologies, patient selection, operative technique, and strategies for spinal cord injuries prevention.[1–9]

The objective of this chapter is to report the incidence and predictors of neurological complications in the early and mid-term period after TEVAR, with a specific focus on the results from GREAT (Global registry of endovascular aortic treatment).

GREAT

GREAT, sponsored by Gore, is a prospective multicentre cohort registry on Gore aortic endografts. It includes 113 centres and 5,023 patients with thoracic, abdominal and thoracoabdominal aortic pathologies. Enrolment began in 2010 and concluded in 2016.

For this analysis, only cases with isolated thoracic aortic pathology were included (n=833), defined as ascending thoracic aneurysm (n=329; 39.5%), type B dissection (n=273; 32.8%), aortic arch aneurysm (n=28; 3.4%), penetrating aortic ulcer (n=88; 10.2%), intramural haematoma (n=19; 2.2%) aortic transection (n=51; 5.9%), and thoracic pseudoaneurysm (n=20; 2.3%).

Proximal landing was in zone 0 in 30 cases (3.6%), zone 1 in 34 (4.1%), zone 2 in 203 (24.4%), zone 3 in 335 (40.2%), and zone 4 in 231 (27.7%). The left subclavian artery was covered with no revascularisation in 169/267 (63.2%) cases. Distal landing was classified as above the level of the coeliac trunk in 806 cases

(96.7%); in 27 (3.2%), the endograft was deployed above the superior mesenteric artery with intentional coeliac trunk coverage. A short thoracic aorta coverage ≤15cm was required in 36.7% of cases (10cm, n=142 [17.1%]; 15cm, n=163 [19.6%]), while 20cm coverage in 21.3% (n=177) and >20cm coverage in 42.1% (n=351). Spinal fluid drainage strategy was primarily based on centre and operator preference and no clear protocol was followed.

Early cerebrovascular accidents

The rate of early cardiovascular accidents in GREAT was 1.5% (n=13: one haemorrhagic, 0.1%; 12 ischaemic, 1.4%). Sixty-one per cent (n=8) were immediate while five occurred 24 hours after the procedure.

Ischaemic stroke rate was 3.7% (n=10) for proximal landing zones 0-1-2, and it was 0.4% (n=2) for zones 3–4 (p<0.001). The specific stroke rate for proximal landing zones (Figure 1) were 13.3% (n=4/30) for zone 0; 2.9% (n=1/34) for zone 1; 2.5% (n=5/203) for zone 2; 0.6% (n=2/345) for zone 3; and 0.4% (n=1/221) for zone 4. The ischaemic stroke rate was 3.7% (n=10) for proximal landing zone 0-1 or 2, and it was 0.4% (n=2) for zones 3 and 4 (p<0.001). Considering the pathology, aortic arch aneurysms had a higher ischaemic stroke rate compared with other thoracic aortic pathologies (14.2% vs. 1%; p<0.001); in cases landing proximal to the left subclavian artery, the cerebrovascular accidents rate was 4.1% (n=6) in case of left subclavian artery revascularisation and 3.5% (n=4) in case of left subclavian artery coverage without revascularisation (p=0.99). Also at the multiple logistic regression, aortic arch aneurysm resulted to be the only significant independent predictor of early ischaemic stroke (odds ratio [OR] = 16.7, 95%; confidence interval [CI] 2.9-67.3; p=0.001).

The number of central neurological complications was lower than previously reported in other large registries (Figure 2). Data extracted from the Talent thoracic retrospective registry showed a 3.7% stroke rate in 422 patients enrolled between 1996 and 2004. Similarly, Buth *et al* reported a 3.1% stroke rate on 606 procedures
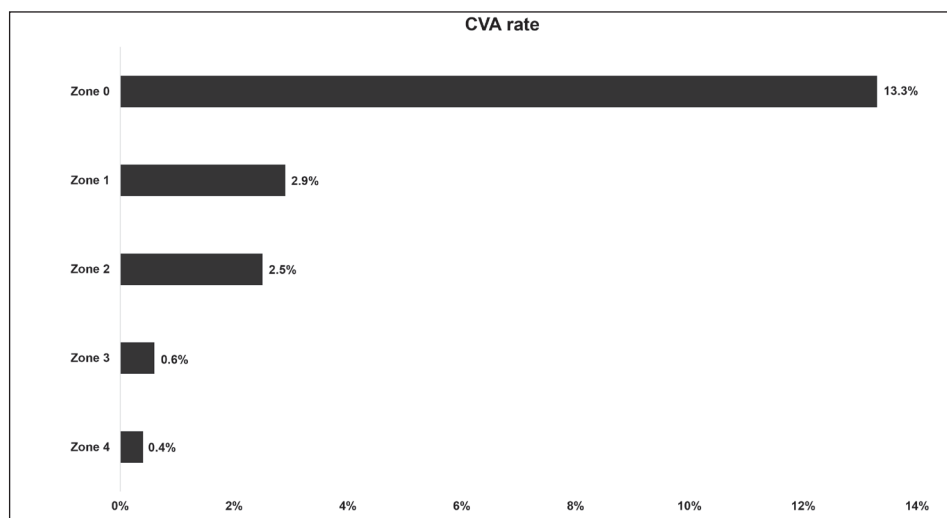
Figure 1: Rate of cerebrovascular complications following TEVAR, stratified by proximal landing zone.

of the EUROSTAR registry in the 2000–2006 period. Also outcomes from the MOTHER (Medtronic thoracic endovascular registry) registry, conducted from 2002 to 2012, and SUMMIT (Study to assess outcomes after endovascular repair for multiple thoracic aortic diseases), collecting data from 2009 to 2013, were consistent with these results with a 4.8% and 3.1% stroke incidence respectively.[4,6,7]

The lesser stroke incidence in GREAT, which was statistically significant when compared with the rates seen in the Talent, EUROSTAR, STABLE, MOTHER, and Vascular Quality Initiative (VQI) registries, may be at least partially explained by the different time periods of patient enrolment and treatment.[8] Another possible explanation is that the Gore thoracic endografts may potentially have a lower risk of air embolism compared with grafts that need to be unsheathed. It is important to note that the risk of cerebral embolisation may also be increased in aneurysms involving the aortic arch compared with other aortic pathologies, because of thrombus dislodgement caused by guidewires and catheters and involvement of supra-aortic trunks ostia. This was confirmed by the multivariate analysis, which identified aortic arch aneurysm as the only independent predictor of 30-day central neurological complications (OR=16.7; p=0.001).

Early spinal cord injuries

In GREAT, the spinal cord injury rate within 30 days was 1.8% (n=15); of these, 14/15 were ischaemic (93.3%), 1/15 haemorrhagic (6.6%), 5/15 were immediate at awakening (33.3%), and 10/15 were delayed (66.7%).

The 1.8% rate of paraplegia/paraparesis (including both permanent and transient events) found in GREAT was lower than the 2.5–4.2% rate generally reported in other registries, even if only MOTHER (GREAT 1.8% vs. MOTHER 4.2%; p=0.002), SUMMIT (GREAT 1.8% vs. SUMMIT 3.5%; p=0.03), and VQI (GREAT 1.8% vs. VQI 9.6%; p<0.001) described a statistically significant higher incidence of spinal cord ischaemia. Considering only early outcomes, the univariate and multivariate analysis failed to identify any independent predictor of
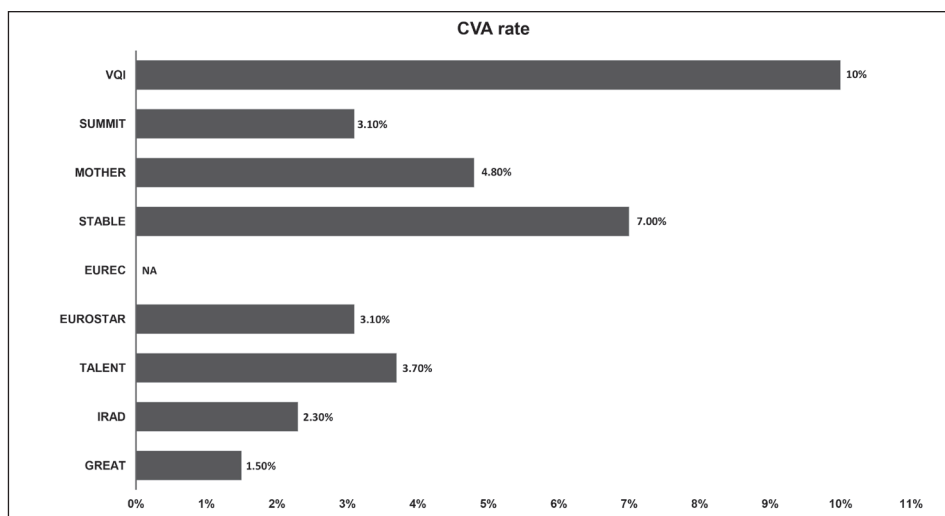
Figure 2: Incidence of cerebrovascular complications following TEVAR in clinical registries.
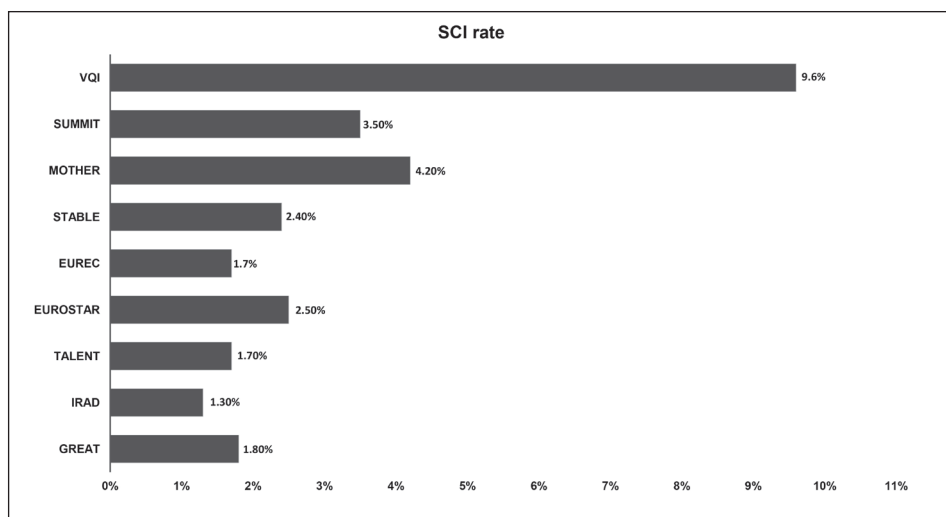
Figure 3: Incidence of spinal cord injuries in clinical registries.

paraplegia in this cohort of patients, and previously described risk factors, as length of coverage, left subclavian artery coverage, female sex, chronic renal insufficiency, and other clinical and anatomical aspects, were not significantly associated to spinal cord ischaemia.[1,9]

Late cerebrovascular accidents

Eleven cases of ischaemic cerebrovascular accidents occurred during follow up (median=255 days; min=76, max=1136), with 4/11 (36%) being in the posterior cerebral territory. Kaplan-Meier estimates of freedom from cerebrovascular accidents at four years was 96.3% (95% CI 94-98). Figure 4A). Multivariate analysis identified left subclavian coverage (HR 3.31, 95%CI 1.44-7.65; P=.005) and hypercholesterolaemia (HR 2.96, 95%CI 1.16-7.57; p=0.024) as independent predictors for ischaemic stroke.

The late cerebrovascular patients in the TEVAR population probably reflects the high prevalence of cardiovascular risk factors among these patients, and this is consistent with the finding that hypercholesterolaemia was significantly associated with these events. However, left subclavian artery coverage without revascularisation also increased the risk of ischaemic cerebrovascular events, suggesting that left subclavian artery revascularisation may have a role in maintaining an adequate cerebrovascular haemodynamic status during a mid-term period following TEVAR.

Late spinal cord ischaemia

Three cases of late spinal cord ischaemia (two paraparesis; one paraplegia) occurred (median=296 days, min=139, max=574), with one case after a hypotensive episode during dialysis. None of these cases was associated to reintervention. Freedom from spinal cord ischaemic events was 97.8% (95%CI 96-98) at four years (Figure 4B). Cox proportional hazards analysis identified length of aortic coverage as the only independent predictor of mid-term spinal cord ischaemia (hazards ratio [HR] 1.24;
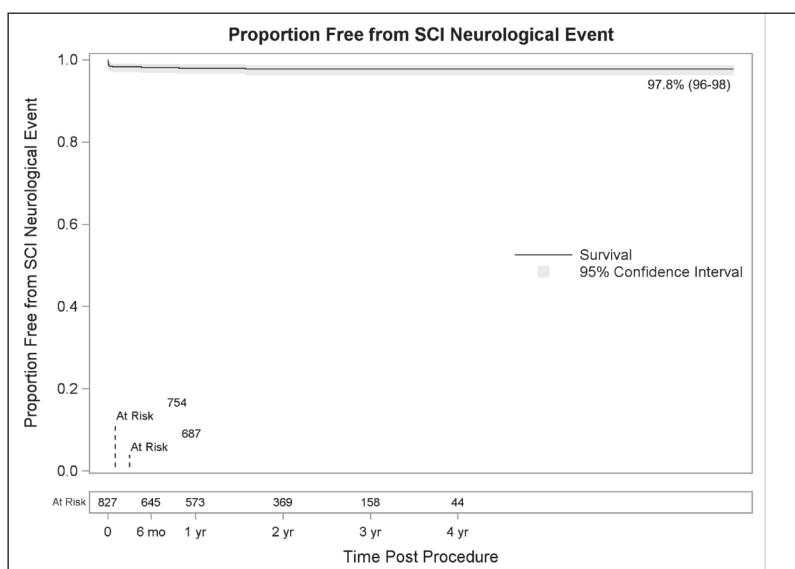
Figure 4A: Kaplan-Meier estimate of four-year freedom from ischaemic stroke after TEVAR.

95%CI 1.01-1.54; p=0.044); left subclavian artery coverage and other clinical and anatomical factors were not significantly related.

The mechanism behind late spinal cord ischaemia, in our opinion, may be primarily related to acute hypoperfusion episodes, especially in those patients with a chronic fleeting compensatory arterial circle to the spinal cord after TEVAR. This phenomenon may have been the cause of the late spinal cord ischaemia that we reported during an acute hypotension (caused by dialysis) case and also the cause of other similar single cases have been reported in the literature.[10,11] However, we do not still have strong and consistent data to support this hypothesis.

Length of aortic coverage, which has already been described as a risk factor for early spinal cord ischaemia, may have a major role in favouring also mid-term spinal cord ischaemia. In our multivariate analysis, endograft length was the only independent predictor, with an HR of 1.24 (p=0.044) every 5cm of increase of aortic coverage.[2,12]

Left subclavian artery management in TEVAR

Left subclavian artery coverage without revascularisation may be responsible for perioperative strokes, spinal cord ischaemia, and left arm ischaemia; however, the optimal management of left subclavian artery in patients requiring left subclavian artery coverage is still controversial.[13] Some studies advocate routine left subclavian artery revascularisation to prevent these complications, while others support a more selective strategy of left subclavian artery revascularisation during TEVAR.[6,14] These discordant data justify the low level of evidence for supporting left subclavian artery revascularisation described in the most recent guidelines.[13] However, one of the limitations of the available literature0 is that previous studies focused only on 30-days or in-hospital neurological complications, and did not analyse possible later events.

On this regard, the results from GREAT seem to underline the concept that left subclavian artery coverage may predispose also to late cerebrovascular
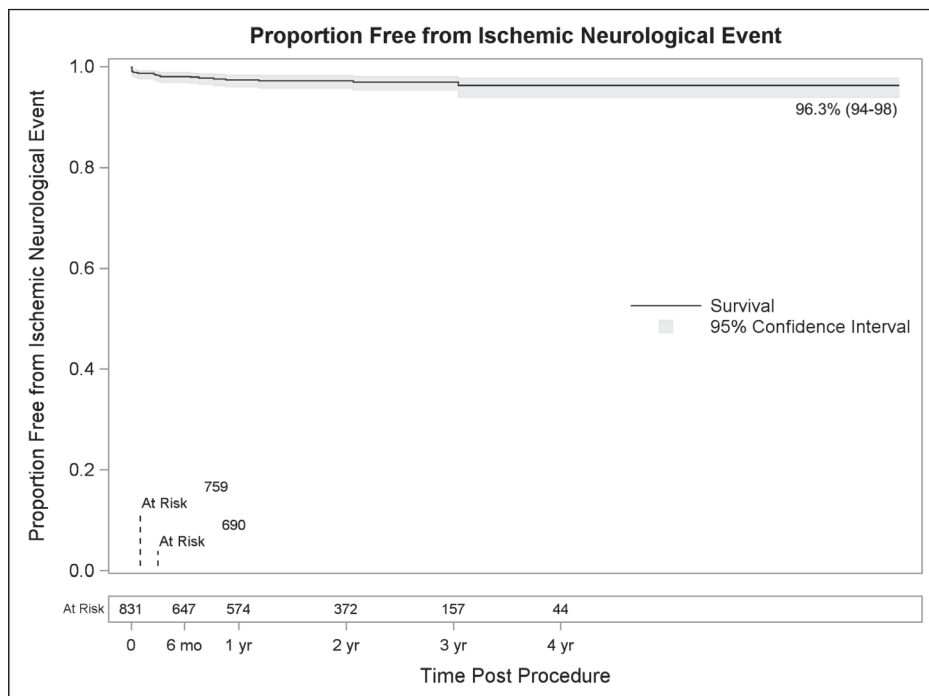
Figure 4B: Kaplan-Meier estimate of four-year freedom from spinal cord ischaemia after TEVAR.

accidents. The multivariate analysis showed that left subclavian artery coverage without revascularisation, together with hypercholesterolaemia, was a strong independent predictor of ischaemic stroke (HR 3.31, p=0.005) in the mid-term follow-up. However, our result does not confirm the role of left subclavian artery revascularisation to prevent early strokes or spinal cord ischaemia.

In consideration of these data, it seems to be advisable during endovascular planning, to consider left subclavian artery revascularisation in order to prevent not only in-hospital neurological adverse events, but also later cerebrovascular accidents.

Conclusion

In this registry, overall neurological complication rate in patients undergoing TEVAR for isolated thoracic pathologies was low. Early risk of stroke was primarily related to proximal aortic extension (aortic arch aneurysm and sealing zones 0-1-2). In the mid-term period, length of coverage resulted an independent predictor of spinal cord ischaemia, as left subclavian artery coverage was associated with a higher stroke rate

Summary

- Results from real-world data of this large multicentre clinical registry show that current rates of early neurological complications following TEVAR are low.

- Aortic arch aneurysms and landing zones 0-1-2 were associated with an increased risk of early cerebrovascular accident.

- Left subclavian artery coverage without revascularisation is associated with an increased risk of ischaemic stroke during mid-term; similarly, length of aortic coverage was a predictor of mid-term spinal cord ischaemia.

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Endovascular therapy for Takayasu's arteritis

IY Soh and SR Money

Introduction

Takayasu's arteritis is a rare, granulomatous transmural vasculitis, primarily affecting the aorta and its major branches. The disease follows an indolent course that leads to both occlusive and aneurysmal disease, and it can be fatal if left untreated. Descriptions of this disease date as far back as 1761, when an Italian anatomist, Giovanni Morgagni, described a 40-year-old female with "pulseless disease." In 1856, William S Savory, a British surgeon, reported on a 22-year-old female with complete obliteration of the main arteries in both upper extremities and left neck who also had vision loss. In 1908, Mikito Takayasu, a Japanese ophthalmologist, presented the case of a 21-year-old female with vision loss and absent radial pulses at an academic meeting where two other professors of ophthalmology shared cases with matching features. An accumulation of case reports was subsequently accrued, and, in 1921, it was proposed that the constellation of ophthalmic findings, pulselessness and end-organ ischaemia be unified under the term "Takayasu's disease". By 1975, the Department of Health and Welfare in Japan renamed the disease "Takayasu's arteritis."

Pathogenesis

The cause of Takayasu's arteritis remains unknown. Immunohistochemical analysis of arterial tissue from Takayasu patients who have undergone open surgery exhibits sequelae of an exaggerated pan-mural inflammatory response and subsequent arterial remodelling. Vessels have hyperplastic vasa vasorum, marked thickening of the adventitial layer, fragmentation of the elastic lamina and fibroblastic proliferation of the intimal and medial layers. The unwavering inflammatory insult causes progressive fibrosis and subsequent luminal narrowing or aneurysmal degeneration.

Medical treatment

Immunosuppressive agents such as corticosteroids are first-line therapy, with the goal of alleviating ischaemic symptoms and preventing progression of vascular stenosis, occlusion or aneurysmal degeneration. Relapses are common, unfortunately, and immunomodulators that target the TNF-alpha and IL-6 pathways are used in refractory cases. There are no randomised trials comparing the efficacy of different immunosuppressive therapies. A meta-analysis, limited to observational studies, found that approximately 60% of patients achieved remission with glucocorticoids combined with either non-biologic immunomodulators (e.g. methotrexate, azathioprine, mycophenolate, cyclophosphamide) or biologic immunomodulators

(e.g. rituximab, tocilizumab).[1] There was a trend towards higher relapse rates for non-biologic agents, but this was not statistically significant.

Indications for interventional or surgical treatment

Surgery may be indicated when maximal medical therapy has failed to prevent or control arterial injury in Takayasu's arteritis. Across a number of series, the predominant indications for surgery are as follows: refractory hypertension or renal insufficiency related to renal artery stenosis; aortic disease including coarctation, ascending aortic aneurysm with aortic valve regurgitation; ischaemic heart disease; supra-aortic disease with cerebral ischaemia; mesenteric ischaemia; and severe limb-threatening claudication.

While there is little in the literature defining what percentage of patients with Takayasu's arteritis will require an intervention, multiple studies report on the safety of both open and endovascular interventions.[2] The durability of each approach varies. Both methodologies have high failure rates, operative complications, and high incidences of restenosis or pseudoaneurysm development.[3]

For patients with mid-aortic syndrome caused by Takayasu's arteritis, angioplasty followed by self-expanding stent angioplasty has been shown to be successful therapy. A retrospective review of 48 such cases included patients presenting with uncontrolled hypertension (n=40; 83.3%), lower limb claudication (n=38; 79.2%), and left ventricular
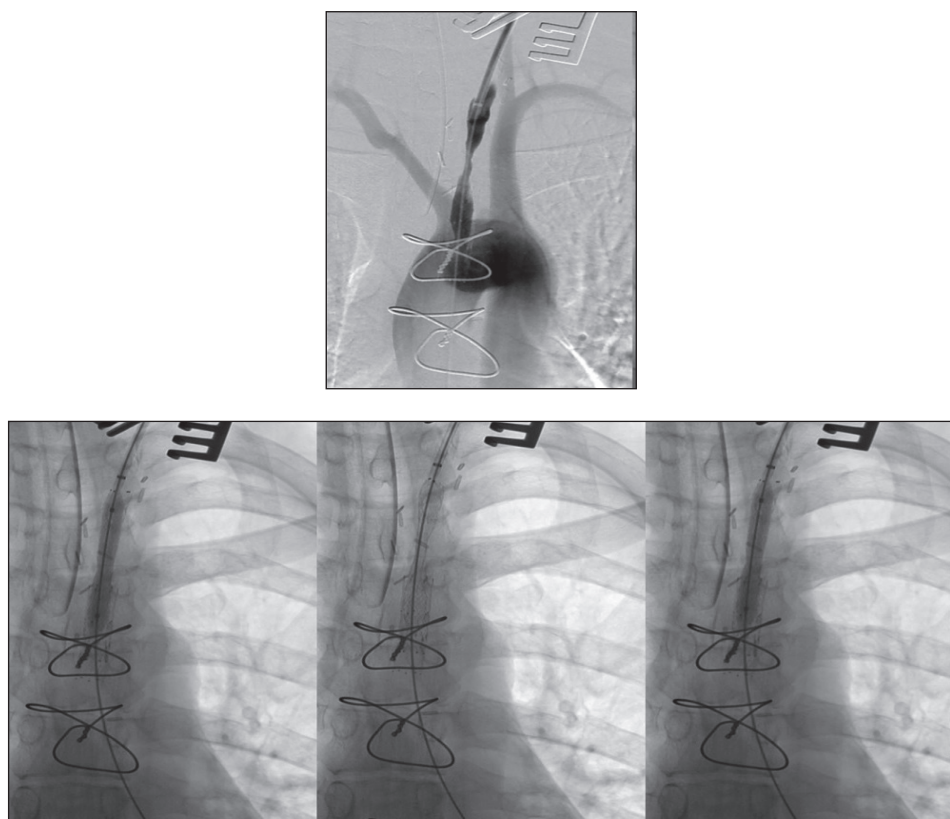
Figure 1: (A) Previous aorto-carotid bypass with in-stent stenosis; (B) predilatation balloon angioplasty 6mm x 40mm; (C) drug-eluting angioplasty 8mm x 60-mm Zilver PTX; and (D) postdilatation balloon angioplasty 6mm x 40mm. No restenosis at seven-year follow up.

dysfunction (n=11; 22.9%).[4] All lesions were predilatated with undersized balloons no greater than 80% of the target aortic diameter, then treated with self-expanding stents (e.g. Wallstent, Boston Scientific). Mean aortic stenosis before and after stent angioplasty was 81% and 15%, respectively. Average peak systolic gradient before and after stent angioplasty was 71mmHg and 14mmHg, respectively. Over an average of 3.1 years follow up, mean blood pressures improved from a mean systolic 179mmHg before stenting to 149mmHg after (p<0.001); mean number of antihypertensive drugs decreased from 3.1 to 1.1 (p<0.001); mean ankle-brachial index values increased from 0.75 to 0.92 (p<0.001); and B-type natriuretic peptide levels decreased from a mean of 1287.8pg/ml to 547.2 (p=0.008).

Patients with severe cerebral ischaemia caused by Takayasu's arteritis have also been successfully treated with endovascular therapy. A retrospective review of 29 patients included 17 who underwent open bypass and 14 who underwent endovascular therapy.[5] Surgical bypass was chosen for long (>5cm) or diffuse lesions, while endovascular therapy was chosen for short (<5cm) lesions. Balloon angioplasty alone was done for nine (64%) of the cases, and a bare metal stent was used in five (36%) cases either because of residual stenosis >50% or dissection after balloon angioplasty. Overall, primary and secondary patency rates in the endovascular group were 85.71% and 92.86% at one-year, respectively; and 68.18% and 75.66% at three years.[5] The only independent risk factor associated with primary patency in surgical or endovascular treatment groups was disease activity (odds ratio [OR] 0.17, confidence interval [CI] 0.03-0.93; p=0.04).

There is a narrow window for survival benefit in Takayasu patients undergoing surgery. After separating Takayasu's arteritis patients by disease severity criteria, a retrospective study including 120 patients reported on outcomes and overall survival.[6] In patients with two or more major complications of Takayasu's (e.g. aortic regurgitation, severe hypertension, aneurysm development), the 15-year survival rate in patients treated medically was 43% compared with 67.5% in patients treated surgically.[6,7] Patients with only one mild/moderate complication had no survival benefit after surgery, and those with uncomplicated disease had a decrease in 15-year survival rate after surgical intervention.

Across a number of series, the best surgical outcomes occur in patients with quiescent disease. This is well conveyed in a retrospective review of 251 patients with Takayasu's arteritis, of which 42 (17%) required open surgical revascularisation.[8] Freedom from surgical revision at five and 10 years was 100% in patients with quiescent disease, no longer on steroid therapy; 95% and 81% in patients with quiescent disease maintained on steroid therapy; 57% in patients with active disease on steroids; and 33% in patients with active disease not on long-term steroids.

The definition of active vs. quiescent disease is difficult to define, however, and it is not uniform in the current literature. Per the US National Institutes of Health (NIH) criteria, disease activity is defined as having at least two of the following criteria:[9]

- Systemic features (e.g. fever, myalgias not otherwise explained)
- Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in the absence of infection or neoplasm
- Features of vascular ischaemia or inflammation (e.g. claudication, diminished or absence pulse, bruit, vascular pain such as carotidynia, asymmetric blood pressures in the extremities)
- Typical angiographic features at onset of disease or worsening of vascular lesion.

In the absence of a uniform indicator of disease activity, many studies rely on serum marker levels as a marker of disease activity. It is important to note, however, that erythrocyte sedimentation rate has been shown to have low sensitivity (36%) and specificity (83%) when compared to pathologic specimen analysis.[8] Moreover, the use of immunomodulators at the time of index surgical intervention trends towards worse patency reads and increase need for reinterventions. Thus, a combination of clinical, pathologic, and laboratory findings must be used in assessing disease acuity prior to surgical intervention.

Endovascular treatment

Stenotic lesions in Takayasu's arteritis are often long and densely fibrotic. Lesion recoil may necessitate increased inflation pressures during balloon angioplasty or supplemental stenting to achieve sufficient luminal diameter. Incidence of post-angioplasty dissection and pseudoaneurysmal degeneration can be reduced by ensuring that endovascular landing zones are beyond inflamed areas. There are several observational studies on the efficacy of percutaneous transluminal angioplasty alone or with stenting in Takayasu's arteritis. While most studies report high rates of restenosis and recurrence rates following the use of stents, this finding is not universal.

In a review of 49 Takayasu's stenosis cases treated endovascularly, renal arteries were the most frequently involved (n=19; 39%), followed by subclavian arteries (n=13; 27%).[10] The majority of cases were treated with stent angioplasty (n=16; 84%) for ostial lesions, long lesions (>3cm), incomplete relief of stenosis, or dissection following balloon angioplasty alone (n=3; 16%). Half of the stent angioplasty cases restenosed, all of which were re-treated with balloon angioplasty. Of these redo cases, 25% (n=2) restenosed again. The overall patency within one- or multistage intervention was 92% over a seven- to eight-year follow up period.

Analysing stent vs. balloon angioplasty, a review of 16 patients with Takayasu's renovascular hypertension cases found equivalent clinical efficacy between the two groups but improved overall patency with balloon angioplasty alone.[11] Technical success was achieved in 21 of the 22 stenotic renal artery lesions. At one, three, and five years respectively, overall patency rates after balloon angioplasty alone were 100%, 91.7% and 91.7%; primary patency rates of stent angioplasty were 55.6%, 33.3%, and 33.3%; and primary-assisted patency rates of stent angioplasty were 88.9%, 66.7%, and 55.6%. These findings were mirrored in a meta-analysis comparing balloon vs. stent angioplasty outcomes in Takayasu's arteritis cases.[12]

By contrast, Lee *et al* reported more durable patency rates with stent angioplasty.[13] Their study analysed 51 Takayasu's arteritis patients, of whom 24 (47%) were selected for endovascular treatment of the renal (n=16), subclavian/innominate (n=11), carotid (n=5) arteries and abdominal aorta (n=3). All 35 lesions were treated with either angioplasty alone (n=18) or with angioplasty plus stenting (n=17). The majority of lesions (n=26; 74%) achieved satisfactory results with no or minimal residual stenosis. In follow-up over an average of 46.8 months, restenosis was observed in eight (44%) lesions treated by angioplasty alone, and three (18%) lesions treated with both balloon and stent angioplasty.

As endovascular technology diversifies, the application of stent grafts vs. bare metal stents, cutting balloons, and drug-eluting technology, are being explored. In a very small retrospective review of four patients who underwent endovascular intervention, although initial outcomes were excellent and directly comparable, stent

grafts remained patent longer than bare metal stents and were less likely to require secondary intervention.[14] Cutting balloon angioplasty may be effective in treating stenotic lesions that are too hard and fibrotic to dilate with appropriately sized complaint or non-compliant balloons. With respect to drug-eluting technology, most randomised clinical data is based upon patients with arterial stenosis of atherosclerotic aetiology. It is unclear whether inflammatory, immune-mediated stenotic lesions of Takayasu's arteritis can be safely and effectively treated by this same technology.

Vigilant long-term follow up is essential after endovascular repair in Takayasu's arteritis patients. In addition to continued immunosuppressive therapy, dual antiplatelet therapy is prescribed after stent angioplasty for one to three months.[15,16] The ever-present risk of disease activation directly correlates with risk of secondary complications after revascularisation, thus surveillance imaging in the form of ultrasound, computed tomography (CT) or magnetic resonance (MR) scans should ensue.

Endovascular techniques

Most short, focal stenoses and occlusions can be crossed using standard hydrophilic guidewires and support catheters. Long and irregular lesions are technically more challenging to traverse. Once the wire and catheter have engaged the lesion of interest, an appropriately sized sheath is introduced and used for localised angiography. Balloon sizing for angioplasty should be conservative and gradually beginning undersized by approximately 80% the normal segment of the target vessel in order to avoid vessel dissection or rupture. When treating supra-aortic lesions, short balloon inflation times can reduce cerebral ischaemic time and risk of hyperperfusion. Should a flow-limiting dissection develop, repeat angioplasty with a prolonged inflation time and a slightly slimmer balloon may provide an adequate result. Rupture should be managed with immediate reinflation of the balloon at the site of the leak and consideration of covered stent angioplasty. Branch points can be treated by kissing balloon angioplasty, or with a safety wire in the branch vessel in order to prevent shuttering of the orifice during angioplasty. When needed, balloon-expandable stents are preferred for use in the visceral and innominate artery lesions, whereas self-expanding stents are preferred for cervical and extremity lesions which are subject to flexion and extension body mechanics. Covered stents, stent grafts, and custom made stent grafts are considered for excluding aneurysmal lesions and for treating aortic stenosis or occlusions. Placement of a Palmaz stent within an aortic stent graft can provide additional radial force in treatment of middle aortic syndrome.[14]

Although technical success with angioplasty is reported in the literature as high as 85–95%, there are limitations on this frontier. Chronic flush occlusions, for example, offer no inherent support for engaging wires or catheters and may oblige open surgical revascularisation. Similarly, symptomatic superior mesenteric and celiac artery lesions are often long and irregular, responding poorly to endovascular intervention. Published literature on endovascular techniques for treatment of mesenteric ischaemia in Takayasu's arteritis is limited, as most of these visceral lesions are approached by open surgical bypass.

Conclusion

Percutaneous transluminal angioplasty has emerged as a safe, minimally invasive and comparable alternative to surgical revascularisation in quiescent Takayasu's arteritis affecting renal arteries and the abdominal aorta. High restenosis and recurrence rates are associated with the use of stent angioplasty and if revascularisation is attempted during active phases of the disease. Thus, balloon angioplasty alone is the preferred initial endovascular approach to treatment, and stringent immunosuppressive therapy is imperative before and after intervention.

Summary

- Endovascular procedures are a safe alternative to open surgery for treatment of Takayasu's arteritis patients who have an unrelenting clinical course despite maximal medical therapy, and who are deemed unfit for open surgery.

- Outcomes are favourable when interventions are performed while the disease is in remission.

- Erythrocyte sedimentation rate is not a sensitive marker for disease activity.

- Accept short-term successes with endovascular therapy as a bridge to open reconstruction should the initial intervention fail.

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Modelling the lifetime risk of malignancy associated with low-dose radiation exposure after endovascular intervention

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Introduction

There is a well-established causal pathway involving exposure to ionising radiation that leads to DNA damage, which then leads to genetic mutations because the damaged DNA is "misrepaired" and subsequently results in the development of malignancies.[1] Population studies on the atomic bomb survivors of Hiroshima and Nagasaki further delineated the dose-associated risks and the latency periods associated with development of various cancers after radiation exposure.[2] There have been concerns about the deleterious effects of radiation exposure, for the patient and operator, since the development of endovascular interventions, and these concerns have only grown with the advent of increasingly complex X-ray guided procedures. However, accurately measuring the radiation dose that a patient receives during endovascular interventions, and then calculating the related risk of malignancy, has proven difficult. In an attempt to quantify these doses and risks, retrospective population studies, biodosimetry and computational models have been used.

Observational studies

Attempts have been made to estimate the risk of radiation-related malignancy associated with endovascular interventions by retrospectively studying cohorts of the relevant population. A recent study used the Hospital Episode Statistics (HES) database to compare the cancer outcomes of patients undergoing endovascular aneurysm repair (EVAR) with those undergoing open aneurysm repair.[3] The authors reported an increased risk of abdominal cancers in the EVAR group, with a hazard ratio of 1.14. Although the findings of these studies are interesting, they are confounded by the fact that non-homogeneous populations were compared. Patients undergoing EVAR are invariably older and more comorbid than surgical patients and, therefore, have an inherently higher risk of malignancy. Additionally, the study could not distinguish between *de novo* and recurrent cancers. Despite attempts to account for confounding factors, establishing that any observed differences in the risk of cancer are related to radiation exposure is difficult. The relatively small, heterogenous population of operators studied to date also means that there is no definitive evidence of an increased incidence of malignancies in operators exposed to radiation, but this may be because of the fact that such studies are not powered

to detect a higher incidence of cancer. This has led to efforts aimed at examining biological surrogates of genomic instability in individuals and modelling the risk of malignancy associated with exposures.

Biodosimetry

Biodosimetry describes the methods used to estimate absorbed radiation dose by observing the molecular, cellular or genetic changes associated with exposure to ionising radiation. Broadly, these techniques either directly examine the tissue damage caused by radiation or measure the products of repair following radiation damage. The dicentric chromosome assay, for example, is based on the theory that after radiation exposure, a proportion of the damaged chromosomes is misrepaired in an arrangement in which one chromosome contains two centromeres (dicentric). The varying microscopic appearances of these chromosomes are demonstrated in Figure 1. The background frequency of dicentric chromosomes in the normal population is very low and rises in a proportional and predictable fashion with absorbed dose of ionising radiation. This assay is the current gold standard of biodosimetry.[4]

Gamma-H2AX is a protein that is formed as a product of DNA repair after radiation-induced damage and can be measured in circulating cells. The predictable rise in the levels of this protein make it useful for estimating dose after acute radiation exposures. Flow cytometry has been used to detect a rise is gamma-H2AX in vascular patients and operators after EVAR, suggesting a significant exposure during this procedure.[5]

Estimating radiation dose and associated risk is complicated by the multifactorial nature of the process, including the source, type of radiation, distance from the source, and any attenuation (e.g. by personal protective equipment). Biodosimetry can be used to estimate an individual's absorbed dose without the need for mathematical adjustment for all of these factors. Therefore, it may arguably give a more accurate estimation of dose compared to other methods. However, it must be noted that individual biodosimetry is a time consuming and costly process and also requires a minimum dose threshold before reliable dose estimates can be achieved.[6] Additionally, we are still in the process of deciphering which biodosimetric
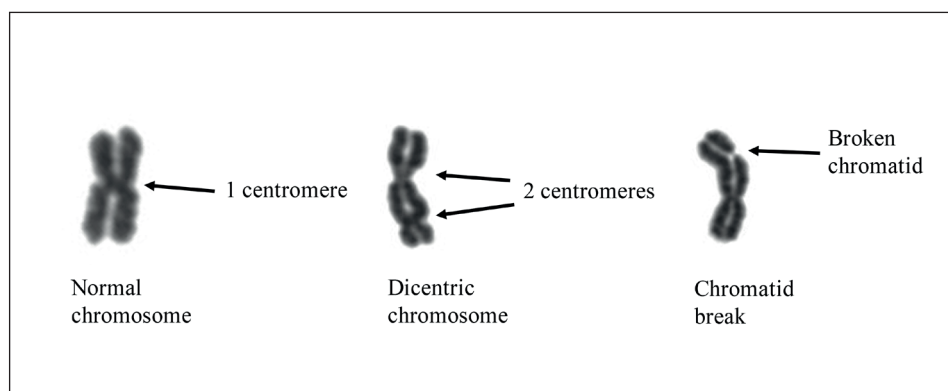
Figure 1: Microscopic images of a normal chromosome (left), a dicentric chromosome (middle), and a chromosome with a broken chromatid (right).

methods are sensitive to the low, chronic radiation exposure that is associated with endovascular procedures.

Estimating cancer risk using modelling

Monte Carlo modelling uses a computational algorithm to simulate the known probabilities of penetrance, absorbance and scatter of each X-ray particle from a given radiation source. Phantom models of the human body, including model organs, are then used to estimate organ doses based on this simulation. Current literature investigating radiation exposure during EVAR with this method almost exclusively uses the Monte Carlo code PCXMC (STUK).[7] There are established limitations associated with the phantom models used in PCXMC.[8,9] For example, separate male and female patient phantoms do not exist, while organ models are very simplistic. As EVAR involves a broad range of beam angles across different planes at different energies, it is important to consider radiation exposure in this context and to incorporate as much procedural data as possible.

To address the deficiencies in previous studies, a Monte Carlo simulated approach has been proposed to estimate organ doses with realistic phantom models and detailed procedural data, including a broad range of beam angles and X-ray data, and including the primary EVAR, perioperative imaging, follow-up CT scans and any subsequent reinterventions.

To estimate procedural organ doses, Monte Carlo simulations may be used to create a look-up table of conversion factors for each organ, adjusted for patient gender and beam angle. The look-up table of conversion factors is produced by synthesising a vast amount of data from anonymised radiation structured dose reports from individual EVARs, including information from both fluoroscopy and digital acquisitions, such as beam angle, dose area product (DAP) per acquisition and tube potential. The conversion factors can then be used to easily convert DAP from future procedures into meaningful organ doses. The main advantage of a lookup table compared with "live" Monte Carlo modelling is the greatly increased computational speed. However, it also confers a lack of flexibility by only allowing an estimation of doses under the clinical conditions in which the initial conversion factors were calculated.

Modelling risk associated with CT imaging

In addition to perioperative imaging, patients may require lifelong follow-up in the form of computed tomography (CT) imaging following EVAR, thus demonstrating the importance of including the radiation exposure associated with imaging in risk calculations to produce reliable organ dose estimates. National Cancer Institute dosimetry system for Computed Tomography (NCICT) is a graphical user interface-based computer programme that can be used to estimate radiation exposure associated with perioperative and follow-up CT imaging.[10] NCICT uses International Commission on Radiological Protection (ICRP) adult phantoms in conjunction with specific CT scanner input data to produce organ dose coefficients and the organ absorbed dose per unit volumetric CT Dose Index (CTDIvol).[11] Studies have suggested that the organ doses produced by NCICT provide realistic anatomy based on ICRP adult phantoms, as well as up-to-date bone marrow dosimetry, which is vital given the susceptibility of rapidly replicating cells such

as bone marrow to carcinogenic change.[11] It is, therefore, important to consider the fact that it is not only the quantity of adsorbed radiation that determines the potential health effects associated with radiation exposure, but also the sensitivity of the specified organ. As such, crude measurements such as dose-length product (DLP) and dose-area product, as used in previous literature, are not sufficient for measuring health risk.[12]

Patient-specific parameters can be inputted into NCICT, such as gender, height and weight, while scanner-specific parameters include dose-length product (DLP) and scan length. The output data, namely effective and organ doses, are extracted and included in the overall calculations to produce organ doses for all imaging associated with the primary EVAR and any reinterventions. These data are combined with EVAR radiation exposure to calculate the overall risk of malignancy.

Modelling cancer risk in patients after EVAR

Organ doses are suspected to be highest for rapidly replicating tissues, such as colon and bone marrow, while effective dose is likely to be significantly higher for the right anterior oblique projection compared to left due to the left-sided anatomical location of the stomach.

Once organ doses from the index procedure have been calculated by one or more of the methods described above, the organ doses from any perioperative and follow-up CT imaging can be incorporated to produce total treatment organ doses. These data can be subsequently inputted into the National Cancer Institute Radiation Risk Assessment Tool (RadRAT) to produce cancer risk estimates. RadRAT is an open access online tool for estimating the lifetime excess risk of cancer incidence amongst various populations with similar cancer incidence rates to the US population. The reported lifetime risks use models obtained for the 11 cancers included in the National Academies of Sciences' BEIR VIII Committee report 2006, as well as additional risk models by the National Cancer Institute.[13]
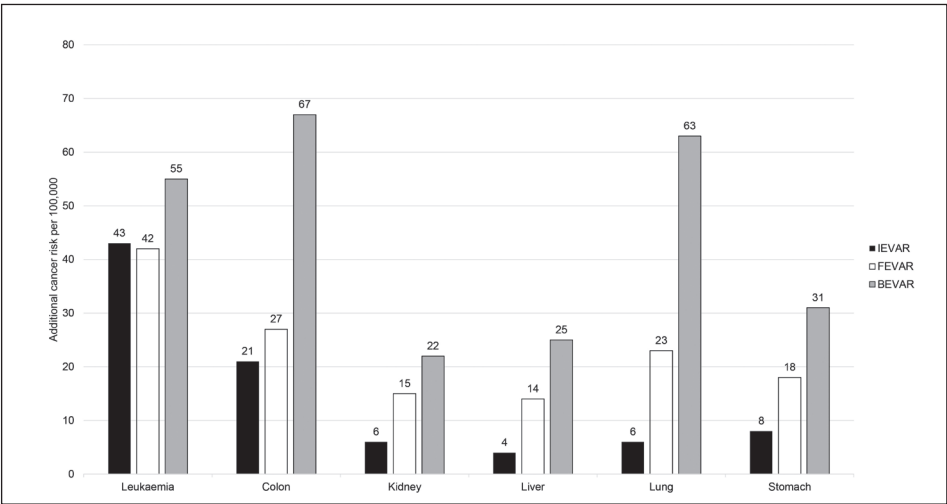
Figure 2: Additional risk of malignancy per 100,000 procedures associated with infrarenal EVAR (black), fenestrated EVAR (white) and branched EVAR (grey).

The additional risk models are based on data from the Japanese atomic bomb survivors. The tool allows calculation of risk using organ dose input data associated with acute and chronic exposures based on 2000–2005 US population and US Decennial Life tables 1999–2001 (and other similar populations). The potential lifetime risk estimates use Monte Carlo simulation methods. Using cumulative organ doses calculated from our own case series, the risk of various malignancies has been estimated by RadRAT as shown on Figure 2.

As with any simulation method, there are key limitations. When incorporating data from atomic bomb survivors, it is important to consider the potential differences in the dose-response curve between a single significant exposure following detonation of a radioactive device and multiple small exposures over a long period of time, particularly when considering additional CT imaging in conjunction with procedural exposure. RadRAT is fundamentally based on estimates calculated using the US general population survival probabilities, whereas for individuals with a shorter life-expectancy such as smokers or comorbid individuals, the lifetime cancer risk secondary to radiation exposure will be lower given the shorter-term life-expectancy conferred by competing risks. Furthermore, patients exposed to medical radiation have been generally found to have lower risk estimates than atomic bomb survivors.[14,15] The precise reasons for this are unknown and it is difficult to disentangle the various potential differences between the study populations.

Conclusion

Precise measurement of the dose of radiation absorbed by a patient during endovascular interventions is difficult. This is partly because of the multitude of contributing physical variables, as well as the individual variations in absorption and sensitivity. We have described some of the available methods to best estimate this dose and, thereafter, estimate the associated risk of malignancy. Biodosimetry offers the most direct measurement of effective dose accumulated over time, but it is time consuming and expensive. Monte Carlo modelling is non-invasive and the use of look-up tables is an efficient method of making a reasonable estimation of dose, although this assumes that the clinical conditions of each case are identical.

Studying the risk of malignancy associated with endovascular interventions is important to better inform patients and protect operators. Modelled risks appear very small and must be viewed in the context of the patient cohort, which is often elderly, multimorbid and requiring a potentially life-saving procedure, which itself generally has a high success rate. It is important to note, however, that modelling does not account for variations in radiation sensitivity between individuals.

Summary

- Endovascular interventions expose patients to an appreciable dose of radiation.

- Consequently, these patients may be at an increased risk of malignancy.

- Precise measurement of absorbed radiation dose is currently difficult.

- Estimating radiation dose and modelling risk is possible by a variety of methods.

- Long-term risk of radiation induced malignancy for the patient must be weighed against the benefits of the procedure.

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Timing of intervention for acute type B dissection in the modern endovascular era

J Budge and I Loftus

Introduction

Acute type B aortic dissection is a life-threatening disease caused by a tear in the intimal layer of the descending thoracic aorta. Early treatment goals focus on reducing the risk of aortic rupture, propagation of the dissection, and visceral malperfusion. Most current guidelines recommend a different management algorithm depending on whether the patient is deemed to have an uncomplicated or a complicated type B aortic dissection.[1] Complicated aortic dissections comprise those with persistent or recurrent pain, uncontrolled hypertension despite maximal medication, early aortic expansion, malperfusion, and signs of rupture (haemothorax, increasing periaortic and mediastinal haematoma). Medical management has historically been the mainstay of treatment for patients with uncomplicated dissection, with the focus on controlling blood pressure, heart rate, and pain; thereby, reducing aortic wall stress and false lumen pressurisation.

The choice of treatment algorithm in the early phase must be balanced with its effect on the mid- to long-term outcomes in these patients. This is especially important in patients with uncomplicated type B aortic dissection, who have relatively low early mortality, but aortic related complications affect their long term clinical outcome. With recent advances in thoracic endovascular aortic repair (TEVAR), earlier endovascular treatment may be of benefit to a greater proportion of these patients. This chapter will focus on the developments on the timing of TEVAR in type B aortic dissection.

Treatment aims, strategies and timing in complicated type B aortic dissection

Complicated type B aortic dissection is a dangerous condition with mortality rates of 16% early follow-up and 40% at five years.[2,3] It is also worth noting that a significant proportion, up to 30% in some trials, of patients with uncomplicated type B aortic dissection may go on to develop complicated dissection.[4]

In complicated type B aortic dissection, surgical intervention should not be delayed; however, a clinical decision must be made as to the optimal repair approach. In patients with disease that is amenable to both open or endovascular repair, several systematic reviews have shown that that TEVAR is associated with lower rates of complications (stroke 0.82 vs. 5.8%; paraplegia 0.48 vs. 4.8%); it also provides a significant early mortality advantage.[5–7]

On the basis of these improved outcomes, TEVAR has become the gold standard for the treatment of complicated type B aortic dissection, as stated in the Society of Thoracic Surgeons (STS) 2008 expert consensus.[8] The evidence for improved outcomes after endovascular therapy has also led to increased interest in the use of TEVAR to manage uncomplicated type B aortic dissection.

Treatment aims and strategies in uncomplicated type B aortic dissection

Traditional management and many current guidelines state that optimal medical management is the first-line approach for uncomplicated type B aortic dissection. This is, initially, often undertaken in a high dependency environment with intravenous agents used to control blood pressure and heart rate as well as providing adequate analgesia.[9] The goal is to convert to using oral agents, which may be required lifelong. It is worth noting that compliance with these medications have been found to be low and this may affect their long-term benefit.[10]

Beyond the early aims of treatment, the role of early TEVAR in the acute period is to assist with inducing false lumen thrombosis and aortic remodelling. The aim is to minimise aortic-related events and long-term reintervention. The use of medical management alone is associated with surgical reintervention rates (because of aneurysmal degeneration) as high as 38%. Therefore, medical management alone may not be sufficient for some patients.[11] The INSTEAD trial, a randomised control trial of optimal medical management vs. TEVAR, showed better five-year survival in the TEVAR arm.[12] It should be noted, however, that no early mortality benefit with TEVAR was gained.

The importance of successfully inducing false lumen thrombosis with TEVAR and its importance in encouraging long-term aortic modelling has been known for some time. Mani *et al,* in 2013, showed that mid-term survival was highest in patients with complete false lumen thrombosis leading to aortic remodelling.[13] This confirms that there is a significant long-term advantage from achieving full depressurisation of the false lumen.

Understanding the optimum intervention timing is key to achieving the best outcomes in these patients. Traditionally, type B aortic dissection has been divided chronologically from time of onset of symptoms into acute (≤14 days), subacute (>14 days to ≤3months), and chronic (>3months).[14] The importance of this categorisation was highlighted by the mid-term outcomes of the VIRTUE registry. This prospective, non-randomised, multi-institution registry showed that the aorta had similar plasticity in the subacute and acute phases, demonstrating similar degrees of false lumen regression after TEVAR for type B aortic dissection. The risk from intervention in the acute phase was much higher than both subacute and chronic stages. False lumen regression, along with other measures of aortic remodelling, was significantly reduced when TEVAR was performed in the chronic phase.[15] This suggested a treatment window in the subacute phase, reducing the risks of early treatment in the acute phase—with its higher rates of retrograde type A dissection—while still allowing for significant plasticity of the aorta and, thus, higher degree of aortic remodelling.[16] This signal of increased complications in the acute period was also noted in other single-centre studies with observations of increased risk of hospital and 30-day mortality, as well as all major complications.[17]

As mentioned, retrograde type A dissection represents a serious complication of TEVAR, especially in the setting of acute type B dissection. Any measures that can be taken to reduce the risk of retrograde dissection are crucial. In recent years, we have gained much better insight into the factors that increase the risk of retrograde dissection. The effect of stent sizing, in particular the risk of oversizing of stent grafts, was demonstrated by Canaud *et al*.[16] In this analysis of the MOTHER Registry, combined with supplementary data from a systematic review, oversizing of >9% was shown to be significantly associated with retrograde type A dissection after TEVAR. Furthermore, each 1% over this threshold of 9% was shown to lead to an increase of 1.14 in the odds ratio (OR) of retrograde type A aortic dissection.

This awareness of the fragility of the aorta in the presence of dissection, and the need to moderate radial forces applied to the vessel wall, has also led to an avoidance of post-deployment dilatation of stent grafts and minimising wire and device manipulation.

Improvements in stent design may have prompted a decrease in the rates of retrograde type A dissection after TEVAR. Though Mani *et al* did not find a statistically significant difference in rates of retrograde type A dissection with either bare or non-bare stent proximal stent graft configurations, there are now stent designs available with dissection as a clinical indication approved for use.[13]

However, despite the evidence regarding timing from the VIRTUE study and others, new studies from America and Japan have challenged the widely accepted algorithm of intervention in the subacute phase. They showed no adverse outcome between early and late intervention but increased aortic expansion in those treated after seven days.[18,19]

Miyairi et al's recent study comprised a retrospective analysis of 680 patients with acute and subacute type B dissections who underwent TEVAR between 2008 and 2013. Ninety-seven of these patients underwent TEVAR between one and 14 days, and 288 underwent TEVAR between 14 days and six weeks. Operative mortality and severe complications, including retrograde aortic dissection, did not differ significantly between the groups in this study. In the hyperacute group (those treated within 24 hours of onset), there was an increase in the rate of stent-related retrograde aortic dissection, though this patient group largely represented complicated type B dissection, recognised as a higher risk group.[20,21]

Wang *et al's* study was a prospective, multicentre registry of 397 patients including 204 acute dissections.[18] Within this study's uncomplicated acute dissection group, there were no clear patterns in mortality or reintervention identified when comparing timing of treatment. There was, however, a statistically significant increase in the rate of rapid aortic expansion in all groups treated after seven days. This, along with the Miyairi et al's study, would indicate that with modern endovascular techniques and perioperative care, earlier intervention may be beneficial.

As with complicated type B patients the role of open repair outside of the acutely unwell patient who is not suitable for endovascular repair is thought to be limited.[22,23] Though a recent meta-analysis showed that the early mortality benefit of TEVAR is not always present by mid-term follow up, thus the treatment of each case should be assessed on its individually merits ideally within a multi disciplinarily team.[24]

Conclusion

The decision to perform TEVAR in patients with type B aortic dissection, and in particular the timing of intervention, depends on multiple physiological, anatomical and demographic variables. A multidisciplinary decision-making process should be encouraged. Early intervention is vital in complicated type B aortic dissection, and TEVAR has been shown to be the gold standard where anatomically possible. In uncomplicated and less urgent type B aortic dissections, without evidence of malperfusion or rapid aortic expansion, current guidance and practice has often indicated to intervene in the subacute phase. However, published analysis of contemporary registry data that indicate that these interventions can, and perhaps should, be considered more often in the acute phase should be taken into consideration.

Summary

- Treatment decisions for TEVAR in type B aortic dissection should be undertaken as part of a multidisciplinary team.

- Early intervention is vital in complicated type B dissecion, with TEVAR being the gold standard where anatomically suitable.

- Report data suggest that TEVAR for uncomplicated type B dissection can be considered in the acute phase.

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The management of acute uncomplicated type B aortic dissection

RE Clough and CA Nienaber

Introduction

Hospital-based studies suggest an incidence of acute aortic dissection of three or four cases per 100,000 per year, which is approximately half the incidence of symptomatic aortic aneurysm.[1,2] A 2018 epidemiological study demonstrated that patients with aortic dissection have more than twice the mortality at five, 10 and 20 years compared with population-based controls.[3]

Aortic dissection was traditionally classified into acute and chronic, where acute dissection was up to 14 days since symptom onset and chronic dissection was more than 14 days. This distinction was made before the advent of modern diagnostic modalities; more recently, the IRAD (International Registry of Aortic Dissection) and VIRTUE study groups have revised this classification. The IRAD group analysed the survival data in its registry and identified four separate time periods: hyperacute (0–24 hours), acute (2–7 days), subacute (8–30 days), and chronic (≥30 days). In the VIRTUE study, patients were defined as having acute (14 days from symptom onset), subacute (15–92 days), or chronic (>92 days) dissection.[4,5] Computed tomography (CT) imaging is usually used in the investigation and management of acute type B aortic dissection because it is widely available.

Complications in acute type B aortic dissection were defined by the expert consensus group as malperfusion resulting in end-organ ischaemia, hypertension despite full medical therapy, periaortic haematoma, haemorrhagic pleural effusion and aortic rupture.[6] Approximately, 25% of patients have complications at the time of presentation. In the absence of these features, the dissection is termed uncomplicated, which has traditionally been managed with best medical therapy alone and close clinical and imaging surveillance. This chapter outlines the current treatment options for acute uncomplicated type B aortic dissection.

Best medical treatment

Medical management is currently the mainstay of treatment for uncomplicated type B aortic dissection and usually consists of a combination of beta-blockers, medications to inhibit the renin–angiotensin system, and calcium channel blockers. In IRAD, 89% of patients were treated with beta-blockers, 47% with angiotensin-converting-enzyme inhibitors, 50% with calcium channel blockers, 29% with diuretics, and 22% with vasodilators. In practice, the specific regimen prescribed is usually determined by a combination of personal experience, expert opinion and the results of historic observational studies. Beta-blockers are commonly used to reduce both the aortic blood pressure and heart rate, as the American College of

Cardiology (ACC) guidelines recommend a target heart rate of 60 beats per minute to achieve the best survival rates.[7]

In-hospital outcome studies demonstrate that in the first 30 days, approximately 12% of patients who were receiving best medical therapy develop significant complications, such as malperfusion, aortic rupture and early expansion, with a intervention-free survival rate of 41% at six years.[8] Survival analyses demonstrate that approximately one quarter of patients are dead at three years, and by five years up to 50% of patients are dead in some series.[9–11]

The importance of good blood pressure control cannot be overestimated and in the ADSORB (Acute dissection stent grafting or best medical treatment) trial the majority of patients required at least three different antihypertensive medications to achieve good blood pressure control.[12] A 2018 study performed outside a trial setting demonstrated that the majority of patients adhere poorly to antihypertensive therapy.[13] Guidelines from the ACC and the European Society of Cardiology (ESC) suggest further studies should be undertaken to refine the therapeutic approaches required for early medical management in patients with type B aortic dissection.[7,14]

Thoracic endovascular aortic repair

The use of endovascular treatment to manage the complications of acute aortic dissection, such as rupture and malperfusion, is well established. The stent graft also helps to induce aortic remodelling by expanding the true lumen, narrowing or obliterating the false lumen, and inducing false lumen thrombosis (Figure 1). Aortic remodelling and thrombosis of the false lumen are associated with improved survival.[15] Endovascular repair of type B dissection can be technically challenging, as vascular access can be difficult due to involvement of the dissection, there may be difficulty when navigating and tracking the device through the dissected aorta, and it can be challenging to find a good proximal landing zone in 20mm of healthy parallel-walled aorta. The procedure is also associated with significant risks such as death, stroke, paraplegia, retrograde type A dissection and distal stent graft-induced new entry tears. A 2019 systematic review and meta-analysis has shown that endovascular repair has a lower early mortality, stroke and spinal cord ischaemia rate and incidence of respiratory complications compared with open surgical repair.[16]

Endovascular treatment in different phases of the disease (acute, subacute or chronic) can result in different outcomes, as demonstrated in the VIRTUE study. In all three groups, the true lumen significantly expanded after endovascular repair and continued to expand over time, with the majority of remodelling complete by six months. Patients treated in the subacute phase showed aortic remodelling that was analogous to the acute group without any incidence of retrograde type A dissection; this occurred in one patient in the acute group. The amount of false lumen area reduction was significantly greater in the acute and subacute groups compared with the chronic group. There was no difference in the amount of false lumen thrombosis between the three groups in the thorax but in the abdomen, there was significantly less thrombosis in the chronic group, which also had a higher rate of reintervention. This temporal variation in outcomes was also found in a 2018 analysis of the Japan Adult Cardiovascular Surgery database. Operative mortality and severe complications were significantly more common in patients

| PRE-PROCEDURE | POST-PROCEDURE | AT 24 MONTHS |
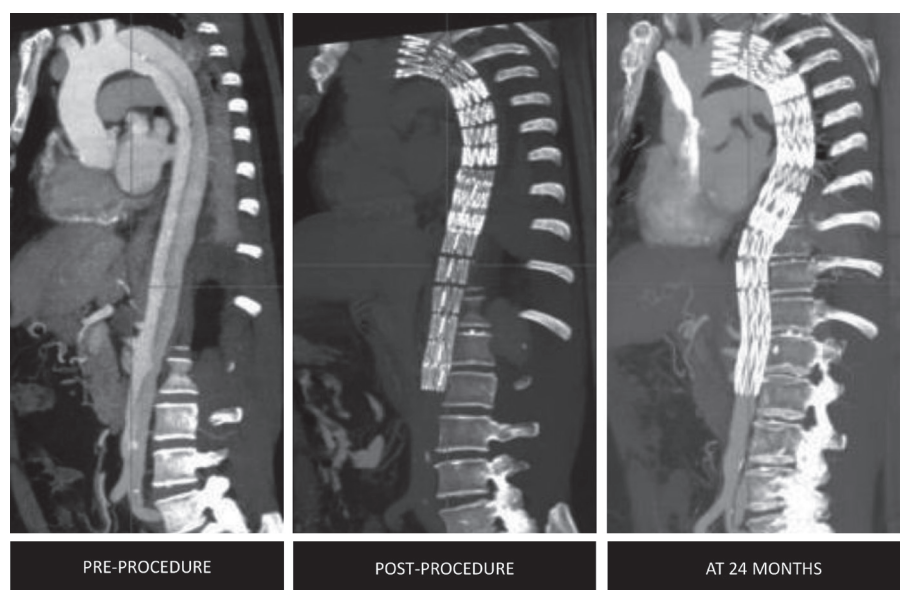
Figure 1: Endovascular stent graft placement induces aortic remodelling by expanding the true lumen, narrowing or obliterating the false lumen and inducing false lumen thrombosis.

treated within 24 hours of dissection compared with those treated in the acute (1–14 days) and subacute (2–6 weeks) phases.[17]

Because of the survival advantages seen with thoracic endovascular repair in complicated cases attention has turned to the use of this technology in uncomplicated cases.

Two randomised controlled trials have been conducted to determine whether endovascular repair combined with best medical treatment for uncomplicated type B aortic dissection would give benefit over best medical treatment alone. In the INSTEAD (Investigation of stent grafts in aortic dissection) trial, the majority of patients were treated in the subacute phase and the longer-term outcomes demonstrated better aortic remodelling and survival in patients receiving endovascular repair (Figure 2).[18] However, there were eight deaths in the endovascular repair group, four of which were aortic-related.

In the ADSORB trial patients were treated within 14 days and the data showed the benefit of endovascular repair in terms of aortic remodelling at one year. There were no deaths within 30 days and one death in the endovascular repair group during follow-up that was related to a cardiac arrest; no autopsy was performed and the death was not reported as dissection-related. The primary endpoints in ADSORB were incomplete false lumen thrombosis, aortic dilatation and aortic rupture. Analysis of this composite endpoint revealed that it occurred significantly more frequently in the group receiving best medical treatment only (100% vs. 50%; p<0.001).[12]

A 2018 meta-analysis of studies evaluating endovascular treatment with best medical treatment vs. best medical treatment alone demonstrated no difference in short, intermediate and mid-term mortality but thoracic endovascular aortic repair (TEVAR) was associated with a lower likelihood of aortic rupture at one year.[19]
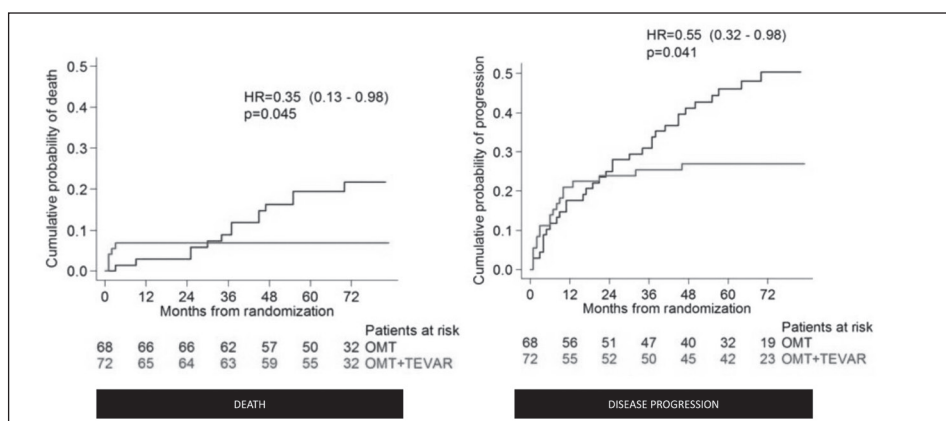
Figure 2: Data from INSTEAD-XL demonstrating reduced disease progression and improved survival in patients receiving endovascular repair.

A multi-institutional retrospective study with a cohort of more than 300 patients showed best medical treatment with endovascular repair results in significantly fewer all-cause and aortic-related deaths compared with best medical treatment alone, with higher early mortality in the best medical treatment group compared with best medical treatment plus TEVAR group.[20]

A further meta-analysis showed that TEVAR increases the early risk of stroke but significantly reduces the risk of late all-cause and aortic-related mortality, as well as late aortic-related adverse events compared with best medical treatment alone.[21]

However, not all patients with uncomplicated type B dissection treated medically will die of aortic-related causes and, therefore, need not be exposed to the risks associated with TEVAR.

Selection of patients for endovascular intervention

Many researchers have tried to identify features that could be used to identify patients with acute uncomplicated type B dissection that are at high risk of aneurysm formation, extension of the dissection and rupture; if the risk of disease progression was known then this could be balanced against the risks of TEVAR.

Increasing aortic diameter is thought to be an important risk factor for dissection and rupture. Prophylactic descending thoracic aortic repair is generally recommended for a descending thoracic aortic diameter of 5.5cm or 6cm.[22] Data from 2016 indicated that an aortic diameter greater than 44mm is a risk factor for mortality and that a false lumen diameter of greater than 22mm is a risk factor for a low rate of intervention-free survival.[23]

Marfan syndrome is an important risk factor for aortic dissection, especially in young patients, and thresholds for prophylactic aortic replacement are typically lower for this specific patient group.[10] Evaluation of the data collected during the ADSORB study demonstrated using multivariate regression modelling that the number of vessels originating from the false lumen is an independent predictor of false lumen growth (odds ratio: 22.1).[24] Other studies have shown that partial false lumen thrombosis, a total aortic diameter greater than 4cm, a large proximal entry tear and presence of the entry tear on the aortic concavity are associated with worse

outcomes.[25] IRAD demonstrated that low rates of aortic expansion are related to Caucasian race, an initial aortic diameter less than 4cm, female sex, the presence of intramural haematoma and the use of calcium channel blockers.[26] Other studies from the same group identified age ≥70 years, a prior history of aortic aneurysm, atherosclerosis, renal failure, pleural effusion and in-hospital hypotension as independent predictors of mortality during follow-up.[27]

In order to detect complications early in patients who present with initially uncomplicated acute type B dissection, some experts now advocate high-intensity serial CT imaging in the first 14 days, with as many as four CT angiograms during this time. If evidence of the development of complications is seen, such as rapid expansion of the aorta, extension of the dissection or end-organ ischaemia, then patients are put forward for endovascular repair, which is performed electively between two and six weeks after symptom onset.

In a 2016 survey, 37% of respondents performed TEVAR in uncomplicated type B aortic dissection based on certain morphological criteria, while 8% performed the procedure routinely for uncomplicated cases.[28]

The current European guidelines recommend TEVAR as the treatment of choice for complicated type B dissection (class I, level of evidence C) and as a treatment that can be considered to prevent aortic complications in uncomplicated acute type B dissection (class IIb, level of evidence B).[29]

Conclusion

Patients with aortic dissection have more than twice the mortality of population-based controls. Management of the condition is challenging and requires a multidisciplinary team approach. Best medical management is the mainstay of treatment for uncomplicated cases but improvements in survival seen with endovascular management of complicated cases has driven interest in this treatment for uncomplicated cases. Contemporary data on this approach are heterogenous but suggest there may be improved late all-cause and aortic-related mortality with TEVAR in addition to best medical treatment. A pragmatic approach is the use of high-intensity serial imaging in the acute phase with selection of uncomplicated patients for endovascular treatment in the subacute phase based on the presence of high-risk features.

Summary

- Management of acute aortic dissection is challenging and requires a multidisciplinary team approach.

- Medical management is the mainstay of early treatment for uncomplicated cases.

- Contemporary data suggest improved late all-cause and aortic-related mortality with TEVAR in addition to best medical treatment.

- A pragmatic approach is the use of high-intensity serial imaging in the acute phase with selection of uncomplicated patients based on high-risk features for treatment in the subacute phase.

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Distal remodelling in type B dissection—balancing patient risk and efficacy

HM Ray and A Azizzadeh

Introduction

Aortic dissection remains the most common aortic emergency with a reported incidence of 2.9 to 3.5 per 100,000 person years.[1–4] Aortic dissections can be further described using two separate classifications schemas: the Stanford classification and the DeBakey classification. The Stanford classification has two subtypes: type A which involves the ascending aorta and type B which does not involve the ascending aorta.[5] The DeBakey classification has more subtypes allowing for more detailed description of the aortic regions involved, the subtypes include: DeBakey 1 (ascending and descending thoracic aorta involved), DeBakey 2 (isolated ascending aortic involvement), DeBakey 3a (descending thoracic aorta involved without extension below the diaphragm) and DeBakey 3b (descending thoracic aorta involved with extension below the diaphragm).[6]

Historically, patients with uncomplicated type B aortic dissection have been managed medically with impulse control with surgical intervention reserved for those meeting criteria for complicated acute type B aortic dissection.[7] More recent evidence suggests that in uncomplicated dissections, some patients may benefit from earlier intervention with thoracic endovascular aortic repair (TEVAR); however, no general consensus has been reached and there remains a lack of prospective randomised data.[8] Patients with complicated acute type B dissection are candidates for intervention with TEVAR as long as no contraindications exist. Despite the lack of definitive evidence, the use of TEVAR in the treatment of Type B aortic dissection has increased over time. The majority of the literature has focused on remodelling over the covered thoracic segment with less in regard to the uncovered abdominal segment.[9–14]

Evidence base

As reported previously by our group, all patients with acute or symptomatic aortic dissections are admitted to the cardiovascular intensive care unit with placement of monitoring lines including a central line, arterial line, and Foley catheter to accurately monitor urine output.[15,16] Optimal medical therapy was initiated with the use of anti-impulse therapy by way of beta blockade, calcium channel blockers, nitroglycerin, or nitroprusside with goal systolic blood pressure <120mm Hg, heart rate <60beats/min, and pain medications as needed for control of pain. Multiple parameters are continuously reassessed including the patient's blood pressure, pain control, and urine output, with adjustments made as needed. Percutaneous or surgical interventions are undertaken for rupture, malperfusion, acute expansion

(aortic growth of 5mm at six months or 1cm at one year), or refractory symptoms, including pain and poorly controlled hypertension.

TEVAR performed for uncomplicated or complicated type B dissections has the same common goal: to seal the entry tear and to induce positive aortic remodelling. Positive aortic remodelling has been quantified in various ways including maximum aortic diameter or area, false lumen diameter or area, true lumen diameter, volumetric analysis or area and a number of ratios comparing various measurements.[11–13, 17] While numerous studies have aimed to address the issue of aortic remodelling, most have focused on the change within the covered thoracic segment of the aorta, with few focusing on the abdominal segment. The PETTICOAT (distal bare metal stent technique), first published in 2006, builds on the idea of entry tear coverage while adding a distal bare metal stent distally in an attempt to augment positive aortic remodeling.[18] The bare metal stent is necessary when covering the visceral segment of the abdominal aorta given the multiple branch vessels within the location. Further complicating the issue is that there is no randomised data in existence comparing simple/standard TEVAR coverage of the entry tear over various lengths of the thoracic aorta with TEVAR plus PETTICOAT. Furthermore, as seen in the INSTEAD-XL trial, five-year results compared with the original INSTEAD trial two-year results, aortic remodelling appears to continue over time as indicated by the survival advantage in the TEVAR group at five years that was not present at the initial two year follow-up.[9,19]

The Zenith dissection endovascular system (Cook) is the first FDA-approved component device in the USA for treatment of aortic dissection with the PETTICOAT technique and is composed of a proximal covered stent graft and a separate distal component which is a bare metal stent.[20] The results with the technique are promising as will be reviewed below; however, recent data from our institution suggests that TEVAR in the thoracic aorta alone appears to allow for continued positive remodelling within the thoracic aortic segment (p=0.0473) over time (Figure 2), with positive remodelling seen within the abdominal aorta initially, but with an overall stabilisation of the abdominal segment with respect to time (p=0.7631). See Figure 3.[21] The question being that if the distal segment of the aorta, the abdominal segment, stabilises with respect to time, what is the
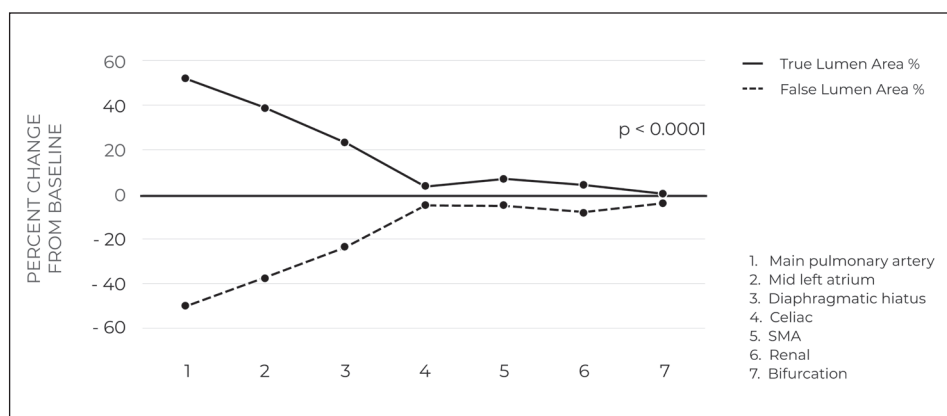
Figure 1: This figure represents the percent change from baseline of the true lumen (TL) area percentage and false lumen (FL) area percentage across different aortic levels with significant increase in TL area (p<0.0001) with concomitant decrease in FL area (p<0.0001) after TEVAR, with largest change noted over thoracic aortic segment with diminishing, but present effect noted further from the distal extent of the device down to the aortic bifurcation.
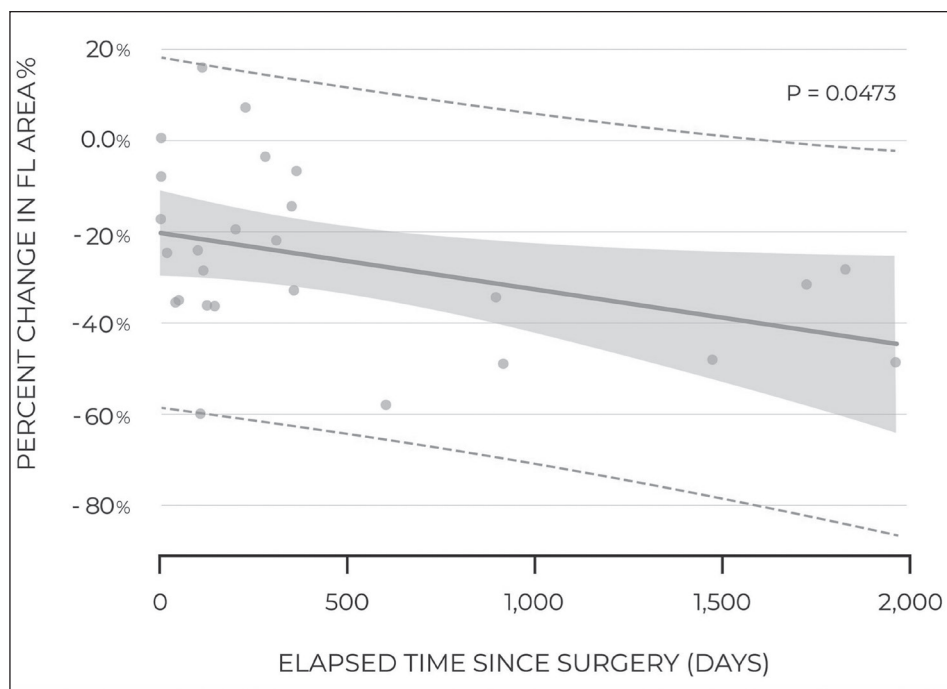
Figure 2: This figure demonstrates that over time the thoracic segment of the aorta continues to remodel in a positive manner (p=0.0473) in terms of percent change in false lumen area percentage

true advantage of the addition of the bare metal stent distally? According to recent systematic review articles that summarise the data, using the PETTICOAT technique demonstrates complete thoracic aortic remodelling—defined as complete false lumen thrombosis in 70.4% of cases at 12 months—while the abdominal segment is noted to be completely remodelled by the same metric to a much lesser degree at 13.5% at 12 months.[22,23]

Our group recently examined 27 patients with DeBakey 3b aortic dissection as well as adequate pre and postoperative CT angiography imaging for analysis.[21] The cohort had an average age of 59.4 years: 81.5% male. With TEVAR, 14/27 (51.9%) patients were in the acute phase (≤14 days) of aortic dissection. The distal Society for Vascular Surgery (SVS) landing zone of attachment was zone 4 in 14.8% and zone 5 in 85.2%. The pre and postoperative measurements at each aortic level including the total vessel diameter and area, true lumen diameter and area, and false lumen diameter and area, were recorded and compared. To examine changes over time, the change in pre vs. postoperative, true lumen area/total aortic area ratio (true lumen area percentage and false lumen area/total aortic area ratio) false lumen area percentage were calculated and examined.

True lumen area and false lumen area percentages were examined, and demonstrated increasing true lumen area percentage (p<0.0001) with concomitant decrease in false lumen area percentage (p<0.0001) after TEVAR for DeBakey 3b Aortic dissection across the length of the thoracic and abdominal aorta as a whole. As demonstrated in Figure 1, the largest changes in both true lumen and false lumen area percentages occur over the thoracic aortic segment with diminishing, but present effect noted further from the distal extent of the TEVAR device down to the aortic bifurcation.
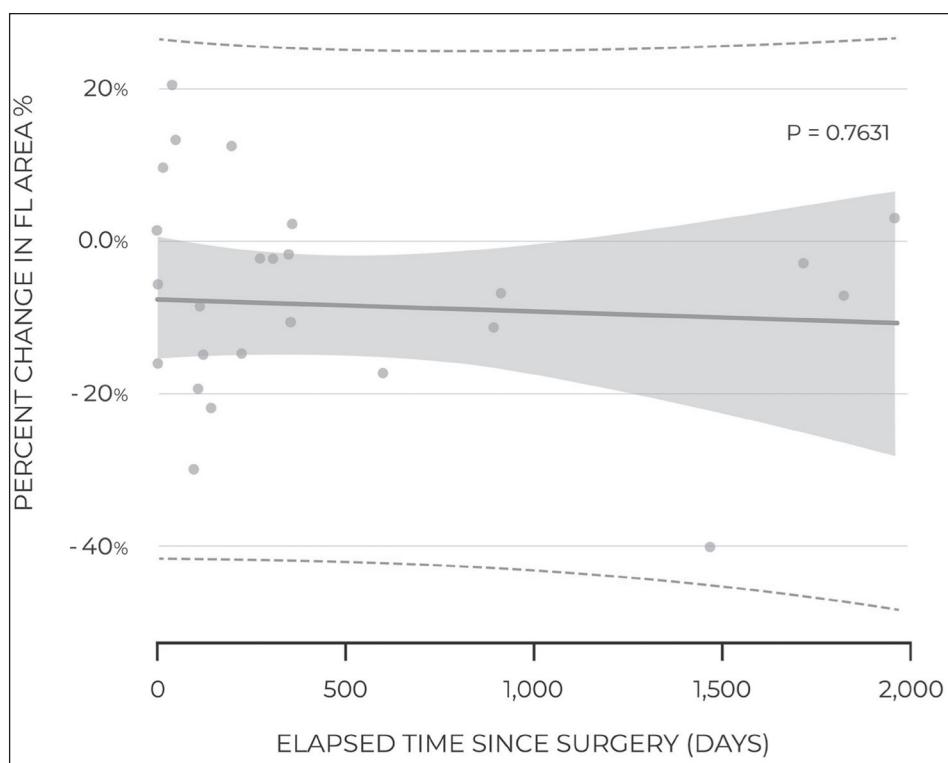
Figure 3: This figure demonstrates that while the abdominal aortic segment demonstrates positive aortic remodelling initially after TEVAR, after this initial remodelling the abdominal aortic segment does not significantly remodel over time in either a positive or a negative manner (p=0.7631) and instead remains largely stable after TEVAR with respect to time.

Positive aortic remodelling is noted over the thoracic and abdominal segments of the aorta in terms of increasing true lumen area percentage and decreasing false lumen area percentage, with the largest effect noted in the thoracic segment. Over time the thoracic segment of the aorta continues to remodel in a positive manner (p=0.0473) in terms of percent change in false lumen area percentage as demonstrated in Figure 2. The abdominal segment on the other hand demonstrates positive aortic remodelling initially after TEVAR, but after this initial remodelling the abdominal aortic segment does not significantly remodel over time in either a positive or a negative manner (p=0.7631) and instead remains largely stable after TEVAR with respect to time (Figure 3).

PETTICOAT technique

Distal remodelling in type B dissection after TEVAR remains a topic of interest. Recently, a Cochrane reviewed whether combined proximal descending thoracic aortic endografting plus distal bare metal stenting (PETTICOAT technique) was superior to conventional proximal descending aortic stent graft repair.[24]

Given the lack of randomised controlled trials, the authors of the review were unable to draw definite conclusions. However, after reviewing the available evidence obtained from non-randomised studies they were able to state that the PETTICOAT technique appears to afford favourable remodelling in the short term. Randomised controlled trials are needed to properly address the question

regarding TEVAR alone vs. TEVAR plus a bare-metal stent in terms of efficacy in inducing positive aortic remodelling in the distal aortic segment.

At the time of the aforementioned Cochrane review, there were seven non-randomised studies that examined standard TEVAR vs. the PETTICOAT technique. Of the seven studies, five were single-arm and all of these showed favourable aortic remodelling in the short-term.[18,20,25–29]

Sobcinkski *et al* found that the PETTICOAT technique was, initially, associated with a significant increase in true lumen (p<0.001) and significant decrease in false lumen (p=0.004) compared with standard TEVAR. However, there was no statistically significant different between them in terms of volume changes in the true and false lumen volumes at 12 months.[28]

Sultan *et al* examined TEVAR (12 patients) vs. the PETTICOAT technique (21 patients) and found that the distal aorta was positively remodelling to a larger degree at the level of the coeliac artery with the addition of the bare metal stent in terms of the true lumen to aortic diameter ratio, which they call the true lumen ratio, at six months.[29]

A recent systematic review of the PETTICOAT technique identified 11 studies that found that the procedure is safe with a 30-day mortality of 4.9% and feasible with a technical success rate of 90.2%.[30] However, with this being said the data remain heterogenous in terms of positive remodelling of the false lumen of the abdominal aorta. The authors also concluded that while the true lumen of the distal aortic segment was improved in the PETTICOAT group vs. standard TEVAR group, there was not conclusive evidence that this led to improved survival in the short- or mid-term follow-up or that the false lumen in the distal aorta is positively remodelled.

Conclusion

Though it appears safe to perform, the true benefit of the PETTICOAT technique (with TEVAR plus a bare metal stent) vs. standard TEVAR remains uncertain with the currently available literature. Our group's recent data suggest that positive aortic remodelling, as measured by increasing true lumen area percentage and decreasing false lumen area percentage, occurs primarily along the segments of the aorta treated by TEVAR. The remodelling benefits diminish distal to the treated segment; however, our recent data demonstrate that the abdominal aortic segment remains largely stable with respect to time in terms of percent change in false lumen area percentage indicating that TEVAR within the thoracic aorta alone may be enough to stabilise the abdominal aorta over time as evidenced by the low aortic event rate in our series.

Summary

- Aortic dissection is the most common aortic emergency with incidence of 2.9-3.5 per 100,000 person year.

- Stanford type B dissection does not involve the ascending aorta.

- Optimal medical therapy: impulse control with goal systolic blood pressure less than 120mmHg and heart rate less than 60 beats per minute.

- Historically, patients with uncomplicated type B aortic dissection have been managed medically with impulse control with surgical intervention reserved for those meeting criteria for complicated acute Type B aortic dissection.

- More recent evidence suggests that in uncomplicated type B aortic dissection, some patients may benefit from earlier intervention with TEVAR; however, no general consensus has been reached and there remains a lack of prospective randomised data.

- Distal remodelling in type B dissection after TEVAR remains a topic of interest with unclear benefit for the PETTICOAT technique with TEVAR plus a bare metal stent vs. standard TEVAR with currently available evidence.

- Our recent data demonstrates that the abdominal aortic segment remains largely stable with respect to time in terms of percent change in false lumen area percentage indicating that TEVAR within the thoracic aorta alone may be enough to stabilise the abdominal aorta over time as evidenced by the low aortic event rate in our series.

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Early and mid-term outcomes of contemporary international endovascular treatment for type B aortic dissection

HL Li, YC Chan, SW Cheng, W Guo and J Xiong

Introduction

Acute aortic dissection is a life-threatening event with an overall incidence of 3.5 per 100,000 person-years.[1] Dissection occurs most commonly in hypertensive patients aged 60 to 80, and is slightly more common in men. It may occur in younger patients, especially those with previously undiagnosed hypertension, with increased incidence especially in cold weather.[2] It also has an association with collagen vascular disease. In historical studies before the use of effective antihypertensive drugs, the majority of patients without any treatment died within three months of presentation, and few survived beyond five years, presumably due to aneurysmal degeneration and aortic rupture.

DeBakey *et al* introduced a revolutionary surgical treatment for aortic dissection in 1955.[3] Open repair was the traditional treatment of aortic dissection, and remains the treatment of choice for acute type A dissection. However, open repair for acute type B dissection typically carries a high risk of perioperative mortality and morbidity, so medical treatment with antihypertensive agents is preferable for uncomplicated cases.[4] Thoracic endovascular aortic repair (TEVAR) was first reported by Dake *et al* and Nienaber *et al* in 1999, and its use reduced short-term mortality and morbidity compared with traditional open surgery.[5–7] However, the role of TEVAR for type B aortic dissection, especially in uncomplicated cases, remains controversial. To date, there are only two prospective randomised trials on uncomplicated type B aortic dissection comparing best medical therapy and best medical therapy with TEVAR: INSTEAD (Investigation of stent grafts in patients with type B aortic dissection) for uncomplicated chronic type B aortic dissection, and ADSORB (Acute dissection stent graft or best medical treatment) for uncomplicated acute type B aortic dissection. In the INSTEAD trial, TEVAR compared with best medical therapy did not improve overall or aorta-related two-year survival or adverse event rates up to two-year follow-up, but did show improved aorta-specific survival and delayed disease progression at five-year follow-up.[8,9] The ADSORB trial documented stent graft induced remodelling with thrombosis of the false lumen and reduction of its diameter; however, long-term results are lacking.[10]

There are a lack of data about the mid-term outcomes of TEVAR worldwide. Most published papers on TEVAR include single-centre studies without adequate follow-up, and the timing of TEVAR in uncomplicated type B aortic dissection remains controversial. Defining mortality and morbidity after TEVAR is critical

in understanding its role in treatment of type B aortic dissection. This chapter describes a meta-analysis that aims to provide an updated review of early and mid-term mortality and morbidity outcomes of TEVAR, and their association with the timing of the intervention and institutional case load.

Methods

This review on TEVAR for type B aortic dissection was performed according to the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement.[11] A comprehensive literature search was conducted in the PubMed, MEDLINE and Science Direct databases, and the Cochrane Library from January 1999 to December 2018. The keywords used were "endovascular repair," "aortic dissection," "stent graft," "descending thoracic aorta" and "TEVAR." References in retrieved publications were also reviewed for related studies.

Studies were considered eligible if they met all of the following inclusion criteria:

- Endovascular treatment for acute/chronic type B aortic dissection
- Minimum case series of 10 patients (this threshold was set to reduce publication bias because these centres were considered to be more experienced in the TEVAR procedure)
- Reporting baseline data of the patients
- Providing information on at least half of the following essential outcome measures: 30-day mortality rate, early type 1 endoleak, perioperative retrograde type A aortic dissection, stroke, spinal cord ischaemia, bowl/limb ischaemia and renal failure, and secondary intervention during follow-up.

Case reports and systematic reviews were excluded; however, their reference lists were reviewed for potentially relevant articles.

Study selection and definitions

The title and abstract of articles screened in the primary search were reviewed, and the full text of selected papers was retrieved for evaluation of their eligibility for inclusion. If both type A and B aortic dissection or other aortic pathologies (e.g. aortic intramural haematoma, penetrating ulcer and thoracic aortic aneurysm) were included in an article, the data were analysed separately with a focus on type B aortic dissection. If the same centre reported a series of patients repeatedly, the most recent one was selected to avoid any duplicated cohort reporting. Aortic dissection was classified according to the Stanford classification, with a Stanford type B aortic dissection originating from the descending aorta distal to the origin of the left subclavian artery.[12] A dissection was considered acute if it was diagnosed within two weeks of onset of symptoms, and regarded as chronic if it was diagnosed more than two weeks after the onset of symptoms.[13] A complicated type B aortic dissection was defined as progression of the dissection with rapid aortic dilation and risk of aortic rupture, imminent rupture as evidenced by extra-aortic blood collection, early expansion by >10mm on serial computed tomography (CT), malperfusion of end-organs due to compression of major arterial side branches which may affect lower extremities as well as visceral organs, refractory hypertension and persistent chest pain. Procedural success was defined as successful deployment of the stent graft at the intended target location as reported in each paper. Secondary intervention was defined as the need for any surgical conversion or additional implantation of endovascular stent/stent graft.

Data extraction

Each article was analysed using a standardised protocol including predefined demographic characteristics, early (30 days) and mid-term (≤5 years) mortality, and perioperative complications. Articles containing insufficient data (<50% of the predefined variables extractable) were excluded from the analysis. Only data clearly obtained from patients with type B aortic dissection subjected to endovascular stent graft implantation were extracted, while data from patients with other thoracic aortic diseases (e.g. type A dissection or thoracic aortic aneurysm) were discarded. Unspecified information was considered as not available. As a result, the number of patients (denominator) varied among the variables reported in the analysis.

Statistical analysis

Rates of events were calculated as the number of events divided by the number of patients with available data. Results are presented as mean ± standard deviation or median and range, when appropriate. The calculations of incidence of in-hospital and follow-up outcome such as mortality and complications were performed using Comprehensive Meta-Analysis software, version 2 (Biostat). Comparisons between patients with acute and chronic aortic dissection were made using the two-sided chi-squared test for categorical variables and the two-sided Student's t-test for continuous variables. Data analysis was performed using SPSS Statistics, version 22.0 (IBM). A p-value of <0.05 was considered statistically significant.

Results

A total of 96 articles with 6,383 patients were selected and included in this meta-analysis. The flowchart for the literature screening process carried out according to PRISMA guidelines is shown in Figure 1. The majority of the studies were on type B aortic dissection alone, while eight studies reported the mixed results of various types of thoracic pathology including Stanford types A and B aortic dissection, aneurysm, penetrating aortic ulcer, intramural haematoma and traumatic aortic injury. Most studies retrospectively analysed single-0centre cohorts, while 19 articles were multicentre studies. In terms of geographical distribution, of the 96 publications selected on TEVAR procedures: 27 (28%) were from the USA; 34 (35%) were from Asia (21 from China, five from Japan, five from Korea, and three from Taiwan); 22 (23%) were from Europe (eight from Germany, five from Italy, three from France, two from Austria, and one each from the UK, Belgium, Sweden and Greece); two (2%) were from South America (Brazil); and one (1%) was from Australia. There were five multicentre studies from European countries, and five from the USA and Europe (10/96; 10%). The largest single-centre series were from China: Li *et al,* Du *et al,* and Zhu *et al,* with 579, 264, and 156 cases, respectively.[14–16] The largest multicentre studies were by Patterson *et al,* Tjaden *et al,*and Jia *et al,* with 309, 264, and 208 cases, respectively.[17–19]

There were 29 studies with 1,055 cases during the 10 years after the introduction of TEVAR in 1999. More than 5,000 published TEVAR procedures were performed between 2011 and 2018 internationally. A total of 4,769 stent grafts had been used in 4,654 patients with available information. The types of stent graft were specified in 77 studies: there were 20 different types of stent graft, including homemade ones. The most commonly used devices were Talent (Medtronic), Zenith (Cook Medical) and Gore TAG (Gore) in 21.4%, 16.6% and 14.5% of cases, respectively.
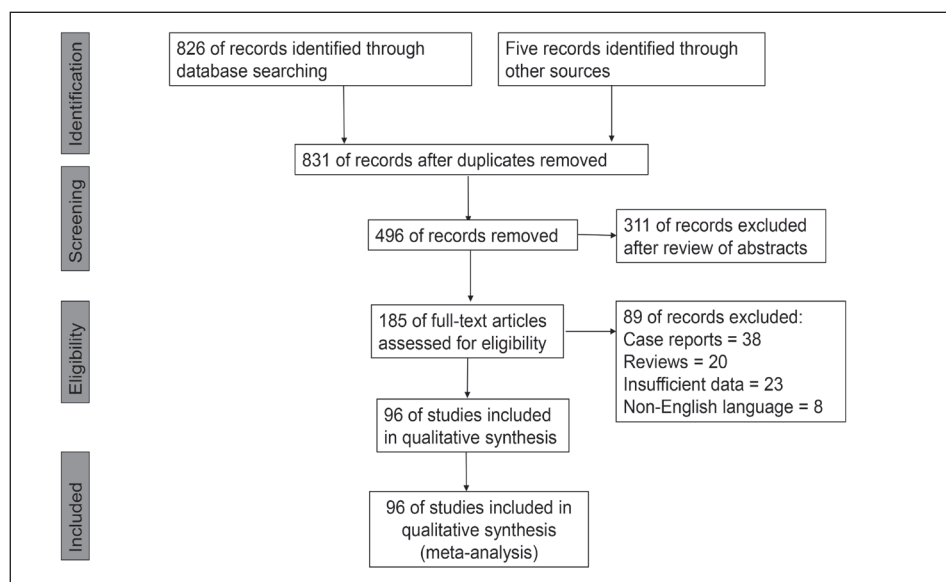
Figure 1: PRISMA (Preferred reporting items for systematic reviews and meta-analyses) diagram.

Among patients with available information, 4,801 of 6,069 patients (79%) were male, and 3,171 of 5,813 patients (55%) were treated during the acute phase (that is <2 weeks). Most patients treated during the acute phase had complicated type B aortic dissection such as aortic rupture, visceral and/or peripheral malperfusion, severe pain and uncontrollable hypertension.

Early mortality was reported in all the 96 studies included. A total of 271 patients died within 30 days after TEVAR. The cause of mortality was specified for 184 patients out of 4,987 patients with available information: 145 deaths were aorta- or procedure- related. Of these, the most common causes of death were aortic rupture (27%), retrograde type A aortic dissection (16%), and cardiac complications (15%) including cardiac arrest, myocardial infarction, and cardiac tamponade.

Pooled estimates for overall mortality, and aorta- or procedure-related mortality were 6.7% (95% confidence interval [CI] 6.0% to 7.5%) and 4.9% (95% CI 4.2% to 5.7%), respectively. Neurological complications, including stroke and spinal cord ischaemia or paraplegia, were reported in 95 studies, with pooled rates of stroke and spinal cord ischaemia of 4.1% (95% CI 3.5% to 4.7%) and 3.3% (95% CI 2.8% to 3.9%), respectively. As another leading cause of early mortality, retrograde type A aortic dissection after TEVAR occurred in 95 of the 6,281 patients with available data, making a pooled incidence of retrograde type A aortic dissection of 3.1% (95% CI 2.6% to 3.7%). Most patients with diagnosed retrograde type A aortic dissection were converted to open repair; and 18 patients (19%) died within 30 days.

In this meta-analysis, the pooled incidence of type 1 endoleak, visceral ischaemia and acute renal failure requiring haemodialysis were 4.9% (95% CI 3.9% to 6.2%), 3.0% (95% CI 2.5% to 3.6%) and 4.8% (95% CI 4.1% to 5.7%), respectively.

During follow-up, a total of 466 deaths were reported in 5,807 patients from 86 studies with available information. The pooled rates of all-cause mortality and aorta-related mortality were 8.6% (95% CI 7.1% to 10.3%) and 4.1% (95% CI 3.5% to 4.8%), respectively. Secondary intervention was performed in 12.6%

(95% CI 10.6% to 15.0%) of the patients. Open conversion was required in 6.0% (95% CI 5.2% to 7.0%) of the patients due to proximal endoleak, type A aortic dissection or aneurysmal dilation of the aortic arch during follow-up. Based on the available cases, the incidence rates of all-cause mortality, aorta-related mortality, secondary intervention and conversion to open repair were 1.76% (95% CI 1.34% to 2.14%), 0.57% (95% CI 0.43% to 0.72%), 3.2% (95% CI 2.59% to 3.81%), and 0.46% (95% CI 0.29% to 0.62%), respectively.

The median number of patients per study was 42. Therefore, centres performing fewer than 42 TEVAR procedures were arbitrarily considered as less experienced, while those performing 42 or more were considered more experienced. The outcome of TEVAR was compared according to case load. Institutions with a case load bigger than 42 patients had significantly better perioperative outcomes in terms of all-cause mortality (4.5% vs. 8.5%; p=0.035), aorta-related mortality (3.1% vs. 6.7%; p=0.012), stroke (3.8% vs. 5.1%; p=0.031), spinal cord ischaemia (3.0% vs. 4.0%; p<0.01), retrograde type A aortic dissection (2.6% vs. 4.6%; p<0.01) and type I endoleak (4.1% vs. 8.5%; p<0.027). There was no significant difference in follow-up outcomes including all-cause mortality, secondary intervention and open conversion between the two groups.

Early and mid-term results of TEVAR performed during the acute phase were specified in 1,965 patients from 34 studies. As mentioned before, most cases undergoing TEVAR during the acute phase had complicated aortic dissections. Pooled estimates for overall mortality, and aorta- or procedure-related mortality were 7.6% (95% CI 5.4% to 10.6%) and 5.8% (95% CI 3.8% to 8.8%), respectively. Regarding in-hospital major complications, the incidence of stroke, spinal cord ischaemia, retrograde type A aortic dissection and postoperative type 1 endoleak were 5.6% (95% CI 4.3% to 7.4%), 3.8% (95% CI 2.7% to 5.4%), 3.5% (95% CI 2.5% to 5.0%) and 4.5% (95% CI 2.9% to 7.0%), respectively. During follow-up, the incidence rates of all-cause mortality, aorta-related mortality, secondary intervention and conversion to open repair were 1.53% (95% CI 0.86% to 2.2%), 0.69% (95% CI 0.42% to 0.97%), 3.0% (95% CI 1.7% to 4.33%) and 0.29% (95% CI 0.07% to 0.52%), respectively.

Compared with the patients with chronic aortic dissection (>2 weeks), patients treated during the acute phase had a higher incidence of in-hospital mortality (7.6% vs. 5%; p=0.012) and renal failure (5.9% vs. 1.7%; p=0.005). There were no significant differences in rates of major complications including stroke, spinal cord ischaemia or retrograde type A aortic dissection.

Conclusion

In this meta-analysis, endovascular repair for type B aortic dissection appeared feasible and safe with a low incidence of mortality and perioperative complications, particularly in centres with a reported case load of more than 42 patients. Compared with patients with chronic aortic dissection (>2 weeks), those treated during the acute phase had a statistically higher incidence of in-hospital mortality, while there were no significant differences in rates of major complications of stroke, spinal cord ischaemia or retrograde type A dissection.

Summary

- This meta-analysis was carried out according to PRISMA guidelines of the contemporary literature on TEVAR for type B aortic dissection from January 1999 to December 2018, and retrieved a total of 96 articles (6,383 patients).

- Overall early and mid-term mortality were 6.7% and 8.6%, respectively. Major perioperative complications including stroke, spinal cord ischaemia, retrograde type A dissection and type 1 endoleak occurred at rates <5%.

- Patients treated during the acute phase (<2 weeks) had a statistically higher incidence of in-hospital mortality compared with those with chronic (>2 weeks) aortic dissection, while there were no differences in major neurological complications or retrograde type A dissection.

- Centres with higher TEVAR caseloads had better outcomes.

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Multidisciplinary team training is effective in reducing error in theatre—it should be mandatory in vascular units

JA Lawson, GFJ Martin, C Riga and CD Bicknell

Introduction

"The swimmer approaches the pool, climbs on the start blocks… silence. Take your marks. Buzzer goes. Launching forward with fingertips streamlined and balanced precision. A fraction of a second later the water tension is separated by his hands, elbows, torso, knees and feet. The underwater undulations take him 15 meters along the pool. The first stroke of the arm and the water surface disturbed once again. Full-force propulsion now overcoming resistance. The desire to breath becomes overwhelming, but streamline is everything, no compromise. The last strokes into the closing metres as an outstretched hand reaches out for impact. The completion of the race. Breathe.

Every movement precise in its chaotic appearance; the result of hours of deliberate practice, rehearsal and collaboration. Technology, analysis, testing, planning. The output of the collaboration of many.

This article questions whether the Olympians are all that different from our patients— the end product of a high performing team.

For most top swimmers, competing and performing optimally at the highest level is of utter importance. However, only a handful of individuals ever reach their maximum capacity in the pool. What then are the attributes that contribute to becoming an elite athlete? A number of studies have reported some similarities. It is believed that anthropometrical characteristics, determined by genetics, work in collaboration with biomechanical and energetic properties which are similarly genetically predisposed, but crucially manipulated by environmental determinants.[1,2] These environmental determinants of performance are manipulated by high performing teams to train, rehearse and reduce error in order to produce optimal performance. This chapter has been written from perspective of an Olympic trial silver medalist swimmer (JA Lawson).

Team training

In the elite sporting world, the idea of a cohesive unit has been a strong area of focus. Members of the world leading teams that function in harmony seem to be able to tap into a zone of performance that elevates their achievements above their competitors. Similarly, on stage, award winning productions are delivered as a

Figure 1: Vascular surgeons can learn from Olympic training approaches.

product of theatrical genius and conceptualised ideas brought together by multiple participants through hours, weeks, and even years of rehearsal and practice.

In surgery, there is an obvious benefit to be able to work as a functional unit. Individual aspects of skill, knowledge and experience may be effectively blended with shared leadership and training in order to maximise collective outputs.

Let us consider an athlete, an elite swimmer, with the coaching team behind their success—the coaches, physiotherapists, nutritionists, sports psychologists, doctors and biokinetisists being directly comparable to the team of vascular surgeons, anaesthetists, nurses, perfusionists, pharmacists and wider multidisciplinary team, that collectively provide care to patients. The outcome of success is dependent on the level of attention to detail each role player can contribute. The team's capability to perform is all that is needed to give the patient—our "athlete"—the optimal outcome, the world record as it were: a successful operation and the return to health. If we take these fundamental concepts into consideration, we conclude that the determinant of success for any intervention is at least materially reliant upon the people behind the athlete, or those treating the patient. The world has continued to produce improved technology and techniques, the benefits of which have tested boundaries in the sporting arena, pushed perceived limits and lowered world records.[3–5] In the medical world, these advancements have led to efficient and structured systems that have revolutionised healthcare. Incurable conditions now have solutions, lengthy operations are now streamlined, and catastrophic diagnoses now have new approaches and promising outcomes.

High-fidelity simulation, virtual reality and gamification are well known approaches that permit routine cases to be trialled and rehearsed. Manipulating routine clinical situations in the simulated environment can also encourage teams to react in a collaborated effort to restore control and order in the face of stressors. These environments promote creativity from faculty and trainees alike, with

flexibility in team training modalities. The sessions should be free from prejudice and encourage versatility in problem solving and situational analysis. Developing a team training programme for vascular units will be effective if it targets the right people, in the right environment, used in the right way.

High-fidelity simulation programmes have already been implemented in the training of vascular surgeons and the wider surgical team at Imperial College, and it would appear that they have been well received. This approach to training a team can potentially bridge the gap that currently exists with new technological advancements, increasing expectations and the need to improve clinical outcomes.[6] Simulation and virtual reality training are valid and effective environments for training that allow deliberate practice as a unified group while removing the patient from potential dangers.[6] It is important, however, to ensure that the goal of any new training technique is always that of improving the quality and safety of care provided to patients in the real world, not just seeking to improve performance in the simulated environment.

Reducing error

With the margin of success or failure being small there is no room for error—a familiar statement in the vascular suite. In the pool, races are won and lost by hundredths of a second. Considering the care of a patient, the entire pathway must be examined in the most exquisite detail to be fully understood and appreciated. Once this has been achieved, collaborative involvement of the team can ensure that each step in the pathway can be optimised. Just as precious time can be lost in a race as the result of inefficient teamwork, one mistake in the pool may result in all being lost. In the vascular surgical operating room, poor teamwork may result in delays and error, and one single mistake can lead to disastrous consequences and failure.

A multitude of examples have shown the importance of the team, but what of the way in which each individual team member is trained? If trained in isolation, with collaboration and team work merely expected in the future, can the attributes of a team be truly integrated to deal with unexpected complications or complex cases where external stressors, accurate decision making, and immediate reactions occur almost reflexively? Most of the errors documented across studies such as the LEAP trial have been shown to be associated with a breakdown in communication and poor displays of non-technical skills.[7] The 185 cases analysed during the trial demonstrated the multifaceted nature of errors, the importance of error categorisation and also a number of potential ways to reduce the rate of such errors. In the various types of errors discussed in the trial, the majority involved equipment usage, and communication and teamwork problems.[7] With a total of 856 errors across the 185 cases, an alarming error rate of 1.2 errors per hour or four per procedure was recorded. Additionally, it was noted that although technical errors do occur, the most pressing and prevalent problems were linked to non-technical aspects of care.[7] Current surgical training has been largely focused and orientated on the purely technical aspects of practice, perhaps accounting for the relatively low frequency of such errors, but a training programme that fails to orientate around the team may also account for why non-technical skills are the biggest contributors to error. Furthermore, inferior teamwork and communication produce more major errors than other non-patient related factors.[7] Multivariate

analysis revealed a direct relationship between errors and the complexity of the procedure, endovascular as opposed to open procedures, and a lack of familiarity with equipment or devices.[7] Fourteen errors directly contributed to patient harm, half of them because of team failures. The consequences of these errors were reoperation, postoperative complications and death.[7] Studies such as this highlight the importance of incorporating equipment familiarisation, communication and system context into training set-up to ensure a focus on the team, rather than the individual.

Learning from error and optimising performance

There are common swimming-specific attributes shared by elite athletes such as coordination, stroke rate and stroke length; these are collectively considered as the efficiency of the swimmer. These physical factors in conjunction with physiological parameters such as bioenergetic efficiency will set some swimmers apart from others.[8–11] Although a large amount of research demonstrates that the athropometric factors of a swimmer contribute to success, it is more the optimisation of physical parameters in context with bioenergetics that truly determines the outcome.[8,12,13] Therefore, it would appear that ultimately the capability of the team to produce superb results is dependent upon the full use of each individual team member's particular strengths. There can be no breakdown in the team-based pathway of preparation for an athlete. Every potential second-saving aspect must be attained to ensure no detrimental outcome to the Olympic campaign. Such teamwork also plays an extremely important role in the prevention of adverse outcomes in the operating room.[14] If this understanding can be implemented into the training of vascular surgeons, then perhaps the team can be optimised through focus on both technical skill, and the often forgotten non-technical. Team optimisation can be achieved through streamlining functionality and improving outcomes using a set of tools and methodologies.[15] These can be integrated to form an instructional strategy, that if learnt and applied as a group, together improves teamwork. The greater the team dynamic, the better the outcome of the athlete and similarly the reduction in the risk of adverse events and errors in patient management.[16] Through team excellence, we can mitigate the impact of comorbidities and practitioner variance to achieve similar success stories despite a patient's 'anthropometric factors'.

In an unpublished series from Imperial College, we have been able to demonstrate that leadership and team skills can be improved through the implementation of structured team training. With sessions focused on both technical and non-technical skills in collaboration, readiness to lead can be established. Once a trainee demonstrates technical competency, they are then given the opportunity to lead the following case. Throughout the training, clinical and educational supervisors observe and guide the learning that is trainee-driven, making sure that objectives are achieved. Discussion around all topics covered includes aspects of situational awareness, good communication and action reinforcement. Additionally, developing effective coping mechanisms surrounding the experience of pressure, external stressors and mistakes is encouraged.

In competitive swimming, optimal performance in the pool is largely influenced by the team's ability to deal with various stressors associated with competition. Maintaining a controlled environment ensures that the athlete is supported and can focus entirely on execution of the plan. In order for the team to develop the

capacity to deal with these environments trial events are attended, racing is done in training, and the dynamic of the team is established prior to the main event. Access to situations that resemble the stressors that may be encountered on the day of competition is paramount. The balance of performance pivots around an inflection point determined by physiological or mental arousal and stress.[7] Stress drives improvement and gains in performance, but determining how much stress is too much and, therefore, detrimental is crucial. Once this point of inflection in stress is understood, tools can be implemented, and the team can act and adapt accordingly. Unified preparation is the key in these examples.

Dealing with stress is one of the areas that can be optimised before competition, or entering the operating room. Targeting preventable failures that frequently occur in operating theatres can be achieved through the implementation of preprocedural team rehearsal. The benefit demonstrated by Morbi *et al* in this regard extended to minimising procedural delays and improving patient safety.[17] Conducting a structured mental rehearsal before taking on an important task may further reduce both the occurrence and severity of error.[18] Each swimmer and patient will be unique, and the team by whom they are supported, equally so. Patient-specific rehearsal techniques incorporate the individual, environmental context and unique team into preparation. This customised approach has shown to reduce the number of angiograms used during stent graft deployment, for example.[19] Ultimately it is apparent that be it poolside or bedside, structured and contextualised team rehearsal reduces error. With the odds of winning an Olympic medal being so small, it is highly probable that there will only be one shot at success. Adopting the mentality that an intervention must be delivered with the same calibre as a single race highlights the importance of the planning, preparation and definitive decision making.[20]

Measuring improvement

During the customised training of an individual, continuous feedback and assessment is beneficial. Historically, assessment has largely been focused on details of the athlete, but it truly is representative of how well a team is functioning during the training process. These measures of performance can then be used as a guide to update the intervention pathway from the team to the athlete. Ultimately, performance markers must demonstrate relevance of teamwork that can be transferred into a competitive environment.[5] During training in vascular surgery, it is imperative that the techniques and approaches used correlate to the benefit observed, with the performance measure being the quality of care delivered and patient outcomes. Clinical benefit, although difficult to study and analyse statistically, is predominantly represented through complications such as infection, length of stay, reoperation rates, procedure failures, return to functional baseline and mortality rates.

The surgical team must demonstrate harmony in the transition from training through to the delivery of care. If this can be done then patient outcomes can be improved and the vital need for the training of the vascular surgeon of today to be done in the context of real life experience demonstrated. In a recent systematic review completed by Robertson *et al,* it was shown that the inclusion of team training in any capacity shows improvement in patient outcome to some degee, although difficult to measure.[14] This is where vascular surgery and swimming are

perhaps dissimilar. The markers of swimming progression and performance can be reflected in improved stroke efficiency or improved lactic acid clearence, and more definitively the time taken to complete the event, all of which are objective and well-defined measures. Due to difficulties in reporting measures of patient outcome, as well as the logistical and resource challenges of getting team members together to conduct training, demonstrating the benefits of team training from an empirical point of view remains a challenge.[14] That being said, current complication rates tend to demonstrate a downward slope as new technologies are better understood and superior skills developed. However, a constant prevalent battle remains with the increasing complexity of the procedures being undertaken and the ever more comorbid and frail patient cohort facing the vascular surgical profession. Perhaps this reflects the importance of treating a patient with a customised and contextualised intervention plan designed by a team with a dynamic training modality.

Another measure of improvement in the pool is a concept refered to as rate of perceived exertion.[21] This is a subjective measure used in swimming performance assessment. It functions as an opportunity to gain insight into the athlete's experience of a training programme or intervention. It can be contextualised for the team through consideration with bioenergetic parameters such as blood lactate and blood glucose, as well as physical parameters, stroke count and rate.[21] This way the team can observe the subjective experience of physiological changes that the intervention evokes. Similarly, when a patient comes into the care of a surgical team, the patient's experience of the intervention and encounter will always be of importance no matter how complex the intervention is. If the team functions smoothly, and each aspect of patient care flows, the "perceived exertion" of the patient will correlate with better outcomes.

Conclusion

Perhaps in summation of team training in vascular surgery we can draw from the words from the book *The Prophet*: "The astronomer may speak to you of his understanding of space, but he cannot give you his understanding".[22]

By this description, it becomes apparent that in order to learn and to improve expertise, continuous learning cultures must be developed and refined. Individuals cannot simply work as a team when the time requires it, they must be trained as a team from the very beginning and throughout their practice. The way in which you experience training must resemble real life in order for an individual to function optimally. That being said, there are contextual aspects that must be considered. There are fewer opportunities for personnel to train as a team due to a combination of less time and resources; the complexity of cases presenting and those amenable to operation. Additionally, greater expectations from procedures due to advancements in technology, methodology and reasonable patient expectation of who is performing their procedure further reduces trainee exposure.

Special consideration must be made to understand the needs of the teams and trainees of today, areas that require improvement, and progression towards a unit with a common goal and purpose. Trainee-led training, social learning and trainee-created content drive the enhancement of both technical and non-technical skills. Accessibility to environments that promote team development must be supported by data analytics and learning experience platforms. This ensures that there is a constant flow of appropriate knowledge and transference of skills that

directly impact the quality of care delivered and patient outcomes. There is a need to generate a training environment that accurately reflects the stressors and expectations of the real-life setting in which the team will be expected to perform. This way there is familiarisation not only with the way in which the procedural aspects are handled, but the cognitive and emotional awareness of the effect of the stressors that team members are subjected to in real-time experiences and how these may impact the patient.

Through the culmination of years of training, the refinement of talent and rehearsal with technical advancements, opportunities for analysis and the establishment of good routine, the team's pathway to success can be reached. Imagine having a team goal to facilitate an athlete to swim a world record time and then realising it. If every patient can be seen as an Olympian, and have a teamwork with them through the course of their management, imagine what could be achieved.

Summary

- There should be a primary importance placed on teamwork and training as a team in surgery.

- There is a direct comparison between the patient and the elite athlete and the surgical team and the coaching team.

- There is a need to align training assessments to meaningful clinical outcomes.

- Training environments need to represent real-life situations with technical and non technical skills vitally important in the generation of optimal outcomes.

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Treatment of thoracic (endo)graft infections

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Introduction

Vascular graft or endograft infections are among the most severe complications in modern vascular surgery. Treatment becomes even more difficult when the graft is located in the thoracic aorta. The mortality associated with this condition depends on the clinical presentation but is estimated to be up to 75%.[1] It is especially high when the infection is associated with the presence of an aorto-oesophageal or aortobronchial fistula.[2–4] Endografts seem at least as prone to infection as surgically inserted vascular grafts so that with the growing use of endografts for a variety of diseases in the thoracic aorta, the incidence of thoracic (endo)graft infections is also rising.[5] Despite this, very few series have been published on the treatment and outcome of this condition; thus, evidence on the optimal approach is rare and often relies on smaller series or systematic reviews of case reports. Taking into consideration the complexity and severity of the treatment, the recently published ESVS guidelines on this subject recommend centralisation of this pathology.[6]

Graft infections are classically divided into early and late infections. The former are mainly caused by a breach in sterility during implantation or the pre-existent presence of bacteria in the aneurysmal thrombus. The latter are mainly caused by haematogenous seeding during a period of bacteraemia or by local bacterial translocation. The reason for the development of aorto-oesophageal or aortobronchial fistulae often remains unclear but ischaemia of the bronchial or oesophageal wall because of occlusion of the feeding arteries, mechanical erosion by the aneurysm, especially when still under pressure due to presence of an endoleak, penetration of an oversized endograft and pre-existing infection are thought to be causative or contributing factors.[6]

Diagnosis

The clinical presentation of a thoracic graft infection can be diverse, ranging from vague symptoms, such as unexplained fever or lethargia, to major bleeding, sepsis and shock. Systemic signs of infection are mostly present but local signs are usually absent due to the deep localisation of the thoracic aorta. Septic emboli can cause secondary foci of infection. Aorto-oesophageal and aortobronchial fistulae are often present with haematemesis or haemoptysis as the first symptom. These bleeds can be massive but are often preceded by self-limiting herald bleedings. Laboratory tests will show elevated inflammatory parameters and it is advised to take haemocultures before antibiotic treatment is installed. The definitive diagnosis is most commonly made by a contrast enhanced CT angiography scan showing perigraft fluid, air bubbles in the aneurysmal sac or signs of inflammation or abscess formation in the surrounding tissues.[7] In low-grade infections or in case of doubt, a PET scan or

white blood cell scintigraphy can be helpful in establishing the diagnosis but should be interpreted with caution.[8] In the presence of an aorto-oesophageal or centrally located aortobronchial fistula the prosthesis or bare stents can sometimes be seen through a defect in the wall of the oesophagus or bronchus on oesophagoscopy or bronchoscopy.

Treatment

Antibiotics

Although rarely indicated as the sole treatment antibiotics should be given to all patients with an infected vascular graft. In the acute phase, and as long as the responsible germ(s) are not known, intensive broad spectrum antibiotherapy or antibiotics directed against the most probable germ is indicated. In specific cases and especially when an enteric fistula is present, additional or antifungal agents should be considered. Once the responsible germ is known the antibiotic spectrum can be narrowed.

No real consensus exists on the optimal duration of antibiotic therapy, which depends heavily on the actual situation, so general guidelines on this issue are largely lacking. On the condition that all prosthetic material is removed and a thorough debridement of all infected tissue can be performed, a minimum of two weeks of intravenous therapy, if possible followed by an oral regimen for another two to four weeks, is mostly considered sufficient if the inflammatory parameters are also under control. If the infected material is replaced by a new synthetic graft, four to six weeks of intensive antimicrobial therapy is usually proposed to prevent recurrent infection. Many authors favour a total treatment time of three to six months in this situation and some even advocate a year's-long treatment. In those patients in whom removal of the infected graft is not possible because of their general condition or the extent of the procedure that would have to be performed, prolonged treatment should be considered. Antibiotics alone will mostly not be able to eradicate the infection completely but low-grade infections without complications can sometimes be kept under control by prolonged antibiotherapy for a minimum of six months up to lifelong. The evolution of inflammatory parameters and computed tomography (CT) angiography and 18F-FDG-PET/CT imaging may help to monitor the success and guide the duration of therapy.[1,9–11]

Drainage and irrigation

If perigraft fluid or abscesses are present these can be drained by a percutaneous approach under ultrasound or CT angiography guidance. This also allows adequate microbiological sampling and identification of the responsible germs. It can be supplemented by the insertion of a pigtail to irrigate the infected space with saline or antiseptic solution. This can be helpful in the acute phase to diminish the burden of infection in septic patients and in those patients where definitive surgery is not an option.[5,11]

In situ reconstruction

Removal of the infected graft, aggressive debridement of the infected area and arterial reconstruction with infection-resistant material remains the cornerstone of definitive treatment of graft infection. Theoretically extra-anatomic reconstructions

offer the advantage of avoiding the infected area but due to the complexity of the procedure most authors prefer an *in situ* reconstruction.

The operative technique will depend on the localisation of the infected graft. If a surgical graft needs to be removed the procedure will at least be similar and often be more extensive than the primary intervention. It is rendered more difficult because of any adhesions after the previous surgery and the inflammatory reaction that will often be present. If an endograft needs to be removed special attention should be given to the management of the landing zones. Although it is advisable to create the proximal and distal anastomoses beyond these landing zones, this is often not possible, in which case care should be taken not to damage these landing zones when removing the endograft.[12]

Partial removal of the graft is usually not an option as in general the whole (endo)graft should be considered as infected. Only in rare circumstances, when on imaging and clinically the infection looks limited and total removal would make the intervention more hazardous, can partial removal be considered. Under these specific circumstances acceptable results with partial explantation can be obtained.[5]

Different graft materials can be used to reconstruct the aorta. As biological material cryopreserved allografts have the advantage of being more infection-resistant and are considered by many as the first choice in thoracic aortic reconstructions.[12–13] However, they are still subject to the risk of degeneration, rupture and bleeding especially in infections with necrotising organisms.[11] Dacron grafts remain the most widely used graft for thoracic aortic reconstructions. Silver coated (with or without triclosan) or rifampin soaked grafts seem to be able to provide some resistance to early reinfection and should be preferred.[13] Growing interest exists in the use of bovine pericardium tailoring a custom-made tube by sewing pericardial sheets.[14]

After completion of the *in situ* reconstruction it is important to cover the newly inserted graft with viable tissue and to prevent direct contact with surrounding organs like lung or oesophagus. Intercostal flaps, pericardial flaps or omentum can all be helpful to achieve this goal if insufficient healthy adjacent tissue is present.[11] More extensive muscular flaps, such as latissimus dorsi or serratus muscle may sometimes be indicated.[15] If no viable tissue is available a bovine pericardial patch may be used to cover the graft.

Extra-anatomic reconstruction

To avoid reconstruction with a new graft in a contaminated field, extra-anatomic reconstructions and aortic ligature followed by removal of the infected graft can be performed in one or two stages. The most commonly used extra-anatomic reconstruction is the so called ventral aorta consisting of a retrosternally placed graft between the ascending aorta and the supracoeliac or infrarenal abdominal aorta.[15] In a second step, during the same intervention or at a later stage, the originally infected graft is removed through a thoracotomy approach. It is advised to cover and reinforce the aortic stump with viable tissue to avoid stump blowout.

Aorto-oesophageal fistula

The treatment of an aorto-oesophageal fistula is even more complex as both the aorta and oesophagus need to be treated. Mortality of this condition is high and patients rarely survive without aggressive treatment.[2,4] Conservative treatment should, therefore, only be considered in a palliative setting. The incidence of

thoracic aortoenteric fistula seems higher than in the abdominal aorta and it occurs earlier and more frequently after endograft placement than after open surgical grafting.[5,13]

In patients presenting with active and life-threatening bleeding from an aorto-oesophageal fistula emergent insertion of an endograft should be considered as the primary strategy to control the bleeding and restore haemodynamic stability.[16] However, this is only a temporary solution that acts a bridge to definitive treatment, which then can be performed in better conditions, because it addresses neither the defect in the oesophagus nor the infected graft.[17] Placement of an oesophageal endoprosthesis alone does not allow control of the bleeding and is only a temporary solution when oesohageal leakage with infection is the only problem.[2]

To avoid persistent or recurrent infection, closure of the defect in the oesophagus is required.[2,4] This can be performed as an isolated procedure or together with the vascular reconstruction. Direct closure of the defect is most often not possible and can only be considered if the lesion is very limited. In most cases, a radical treatment with partial or total resection of the oesophagus is necessary. In acute situations, this can be done in a staged fashion with cervicectomy, closure of the cervical oesophagus and creation of a nutritional gastro- or jejunostomy (e.g. at the moment a thoracic endograft is inserted to control the bleeding). This is then followed by removal of the oesophagus and vascular reconstruction when the patient is stabilised. Reconstruction of the intestinal continuity with gastric or colonic pull-up can be performed in a third stage. Reconstruction of the aorta is performed *in situ* or extra-anatomically following the same principles as described above. Whether to perform the whole treatment in one, two or three stages will often be dictated by the circumstances, the possibility to control the infection and the condition of the patient.[1,12] Besides complex surgery these patients will also need intensive medical support.

Aorto-bronchial fistula

Aortobronchial or aortopulmonary fistulae are less common than aorto-oesophageal fistulae but are, if left untreated, also almost uniformly fatal.[3] A difference should be made between (proximal) aortobronchial fistulae with fistulisation to the bronchial system and aortopulmonary fistulae with fistulisation to the pulmonary parenchyma. The latter is thought to have a more benign course and better prognosis.[3]

Just as in acute bleeding due to an aorto-oesophageal fistula, emergent implantation of a thoracic endograft may be indicated to stabilise the patient. As a definitive treatment, repair of the bronchial defect with an intercostal muscle or pericardial flap can be an option but in many cases bronchial resection with anastomosis or lung resection is indicated. Recently acceptable results have been described in aortopulmonary fistulae with insertion of an endoprosthesis alone, pulmonary resection and coverage of the endograft with a muscle or pleural flap in a single or staged procedure.[18] This can only be considered when the infection is limited and still entails the risk of recurrent fistula or persistent infection. In case of overt infection or when the condition of the patient allows removal of the infected graft and *in situ* reconstruction remains the preferred treatment as this still yields the best results in the long term.[3]

Conclusion

Even after successful repair an increased risk of persistent or recurrent infection remains present. When cryopreserved allografts have been used early degeneration can occur. Recurrence or persistence of infection and subsequent organ failure are the main reasons for final demise of the patients. Reoperations due to infectious or bleeding complications can be needed in up to 50% of patients.[19] Also in the longer term follow-up, including monitoring of inflammatory parameters and repeated imaging with CT angiography and/or 18F-FDG-PET/CT remain indicated.

Summary

- Infection of a thoracic (endo)graft is a serious complication with high morbidity and mortality. Symptoms and presentation can be very diverse. Treatment should be individualised and concentrated.

- Adequate antibiotic treatment is necessary in all patients with infected grafts. The optimal duration of therapy depends on the individual situation and should be determined after multidisciplinary discussion.

- Definitive cure can only reliably be expected when all graft material is removed. Partial removal should only be considered in very specific situations.

- Conservative treatment should only be considered if the patient's condition prevents an aggressive approach, as a temporary treatment or in a palliative setting.

- The presence of an aorto-oesophageal or aortobronchial fistula further increases mortality and complicates treatment. If massive bleeding is the presenting symptom, insertion of an endograft to stabilise the patient is advised as a bridge to definitive treatment. In an aorto-oesophageal fistula, resection of the oesophagus and removal of the infected graft in a two or three stage approach will mostly be needed to cure the patient. In an aortobronchial fistula, especially when the fistula is to the pulmonary parenchyma, a less aggressive approach might sometimes be taken.

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Open or endovascular treatment of downstream thoracoabdominal pathology in patients previously treated with frozen elephant trunk

A Grandi, A Melloni, D Loschi, G Mellissano, R Chiesa and L Bertoglio

Introduction

Aortic pathology of various origins might warrant extensive aortic replacement starting from the aortic arch and extending into the thoracoabdominal segment. Therefore, surgical approaches have been developed to facilitate second-stage thoracoabdominal aortic repair.[1,2] In 1983, Hans Borst changed the two-stage approach by introducing the elephant trunk technique.[3] This made the downstream operation easier by placing a Dacron prosthesis into the descending aorta during the arch repair. The introduction of the frozen elephant trunk technique with the idea of "freezing" the distal end of the trunk with a stent graft was pioneered by Suto *et al* and Kato *et al,* and then popularised by Usui *et al* and Karck *et al.*[1,4–6] The frozen elephant trunk procedure was initially performed using a combination of conventional Dacron surgical grafts and thoracic stent grafts until manufactured hybrid prostheses became available. The frozen elephant trunk technique was meant to treat the entire thoracic aortic disease in one step; however, it can also be performed as a proximal platform for second-stage open or endovascular treatment of downstream thoracoabdominal pathology (Figure 1).

Current evidence

Only a few articles describe the outcomes of treatment of downstream aortic pathology after the frozen elephant trunk technique.

Rustum *et al* report 53 patients receiving a second-stage operation with median time to the intervention of seven months (range 0–78 months) for the entire cohort.[7] The authors compare differences between the standard elephant trunk and frozen elephant trunk procedure, rather than open repair and endovascular treatment. Indications for second-stage repair were progression of the diameter of the downstream aorta due to atherosclerotic aneurysms (39; 74%), aortic rupture (5; 9%), fistula (5; 9%), residual aortic dissection (3; 6%) and malperfusion (1; 2%). Twenty-eight (53%) patients underwent endovascular treatment while 25 (47%) underwent open repair. There were eight in-hospital deaths.

Haensing *et al* report 10 patients receiving a second-stage operation with median time to the intervention of 136 days (range 14–282 days).[8] Indications for second-stage repair were thoracoabdominal aortic Crawford type I (3; 30%) or Crawford type 2 (4; 40%) and complicated residual aortic dissection after the frozen elephant trunk technique (3; 30%). All patients underwent endovascular treatment with a complex endovascular aortic procedure (fenestrated or branched endovascular aneurysm repair), with four custom-made devices (40%), four off-the-shelf devices (40%) and two using a provisional extension to induce complete attachment (PETTICOAT) technique (20%). There was one aortic-related in-hospital death (10%). The median intensive care unit stay was one day (range 0–3 days), and median hospital stay was seven days (range 5–12 days). Spinal cord preconditioning was performed in seven patients with no paraplegia at 30 days. Computed tomography (CT) scans at 8.5±11.4 months of follow-up showed
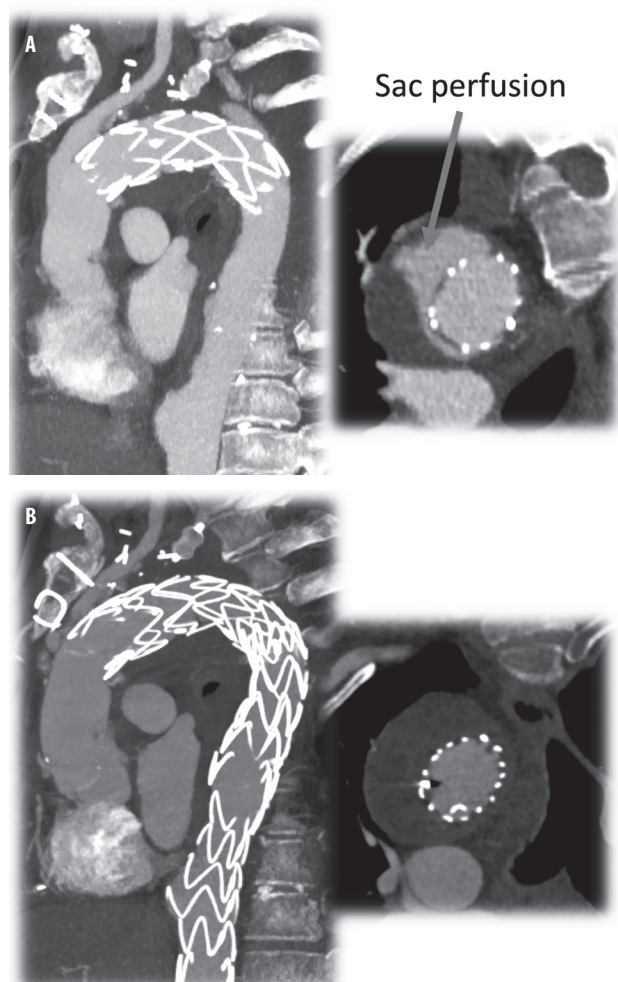
Figure 1: (A) CT scan after frozen elephant trunk procedure with a distal sac reperfusion. (B) CT scan after second-stage thoracic endovascular aortic repair with a complete exclusion of the aneurysm sac.
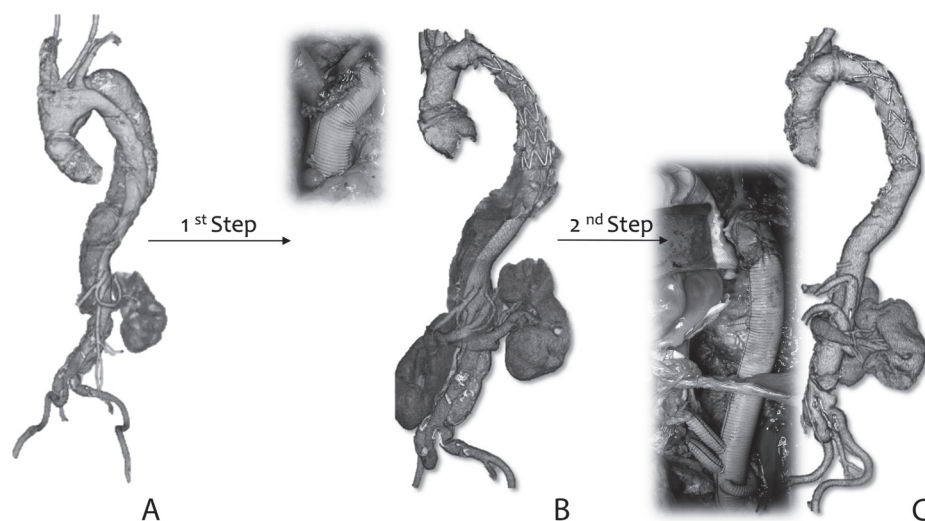
Figure 2: (A) 3D reconstruction of a residual type A dissection after ascending aorta open repair. (B) 3D reconstruction after aortic arch repair using the frozen elephant trunk technique. (C) Intraoperative photograph and postoperative 3D reconstruction of complete aortic reconstruction with proximal anastomosis performed on the previous frozen elephant trunk with reimplantation of the visceral and renal vessels with a direct bypass.

complete false lumen thrombosis of all type B aortic dissections and one (11%) type 3 endoleak with constant aneurysm diameter. Branch patency was 100%.

Folkmann *et al* report nine patients receiving a second-stage operation with median time to the intervention of 423 days (range 19–1979 days).[9] Indications for the second-stage repair were progression of the diameter of the downstream aorta due to atherosclerotic aneurysms (6; 67%), patients with Marfan syndrome after previous aortic dissection (2; 22%) and giant cell aortitis (1; 11%). All patients underwent open repair with a distal anastomosis at the iliac bifurcation. There were no in-hospital deaths. The median intensive care unit stay was 3.5 days (range 1–12 days) and median hospital stay was 22 days (range 14–132 days). No symptomatic spinal cord ischaemia or stroke was observed. One patient developed acute renal failure that required haemodialysis.

The San Raffaele experience

Between January 2011 and 2020, 703 patients underwent thoracoabdominal aortic open repair or endovascular treatment at the authors' institution. Of these patients, 47 (31 males) underwent thoracoabdominal aortic repair after the frozen elephant trunk technique: 27 (57.4%) underwent open repair and 20 (42.6%) endovascular treatment.

Open treatment

Open thoracoabdominal aortic repair after frozen elephant trunk is performed in a standard fashion. Extracorporeal circulation or left heart bypass is usually established via femorofemoral access or via the femoral artery and the pulmonary vein, and patients are usually cooled to between 32 and 34 degrees Celsius. A left thoracotomy, in case of thoracic aneurysm, or thoraco-phreno-laparotomy, in

Figure 3: (A) 3D reconstruction of a mega aorta. (B) 3D reconstruction after aortic arch replacement using the frozen elephant trunk technique. (C) 3D reconstruction of the endovascular exclusion of the downstream aorta using a custom-made branched prosthesis.

case of thoracoabdominal aortic repair, is used to isolate the entire aorta and its visceral vessels. After distal and proximal clamping, the aorta is replaced with a Dacron graft prosthesis, with the proximal anastomosis being performed on the previously positioned frozen elephant trunk endovascular graft. Even in patients with a previous frozen elephant trunk, it is possible to clamp the aorta without difficulties or damage to the stent graft. The intercostal arteries are reimplanted depending on the position, the size and backflow and motor and somatosensory evoked potentials. The visceral and renal arteries are reimplanted via islands/patches or individual anastomoses, depending on the type of prosthesis used (Figure 2). Perfusion of the visceral and renal arteries is always ensured. The incision is then

closed in a standard fashion. Patients are usually transferred to the intensive care unit after the operation. Cerebrospinal fluid can be positioned the day of or the day before the operation and is used and maintained for three days after the operation if there are no neurological deficits.

Endovascular treatment

The endovascular approach is tailored according to the extent of the pathology, with a simple thoracic endovascular aortic repair (TEVAR), or the addition of a candy plug or fenestrated or branched endovascular aneurysm repair. These procedures are performed under local or general anaesthesia in the hybrid operating room. Arterial access can be established through surgical cutdown or percutaneous puncture of the femoral and upper extremity arteries. For a simple thoracic endovascular aortic repair, sheaths are introduced, and a guidewire is advanced retrogradely to enter the aortic arch. The stent graft prosthesis is deployed under fluoroscopic guidance. Sufficient overlap between the frozen elephant trunk prosthesis and the stent graft prosthesis is ensured. In the case of residual dissection, a candy plug can be deployed in the false lumen to exclude it and avoid any retrograde reperfusion (Figure 3).[10,11]

For a complex aortic procedure with the involvement of the visceral vessels, the repair can be performed using off-the-shelf or custom-made devices. The intraoperative sequence is the same, although fenestrated or branched endovascular aneurysm repairs require the cannulation and bridging of all the visceral vessels through the corresponding fenestrations/branches. Finally, the deployment of a stent graft in the infrarenal aorta or in the iliac arteries may be needed to obtain adequate sealing if there are extensive thoracoabdominal aortic repairs or residual dissections. Different cerebrospinal fluid drainage and staging procedures have been proposed to reduce the incidence of spinal cord injury.[12]

Results

The median time to the second-stage intervention was of 50 months (range 1–196 months). Indications for second-stage repair were residual aortic dissection (26; 55.3%), progression of the diameter of the downstream aorta due to atherosclerotic aneurysms (20; 42.6%) and aortic rupture (1; 2.1%). There were four in-hospital deaths. There were three (6.4%) cerebrovascular, six (12.8%) cardiac, and 17 (36.2%) pulmonary compilations; seven (14.9%) patients presented postoperative renal insufficiency. Seven (14.9%) spinal cord injuries were reported.

Compared with the open repair group, patients in the endovascular treatment group had fewer cardiac (0 [0%] vs. 6 [22.2%]; p=0.031] and pulmonary (1 [5.0%] vs. 16 [59.2%]; p<0.001) complications. Composite major adverse events were statistically significantly lower in the endovascular treatment group (1 [5.0%] vs. 13 [48.1%]; p=0.001) and fewer patients in the endovascular treatment group were transfused than in the open repair group (0 [0%] vs. 23 [85.1%]; p<0.001). Despite the difference in perioperative outcomes, there was no statistical significance in the reintervention rate (0 [0%] vs. 4 [14.8%]; p=0.12) or death between the two groups (1 [5.0%] vs. 4 [14.8%]; p=0.37).

Conclusion

Thoracoabdominal aortic repair is feasible after the frozen elephant trunk procedure as either an open or endovascular option and can be considered a safe procedure in referral centres. Despite the decreased perioperative complication rates in the endovascular treatment group, both techniques should be considered and tailored to the patient.

Summary

- The frozen elephant trunk procedure can be used as a single-stage repair or as a proximal platform for downstream aortic pathology treatment.

- Second-stage procedures can be either open or endovascular and unplanned.

- In the literature, both open repair and endovascular treatment of downstream thoracoabdominal aortic pathology are reported with satisfactory results.

- Both techniques should be considered and tailored to the patient, in high-volume and referral centres.

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Abdominal aortic consensus

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Guideline compliance is associated with improved outcomes for abdominal aortic aneurysm repair

J Eldrup-Jorgensen and LW Kraiss

Introduction

The purpose of clinical practice guidelines is to improve care. Clinical care is improved by following evidence-based recommendations and reducing variations in care.[1] Almost all professional societies put considerable effort into creating clinical practice guidelines that are intended to be a readily available resource that provide direction and support for different clinical scenarios.[1] Creating such guidelines is a labour-intensive and time-consuming process.[2] Recognised experts in the field are identified to form a writing committee. The process begins with an extensive literature review followed by synthesis and grading of the data. All professional societies put in considerable time and effort to create guidelines for their membership. Clinical practice guidelines are published and distributed to members to facilitate adoption and implementation. However, it is not clear whether practitioners follow the guidelines or whether compliance with guidelines impacts patient outcomes.[3] The goal of this chapter is to assess compliance with guidance on treating abdominal aortic aneurysm.

Society for Vascular Surgery aneurysm guidelines

The Society for Vascular Surgery (SVS) has a structured methodology for guideline creation consisting of committee selection, identification of critical clinical questions, evidence synthesis including systematic review and meta-analysis, grading of strength of recommendation, voting, peer review and publication.[4] In January 2018, the SVS published its practice guidelines on the care of patients with an abdominal aortic aneurysm in the *Journal of Vascular Surgery*.[5] The SVS guidelines document was a huge task written by 14 international experts and includes 111 recommendations.

In an effort to measure the degree of compliance by practising vascular surgeons to the SVS abdominal aortic aneurysm guidelines, the Vascular Quality Initiative (VQI) abdominal aortic aneurysm registry was used as the reference source. The VQI is a clinical registry organised under the structure of a patient safety organisation, which collects data for vascular procedures to improve the quality, safety, effectiveness and cost of vascular healthcare.[6,7] Patient data are collected in hospital and at one year on 12 different procedures.[8] More than 200 centres throughout the USA participate in the open abdominal aortic aneurysm and

endovascular aneurysm repair (EVAR) registries, with more than 10,000 and 40,000 cases entered, respectively.

The SVS abdominal aortic aneurysm guidelines were reviewed to select those captured by variables in the VQI registry. After determining which guideline recommendations could be found in the pertinent VQI registries (open abdominal aortic aneurysm repair and EVAR), the degree of compliance and the association with outcomes were then measured.[9] The study cohort included elective and emergent open abdominal aortic aneurysm repairs and EVAR enrolled in VQI from 2003 to March 2019. Outcome measures included surgical site infection, respiratory complications, major adverse cardiac events (MACE; myocardial infarction, congestive heart failure and dysrhythmia), conversion to open repair, in-hospital and one-year mortality, and any adverse event. The degree of compliance with these individual recommendations was calculated by centre and correlated with clinical outcomes. The statistical analysis has been previously described.[9]

Measuring compliance with SVS aneurysm guidelines

The SVS abdominal aortic aneurysm guidelines offer 111 recommendations and suggestions categorised according to the GRADE method of assessing strength of recommendation and quality of underlying evidence.[10,11] Based on the GRADE scheme, 29 of the SVS abdominal aortic aneurysm guidelines were 1A (strong/high), 23 were 1B (strong/moderate), 17 were 1C (strong/weak), 13 were 2B (weak/moderate) and 33 were 2C (weak/weak). Six were ungraded good practice statements. Because of a mismatch between variables in the recommendations and the VQI registry, only a small number could be analysed using the VQI registry. Of the 69 GRADE 1 guidelines, five could be measured in VQI. Of the 46 GRADE 2 guidelines, three could be measured in VQI.

Recommendation 1

"We recommend elective repair for the patient at low or acceptable surgical risk with a fusiform abdominal aortic aneurysm that is greater or equal to 5.5cm in males and greater or equal to 5.0cm in females (level of evidence 1A)."

For EVAR procedures, 71.3% (range 36–92%) were performed in compliance with the size threshold or documented the presence of an iliac aneurysm. For open abdominal aortic aneurysm procedures, 83.1% (range 40–100%) were in compliance. Some cases performed for saccular morphology or because of rapid growth may have appropriate indications but will not be strictly compliant with size criteria. As such, the VQI assessment of compliance will underestimate the number of appropriate cases performed by a centre.

When considering all cases performed, compliance with the size threshold guideline inversely correlated with adverse outcomes. After multivariable analysis, compliance in the EVAR registry for size threshold was associated with increased one-year mortality (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.24 to 1.64; p<0.0001) and any adverse event mortality (OR 1.27, 95% CI 1.14 to 1.41, p<0.0001) and there was a trend towards increased MACE (OR 1.15, 95% CI 0.98 to 1.36; p=0.084). In open abdominal aortic aneurysm, there was an association with increased respiratory complications (OR 1.34, 95% CI 1.02 to 1.77; p=0.039) and any adverse event (OR 1.23, 95% CI 1.01 to 1.49; p=0.042). The negative

association of size threshold compliance with outcomes should not be interpreted as support for treatment of smaller abdominal aortic aneurysm because multiple previous studies have shown the validity of the size threshold as an indication for abdominal aortic aneurysm repair including EVAR.[12–15]

This guideline is incompletely measured in VQI and consideration should be given to revising the registry to capture sac morphology and increasing size. Despite the inverse association with outcomes, compliance with this guideline is appropriate.
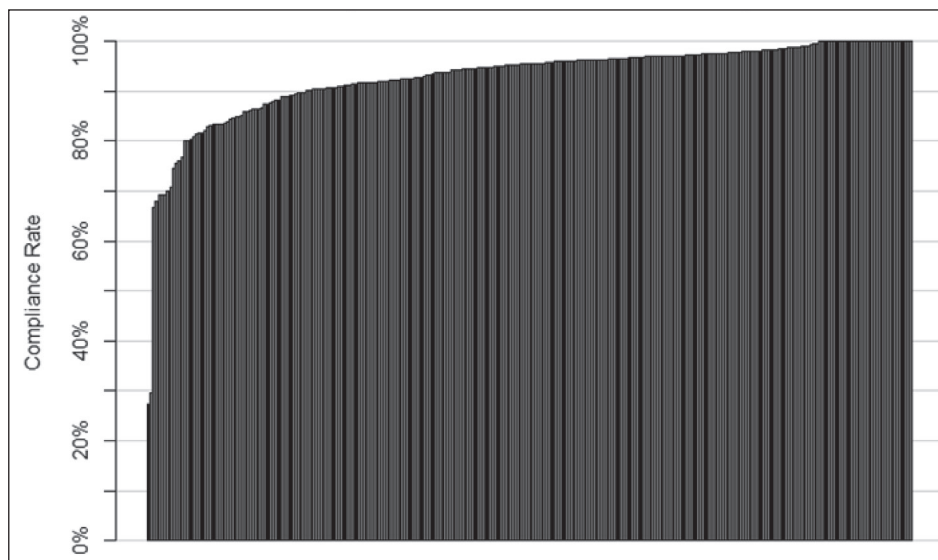
Figure 1A: Compliance with antibiotic recommendation 3 by centre in EVAR.
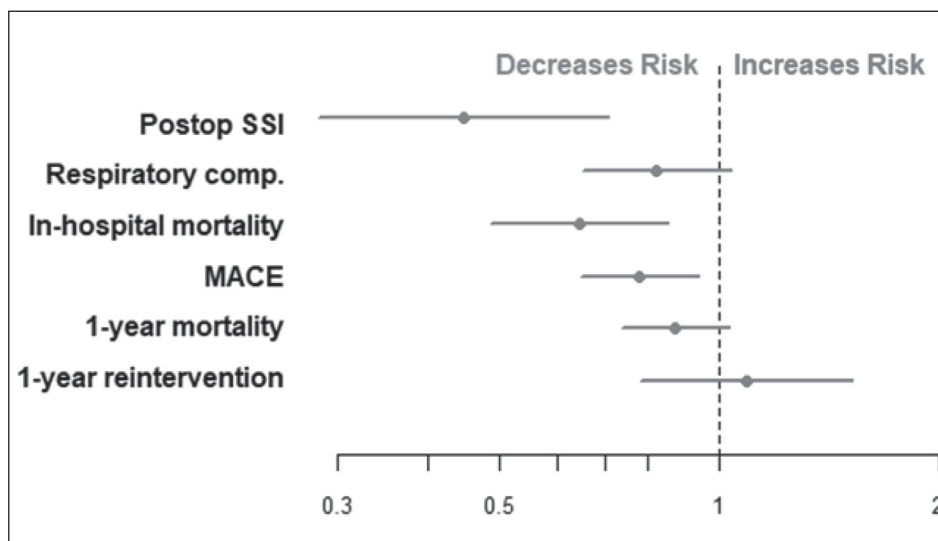
Figure 1B: Multivariate logistic regression analysis of compliance with antibiotic recommendation 3 in EVAR.

Recommendation 2

"We recommend preservation of flow to at least one internal iliac artery (level of evidence 1A)."

Flow to at least one internal iliac artery was preserved in 99.2% of EVAR procedures (range 75–100%) and 96.8% of open abdominal aortic aneurysm procedures (range 51–100%). After multivariable analysis, there was an association with decreased MACE (OR 0.49, 95% CI 0.29 to 0.83; p=0.008) in compliant EVAR cases, and there was a trend towards decreased in-hospital mortality (OR 0.62, 95% CI 0.37 to 1.02; p=0.060) and one-year mortality with compliance in open abdominal aortic aneurysm (OR 0.66, 95% CI 0.42 to 1.04; p=0.073).

This guideline has high compliance and improved outcomes but there is wide variation between centres. There may be anatomic restrictions to compliance but providers and centres should pay attention to this guideline and try to improve performance in the future.

Recommendation 3

"We recommend intravenous administration of a first-generation cephalosporin or, in the event of penicillin allergy, vancomycin within 30 minutes before open surgical repair or EVAR. Prophylactic antibiotics should be continued for no more than 24 hours (level of evidence 1A)."

Compliance with the antibiotic guideline for EVAR cases was 93.8% (range 27–100%) (Figure 1a) and for open abdominal aortic aneurysm was 93.3% (range 60–100%). After multivariable logistic regression in the EVAR registry, compliance with the guideline was associated with decreased surgical site infection (OR 0.45, 95% CI 0.28 to 0.74, p=0.0005), MACE (OR 0.78, 95% CI 0.65 to 0.94; p=0.009), inpatient mortality (OR 0.64, 95% CI 0.49 to 0.85; p=0.002) and any adverse event (OR 0.81, 95% CI 0.70 to 0.93; p=0.002) and marginally decreased respiratory complications (OR 0.82, 95% CI 0.65 to 1.04; p=0.099) and one-year mortality (OR 0.87, 95% CI 0.74 to 1.03; p=0.112) (Figure 1b). After multivariable logistic regression, there were no significant findings in the open abdominal aortic aneurysm registry for antibiotic non-compliance.

Overall compliance is high but there is a wide range of compliance with this 1A evidence level guideline, which is a readily achievable process measure. Compliance with this guideline may provide a focus for quality improvement for many centres (Figure 1a). Centres and physicians should be aware of their performance.

Recommendation 4

"We recommend using cell salvage or an ultrafiltration device if large blood loss is anticipated." (level of evidence 1A)

Compliance with the cell salvage guideline in open abdominal aortic aneurysm was 92.3% (range 25–100%) in patients with blood loss >500ml. After multivariable logistic regression, compliance with the guideline was associated with improved one-year survival (OR 0.63, 95% CI 0.46 to 0.85; p=0.003) and a trend towards decreasing any adverse event (OR 0.81, 95% CI 0.64 to 1.03; p=0.090).

This guideline also has high compliance overall and is associated with improved outcomes but there is wide variation with this process measure. As it should be

readily achievable, select centres should focus their efforts and try to improve compliance in the future.

Recommendation 5

We recommend smoking cessation for at least two weeks before aneurysm repair (level of evidence 1C)."

Compliance with the smoking cessation guideline in EVAR cases was 54.6% (range 13–100% (Figure 2) and in open abdominal aortic aneurysm cases, 40.1% (range 0–83%). After multivariable logistic regression in the EVAR registry, compliance with the guideline was associated with decreased respiratory complications (OR 0.66, 95% CI 0.53 to 0.83; p=0.0002), inpatient mortality (OR 0.64, 95% CI 0.44 to 0.92; p=0.016) and one-year mortality (OR 0.88, 95% CI 0.78 to 0.99; p=0.043), and any adverse event (OR 0.86, 95% CI 0.78 to 0.95; p=0.002). After multivariable logistic regression, the findings in the open abdominal aortic aneurysm registry for tobacco cessation were associated with decreased respiratory complications (OR 0.74, 95% CI 0.60 to 0.91; p=0.004), one-year mortality (OR 0.68, 95% CI 0.52 to 0.90; p=0.007) and any adverse event (OR 0.75, 95% CI 0.64 to 0.88; p=0.0003).

Compliance with tobacco cessation was much poorer possibly because of the difficulty of implementation, which is partly outside of the influence of the practitioner. These findings support the importance of tobacco cessation before the operation and may warrant greater attention on the part of providers.

Recommendation 6

"In patients with significant clinical risk factors, such as coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic renal insufficiency, and unknown or poor functional capacity (metabolic equivalent <4), who
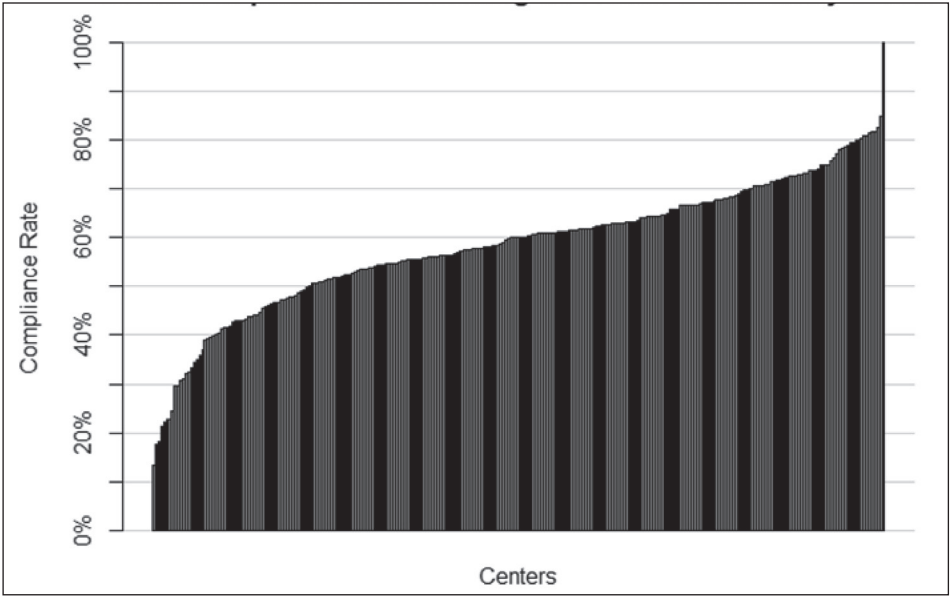
Figure 2: Compliance with smoking cessation recommendation 5 by centre in EVAR.

are to undergo open surgical repair or EVAR, we suggest non-invasive stress testing (level of evidence 2B)."

In the VQI registries, there are variables for coronary artery disease, congestive heart failure, diabetes mellitus, chronic renal insufficiency and functional status. For this analysis, it was considered that stress testing indicated whether any single comorbidity was listed as being present. Compliance with the stress testing guideline was 43.7% for EVAR (range 0–100%) (Figure 3) and 60.3% for open abdominal aortic aneurysm (range 6–100%). After multivariable logistic regression, the patients treated according to the guideline in the EVAR registry had improved survival at one year (OR 0.83, 95% CI 0.71 to 0.97; p=0.022), lower rates of any adverse event (OR 0.86, 95% CI 0.76 to 0.98; p=0.023) and marginally decreased MACE (OR 0.84, 95% CI 0.69 to 1.01; p=0.067). In the open abdominal aortic aneurysm registry, compliance with the guideline was associated with marginally increased MACE (OR 1.31, 95% CI 0.99 to 1.73; p=0.062).

Stress testing before repair had a wide range of compliance (0–100%) (Figure 3) but a minimal impact on outcomes. This wide variation suggests that there is little consensus on the approach to preoperative cardiac evaluation and highlights the need for further investigation as to which patients would benefit from cardiac stress testing before abdominal aortic aneurysm repair.[16]

Recommendation 7

"We suggest that elective EVAR be performed at centres with a volume of at least 10 EVAR cases each year and a documented perioperative mortality and conversion rate to open surgical repair of 2% or less (level of evidence 2C)."

"We suggest that elective open abdominal aortic aneurysm be performed at centres with a volume of at least 10 open aortic cases (of any type) each year and a documented perioperative mortality of 5% or less (level of evidence 2C)."
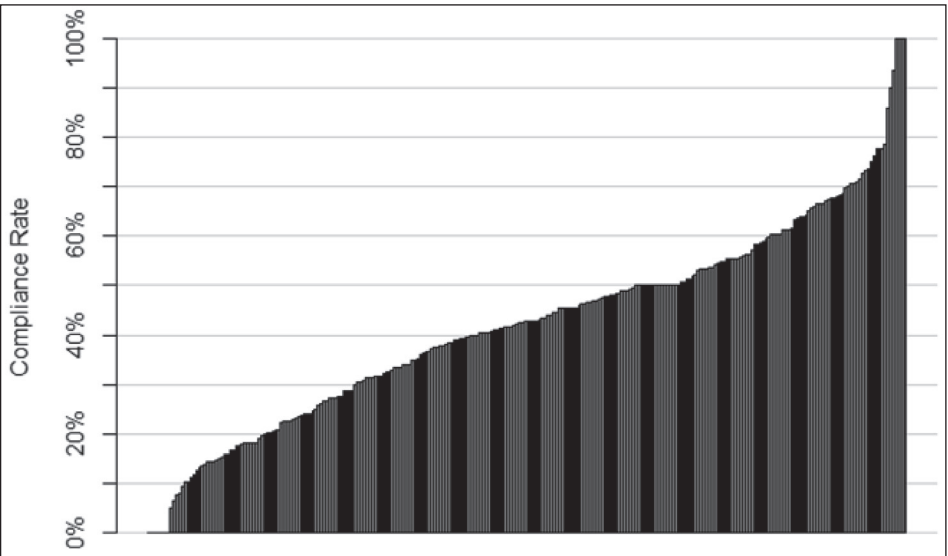
Figure 3: Compliance with stress test recommendation 6 by centre in EVAR.

Of all EVAR, 95.8% were performed in centres equalling or exceeding the volume threshold of 10 EVAR cases per year. However, only 78% of centres in VQI met this volume threshold. Of all open abdominal aortic aneurysms0, 68.3% were performed in centres equalling or exceeding the volume threshold of 10 open abdominal aortic aneurysm cases/year. However, only 51% of centres in VQI met this volume threshold. After multivariable logistic regression, there was no correlation between outcomes and compliance with volume in the EVAR registry. Patients treated at hospitals compliant with the open abdominal aortic aneurysm volume guideline had improved in-hospital survival (OR 0.59, 95% CI 0.41 to 0.86; p=0.005) and marginally improved survival at one year (OR 0.77, 95% CI 0.58 to 1.01; p=0.061).

The volume–outcome conundrum continues. Most EVAR procedures were performed in volume-compliant centres but one in five centres performing EVAR did fewer than 10 cases per year. Compliance with the volume standards for open abdominal aortic aneurysm was associated with improved survival but compliance with the volume threshold was poorer.

Recommendation 8

"We suggest a retroperitoneal exposure or a transperitoneal approach with a transverse abdominal incision for patients with significant pulmonary disease requiring open surgical repair (level of evidence 2C)."

The guidelines do not define significant pulmonary disease, so we defined it as patients on home oxygen (n=300). Compliance with the guideline for patients on home oxygen was 29%. On univariate analysis, there was a trend towards decreased inpatient mortality in patients who received a retroperitoneal incision: 12.6% vs. 19.2% (p=0.18). There was no association with respiratory complications.

While a retroperitoneal incision for severe pulmonary disease had no statistically significant impact on outcomes (p=0.18), there was a >50% increase in mortality in non-compliant cases. The lack of statistical significance may be due to a type 2 statistical error. The observed trend suggests there may be value to a retroperitoneal incision for patients with severe pulmonary disease and warrants further investigation.

Improving care with professional society guidelines

As measured in the VQI registries, compliance with select SVS abdominal aortic aneurysm guidelines varied from 0 to 100%.[9] Compliance with guidelines with high levels of evidence was associated with improved outcomes, which is to be expected based on the quality of evidence. However, there are many centres with compliance rates below 50% for these high-quality guidelines. Antibiotic administration and cell salvage are process measures that make a difference and should be readily achievable so there is good reason to adhere to them.

This is not the first effort to use a registry to monitor compliance,[17] and associate compliance with improved outcomes.[18] The emphasis of this chapter is to highlight the role of a clinical registry. The value of any clinical registry is contingent on improving care. There is a business maxim that "If you can't measure it, you can't improve it" attributed to W Edwards Deming.[19] Providers and centres should be aware of their compliance with guidelines and they should also be aware of their

outcomes. Participation in the VQI or a clinical registry provides benchmarking reports to allow providers and centres to focus their quality improvement efforts.

Compliance with clinical practice guidelines is intended to reduce variation and improve care. Currently, there are few incentives to follow or adopt practice guidelines other than individual provider efforts to adopt best practices. There may be linkage to payment in the future. The Centers for Medicare and Medicaid Services has developed a programme for provider-led entities to develop appropriate use criteria to encourage best practices. The SVS is currently developing appropriate use criteria that could be used to encourage adoption of clinical practice guidelines. Additionally, the SVS is developing a verification programme that may use clinical practice guidelines as certification checkpoints.

Conclusion

The impact of abdominal aortic aneurysm guideline compliance as measured in the VQI registries is dependent on the grade of the evidence. Compliance with guidelines is supported and encouraged. Registry assessment may confirm the value of a clinical practice guideline and may help inform guideline writing committees. The corollary is also true: the guidelines may be used to inform registry writing committees regarding selection of variables. Participation in a clinical registry allows providers and centres to have an objective assessment of their performance and compliance with guidelines. Provider and centre reports from the registry may be used as a focus for quality improvement efforts.

Summary

- Overall compliance with SVS abdominal aortic aneurysm guidelines was high and associated with improved outcomes.

- There was significant variation in the degree of compliance even with guidelines with high levels of evidence.

- Centres and providers should be aware of their compliance and their outcomes.

- Low compliance can be used as a focus for quality improvement.

- Participation in a clinical registry, such as VQI, allows easy assessment of compliance and performance

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Early results from the AAA Get Fit Trial

A Haque and C McCollum

Introduction

Abdominal aortic aneurysm affects up to 8% of men aged over 65 and accounts for 5% of all sudden deaths.[1,2] Mortality from abdominal aortic aneurysm is mainly related to rupture, and the aim must be to repair the aneurysm before this occurs. Pivotal to this is early detection, which is usually either incidental or through a national abdominal aortic aneurysm screening programme. As small aneurysms are much more common than those >5.5cm in diameter requiring repair, most patients are managed with surveillance in which they will have regular assessment until their aneurysm grows to a size necessitating repair. Despite recent advances in repair technology, elective repair still carries a significant perioperative mortality of 2.6% for open surgery and 0.6% for endovascular aneurysm repair (EVAR).[3] There is also an in-hospital morbidity approaching 25% that impairs quality of life and adds to the already substantial procedural cost of more than £10,000.[4,5] The risk of surgery can be determined through cardiopulmonary exercise testing with those parameters that predict outcome being well defined.[6] Improving these parameters through exercise training should reduce perioperative risk and increase quality of life.

Cardiopulmonary exercise testing in AAA

Most UK vascular centres employ cardiopulmonary exercise testing in their preoperative assessment of patients requiring elective abdominal aortic aneurysm repair. The clinically important variables include induced myocardial ischaemia, oxygen uptake at maximal effort (peak VO_2), oxygen uptake at the anaerobic threshold, and the ventilatory equivalent ratio for carbon dioxide at anaerobic threshold (VE/VCO2). The Manchester Cardiopulmonary Exercise Testing Study Group performed the largest studies worldwide demonstrating that a peak VO2 <15ml/kg/minute, oxygen uptake at the anaerobic threshold <10.2ml/kg/minute and VE/VCO2>42 all convey increased 30-day and 90-day operative risk.[7] Long-term survival could be predicted independently by peak VO_2, VE/VCO2, and the total number of abnormal cardiopulmonary exercise testing variables for each patient. These important variables also predicted morbidity and length of stay.

These parameters can be improved by exercise training, which also has also been shown to reduce cardiovascular risk and improve quality of life.[8,9] It is becoming widely accepted that reducing perioperative risk through exercise training should be an important step in the management of the patient with abdominal aortic aneurysm but there are currently no well-defined strategies to achieve this.[10]

Exercise training has been shown to be safe in abdominal aortic aneurysm patients and does not influence growth rate or increase cardiovascular risk.[11,12]

Despite this, the optimal type and duration of exercise training required to improve cardiopulmonary exercise testing measures of fitness in elderly patients with cardiovascular disease remains unknown, with published trials impaired by poor compliance, low numbers and methodological flaws.[10,13–15]

Exercise for abdominal aortic aneurysm patients

Exercise training could be initiated either during the time that the patient is under surveillance or when they reach the threshold for repair. Leaving initiating exercise until a repair is required unnecessarily enforces a limit on the time that is available to improve fitness and fails to address the increased risk of cardiovascular events in patients with small aneurysms.[9] Exercise training should ideally begin as soon as patients enter surveillance, allowing the opportunity to reduce all-cause mortality. This should also achieve improvements in quality of life and general well-being.

Although there has been little research on exercise training in the abdominal aortic aneurysm population, studies in other similar patient groups informs us that it should incorporate warm-up, stretching, resistance, cardiovascular exercises and cool-down exercises, and be at a moderate intensity, which allows improvements in fitness to be maintained while being realistic for an elderly person.[16,17]

Older adults should aim to exercise in this way for at least 150 minutes per week and there is good evidence to support an overall duration of training of at least 20 weeks.[18] This time, and more, is available to abdominal aortic aneurysm patients in surveillance because repair may not be indicated for months or even years. Despite this, the longest published exercise programme is only 12 weeks.[14]

The key to establishing exercise training in this population is that it must be acceptable to both the patient and the organisation. A patient and public involvement group advised they would prefer to exercise either at home or within their local community rather than at a hospital; a desire that is echoed elsewhere in the literature.[19] The advantages are that patients are able to do exercise at their own convenience, which should improve compliance and reduces the burden on the health organisation.[20] Exercise training programmes designed in this way should be easily scalable and likely more cost-effective.

The AAA Get Fit Trial

This chapter describes the results of the AAA Get Fit trial, which was a randomised controlled trial of patient-directed exercise in patients with abdominal aortic aneurysms. The study hypothesis was that patient-directed, community exercise training, at home or in a gym, would achieve greater improvements in fitness in elderly aneurysm patients than the advice currently given in standard clinical practice. It was also hypothesised that fitness would continue to improve throughout the duration of the programme, although this may plateau over time, and that fitness improvements would be maintained after the programme has finished. Exercise training may also reduce cardiovascular risk while achieving improved habitual activity levels and quality of life.

Power calculation

Increasing peak VO2 (our primary outcome measure) by 1.5ml/kg/minute equates to a reduction in perioperative mortality of up to 24%.[21] Using this as the primary

outcome measure and allowing for a 35% attrition rate, a total of 56 patients (28 in each group), achieves an 80% power of achieving a result statistically significant at the 5% level.

Methods

Consecutive eligible patients attending the abdominal aortic aneurysm surveillance clinics at Manchester University NHS Foundation Trust Wythenshawe Hospital were reviewed for eligibility before being given written and verbal information about the study. Interested patients were there invited to baseline assessment, which included:

- Discussion of the research protocol and consent in writing
- Detailed past medical and drug history
- Clinical examination including anthropometric measures of cardiovascular risk[22]
- Cardiopulmonary exercise testing as previously described by the Manchester Cardiopulmonary Exercise Testing Study Group[7]
- Venous blood sample for biomarkers of cardiovascular risk[23–25]
- A validated health-related quality of life questionnaire (Medical Outcomes Study SF-36v2 HRQoL).

Inclusion criteria for recruitment were:

- Men with abdominal aortic aneurysm ≥3.0 and <5.0cm, and women with abdominal aortic aneurysm ≥3.0 and <4.5cm
- Potentially fit for elective abdominal aortic aneurysm repair (open or endovascular aneurysm repair)
- Aged 60–85 years inclusive
- Willing and able to complete cardiopulmonary exercise testing and engage in gym and/or home-based exercise training.

Exclusion criteria for recruitment were:

- Patients deemed not fit for elective abdominal aortic aneurysm repair (open or endovascular aneurysm repair) even following exercise training and weight loss
- Unable or unwilling to undertake cardiopulmonary exercise testing or exercise training
- Severe liver disease (international normalised ratio >2, serum albumin <3.0g/dL, bilirubin >50µmol/L)
- Unstable angina occurring more than once daily, angina that is increasing in frequency or precipitated by less exertion, angina at rest or of recent onset (<2 months)
- Uncontrolled (heart rate >90 beats/minute) atrial fibrillation or other arrhythmia; untreated paroxysmal atrial fibrillation
- Moderate or severe aortic valve stenosis (peak systolic pressure gradient >40mmHg or with an aortic valve area <1cm2)
- Pericarditis or myocarditis within the previous six months
- >2mm ST depression during the initial cardiopulmonary exercise testing. Any such patient will be referred to a cardiologist
- Diagnosis or treatment for a malignancy, other than basal cell carcinoma, within the previous 12 months.

Randomisation and allocation

A total of 56 patients were randomly allocated (one-to-one ratio) to either standard clinical care or community exercise training using computer randomisation with minimisation to stratify for:

- Age <75 years or ≥75 years
- Sex
- Body mass index (<30 or ≥30)
- Baseline peak VO2 (<15ml/kg/minute or ≥15ml/kg/minute).

Patients randomised to the study intervention attended an induction at a local gym where they were shown how to perform a bespoke exercise programme designed for elderly patients, consisting of warm-up, aerobic, resistance, stretching and cool-down exercises. Modified exercises to enable the participant to perform the programme at home were also demonstrated. Each patient was then instructed to perform the exercises at a moderate intensity, based on a score of 12–14 on the Borg's perceived exertion scale (which was also provided), spread out over the week for a total of at least 150 minutes of exercise per week. They were also given a free gym membership for 24 weeks, although they were able to choose whether to perform the exercises in the gym or in their own home.

All patients will be given clear verbal advice on diet, regular exercise, weight loss and smoking where applicable, based on current NHS guidance for patients with abdominal aortic aneurysm.[26]

Follow-up

Follow-up at 8, 16, 24 and 36 weeks included cardiopulmonary exercise testing, anthropometric and biomarkers of cardiovascular risk, health-related quality of life and physical activity levels.

Early results
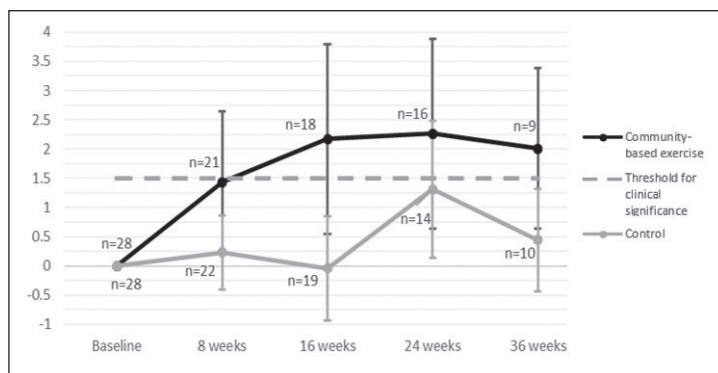
Figure 1: Mean (95% CI) change in peak VO2 (ml/kg/minute) from baseline comparing patients in the community-based exercise group with control patients, indicating a statistically significant result at all time points in the intervention group but only at 24 weeks in the control group. Increase in peak VO2 exceeding the 1.5ml/kg/minute clinically significant change assumed in our power calculation was achieved in the intervention group at 16 weeks and has so far been maintained to 36 weeks, indicating that we are likely to achieve both clinical and statistical significance when our target population of 56 patients have completed the study.

All 56 patients have been recruited with data complete to 16 weeks (n=37), with 20 patients completing the study to 36 weeks so far.

Baseline demographics were evenly distributed with 24 men and four women in each treatment group. Mean body mass index was 27.8kg/m2 (standard deviation [SD] 4.1) in the exercise patients and 27.6kg/m2 (SD 3.1) in controls, with an average age of 73.3 years (SD 5.3) in the exercise group compared with 72.4 years (SD 6.2) in the control group. Baseline mean peak VO_2 was 15.2ml/kg/minute (SD 3.8) in the exercise group and 18.1ml/kg/minute (SD 5.9) in the control group.

As these are early results, only the primary outcome measure, peak VO_2 and for interest, health-related quality of life (HRQoL) are reported.

Peak VO_2

Peak VO_2 in controls increased from baseline by a mean 0.23ml/kg/minute (95% confidence interval [CI] –0.4 to 0.86) at eight weeks, –0.04ml/kg/minute (95% CI –0.93 to 0.85) at 16 weeks, 1.31ml/kg/minute (95% CI 0.14 to 2.48) at 24 weeks and 0.44ml/kg/minute (95% CI –0.43 to 1.31) at 36 weeks, only reaching statistical significance at 16 weeks. However, in the exercise patients, the increase in peak VO_2 was 1.43ml/kg/minute (95% CI 0.22 to 2.64), 2.17ml/kg/minute (95% CI 0.55 to 3.79), 2.26ml/kg/minute (95% CI 0.64 to 3.88) and 2.01ml/kg/minute (95% CI 0.63 to 3.39) at the same time intervals. This was statistically significant at each follow-up (Figure 1).

Health-related quality of life

HRQoL was scored using the Medical Outcomes Study SF-36v2 HRQoL questionnaire, which included both a physical component score and mental component score.

HRQoL physical component score

HRQoL physical component score in controls changed from baseline by a mean of –0.34 (95% CI –3.27 to 2.60) at eight weeks, –0.51 (95% CI –3.75 to 2.73) at 16 weeks, –0.16 (95% CI –2.78 to 2.45) at 24 weeks, and –1.10 (95% CI –4.32 to 2.12) at 36 weeks. In the exercise patients, the increase in HRQoL physical
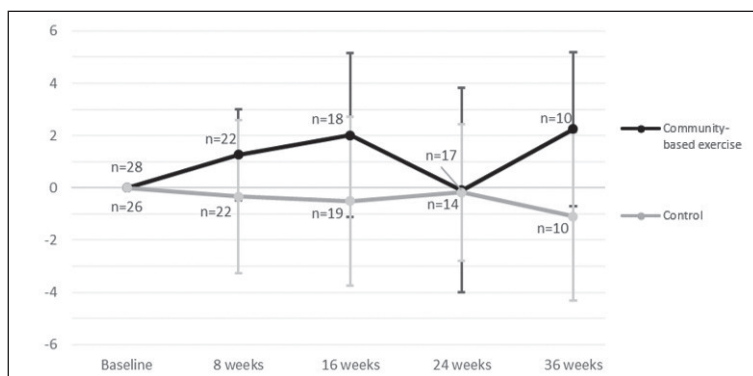
Figure 2: Mean (95% CI) change in health-related quality of life physical component score comparing patients performing community-based exercise with controls, showing an overall increase in health-related quality of life physical component score by 36 weeks in the exercise group but a slight decrease in the control group over the same period.
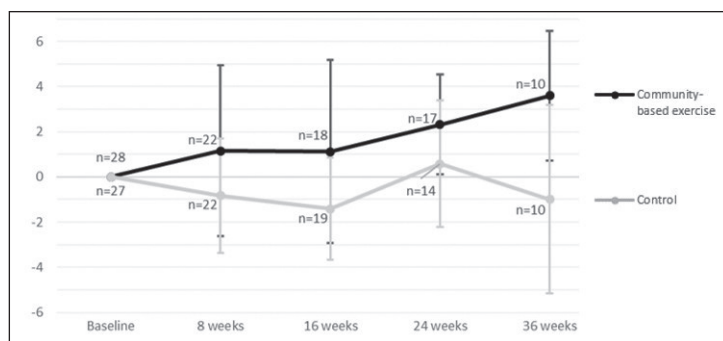
Figure 3: Mean (95% CI) change in health-related quality of life mental component score comparing patients performing community-based exercise with controls, showing a statistically significant improvement in health-related quality of life mental component score from 24 weeks onwards in the community-based exercise group

component score was 1.27 (95% CI –0.47 to 3.01), 2.02 (95% CI –1.12 to 5.16), –0.09 (95% CI –3.99 to 3.81) and 2.26 (95% CI –0.69 to 5.20) at the same time intervals (Figure 2). None of these results reached statistical significance at any time interval.

HRQoL mental component score
HRQoL mental component score in control patients increased from baseline by a mean of –0.83 (95% CI –3.36 to 1.70) at eight weeks, –1.41 (95% CI –3.67 to 0.86) at 16 weeks, 0.58 (95% CI –2.23 to 3.39) at 24 weeks and –0.97 (95% CI –5.15 to 3.17) at 36 weeks, with no significant change at any time interval. However, in the exercise patients, there was a steady increase in the HRQoL mental component score of 1.16 (95% CI –2.63 to 4.94), 1.12 (95% CI –2.94 to 5.19), 2.31 (95% CI 0.10 to 4.52) and 3.60 (95% CI 0.73 to 6.46) at the same time intervals, reaching statistical significance at 24 weeks that was maintained to 36 weeks (Figure 3).

Discussion
The results suggest that this exercise strategy for abdominal aortic aneurysm patients is likely to achieve statistically and clinically significant improvements in peak VO_2. The way the improvements in fitness continued up to 24 weeks and are maintained by 36 weeks justifies the longer duration of exercise programme.

It is interesting to note that there was a statistically, and near clinically, significant improvement of 1.31ml/kg/minute in peak VO_2 in the controls at 24 weeks. This could be attributed to the control group being subjected to focused advice, four follow-up appointments with a clinician and repeated objective fitness testing, which was required to allow meaningful comparison between control and intervention but is clearly far different from current standard practice. Indeed, participation in the study seemed to motivate the control patients to take up exercise, with more than half of the 28 control patients making an exercise-focused behaviour change such as joining a gym or buying home equipment.

The mental component of HRQoL improved significantly by 24 weeks and was maintained at 36 weeks in the exercise group but had declined in the control group by the end time point. The change in the physical component of HRQoL did not reach statistical significance in either group, although there was an improving trend

in the exercise group, which may well reach statistical significance when all patients have completed follow-up, compared with an overall decrease in this component score in controls. The physical component score is calculated based on an individual's subjective perception of their ability, whereas the mental component is calculated based on their perception of how their health affects their general mental well-being. The difference in improvements between these components in the exercise group could be explained by the individual having increased awareness of their physical deficiencies, which they were previously oblivious to, once they began exercising and so downscoring this component despite mentally feeling healthier.

Conclusion

These early results suggest that a patient-directed, community-based exercise programme may produce long-term improvements in mortality-related cardiopulmonary exercise testing parameters of fitness and health-related quality of life compared with current standard care. If these results are confirmed on completion of the study, they will provide the evidence base needed to design definitive clinical trials on exercise training designed to reduce all-cause mortality.

Summary

- Elective abdominal aortic aneurysm repair carries significant perioperative risk.

- Peak VO_2 oxygen uptake at the anaerobic threshold and $VECO_2$ at the anaerobic threshold, measured by cardiopulmonary exercise testing, predicts this risk and long-term survival.

- Exercise training to improve these cardiopulmonary exercise testing variables should reduce risk.

- The AAA Get Fit Trial is a randomised controlled trial of community-based patient-directed exercise over 24 weeks to determine the optimal exercise training and its duration for elderly patients with arterial disease.

- On interim analysis, there was a clinically and statistically significant improvement in peak VO_2 in the exercise group at all follow-up intervals, which was not seen in the control group.

- There was a significant improvement in the mental component of health-related quality of life in the exercise group at 24 and 36 weeks, which was not seen in the control group.

- These results will inform the design of a definitive multicentre randomised controlled trial on exercise training in abdominal aortic aneurysm surveillance patients with a primary outcome of all-cause mortality and secondary outcomes of aortic mortality, cardiovascular risk and quality of life.

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Cardiac risk assessment in patients with AAA: A fundamental tool for adequate selection between open and endo repair

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Introduction

Cardiovascular and pulmonary diseases are the major causes of mortality and morbidity associated with abdominal aortic aneurysm repair, with myocardial infarction, arrhythmias and heart failure the most common complications. Furthermore, mortality from cardiovascular events is high, with an overall five-year survival rate after intervention of less than 70%. [1,2]

This chapter describes a systematic and standardised preoperative cardiac evaluation and an analysis of its efficacy in reducing postoperative cardiac morbidity and mortality.

Patient selection

Between January 2008 and December 2018, 851 consecutive elective infrarenal aneurysm repairs were carried out at our centre. A total of 421 patients underwent open surgical repair and 432 patients underwent endovascular aneurysm repair (EVAR). Only patients with infrarenal aneurysms undergoing elective repair were included in the current analysis.

Patients undergoing the procedure before 2012 received a preoperative cardiologic evaluation according to the American Heart Association and European Society of Cardiology/European Society of Anaesthesiology guidelines; patients undergoing the procedure after 2012 underwent a routine preoperative cardiology consultation.[3,4] Therefore, patients in open surgical repair and EVAR groups were each further divided in two groups. Group A included patients undergoing the procedure between January 2012 and December 2018, and group B included interventions between January 2008 and December 2011. In the open surgical repair group, there were 258 patients in group A (61%) and 163 patients in group B (39%); in the EVAR group, there were 261 patients in group A (60%) and 171 patients in group B (40%).

Statistical analysis

Continuous data are expressed as mean ± standard deviation and were compared using a Student's t-test or Wilcoxon rank-sum test. Categorical data are expressed as number and percentage and were compared using a Chi-squared or Fisher's exact test as appropriate.

Method

Considering the incidence of cardiac complications after aneurysm surgery,[5] patients undergoing repair at the authors' centre (University of Padova) have all been evaluated preoperatively by the same cardiologist since January 2012.

The basic cardiology evaluation includes a medical history, physical examination, ECG and rest echocardiography. An important goal when taking a history is to define the patient's functional capacity and the metabolic equivalents scale rating.[6] This information is used by the cardiologist to determine whether or not to proceed with second-level examinations.

Patients who are eligible for an open surgical repair often then undergo a second-level examination, such as a stress test, or coronary angiography. Stress tests consist of dobutamine stress echocardiograms or myocardial perfusion scintigraphy tests. If the stress test is positive, the patient will be recommended for coronary angiography.

Patients with a contraindication to stress testing (e.g. severe aortic stenosis or severe arrhythmias) or with cardiac symptoms, or patients for whom a stress test would not be productive, are recommended to undergo coronary angiography. Finally, a Holter ECG is requested in the case of suspected arrhythmia.

Patients who are eligible for EVAR undergo the same initial basic cardiology evaluation as described above, but whether they need a second-level examination or coronary angiography depends on the combination of several factors: metabolic equivalents evaluation and a pre-existent cardiac pathology, such as congestive heart failure (including compensated heart failure), arrhythmia or a previous myocardial infarction. If the patient has metabolic equivalents ≥4 and a normal left ventricular ejection fraction, no further investigations are recommended. If the patient has metabolic equivalents <4, initial cardiac symptoms or several risk factors such as diabetes, a stress test is proposed. Again, if stress testing is contraindicated or it would not be useful, a coronary angiography is directly proposed.

Patients who have coronary angiography showing a coronary stenosis are discussed in a multidisciplinary heart team with the cardiologist, the cardiac surgeon and the vascular surgeon to determine the best choice of treatment.

This extended cardiologic evaluation enables the patient to be assigned to the lower-risk intervention. In fact, if the patient still does not have an acceptable surgical risk at the end of the overall evaluation and after the treatment of active cardiac conditions, an endovascular treatment can be proposed if there is a suitability assessed by anatomical criteria. Figure 1 shows the cardiac flowchart used to decide which procedure is best for each patient.

Patients who had the procedure before 2012 were not systematically evaluated in this fashion; instead, they were evaluated by an anaesthesiologist and risk stratification was based on the American Heart Association and European Society of Cardiology/European Society of Anesthesiology guidelines.[3,4] Patients with a functional capacity with metabolic equivalents ≥4 were sent for surgery without further investigation,
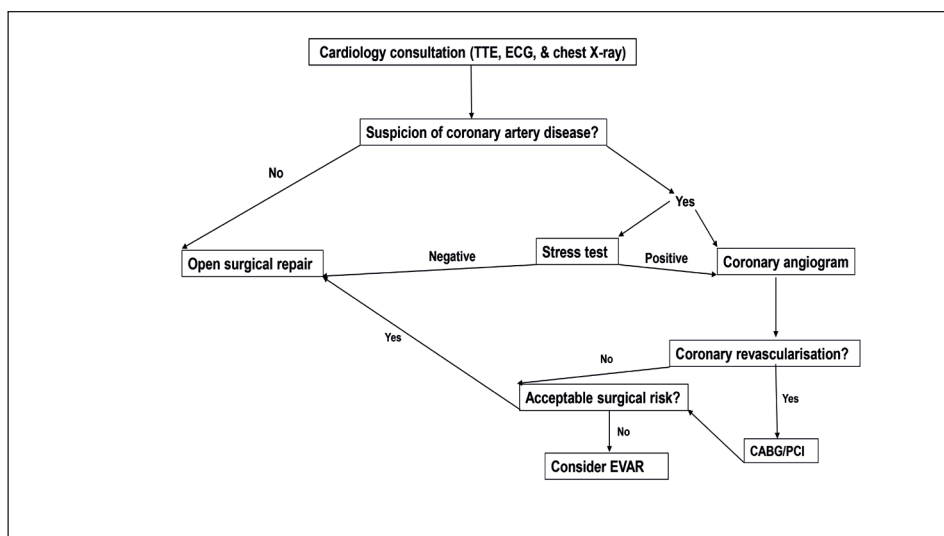
Figure 1: Preoperative cardiology flowchart in patients eligible for open surgical repair.

regardless of whether the procedure was open or endovascular, unless they presented with three or more clinical risk factors, in which case they were referred to a cardiologist. Further instrumental tests and a cardiology evaluation were required for patients with signs or symptoms of an active and/or unstable cardiac disease: angina pectoris, heart failure, significant cardiac arrhythmia, symptomatic valvular heart disease, myocardial infarction within the past 30 days, or residual myocardial ischaemia.

Results

Groups A and B were compared in each cohort (open surgical repair and EVAR) to assess the usefulness of the systematic cardiac flowchart evaluation.

Open surgical repair

In the open surgical repair group, the mean age of patients was 69±7.45 years. Preoperative data showed a statistically significant difference between the two groups in terms of prevalence of dyslipidaemia (60% for group A vs. 31% for group B; p<0.0001) and previous myocardial revascularisation with percutaneous transluminal coronary angioplasty (16% for group A vs. 8% for group B; p=0.01). The Society for Vascular Surgery (SVS) medical comorbidity grading system (SVS score)[7] was calculated for each patient.[7] The two groups were significantly different for the SVS cardiac score (1.17±0.92 for group A vs. 0.68±0.91 for group B; p<0.0001), showing that patients undergoing the procedure between 2012 and 2018 were more likely to have had a previous cardiac disease that may or may not have been associated with a myocardial revascularisation and must be considered higher-risk patients.

Patients in group B only underwent rest echocardiography and did not receive a second-level cardiac test, such a stress test or a coronary angiography.

In group A, 128 patients were subjected to a stress test and 39 patients to a coronary angiography. Of those who underwent coronary angiography, 14 patients (35.9%) underwent preoperative percutaneous transluminal coronary angioplasty

and three patients (7.7%) underwent coronary artery bypass graft surgery. Finally, Holter ECG was performed on 7% of patients in group A.

Analysis of the open surgical repair cohort revealed no significant between-group difference in the overall rate of cardiac complications (p=0.11). The overall rate of early (<30 days) mortality was 0.48%.

EVAR

Of 432 patients who underwent EVAR during the study period, 261 were in group A and 171 were in group B. The mean age was 75±7.47 years. The EVAR cohort was relatively homogeneous and only differed significantly in terms of the incidence of hypertension (88% for group A vs. 80% for group B; p=0.02). Mean SVS cardiac score was slightly higher in group A (1.03±0.97) than in group B (0.87±0.95), but this difference was not significant (p=0.11).

A stress test was performed in 43 patients in group A and 22 patients in group B. A total of 26 patients underwent coronary angiography in group A and five did so in group B (p=0.006). In group A, 13 patients underwent preoperative percutaneous transluminal coronary angioplasty, one patient underwent coronary artery bypass grafting (CABG) prior to repair, and one patient underwent CABG after EVAR. In group B, only one patient underwent preoperative percutaneous transluminal coronary angioplasty.

Analysis of the EVAR cohort revealed no significant between-group difference in the overall rate of cardiac complications (p=0.82). There were no specific between-group differences in acute heart failure or arrhythmia, whereas there was a difference in postoperative troponin elevation (p=0.03). In group A, only one patient exhibited elevated troponin values without ECG signs or clinical signs of recent myocardial ischaemia. This patient had undergone preoperative percutaneous transluminal coronary angioplasty before EVAR, at which point they exhibited only a slight elevation in troponin. Accordingly, it was elected not to perform further examinations. In contrast, five patients in group B had elevated troponin values post-procedure. No further examinations were performed in two patients, one patient had an ECG (normal result), one patient underwent a stress test (positive, but the patient was subsequently lost to follow-up), and one patient was advised to undergo further examination after discharge. Troponin elevation was not considered as a valuable result, since troponin was rarely measured in asymptomatic patients before 2012, unlike in group A where troponin was systematically measured in patients with a history of cardiac disease.

Discussion

Since its first report in 1951, abdominal aortic aneurysm repair has evolved enormously and current techniques permit the treatment of even high-risk patients. Repair is increasingly important, given its role in prolonging life expectancy, and a growing population of older patients worldwide, whose care poses important challenges for vascular surgeons.

Current SVS guidelines recommend a preoperative cardiac evaluation where key points are metabolic equivalents score and the presence of a pre-existing cardiac condition.[2] The metabolic equivalents scale categorises a patient's functional capacity based on score as poor (<4), moderate (4–7), good (7–10), or excellent (>10).

In the case of satisfactory functional capacity (metabolic equivalents ≥4), the patient can be recommended for intervention, with a simple adjustment in medical therapy, for example, the introduction of a beta-blocker to address a coexisting risk factor such as mild angina pectoris, previous myocardial infarction, compensated or previous congestive heart failure, diabetes mellitus or chronic kidney injury.

For patients with metabolic equivalents <4, non-invasive testing may be considered if the outcome has potential to influence the management of aneurysm repair.

Coronary angiography (alongside adjustments in medical therapy) is indicated in cases of unstable coronary syndrome (unstable angina or myocardial infarction within the past month), decompensated congestive heart failure, severe valvular disease, and significant arrhythmias. In contrast, all patients should undergo 12-lead ECG and, when indicated (e.g. history of congestive heart failure and unknown origin of dyspnoea), echocardiography before surgery. As a rule, a more extensive cardiac evaluation is suggested in patients with an active cardiac condition.[3]

With regard to open repair, the data analysis did not show a significant reduction in postoperative cardiac complications in patients undergoing the procedure after the implementation of the systematic cardiac evaluation in 2012; however, patients having the procedure after 2012 had a significantly higher average SVS cardiac score, indicating that they were predisposed to a higher rate of cardiac complications in the postoperative period. Consequently, we can theorise that performing a routine cardiac evaluation and, as necessary, second-level examinations and myocardial revascularisation, enables high cardiac risk interventions with an acceptable rate of postoperative cardiac complications.

In contrast, the EVAR cohort was homogeneous for cardiac risk. A statistically higher number of coronary angiographies was performed in group A compared with group B. Analysis of postoperative cardiac complications showed a significantly lower incidence of troponin elevation in patients undergoing procedures after 2012. However, this was not considered to be a valuable result, because before
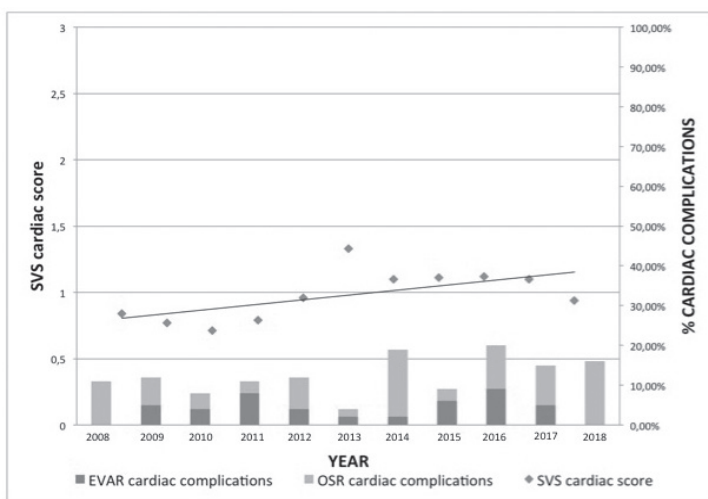
Figure 2: The figure compares the trend of the overall SVS cardiac score during the study period to the total cardiac complications in each group (open surgical repair and EVAR). Whereas the score increases, the percentage of cardiac complications remains stable.

2012 troponin was not routinely measured in asymptomatic patients with a history of cardiac disease.

Finally, the importance of postoperative cardiologic follow-up should be emphasised. In the presence of signs or symptoms of a cardiac event such as troponin elevation, chest pain, dyspnoea or new ECG findings, a postoperative cardiac consultation can improve follow-up of the patient and ultimately reduce late cardiac-related morbidity and mortality.

Conclusion

Preoperative cardiac evaluation is important in patients undergoing significant non-cardiac surgery. In the authors' experience, a systematic and standardised cardiologic visit, the appropriate performance of second-level examinations such as stress tests and coronary angiography, and appropriate patient selection for each type of treatment can reduce the rate of cardiac complications after both EVAR and open surgical abdominal aortic aneurysm repair. Future research should confirm the utility and patient benefit of more extensive cardiac examination as part of the preoperative evaluation for abdominal aortic aneurysm repair.

Summary

- Cardiovascular and pulmonary postoperative complications are major causes of morbidity and mortality following abdominal aortic aneurysm repair.

- Use of a systematic cardiologic flowchart evaluation allows patients with high SVS cardiac scores to undergo open abdominal aortic aneurysm repair with an acceptable rate of complications.

- Performing additional preoperative cardiologic exams, such as stress testing and coronary angiography, should be considered even in patients eligible for EVAR.

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Open conversion of failed EVAR is the new training ground for open aortic surgery

A Mohapatra, N Liang and MS Makaroun

Introduction

Abdominal aortic aneurysm, once treated exclusively by open surgical repair, is now primarily treated by endovascular aneurysm repair (EVAR). National and international vascular surgery conferences are typically headlined with reports of new and innovative endovascular solutions, designed to overcome limitations of existing endografts and to eliminate the need for open repair in patients with high risk anatomical features. Across the world, EVAR has become the most attractive treatment option for abdominal aortic aneurysms, though the recent draft UK National Institute for Health and Care Excellence (NICE) recommendations encouraging open repair are a notable exception.

Current indications for open aneurysm repair over EVAR are rapidly evolving. In some practice settings, open repair is considered to be the optimal therapy for younger, fitter patients with low perioperative risk and long life expectancy. In some patients with anatomical features precluding EVAR or making it higher risk—such as stenotic access vessels, an infrarenal seal zone that is short, wide, angulated, calcified, or containing mural thrombus, or an aneurysm involving the renal/visceral segment—open repair is more strongly considered. In addition to these traditional roles, late conversion of failed EVAR is an operation that is rapidly expanding into one of the most common indications for open aneurysm repair.

Diminishing role of primary open aneurysm repair

As EVAR becomes more widespread and able to handle more anatomical complexity, open abdominal aneurysm repair is becoming less common. Suckow *et al* examined Medicare trends over a decade and found a 76% decline in open repairs in the US between 2003 and 2013, with a concomitant rise in both standard EVAR and fenestrated/branched EVAR.[1] Unsuitable anatomy for EVAR has long been an indication for open repair, but this is a shrinking segment of the population. For short necks, for example, commercial devices including the Zenith Fenestrated (Cook Medical) and the Endurant with EndoAnchors (Medtronic) now carry indications to treat patients with an infrarenal neck as short as 4mm. Off-label use has been prevalent since the early days of EVAR. Schanzer *et al* have previously shown that a large number of EVAR devices are placed outside their specific indications for use, and this factor alone can predict late complications.[2] Newer techniques such as parallel grafting and physician-modified endografts further expand the ability to provide off-label solutions in patients who would previously have undergone open repair. While there is ongoing debate regarding
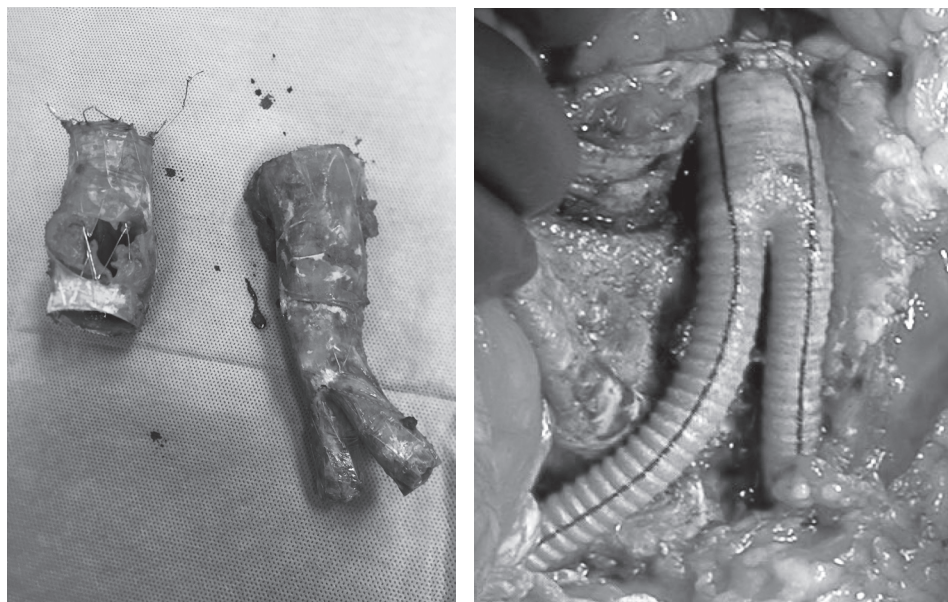
Figure 1: Total graft explantation and aorto-bi-iliac reconstruction.

the long-term durability of such solutions in patients with unfavourable anatomy, there is no question that the existence of such therapies will continue to erode the total volume of primary open repairs performed.

Young, fit patients may also benefit from open repair, owing to lower perioperative risk and greater life expectancy than older patients with greater comorbidity burden. Our group has previously shown from Vascular Quality Initiative data that younger patients (those under age 65 or 70) have very low perioperative mortality with both open repair (0.9%) and EVAR (0.2%; p<0.001) and that the early survival difference is eliminated within one year.[3] Long-term follow-up outcomes from the EVAR-1 study showed a survival benefit at 15 years after open abdominal aneurysm repair compared to those undergoing EVAR, suggesting that younger patients should be more strongly considered for open repair.[4] In our experience, however, this is often not the case, and even exceptionally young healthy patients are offered EVAR as a first-line therapy.

The end result of the evolution in treatment paradigms for abdominal aneurysm repair is that today's vascular surgeons and their trainees perform very few open repairs. Dua *et al* examined trends in open repair volume in teaching institutions. A 2014 study by the group projected that vascular surgery trainees in the US would graduate with 10 open repairs in 2015 and five in 2020—far fewer than those performed by their predecessors.[5] The group then updated this projection in 2017 to account for the impact of fenestrated/branched EVAR, and concluded that by 2020 the typical vascular trainee will complete only two to three open abdominal aneurysm repairs before graduation.[6] While this shortfall will be variable across training programmes, it is clear that many trainees will complete residency or fellowship not being comfortable performing open aortic procedures independently.

Open conversion: Increasing role, indications, and technical considerations

Contrary to primary aortic repair, late open conversion after a failed EVAR is becoming increasingly common worldwide. We have described our own institutional experience with conversion, noting a large increase in annual volume between 2002 and 2017, with 42% of cases performed in the last three years of the 16-year period.[7] In the first nine months of 2019 at our institution, 34% of all open aortic cases were late conversions, more common than any other abdominal vascular operation performed (including primary open repair and aortobifemoral bypass for occlusive disease).

We attribute this increase in open conversion volume largely to ineffective EVAR performed in patients with hostile anatomy and to ineffective secondary interventions for endoleaks. The most common indications for open conversion include aortic rupture, endograft infection, or an endoleak not amenable to an endovascular intervention. Type 1A and 3 endoleaks often fall into the latter category. Additionally, we have noted a rise in our practice in conversion for recalcitrant type 2 endoleaks with ongoing sac expansion. Type 2 endoleaks, though often thought to be benign, can indeed lead to sac expansion.[8] We have shown from our own institutional experience that many type 2 endoleaks, especially those requiring multiple secondary interventions or those with rapid sac enlargement, are later found to be occult type 1A or type 3 endoleaks.[9] In our practice, we have found an increasing role for open conversion for late type 2 endoleaks with sac expansion despite multiple attempts at coil embolisation.

There are a number of technical considerations that make open conversion more challenging for the surgeon and have greater mortality for the patient. A clearly defined operative plan is crucial to a safe and successful repair. Supracoeliac aortic control is often necessitated by suprarenal endograft fixation even when an infrarenal repair is being performed.[10] The endograft should be explanted in its
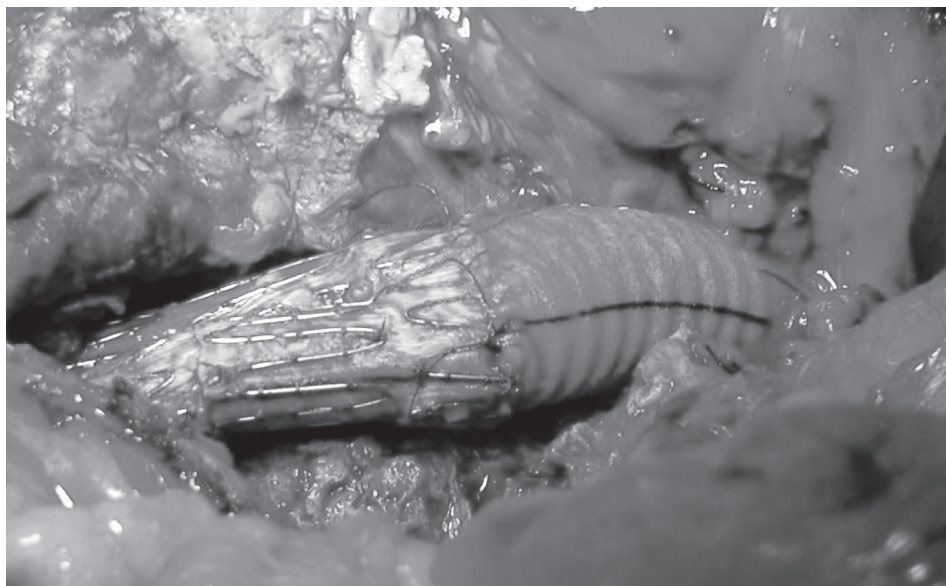
Figure 2: Partial explantation of the proximal endograft to treat a type 1A endoleak with distal main body and limbs left in place.
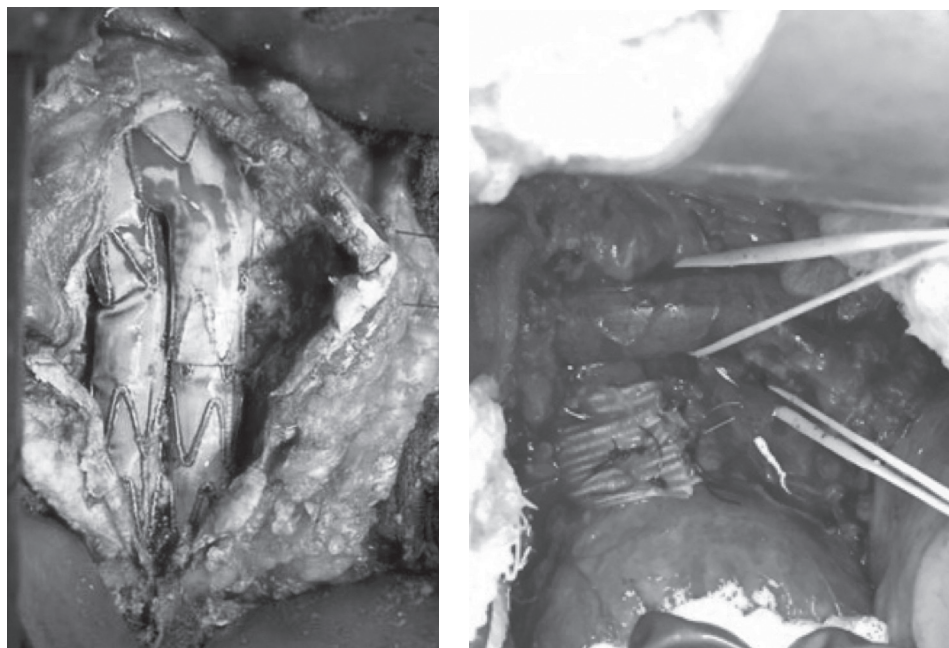
Figure 3: Graft-preserving interventions, including sacotomy and ligation of branch vessels without removing the endograft (left) and external plication for reinforcement of the proximal seal with a Dacron graft (right).

entirety if undergoing treatment for infection; care should be taken in removal of the proximal stents to avoid injury to the perivisceral aorta. In other cases, a proximal fabric cuff or a portion of the limb distally can be left in place, in which case the anastomosis should ideally incorporate both the endograft and the arterial wall.

We have also found it feasible in many cases to treat endoleaks without graft explantation. Graft-preserving interventions involve either external reinforcement of the proximal seal for a type 1A endoleak, ligation of branch vessels for a type 2 endoleak, or both. The proximal seal can be reinforced directly with external sutures or, more commonly, wrapping a Dacron cuff around the neck to plicate the native aortic tissue around the endograft. To treat type 2 endoleaks, the aneurysm sac is opened and lumbar arteries are ligated from within the sac, taking care not to disrupt the main body or limbs of the endograft. Graft-preserving interventions in our experience may reduce the procedural mortality and are generally durable.[7]

Conclusion

Primary open abdominal aortic aneurysm repair has become significantly less common as EVAR has become more widely performed and for broader anatomic indications. This in turn is leading to an erosion in volume of open aortic operations for vascular surgeons and their trainees. Open conversion is on the rise, however, to treat late complications after EVAR including infection and endoleaks, with or without aortic rupture. These operations are more technically complex for the surgeon and more morbid for the patient than *de novo* repair. As the field of open aortic surgery shifts from primary open abdominal aneurysm repair to an endovascular-first approach with open surgery treated as a bailout option, future

generations of vascular surgeons will increasingly rely on open conversion to build or maintain their skills in open aortic surgery.

Summary

- Primary open abdominal aortic aneurysm repair is becoming less common as EVAR expands its indications to patients with more hostile anatomy.

- Open conversion after failed EVAR is becoming more common as a treatment for endoleaks not amenable to an endovascular secondary intervention, or for endograft infection or aortic rupture.

- As trainees perform fewer primary open aortic procedures, they will become more reliant on open conversion to learn both the fundamental and more advanced technical aspects of open aortic surgery.

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Consensus on the future for EVAR

MP Jenkins

Introduction

The concept of endovascular aneurysm repair (EVAR) is an extremely attractive one. Whereas open surgical repair necessitates a laparotomy and mandates aortic cross-clamping, EVAR is minimally invasive and is associated with far less physiological stress to patients who are often frail and elderly. Not surprisingly, early results were superior in terms of mortality, morbidity and recovery.

The original homemade grafts of the mid 1990s were quickly superseded by commercially made devices, and rapid development led to lower profile devices that were easier to introduce and more accurate to deploy. The first randomised controlled trials confirmed what everyone was already experiencing clinically—patients were more likely to survive after EVAR and recovered much faster. All stakeholders seemed to benefit; patients preferred EVAR, health organisations benefited from a reduced length of hospital stay, industry profited from the sale of devices, and clinicians could treat sicker and older patients than previously. The development of EVAR also fostered a new relationship between clinicians and industry, and competition meant that a large number of devices were available on the market. Although there were differences between the devices, the main concept of aneurysm exclusion remained the same—proximal and distal sealing by stent graft radial force.

Vascular surgery was not alone in this approach, which, aided by technological advances was mirrored in many other surgical specialties where laparoscopic, robotic and radiological techniques allowed more patients to benefit from less invasive surgery.

Beyond the learning curve

EVAR flourished and rapidly became a topic to be investigated, researched and discussed at conferences. A new language was needed to describe how devices performed and the natural history of post-EVAR imaging appearances. Most clinicians accepted that the results form EVAR were better in some anatomies than others and industry partners produced guidelines or "instructions for use" to describe the anatomy (mostly the proximal neck) in which their device would reliably allow aneurysm exclusion.

Early outcomes dominated the literature and registries rarely progressed much beyond two years. The increasing usability of new devices encouraged their use in more difficult anatomy and older patients and there was little concern about durability. It became clear that EVAR seemed to work (at least in the short term) even in patients who had anatomy outside the instructions for use of devices, and clinicians became adept at using devices in more difficult scenarios.

Over a period of 25 years, although stent grafts evolved, with one noticeable exception, the main technique and device concept has changed very little. That exception was the technique of endovascular aneurysm sealing (EVAS) which focused on treating the sac using polymer-filled bags rather than relying on the radial force of a stent graft. Its ease of use and early promise precipitated rapid uptake before sound longer term outcome data were available. When it then failed, it came as a shock and something of a wake-up call to the vascular world.

The present

At the same time that EVAS was seen to be failing, clinicians were also noticing late problems following conventional EVAR in some patients—increasing sac diameters, late endoleaks and even ruptured aneurysms. These anecdotal findings were seen in a new light with the publication of the late outcomes from the EVAR and DREAM (Dutch randomised endovascular aneurysm management) trials. These trials suggested that the early survival benefit from EVAR was lost by four years and patients who had received open surgical repair survived for longer and with fewer interventions after eight years.[1]

While the trials investigated patients treated within instructions for use, those outside these criteria, with short, conical, angulated or wide necks fared even worse. Large cohort studies from the USA revealed rates of aneurysm growth of over 40% in five years and significantly increased rates of reintervention and late rupture post-EVAR compared with open surgical repair.[2,3] Despite such data, the vascular fraternity remained reluctant to acknowledge the shortcomings of EVAR and the seduction by the technology and its clear early benefits for patients continued.

In the summer of 2018, however, the National Institute for Health and Care Excellence (NICE) issued draft guidelines on the management of abdominal aortic aneurysms.[4] NICE is a well-respected body, independent of the UK government and Royal Colleges, with a long history of advisory publications regarding new drugs, new medical techniques and the management of a wide range of conditions. The first draft concerning abdominal aortic aneurysm management, however, resulted in an unprecedented response from individuals, hospitals, specialist societies (including the Vascular Society of Great Britain and Ireland, the British Society of Interventional Radiology and the British Society for Endovascular Therapy) and industry partners.

The main reason for the magnitude of the response was the controversial recommendation that elective EVAR should not be offered in any circumstances. Bearing in mind that EVAR is regarded as a mature technology and is established as a treatment for abdominal aortic aneurysms in all UK vascular units, the potential impact would be significant. The draft guidance suggests that patients deemed fit for open surgery should undergo such surgery, but those thought to be unfit (not actually defined), should not be treated at all, other than control of risk factors. Amongst other recommendations, it was also suggested that surveillance post EVAR should be by annual computed tomography (CT) angiography, even though the majority of institutions employ non-invasive duplex surveillance as first line. These recommendations are out of tune with guidelines from the European Society for Vascular Surgery (ESVS) and Society for Vascular Surgery (SVS), and they are contrary to the direction of travel for surgical intervention in general.

At the time of writing (March 2020), the draft guidelines have still not been ratified and published. Deadlines for publication have been missed in November and December 2018, January and July 2019, and (most recently) January 2020. The subject has been commented on and debated extensively with various criticisms largely centred on the advice being a retrograde step, the findings being based on out-of-date data and perhaps unfairly that the clinicians on the committee were not actually expert in the field of aortic intervention.

Despite all the criticism, there is some clear sense in what has been proposed. Aortic aneurysms are largely asymptomatic and occur in the elderly, who often have limited life expectancy secondary to comorbid conditions such as ischaemic heart disease, chronic obstructive pulmonary disease, cancer and dementia. As there is no symptomatic benefit in abdominal aortic aneurysm treatment, we have to be sure that treatment does prolong useful life. Moreover, in the financial austerity of the NHS, it has to achieve this in the most cost-effective way possible. Furthermore, treatment must preserve quality of life and, therefore, ongoing surveillance or further reinterventions should not be intrusive.

So, what is the main concern? There is a feeling that the standard prescriptive NICE approach in only considering evidence from randomised control trials means it has relied on the late findings of the EVAR trials (which revealed an increase in aortic-related mortality in the EVAR group compared with the open group) and has, thus, inappropriately extrapolated this to modern day practice. Crucially, NICE has ignored the better results in patients with good anatomy within the instructions for use of most EVAR devices where durability is much improved. Although patients randomised within this trial were within instructions for use of the devices available at the time, whether the imaging equipment of the day combined with the accuracy of device deployment allowed the preintervention landing zones to be actually achieved is doubtful.

What is the future?

Despite the furore, in the short term at least, we will probably see some rebalancing in the ratio of EVAR to open surgery. In my opinion, the question of anatomy is vitally important here. Almost all reports on the subject show that the outcome for EVAR procedures performed in patients with adverse proximal neck anatomy (angulated, conical, short landing zone or larger diameter) is worse than for those with straighter, parallel-walled, longer and narrower necks. Previously, neck length was seen as the main determinant of instructions for use and, therefore, durability, but increasingly, I believe neck diameter may be more important. Aortic neck dilatation is now a recognised entity and is thought to occur in approximately 25% of cases.[5] This means that a well sized graft deployed perfectly in a proximal seal zone eight or 10 years ago may ultimately fail if the neck dilates beyond the maximum diameter of the graft. Whether this is secondary to the ageing process of the aorta or precipitated by radial force from the stent is uncertain, but it is acknowledged that aortic diameter does increase over time and dilatation also occurs after open repair, meaning that excess radial force is unlikely to be the main reason. Even within what is currently considered compatible with instructions for use, I think we need to reconsider the use of larger grafts. A 36mm graft could be used for a 30mm diameter neck within instructions for use, but an aorta with a diameter of 30mm is actually an aneurysm and if diagnosed with an aneurysm

screening programme, would be expected to dilate over time. It is, therefore, not surprising that a proportion dilate to such an extent that the seal is lost.

However, durability concerns longer term have to be offset against the upfront benefits of an endovascular approach for elderly patients. Patients' wishes have to be prioritised and the NICE recommendations in their current (draft) form do not acknowledge this or the greater importance an elderly population attaches to early benefit compared with what might happen in a decade's time. The benefits of a minimally invasive approach that results in reduced perioperative mortality and allows a faster recovery and return to normality cannot be underestimated. In a world where global information is available instantly, patients will no doubt feel they are entitled to at least be considered for treatment modalities that are not only available but are often first choice in most European countries, Australia, and the USA. Also, in this digital age, many patients are attuned to available treatments and, therefore, to deny them the consideration of an endovascular approach may seem to them to breach the principles of consent for treatment currently used in the UK. From a legal perspective, the proposed guidelines are just that—practice guidelines and not mandatory. However, the previous high quality and evidence-based publications from NICE (across a wide range of health conditions) mean that they have been viewed as a marker of best practice; a lack of adherence to them has sometimes been seen by the legal profession as a breach of duty. Whether commissioners will decide to apply them in this case is uncertain. A difference of opinion could result in piecemeal adoption and a postcode lottery for patients, who could then attempt to procure treatment outside their immediate area.

So, what would the immediate impact be if the NICE abdominal aortic aneurysm guidelines were published in their current format and endorsed by commissioners? The ratio of EVAR to open surgery for elective infrarenal abdominal aneurysm treatment in the UK has been about 70/30 for a number of years now. In the screen-detected cohort, however, the ratio is about 50/50 as screen-detected patients (who tend to be up to a decade younger) are generally fitter and have a longer life expectancy thereby mandating better durability. Even though the draft guidelines have not yet been published, there has already been a shift in practice in favour of open surgery with data from the latest National Vascular Registry (NVR) report showing that the ratio of EVAR/open was 68/32 in 2018, but has changed to 63/37 in the 2019 report. Although there was a marginal increase in open surgery, there were 520 fewer EVARs performed, suggesting a shift towards conservative management in some. Although there has been a gradual decline in abdominal aneurysm numbers, the magnitude of this change is too large to be secondary to a year-on-year prevalence change and, therefore, does represent a real change in practice.

If we concentrate on the group currently undergoing elective EVAR (and indeed fenestrated EVAR), then a proportion of them would be turned down for open treatment. An objective tool to accurately estimate perioperative mortality and longevity (treated or untreated) is lacking, but extrapolating the findings of NAAASP (National abdominal aortic screening programme), I would estimate that 20−30% of these patients would not be offered open surgery. The cost of this would be measured in two ways—the decrease in quality of life amongst those diagnosed with a potentially fatal condition for which no treatment can be offered, and the increased fiscal cost and poorer outcomes of the emergency treatment necessary when a proportion of them present with a ruptured aneurysm in the future. Moreover, a

change in policy such as this may render the NAAASP redundant. The hallmark of any successful screening programme is that there is an acceptable and effective treatment modality for the disease screened for. Already, up to 20% of screen-detected abdominal aneurysm patients do not undergo intervention, mostly as a result of fitness. If this was increased further (inevitable with the guidelines in their current form), the utility, not to mention the cost effectiveness of the NAAASP would have to be reconsidered.

The impact on hospitals could be significant in the current climate. Data from the King's Fund show that the UK bed base has halved in the last 40 years. Many currently struggle with both bed and critical care capacity and the conversion of even a proportion of abdominal aneurysm patients from EVAR to open surgery is likely to impact significantly on length of stay and critical care use of these patients. NVR data reveal that the mean length of stay for EVAR patients is only two days compared with seven for open cases. If all current EVAR cases (approximately 2,300) were considered for open surgery, a proportion would not be fit. About 50 units in the UK offer open abdominal aneurysm surgery, so even if 2,000 extra open cases had to be performed this would only amount to 40 per unit per year or less than one per week. Although not a huge burden in terms of theatre time, it would add to the pressure on beds. A potential increase in emergency presentations both by those turned down for surgery and potentially by those with undetected aneurysms as a result of the demise of the screening programme would also add to this problem. Moreover, the advised changes to surveillance imaging—CT angiography to replace duplex—would increase the pressure on imaging lists and increase the radiation burden for the patient at a time when there are already concerns regarding an increased risk of abdominal cancers following EVAR treatment.

I, therefore, believe, for the reasons outlined above, that the draft guidelines, if published unabridged, cannot be fully implemented in the UK. They are, however, a wake-up call for aortic endovascular practice, and the vascular community would be foolish to completely ignore them. There are patients who do not benefit longer term from EVAR, but survive the procedure itself as a result of advances in perioperative management and the minimally invasive nature of the technique. Such patients, with reduced life expectancy, need to be identified and not subjected to unneeded intervention. At the other end of the spectrum, those in their 60s who may live another 25 years should be better counselled and an open approach considered in light of the recent evidence regarding EVAR durability in some. Clearly those with adverse anatomy should not now be treated with conventional EVAR based on our knowledge of the potential sequelae. During surveillance, in my view, we should be no longer satisfied with sac stability, but see sac shrinkage as an important marker of depressurisation and successful aneurysm exclusion.

If there was an opportunity to revise the NICE guidelines, I would like to see anatomy prioritised as an important consideration. We have to accept that although some patients are good candidates for an endovascular solution, they are a much smaller group than the one currently treated with EVAR. But, just because EVAR does not work in all patients, it should not be denied to those where it is both effective and durable. The concept has matured and endured and its ongoing use in appropriate patients would facilitate ongoing research and industry development into solutions more applicable to adverse anatomy in order that a greater proportion of aneurysm patients will have an endovascular solution in the future.

Conclusion

What that future will look like, I am not certain, but I am hopeful it will continue to involve some form of endoluminal approach to the aorta. I suspect it may involve a combination of techniques to exclude the aneurysmal sac by fixation and sac management to eliminate endoleaks and take account of ongoing anatomical changes. In the shorter term, we need to use both EVAR and open surgery wisely and ensure that the next generation of surgeons is appropriately trained to do this.

Summary

- The early advantages of EVAR are indisputable.

- However, aneurysm exclusion remains unreliable in a proportion of patients leading to the need for reinterventions.

- Anatomical suitability for stent graft sealing seems to be protective against the need for reinterventions.

- Stent grafts used outside of manufacturers' recommended anatomical parameters result in the need for more reinterventions, have poorer durability and eventually can lead to sac expansion and rupture.

- The evidence for poor longer-term stent performance in adverse anatomy needs to be acknowledged and precipitate a change of practice to either open surgery or custom endovascular solutions as appropriate in such cases.

- The proposed draft NICE guidance for abdominal aortic aneurysm management highlights durability concerns, but goes too far in suggesting that EVAR should not be used at all.

- Appropriate use of EVAR, combined with surveillance, is safe in many patient groups and its continued use will allow the research and development needed for further improvements in durability and applicability to cases with adverse anatomy.

- Endovascular aneurysm exclusion remains an elegant solution and is preferred by patients, but current technology is not the finished article and further work is needed to solve the durability problems that are now evident and cannot be ignored.

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Mortality of ruptured common iliac aneurysms: Lessons learned about which ones are at risk

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Introduction

Common iliac artery aneurysms (CIAA) are defined as a permanent focal dilatation ≥1.8cm in men and ≥1.5cm in women, and they represent the most frequent abdominal localisation after infrarenal aortic aneurysms.[1] Most CIAA develop in patients with infrarenal aneurysms whereas isolated iliac aneurysms are rare—constituting only about 2% of all abdominal aneurysms, with a prevalence of 0.03% in autoptic studies.[2–4] According to the anatomic classification of isolated CIAA, proposed by Reber, type I is the most frequent presentation.[5] Iliac and aortic aneurysms share many similarities regarding aetiology, natural history and risk factors. The most frequent aetiology is degenerative/atherosclerotic, followed by pseudoaneurysms, penetrating ulcers, post-dissection, post-traumatic or post-infective aneurysms.[6] The majority of patients with CIAA are males (90%) and diagnosis often occurs between the seventh and eighth decade.[7]

Which aneurysms are at risk of rupture?

The natural evolution of CIAA is to grow with time, with reported expansion rate ranging between 1.1mm per year and 4mm per year.[4,8–9] Their diagnosis is often incidental during abdominal imaging, as most of them are asymptomatic; however, symptomatic and ruptured aneurysms are a life-threatening emergency due to the haemorrhagic shock and significant risk of death in absence of a prompt intervention. Most of the ruptures are retroperitoneal; however, rupture into the inferior vena cava or iliac vein may occur due to their close anatomic relationship.

CIAA growth rate, according to initial diameter, rupture risk, and its association with size, are not as well established as for abdominal aortic aneurysms, but most of the reported ruptures in literature occurred in aneurysms ≥5cm of diameter, and rarely in CIAA of <4cm.[8-11] McCready *et al* reported a mean diameter of both symptomatic and ruptured aneurysms of 7.8cm at presentation.[4] Richardson *et al,* in a cohort of 72 iliac ruptured aneurysms, reported a range of diameter from 3.5cm to 18cm.[12]

Similar results have been found for isolated hypogastric aneurysms: in a multicentre retrospective analysis of 63 ruptured internal iliac aneurysms, Laine
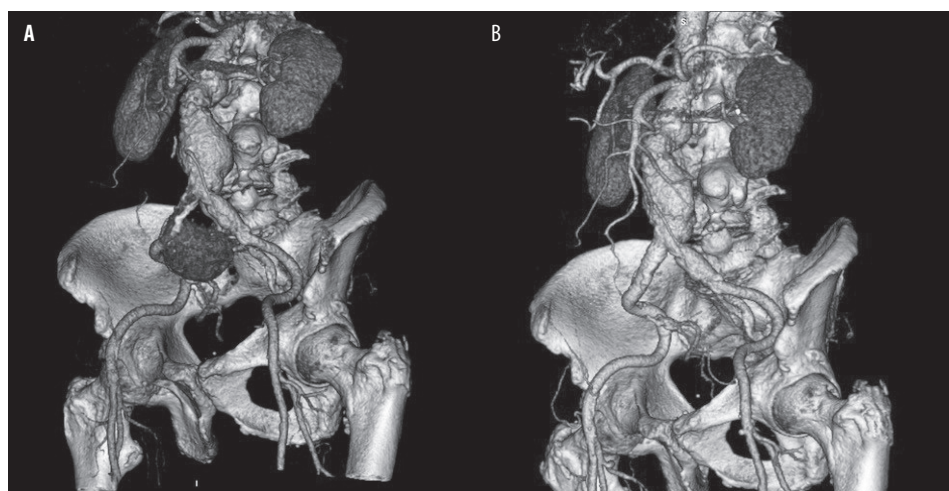
Figure 1: (A) A 82-year-old man presented with a 71mm ruptured saccular right common iliac aneurysm and concomitant 55mm juxtarenal aneurysm. (B) Due to the absence of a proper proximal infrarenal aortic neck and a suitable proximal common iliac neck, a common to external self-expandable covered stent graft was deployed under local anaesthesia after the exclusion of the hypogastric artery origin with an Amplatzer Plug.

et al found that only 8% presented with a diameter <4cm, a rate that is similar to that of ruptured small abdominal aortic aneurysms (<55mm), leading authors to suggest that it is safe to monitor patients with small (<4cm) iliac aneurysms without early intervention.[13]

Clearly, other anatomical factors may play a major role on the risk of CIAA rupture: saccular aneurysms (Figure 1) or aneurysms on chronic dissection may well be at higher risk of complication and should be corrected surgically without delay, even if a clear evidence in the published literature is still lacking due to rarity of the disease.

Among cardiovascular risk factors, hypertension was the sole predictor of faster growth in a population of 438 patients.[9] Despite the increasing use of abdominal ultrasonography and the awareness of the pathology, data extracted from the Nationwide inpatient sample (NIS) database from 1988 to 2011 showed how the number of urgent procedures has remained stable over time (15 procedures per 10 million of the US population).[14]

As for patients with infrarenal aortic aneurysms, both open repair and endovascular iliac repair are feasible options even in an urgent setting.

Open repair

Open repair of CIAA includes the use of bifurcated or straight polyester grafts through a transperitoneal or retroperitoneal approach. This technique could be highly challenging particularly in ruptures because of the deep location of the aneurysm (especially in obese patients) or in the presence of scars from previous surgery or radiotherapy. Moreover, the haematoma often dislodges and disguises the ureters. Simultaneous infrarenal aortic and common iliac artery repair is performed in case of concomitant aneurysms. In case of bilateral need for hypogastric exclusion, reimplantation of the inferior mesenteric artery is usually advocated when feasible to avoid pelvic malperfusion.

The presence of extensive hypogastric aneurysmal involvement usually increases the perioperative risks and it is often managed with hypogastric monolateral occlusion.

Endovascular repair

In the last two decades, endovascular treatment of isolated CIAA or in combination with infrarenal aortic aneurysms has become a valuable alternative to open surgery in most patients with suitable anatomy. As a matter of fact, the endovascular approach to aortoiliac repair increased steadily over time and surpassed open repair in 2003 in the USA.[14] The advantage of endovascular iliac repair is the possibility to perform it percutaneously under local anaesthesia; however, aneurysm involvement of the distal common iliac artery often complicates endovascular repair planning and deployment, especially for urgent procedures.[15] In case of absence of a proper non-dilated distal common iliac artery, distal sealing must be achieved in the external iliac artery with the sacrifice and coverage of the internal iliac artery at its origin. The alternative use of an iliac branch device to preserve hypogastric flow is increased reported, especially in patients with high risk of pelvic ischaemia due to contemporary occlusion of the contralateral hypogastric artery and the inferior mesenteric artery in elective procedures.[16] This procedure, however, may be lengthy and difficult in case of excessive tortuosity of the iliac arteries, as is often the case in large, ruptured common iliac aneurysms, therefore, we did not adopt such a solution in any of our rupture cases.

Mortality and morbidity in ruptured CIAA

Deaths from isolated iliac artery aneurysm have decreased over time, despite the increase in total repairs.[14] According to literature, open repair mortality in the case of ruptured common artery aneurysms ranges between 27% and 60%.[9,17-18] Endovascular iliac repair has emerged as a safe and minimally invasive procedure to treat ruptured CIAA. Buck *et al* reported a lower in-hospital mortality rate with endovascular compared to open repair (1.1% vs. 7.5% respectively; p<.001).[14] Chaer *et al* showed no significant differences in mortality rates between the two groups; however, the need for blood transfusion and hospital stay was significantly lower in the endovascular group.[19] Nevertheless, Kobe *et al* reported a 15% conversion rate to open surgical repair in emergency patients with uncontrollable bleeding or development of abdominal compartment syndrome after endovascular repair.[17] For all these patients, a regular postoperative intra-abdominal pressure measurement is crucial to avoid ischaemic complications. Huang *et al* reported a 34% five-year survival rate in 175 symptomatic CIAA, independent of the type of procedure. In their multivariate analysis, emergency intervention, chronic obstructive pulmonary disease and age resulted significant predictors of poor long-term outcomes, with hazard ratios of 2.55 (95% CI: 1.75−3.70), 1.96 (95% CI: 1.49−2.56) and 1.53 (95% CI: 1.19−1.91) respectively.[9] The concomitant presence of infrarenal aneurysm seems not to affect short-term and long-term mortality.[9]

Endovascular iliac artery repair has shown encouraging results in the treatment of ruptured common artery aneurysms for fit patients; however, some concerns are still related to durability, endoleaks, stent graft thrombosis, and preservation of

Figure 2: Same patient as in Figure 2. Three months later, in an elective setting, a second-stage procedure was performed to complete the endovascular exclusion of the abdominal aneurysm through a fenestrated endograft three fenestrations and one scallop).

the internal iliac artery perfusion. Endovascular repair reintervention rate ranges between 11% and 19%, essentially due to endoleaks.[7,10,20]

Of the 150 patients treated for ruptured aortoiliac aneurysms in our centre between 2010 and 2019, only seven patients (4%) had an isolated CIAA rupture. All the patients were males, the mean common iliac artery diameter was 5.5cm, four patients presented with a concomitant infrarenal aneurysm. Five patients were treated with open repair, the remaining two were treated percutaneously with endovascular repair and hypogastric embolisation. One early reintervention was required for postoperative bleeding in a patient treated with open repair, whereas no 30-day mortality or late iliac-related mortality was reported at a mean follow-up of 38 months (9–98).

Preservation of the pelvic perfusion should be of primary importance in case of bilateral involvement of the iliac bifurcation, in order to avoid buttock claudication, colonic ischaemia and erectile disfunction.[21] In the urgent setting, however, both open and endovascular repair could require the sacrifice of the origin of the hypogastric artery. In such cases, it is crucial to maintain patency of the collateral networks (reimplantation of inferior mesenteric artery, use of iliac branch devices or other endovascular techniques like double barrel endografts) in high-risk patients, in order to reduce the risk of complications. Bilateral, simultaneous hypogastric exclusion together with inferior mesenteric artery occlusion should be avoided in the acute setting if possible, eventually with a planned staging strategy (Figure 2).

Conclusion
Ruptured CIAA represent a rare but life-threatening pathology with high mortality and morbidity.

Open repair has been replaced as the gold standard treatment by the introduction of endovascular repair that demonstrated comparable results in terms of mortality with reduced blood loss and hospital stay in non-randomised studies. Still, endovascular repair presents a higher risk of reintervention rate if compared to open repair, but undoubtedly confers benefits especially in fragile, elderly patients and in emergency settings.

To avoid rupture, an aggressive approach with endovascular repair should be offered and discussed with patients with a common iliac artery aneurysm diameter greater than 3.5cm, or with saccular or dissected iliac aneurysms, when feasible.

Summary

- Rupture of common iliac aneurysm is a life-threatening condition with high mortality and morbidity even in high-volume centres.

- Diameter is the principal predictor of rupture; patients presenting with common iliac aneurysms <3.4cm are safely managed conservatively while larger aneurysms should be considered for repair.

- If feasible, endovascular repair is the best treatment option. Endovascular results are comparable to open repair in terms of early and late mortality, while blood loss and hospital stay are reduced.

- High risk of reintervention still remains an issue in endovascular repair.

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Pre-emptive embolisation of aortic side branches for type 2 endoleaks

HYH Yu and K Mani

Introduction

Type 2 endoleaks continue to be the Achilles heel of endovascular aneurysm repair (EVAR). Although their associated risks are a matter of much debate, according to the evidence, they are linked to a small risk of aneurysm rupture; a meta-analysis showed a 0.9% rupture risk.[1] The general consensus is to treat persistent endoleaks, particularly when sac size increases; however, there are no uniform indications in either the latest European Society for Vascular Surgery (ESVS) or the latest Society for Vascular Surgery (SVS) guidelines.[2,3] Generally, indication for treatment includes sac expansion of 5mm to 10mm measured with the same imaging modality during follow-up after EVAR. Intervention for type 2 endoleaks can be performed with various techniques, including transarterial embolisation of the feeding vessel, translumbar or transabdominal direct puncture of the aneurysm sac and embolisation of the endoleak nidus, or transcaval sac access. There are also an abundance of publications on various endovascular materials that can be used for embolisation, including coils, glue, and onyx. The various techniques and materials used in this context demonstrate the difficulties involved in achieving success when treating type 2 endoleaks with sac expansion. Success in treating these endoleaks is suboptimal. Technical success, which is defined as freedom of reintervention, is only around 72% with great variation in different reports.[1]

Studies have identified anatomical risk factors that increase the risk of type 2 endoleak, and these factors include: inferior mesenteric artery >3mm; lumbar artery >2mm; multiple patent lumbar arteries; aortoiliac aneurysm; and abdominal aortic aneurysm >7cm (Figure 1).[4–6] As a result of these findings, some advocate pre-emptive embolisation of aortic side branches to prevent the development of type 2 endoleaks.

Indications for embolisation

Currently there are no guidelines on the use of pre-emptive embolisation of aortic side branches. In the literature, indications for pre-emptive embolisation mainly include patent inferior mesenteric artery and lumbar arteries (diameter >2–3mm). The procedure can be performed, in a separate session, prior to EVAR; however, performing pre-embolisation during the same session as EVAR is more common. Overall, the aim is to reduce the risk for persistent type 2 endoleaks post-EVAR and, thus, reduce the risk for sac expansion and endoleak-related complications over time.
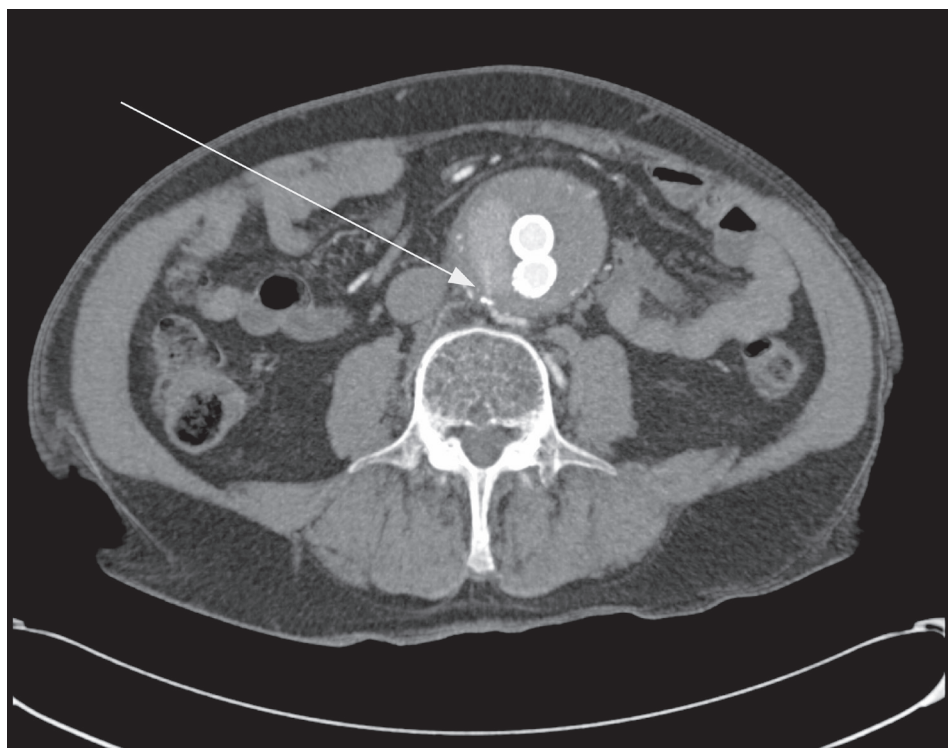
Figure 1: Type 2 endoleak post-EVAR of a 7.5cm abdominal aortic aneurysm, originating from a lumbar artery >3mm in size. This patient thus had two risk factors for persistent type 2 endoleak (aneurysm >7cm, large feeding vessel >3mm).

Technique for pre-emptive embolisation of aortic side branches

Embolisation is performed via the transfemoral approach. The ostium of the targeted aortic side branch is cannulated with a 4F or 5F catheter. After confirmation of position, embolisation can be performed with use of coils or plugs. Generally, coiling is reserved for patients with unfavourable anatomy (for plugs) or when there is an unstable catheter position. An extra microcatheter and a microwire is required to deploy the coil. Technical success is defined as thrombosis of main trunk of targeted vessel without occlusion of its distal branches on control angiography.[7] Caution should be exercised to avoid plug insertion beyond the first branches of the target artery, as this could potentially enable persistent type 2 endoleak despite embolisation.

Is pre-emptive embolisation successful?

The use of pre-emptive embolisation vs. that of EVAR without embolisation has been primarily analysed in single-centre reports, in which embolisation was performed in selected cases. The primary outcome used in these studies varies, from the incidence of type 2 endoleak in the embolisation cohort vs. that in the conventional EVAR cohort to the rate of reintervention. Occasionally, the evolution of sac diameter or volume is also assessed.

Our group performed a systematic review and meta-analysis of pre-emptive embolisation of aortic side branches. In line with the PRISMA guidelines, we

found that technical success was higher for inferior mesenteric artery (82%) than for the lumbar arteries (69%). In 13 studies, including >1,400 patients overall, pre-emptive embolisation of aortic side branches significantly reduced the incidence of type 2 endoleaks by two thirds and reduced the incidence of reintervention by 90%.

Another meta-analysis, by Li *et al,* included nine studies. The authors' findings regarding the rate of type 2 endoleaks (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.21–0.60) and that of reintervention (OR 0.10, 95%CI 0.04–0.27) were similar to the findings of our group. Their study also reported a similar incidence of type 1/3 endoleaks regarding pre-emptive embolisation.[8] Importantly, data in a randomised, non-biased setting for the role of pre-emptive embolisation are lacking.

Complications related to pre-emptive embolisation

The incidence of type 1/3 endoleaks after pre-emptive embolisation (plus EVAR) is comparable to that after conventional EVAR. Nevala *et al* reported eight (20.5%) of 39 patients with type 1 endoleaks following conventional EVAR compared to five in 40 patients (12.5%) who had undergo pre-emptive embolisation group.[9] Müller-Willie *et al* reported one type 1 endoleak (3.2%) and one type 3 endoleaks (3.2%) in an embolisation group of 31 patients compared to four of 43 patients (9.3%) with type 1 endoleak in a conventional EVAR group.[10]

In the literature, two mortalities following pre-emptive side branch embolisation (prior to EVAR) have been reported. One patient died because of iliac rupture during the procedure and the other because of a colonic infarct.[11,12] The patient who died of a colonic infarct had previously undergone right hemicolectomy, sacrificing the middle coeliac artery. Ward *et al* reported that he had undergone an inferior mesenteric artery embolisation and was found to have colonic infarct after the operation. He died of multiorgan failure within 72 hours.[12] Therefore, special attention to Arc of Riolan is encouraged before contemplating such embolisation. The patency of Arc of Riolan is particularly important when the length of inferior mesenteric artery main trunk is short and, if planned, embolisation is to be done by coiling.

In their study, Ward *et al* also reported non-specific abdominal pain. Ten of 108 patients (9.3%) complained of abdominal pain after the procedure. They had all undergone flexible sigmoidoscopy and colonic infarction was ruled out. Their symptoms subsided with overnight intravenous hydration.[12]

Cost-effectiveness of pre-emptive embolisation

Although there are only limited data, selective application of embolisation of aortic side branch to prevent type 2 endoleak may well be cost-effective. Generally, embolisation of aortic side branches only takes about 30–60 minutes (compared with two hours for reintervention). Plus, the plug or coils (with their microcatheters) are the only additional cost for embolisation; so, the cost of pre-emptive embolisation is only a fraction of that of standard EVAR.[13]

Based on a meta-analysis, in which the indication of embolisation was a patent (>2–3mm diameter) inferior mesenteric artery and/or lumbar arteries, the absolute risk reduction for the need of reintervention for type 2 endoleak is approximately

10%. This suggests that the number needed to treat to avoid one reintervention is <10. Assuming that the technique can reduce the frequency of type 2 endoleaks, pre-emptive embolisation may reduce overall health expenditure because of the reduced need for imaging follow-up and reinterventions. However, the cost-effectiveness of such an intervention would still need to be evaluated in a randomised setting.

Conclusion

Pre-emptive embolisation of aortic side branches prior to or during EVAR is a promising strategy to prevent type 2 endoleak. Current evidence suggests that the technique is safe and effective to reduce incidence and reintervention for type 2 endoleak. Further evaluation of the technique in terms of cost-effectiveness and unbiased evaluation of its effect on sac dynamics would be of value prior to general recommendation regarding its use.

Summary

- Type 2 endoleaks is not always benign and carries a small risk of rupture.

- There is no global consensus on treatment for type 2 endoleaks.

- Success rate for treatment of type 2 endoleaks is not satisfactory.

- Pre-emptive embolisation of aortic side branches to prevent type 2 endoleaks appears to reduce the risk of type 2 endoleaks and risk for reintervention.

- General indication for pre-emptive embolisation is patent inferior mesenteric artery (>3mm) and/or lumbar arteries (>2mm).

- The technique appears safe but special attention should be made towards colonic circulation, including prior colonic operation and Arc of Riolan.

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Abdominal aortic aneurysm controversies (ESVS 2019)

A Wanhainen

Introduction

The first European Society for Vascular Surgery (ESVS) guidelines for the treatment of abdominal aortic aneurysms, published in the *European Journal of Vascular and Endovascular Surgery* (*EJVES*) in 2011, have had a major impact on clinical practice and research in aortic disease.[1] In light of the extensive developments in the field of abdominal aortic aneurysm that have occurred since then, steps were taken to update these guidelines; a process that started in 2015.

A writing committee, consisting of 16 European vascular surgeons, produced a comprehensive document that included a total of 125 recommendations based on 790 references. The document was thoroughly reviewed by 13 external reviewers from Europe, the USA, Asia and Australia (as well as the 10 members of the ESVS guidelines committee) to ensure that its recommendations were up to date and reflected current practice and knowledge worldwide.

The resultant ESVS 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysm were published in the 2019 January issue of the *EJVES*.[2] They review several new topics that were not addressed in the previous 2011 guidelines, such as: treatment of juxtarenal abdominal aneurysm, isolated iliac aneurysms, mycotic and inflammatory aneurysms, and management of aneurysm patients with concomitant malignant disease. New treatment concepts, such as modern endovascular techniques including fenestrated endovascular aneurysm repair and chimney EVAR are also covered. Furthermore, service standard and surgical volume requirements are addressed in the document. Another new aspect is a dedicated chapter on the patient's perspective, which was written in collaboration with patient representatives.

The new recommendations, based on the latest evidence and considerations, include a less frequent surveillance protocol for small aneurysms, an "EVAR-first" strategy in most scenarios, and a stratified less frequent follow-up regimen after EVAR. This chapter summarises important news in the new ESVS 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysm and discusses outstanding limitations and controversies. Of note, the European Society of Cardiology (ESC) grading system for specifying the strength/level of evidence for each recommendation was used in the ESVS 2019 guidelines.

Service standard

With the rapid and extensive introduction of endovascular techniques, the management of infrarenal aneurysms has profoundly changed. Randomised controlled trials and cohort studies have convincingly shown the benefit of endovascular management for elective as well as emergency aneurysm repair in

Level of evidence	Definition
A	Data derived from multiple randomised clinical trials or meta-analyses
B	Data derived from a single randomised clinical trial or large non-randomised studies.
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Table 1: Levels of evidence.

patients with suitable anatomy. However, not all patients are suitable for standard EVAR or more complex endovascular treatment options; thus, open surgery is still the best treatment option for some patients. Consequently, endovascular techniques cannot entirely replace open surgical repair and vice versa. Overlooking the anatomical requirements for standard EVAR, by using complex and partially experimental endovascular techniques, to avoid using established open surgical solutions is not recommended. In the same manner, offering major open surgery when there are proven minimally invasive options, just because of lack of resources or local knowledge, is not in accordance with good clinical practice. Thus, at present, performing any form of aneurysm interventions without the ability to offer both open and endovascular approaches 24/7 is not acceptable (recommendation 2; class I, level B).

The firm evidence of a volume-outcome relationship in surgery, in general as well in aneurysm repair, means that a recommendation on minimal surgical volume is both necessary and justifiable. However, no clear threshold volume for aortic surgery at the surgeon or centre level can be identified in the literature. Various cut-off levels have been suggested, and other aspects affecting the possibility for centralisation of aortic services have to be taken into account, such as population density and geographical distances. Therefore, based on available the literature, the ESVS guidelines writing committee concluded that there is enough evidence for a "weak" recommendation for a desired minimum hospital volume of at least 30 cases annually (recommendation 3; class IIa, level C) but more evidence for a stronger recommendation on a minimum yearly case load of at least 20 repairs to perform aortic surgery at all (recommendation 4; class III, level B).

Of note is that although the literature suggests that the volume-outcome relationship is primarily applicable to open surgical repair, the committee has chosen not to specify the volumes for the respective surgical method. It instead refers to the total surgical volume regardless of the surgical technique. Studies of the volume-outcome relationship for aneurysm repair have mainly focused on short-term outcome, which tends to be more relevant for open procedures. However, assuming that experience also plays a role for EVAR—with short-term outcomes being late failures, such as endoleaks, migration and kinking—is reasonable. Thus, the significance of the volume-outcome relationship needs further analysis, including also focusing on long-term results, to guide future updates of recommendations.

An increasingly burning, yet unanswered, question regarding centralisation of services is how open surgical skills can be acquired and maintained if more and

more cases are treated with endovascular technology at the expense of open repair. We already know that many trainee vascular surgeons only observe a few surgical repair techniques during their education let alone actually perform them. Should perhaps open surgery be centralised in the near future?

Screening

Evidence from several randomised controlled trials, conducted in the 90s, showed that screening elderly men for aneurysms effectively and cost-effectively reduced aneurysm-specific mortality. Recent data from the Sweden and UK national screening programmes, which both target 65-year-old men, have confirmed the benefit of screening in a contemporary setting. These findings are despite the fact that they found a much lower prevalence of the disease. Consequently, the ESVS guidelines issue a strong recommendation that all men at age 65 years should be offered an ultrasound screening for abdominal aortic aneurysm (recommendation 12; class I, level A).

The changing epidemiology, nevertheless, continues to challenge the future of aneurysm screening. General screening of all 65-year-old men is highly cost-effective today, but what if the prevalence continues to decline? Would targeted high-risk screening in smokers or in patients with established atherosclerotic cardiovascular disease be a more cost-effective alternative? Also, secondary cardiovascular prevention programmes, applied within the framework of aneurysm screening, could have a major impact on the overall health-promoting effect of an aneurysm screening programme and need to be evaluated properly. Recently, extended screening programmes, targeting multiple disease processes, have been proposed and need further assessment.

Another much needed research initiative of relevance for screening is the development of medical treatment options to slow aneurysm growth. Currently, the most promising candidate is metformin.

The MetAAA-trial is an ongoing small pilot and feasibility randomised controlled trial in Austria, and recently the MAAAGI-trial—a larger randomised controlled trial that is aiming to recruit 500 non-diabetic patients with small aneurysms—started in Sweden. Further metformin trial initiatives are expected from Australia.

Aneurysm repair

The diameter threshold for elective aneurysm repair in men has convincingly been established by four randomised controlled trials and two trials comparing EVAR to surveillance of small aneurysm, which is why the recommendation for repair remains ≥5.5cm in men (recommendation 22; class I, level A). Regardless, the debate is still alive as to whether aneurysms should be operated at a smaller size; more recently, the debate has focused on whether a larger diameter threshold may actually be more appropriate. Clearly, the studies that form the basis of the current recommendation are old, and recent analyses from the English screening programme indicate that the rupture risk of small aneurysms is lower than expected. Less data are available for women, but the reported higher rupture rate justifies a weak recommendation to consider aneurysm repair at lower diameters (5cm) in women (recommendation 23; class IIb, level C). More data are, however,

Classes of recommendations	Definition
I (is recommended)	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
IIa (should be considered)	Weight of evidence/opinion is in favour of usefulness/efficacy.
IIb (may be considered)	Usefulness/efficacy is less well established by evidence/opinion.
III (is not recommended)	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful.

Table 2: Recommendation classes.

needed to better guide us in the future regarding the threshold for elective repair in women.

Due to the rapid technological and medical development, the existing randomised controlled trials comparing elective open surgical repair and EVAR are partly outdated and, thereby, not entirely relevant for the current situation. Additionally, several of the randomised controlled trials are limited by the fact that they mainly included patients <80 years of age, whereas the greatest increases in aneurysm repair are now among those >80 years. This group of patients has also seen the most pronounced improvement in outcome after aneurysm repair, probably related to the preferential use of EVAR for treatment among octogenarians. It is, therefore, necessary to also include more recent cohort data in the overall evaluation of the evidence base when comparing open surgical repair to EVAR. Thus, despite data from multiple randomised controlled trials and meta-analysis, representing the highest level of evidence, the writing committee rated the existing level of evidence of medium strength (level B). Overall, the currently available evidence suggests a significant short-term survival benefit of EVAR over open surgical repair, with similar long-term outcomes until 10–15 years of follow-up. So in patients with suitable anatomy and reasonable life expectancy, EVAR should be considered as the preferred treatment modality (recommendation 60; class IIb, level B). Yet, there are indications that there may be an increased rate of complications after eight to 10 years with earlier generation EVAR devices and the durability of current devices is uncertain (particularly, the low-profile devices). Although EVAR should be considered the preferred treatment modality in most patients, open surgical repair as the first-line strategy in younger, fit patients with a long life expectancy (i.e. >10–15 years) is reasonable (recommendation 61; class IIa, level B).

Nonetheless, the debate about open surgical repair vs. EVAR seems to be a never-ending story. The rapid technological development is an inherent challenge within the endovascular field. Constant upgrades/modifications and the several actors involved make it extremely difficult to ensure reliable data about durability,

which is of utmost importance. Device-related complications or problems are rare and difficult to detect in single-centre environments. Randomised controlled trials, although representing the highest level of evidence, will eventually become outdated under these circumstances; therefore, cohort data and registry data will be the main means of continuously updating our knowledge. The behaviour of the later generation of low-profile stent grafts is an ongoing research area of great importance.

Pooled one-year results of the three recent randomised controlled trials comparing open surgical repair and EVAR for ruptured aneurysms suggest that there is a consistent but non-significant trend for lower mortality post EVAR. The largest and most recent randomised controlled trial, the IMPROVE trial, found that patients treated with EVAR were discharged earlier from hospital to independent living, with better quality of life post procedure, which, therefore, was cost-effective. The recently published three-year results of the IMPROVE trial suggest that, compared with open surgical repair, an endovascular-first strategy for suspected ruptured aneurysm was associated with a survival advantage, a gain in quality of life adjusted years, similar levels of reintervention, and reduced costs. Overall, an EVAR-first strategy for ruptured aneurysm suitable for endovascular repair was cost-effective. These findings, together with observational studies and registry data, support a strong recommendation of an EVAR-first strategy for ruptured aneurysm repair (recommendation 74; class I, level B). The subsequent debate has primarily focused on whether an early survival benefits exists after EVAR, as many cohort studies indicate, or not, as the randomised controlled trial show. However, in practice, this question is of minor importance as everyone now agrees that EVAR should be the first method; no matter how one looks at the evidence.

New devices

In recent years, manufacturers have developed new stent grafts and delivery systems with lower profiles to allow an endovascular approach even in patients with small access vessels. Although this development is desirable, it is important to underline that demonstrable track records based on previous generations devices becomes less and less applicable for each modification. There are some series reporting favourable mid-term outcomes for the latest-generation low-profile stent grafts compared to standard profile stent grafts; but, more experience and longer-term outcome data, especially about the durability of these new devices, are needed to confirm those findings. Therefore, when upgrades of existing platforms are used in clinical practice, the need for long-term follow-up should be recognised. An evaluation of modified devices in prospective registries, with complete follow-up is strongly recommended (recommendation 57; class I, level C).

The role for several new innovative CE-marked technologies on the market is still unclear and further data are needed before these can be recommended to be used in routine clinical practice. CE marking (or approval) is a certification mark for products sold within the European Economic Area (EEA), i.e. European Union (EU) and European Free Trade Association (EFTA). Unlike the rigorous evaluation of efficiency and safety required for Food and Drug Administration (FDA) approval in the USA, CE marking has nothing to do with efficiency or safety. In fact, there are many unproven, ineffective, or even inappropriate medical devices

that are CE marked. Consequently, it is up to the professional societies (such as ESVS) to make proper recommendations based on science (or lack of science) and experience. The role for several new innovative CE-marked technologies on the market is still unclear and further data are needed before these can be recommended for use in routine clinical practice. The ESVS guidelines issue a strong negative recommendation against the use of new unproven devices in clinical practice outside studies approved by research ethics committees and with informed consent from the patients, until adequately evaluated (recommendation 58; class III, level C). Notably, the revised EU recommendations regarding introduction of new medical devices in the market are in line with this recommendation.

Follow-up after EVAR

Regular imaging follow-up post EVAR is routine practice, due to the risk of graft-related complications and rupture after EVAR. On the other hand, the true value of prophylactic regular follow-up imaging after EVAR is unclear. Routine surveillance seldom identifies significant findings requiring reintervention, and there are studies suggesting that most patients who require reintervention after EVAR present with symptoms. Furthermore, several studies show that compliance with annual prophylactic imaging guidelines is suboptimal, and lack of adherence to follow-up does not seem to affect long-term mortality or post-implantation rupture rate. Thus, annual imaging after EVAR for all patients is neither evidence-based nor feasible. Yet, an early postoperative clinical and imaging follow-up after EVAR is required to assess the success of the performed intervention (recommendation 91; class I, level B). Recent observational data suggest that patients considered at low risk for endovascular aortic repair failure after their first postoperative computer tomography (CT) angiography, i.e. anatomy within instructions for use, no endoleak, adequate overlap and seal of ≥10mm proximal and distal stent graft apposition to arterial wall, may be considered to be stratified to less frequent follow-up. Patients who fulfil the aforementioned criteria at early follow-up imaging may be considered for delayed imaging up till five years after repair (recommendation 92; class IIb, level C). Patients who do not meet these requirements should be assessed for the need for reintervention or continued frequent monitoring. However, this change in practice needs to be carefully monitored and evaluated. Setting up a randomised controlled trial to address this issue is, however, not realistic because of the low frequency of the main endpoint (aneurysm rupture) after EVAR. Instead, we have to rely on careful monitoring of the long-term outcome, preferably in prospective cohort studies and registry studies with complete reporting.

Juxtarenal aneurysm

Given the rarity and complexity of juxtarenal aneurysm treatment, it is recommended that these patients are treated at specialised high-volume centres that can offer both open and complex endovascular repair (recommendation 94; class I, level C).

Complex endovascular techniques have emerged as a promising option for the treatment of juxtarenal aneurysm. However, there are currently no reliable comparative and health-economic studies comparing open surgical repair to

complex EVAR in these patients. With today's rather extensive experience of complex EVAR (especially fenestrated EVAR), showing generally good results, and the ability to offer treatment to many patients less suitable for major open surgery; it is difficult to motivate a strong preference for open surgical repair over complex EVAR for juxtarenal aneurysm. Instead, the guideline committee suggests a more pragmatic approach; open surgical repair and EVAR are complementary techniques for treatment of these patients. Decision making should be tailored to each individual patient and local health economies. Stratification of cases by anatomy and surgical risk may be useful in patients with juxtarenal aneurysm (recommendation 95; class IIa, level C). Open surgical repair with an anastomosis below the renal arteries and short renal clamping time may be a preferable, as well as a more durable option, for fit patients with a short aortic neck. With more complex anatomy or high surgical risk due to comorbidities, an endovascular solution with suprarenal proximal landing zone may be preferable. Despite limited data, the ESVS guidelines committee believes that fenestrated technology has a small advantage over parallel graft technique when it comes to proven feasibility and durability. There are more multicentre reports and longer follow-up data available supporting fenestrated technology, and thus it should be the preferable endovascular technique for elective juxtarenal aneurysm repair (recommendation 96; class IIa, level C). Parallel graft techniques may, however, be considered as an alternative technique in the emergency setting or as a bailout (recommendation 97; class IIb, level C).

As for standard aneurysm repair, novel new techniques and treatment principles, such as EVAS, EndoAnchors and *in situ* fenestration are not recommended in clinical practice for juxtarenal aneurysm repair but should be limited to studies approved by research ethics committees and with informed consent from the patients (recommendation 98; class III, level C).

Data are scarce for ruptured juxtarenal aneurysm, but the risk aversion is low in such an immediate life threatening and complex situation. Therefore, in patients with ruptured juxtarenal aneurysm open repair or complex endovascular repair (with physician modified fenestrated stent grafts, off-the-shelf branched stent graft, or parallel graft) may be considered based on patient status, anatomy, local routines, team experience and patient preference (recommendation 99; class IIb, level C).

Conclusion

The new ESVS aortic guidelines are an extensive document offering many recommendations of clinical importance on the management of aneurysm. Each recommendation is accompanied by a comprehensive supporting text that summarises the literature and motivates the positions made. Hopefully, it will guide both clinicians in the everyday work as well as researchers and decision makers and contribute to the care and understanding of patients with abdominal aorto-iliac artery aneurysms.

Summary

The ESVS 2019 aneurysm guidelines include a total of 125 recommendations. Some of the more important ones are:

- It is recommended that centres or networks of collaborating centres treating patients with abdominal aortic aneurysms can offer both endovascular and open aortic surgery at all (recommendation 2; class I, level B).

- Abdominal aortic aneurysm repair should only be considered in centres with a minimum yearly case load of 30 repairs (recommendation 3; class IIa, level C); and, abdominal aortic aneurysm repair should not be performed in centres with a yearly case load <20 (recommendations 4; class III, level B).

- In men, the threshold for considering elective abdominal aortic aneurysm repair is recommended to be ≥5.5 cm (recommendation 22; class I, level A); and in women with acceptable surgical risk, the threshold for considering elective abdominal aortic aneurysm repair may be considered to be ≥5.0cm diameter (recommendations 23; class IIb, level C).

- For newer generations of stent grafts based on existing platforms, such as low profile devices, long-term follow up and evaluation of the durability in prospective registries is recommended (recommendation 57; class I, Level c); and new techniques/concepts are not recommended in clinical practice and should only be used with caution, preferably within the framework of studies approved by research ethics committees, until adequately evaluated (recommendation 58; class III, level C).

- In most patients with suitable anatomy and reasonable life expectancy, endovascular aneurysm repair should be considered as the preferred treatment modality (recommendation 60; class IIa, level B); and in patients with long life expectancy, open aneurysm repair should be considered as the preferred treatment modality (recommendation class IIa, level B).

- Early (within 30 days) postoperative follow-up after endovascular aortic repair including imaging of the stent graft to assess presence of endoleak, component overlap and sealing zone length is recommended (recommendation 90; class I, level B); and patients considered at low risk of endovascular aortic repair failure after their first postoperative CT angiography, may be considered for stratification to less frequent imaging follow-ups (recommendation class IIb, level C).

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Official centralisation of abdominal aortic aneurysm care improves early clinical outcomes

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Introduction

Hospital and 30-day mortality is an essential quality parameter for both endovascular aneurysm repair (EVAR) and open repair procedures. The relationship between higher case volume and lower patient mortality following treatment for abdominal aortic aneurysm has been well described in previous studies. Clearly, the link between volume and better results is a fundamental aspect and it is evident that high-volume centres can benefit not only from high-volume surgeons, but also from multidisciplinary teams, resources and easier access to the resources themselves.[1,2]

Although the observation of better outcomes in high-volume centres resulted in centralisation in countries such as the UK, there are few available data supporting the benefit of such reconfiguration.[3] The reorganisation of associated services, quality of care for surgery, patient preference, and healthcare delivery should be considered as well as the surgeon or hospital threshold operative case load. Therefore, we cannot universally state that centralisation should be implemented at any level and in any territory. Patient outcomes and other quality-of-care parameters should be considered for the decision and serve as an instrument to assess the effects of such reconfiguration.[4] One of the principal challenges in healthcare systems is deciding which services have to be concentrated, taking into account, among other parameters, their frequency, complexity, risk, accumulated experience and costs.[5]

Volume relationship for elective repair

One of the main arguments in favour of centralisation is the relationship between volume and better outcomes, considering that high-volume centres consequently have lower mortality and morbidity. The minimum case load volume cannot be considered as a large-scale applicable value. In fact, the population as number of inhabitants, population density, or aspects concerning infrastructure or resources must be taken into account.

It seems that the available literature would support the centralisation of aneurysm procedures, but not equally for EVAR and open repair. A report of 122,495 Medicare beneficiaries confirms the importance of hospital and surgeon volume in patients who underwent elective repair for an intact aneurysm. This study found a strong association between hospital and surgeon volume and mortality after open

repair, while only a minimal impact between hospital volume and mortality with no such association for surgeon volume was seen after EVAR.[6]

These results have been confirmed by a German study that collected a total of 96,426 cases, of which 11,795 (12.6%) presented as ruptured aneurysm, treated in more than 700 hospitals (annual median: 501). Volume was inversely associated with mortality after open repair and EVAR:

- EVAR—mortality 3.0% in lowest quintile, 1.6% in highest quintile, p=0.011
- Open repair—mortality 7.6% in lowest quintile, 4,5% in highest quintile, p=0.005.

Complication rates, length of stay, and use of blood products were lower in high volume hospitals, identifying an annual case load of 75–100 elective cases associated with the lowest mortality risk.[7]

On the contrary, a population-based time-series analysis of elective and urgent repairs in Ontario (Canada) demonstrated that the spread of endovascular surgery in community hospitals since 2010 has led to the start of decentralisation of aneurysm care. The authors state that training in endovascular surgery, minimally invasive surgery and lack of need of intensive postoperative care may favour the performance of these procedures even in community hospitals without having a negative impact on mortality. They also suggest that teaching centres may focus on performing complex procedures such as branched and fenestrated endovascular aortic repair.[8]

Although the volume does not have such a clear impact on mortality after elective EVAR, the impact on the rate of reinterventions, medium-long term morbidity, and mortality and length of stay is not clear, as these factors will probably reduce the quality of care and increase costs.

Interestingly, a study by Gafheri et al reports that the complication rate after surgery was not significantly different between low-volume and high-volume centres; however, mortality after major complications was higher in low-volume centres, suggesting that there are other factors such as institutional facilities, application of protocols, competence of other specialists (ex. intensive care specialist) and medical staff facing challenging management of complex interventions.[9]

In fact, mortality after aneurysm surgery is in general not directly related to the procedure itself, but depends on the failure to recognise, manage and treat major complications and morbidity following procedures, defined as "failure to rescue" after surgery.[10] This concept assumes greater importance in open repair, as demonstrated by a study from Scali et al. The authors reported that failure to rescue/30-day mortality odds for hospitals with three-year volumes of 50, 100, 150, and 200 cases were 1.4, 2.0, 2.7, and 3.0 times lower, respectively, than hospitals performing ≤25 cases/three years, concluding that in open repair failure to rescue/30-day in-hospital mortality strongly correlated with annual case volume and higher volume centres have the lowest risk.[11]

Although European Society for Vascular Surgery (ESVS) guidelines recommend that abdominal aortic aneurysms treatment should only be considered in centres with a minimum yearly case load of 30 repairs (recommendation 2a C), the minimum volume threshold cannot be considered as an absolute numeric value, because vary considerably among countries.[12] Thus, centralisation requires a shift towards improving procedures and infrastructures, rather than planning based solely on the volume threshold.[13]

Furthermore, centres must demonstrate an acceptable short-term mortality. Actually, regarding aneurysm repair-related short-term mortality, Society of Vascular Surgery (SVS) guidelines recommend not to exceed mortality by 5% following elective open repair and 2% following elective EVAR.[14] Moreover, Leapfrog group standards for high-risk procedures recommend that only institutions with short-term survival of 97.3% or greater should perform aneurysm repairs.[15]

Therefore, a territorial reorganisation must take into account and associate a minimum volume that guarantees not only an acceptable mortality with other quality of care parameters.

Volume relationship for urgent repair

ESVS guidelines recommended that EVAR should be considered the first option in the treatment of ruptured aneurysm, provided that the anatomy is suitable and that centres or networks of collaborating centres treating patients with abdominal aortic aneurysms can offer both EVAR and open repair at all times (recommendation class I, level B).[12]

Although the IMPROVE trial showed no significant reduction in either 30-day mortality or cost when using EVAR vs. open repair for ruptured aneurysm, significant bias and crossover cases have been described.[16] Also, the long-term results showed a better survival and quality of life, reduced costs, and a cost-effective strategy for EVAR.[17]

A recent large multinational registry confirms that mortality in treatment of ruptured aneurysm has been reduced in recent years thanks to the greater use of EVAR. Care of ruptured aneurysm varies between countries: Denmark, for example, which has the highest degree of centralisation and uses EVAR in only 5.1% of cases has an overall mortality of 25.9%, while in Australia, where vascular services are less centralised, almost 40% of patients are treated by EVAR and mortality is similar (24.5%). Therefore, we cannot consider centralisation the sole way for a large-scale benefit for ruptured aneurysm. Territorial variability, including population, population density, distribution of centres, times and transport systems should be considered. Finally, there is variability between the various countries in the definition of high-volume.[18]

Typical controversial arguments about centralisation in the emergency treatment of ruptured aneurysm are the turn-down rate and the poorer skills of vascular surgeons of low-volume hospitals, who are not allowed anymore to operate on an elective aneurysm. The turn-down rate is a determining factor in the population outcomes, because survival is close to 0% without treatment. Currently, we have few data to establish the impact of centralisation on turn-down rate; however, it is probable that peripheral centres without availability of EVAR have a higher percentage of patients considered unfit of surgery. On the other hand, the delay in receiving treatment for patients who are transferred from one centre to another in an emergency situation must be taken into account.[19]

Data from a Spanish registry analysing the impact of centralisation in urgent repair reported 662 ruptured aneurysms, 421 before centralisation and 241 afterwards. The rate of ruptured aneurysm submitted to surgery (open repair or EVAR) was similar in both periods: 60.3% before and 64.3% after centralisation (p=0.310), showing a non-significant decreasing in the amount of non-treated patients.[20]

Interim impact on outcomes of the official centralisation process for aneurysm management in Catalonia

In 2014, the Catalan Health Service (CatSalut), responsible for the public health service system in Catalonia (Spain), integrated into the Spanish National Health System, formally designed a model of reorganisation of the high specialised procedures. In vascular surgery, therapeutic procedures considered as highly specialised, following criteria of number of cases and treatments that require a degree of high expertise, both professional and technical, and that carry a high risk to the patients, where identified: aortic and carotid repairs. The Department of Health, in collaboration with vascular surgeons, have been reviewing the complexity levels of the portfolio of vascular surgery services, activity volume, as well as the necessary requirements for procedures depending on the complexity. It has been determined 30 annual procedures on recommended minimum volume for both elective aneurysm and carotid repairs.

It was considered that this model of reorganisation in accordance with required level of complexity, contributed to sustainability of the healthcare public system, to the best rationalisation and appropriate use of resources, to the improvement of the level of quality of care and to the outcomes. Then, since January 2015, only 10 selected hospital units with more than 30 cases per year were allowed to treat and follow-up aneurysm.

Through in a retrospective observational study, the outcomes of patients undergoing aneurysm repair, based on pre and post-centralised Official Public Healthcare Registry data in Catalonia, were examined (2009–2014 pre-centralisation 2015–2017 post-centralisation). The purpose was to analyse the impact of centralisation in terms of in-hospital and 30-day mortality (short-term mortality) and length of stay in elective and urgent repairs of aneurysm among the Catalan population. Secondary outcomes included comparison of mortality and hospital stay in subgroups: ruptured aneurysm and intact aneurysms, low and high-volume centres, and outcomes improvement in high volume centres after centralisation.

In the study, 3,501 intact aneurysms—including 1,124 open repair (32.1%) and 2,377 EVAR (67.9%) and 409 ruptured aneurysm including 218 open repair (53.3%) and 191 EVAR (46.7%)—were identified. An increase in EVAR/open repair ratio was observed after centralisation (from 62.3% to 78.0% for intact aneurysms, p<.001; and from 35.4% to 65.2% for ruptured aneurysm p<0.001). After centralisation, a significant decrease in overall mortality in intact aneurysm repair (4.7% vs. 2.0%; p<.001) and ruptured aneurysm repair (53.1% vs. 41.9%; p=.028) was observed. Mortality reduction in intact aneurysm was significant for open repair (8.7% vs. 3.6%; p=.005) but not for EVAR (2.2% vs. 1.5%; p=.246). Overall, length of stay decreased as well—mainly in intact aneurysm (9.49±10.84 vs. 7.44±12.23; p<.001) and, in particular, in elective EVAR (7.32±7.73 vs. 6.00±8.97; p<.001). After centralisation, short-term mortality significantly decreased for both intact aneurysm and ruptured aneurysm, mainly for elective open repair. Length of stay also significantly decreased, mainly for elective EVAR.

These results support the benefit of centralisation of AAA repair procedures and reinforces results of previous studies, in particular regarding mortality after elective open repair and the positive impact of the increased ratio of EVAR in urgent repair. Also, reduction of length of stay reflects a positive result in terms of resource use and improved clinical outcomes.

Conclusion

The vast majority of the studies support that centralisation of aneurysm repair reduces mortality rates, in particular for open repair. Beyond mortality, there are other non-minor benefits that affect other ethical, economical, teaching and research aspects. Centralisation could provide greater experience in the prevention, detection and treatment of complications, with the best result at the lowest cost.

Summary

- Perioperative risk after aneurysm surgery must be acceptably low and the intervention itself should be assumed to prolong patients' life expectancy.

- Centralising of aneurysm treatment has been associated with improved outcomes and conformity with clinical guidelines.

- The relationship of volume/outcome with quality is complex. It is necessary to focus toward infrastructural and procedural improvements that drive high-quality services rather than the concentration of planning exclusively around an operative volume threshold.

- The process of centralising aneurysm treatment is not disconnected from a healthcare system organisation perspective.

- Together with quality of care outcomes, implementation of centralisation should be examined also at the health economic levels.

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Misdiagnosed ruptured aortic aneurysm in the emergency department is associated with a high mortality rate

K Smidfelt and M Langenskiöld

Introduction

Rapid diagnosis, upon presentation in the emergency room, of a ruptured abdominal aortic aneurysm is, intuitively, of the utmost importance given the mortality risks of such an aneurysm.

However, making the correct diagnosis at the first assessment is not always easy. Many physicians have encountered patients with ruptured aneurysms who were initially misdiagnosed. Studies have shown that an initial misdiagnosis is common and occurs in 25–62% of cases.[1–13]

Contemporary frequency of misdiagnosis in ruptured aneurysms and the impact of misdiagnosis on complication rate, lead times and mortality

The consequences of misdiagnosis or a delayed diagnosis in patients with ruptured aneurysm have historically been largely unreported. However, a Swedish group recently performed a retrospective review of the associated outcomes of delayed or misdiagnosed ruptured aneurysm.[11,14] The group investigated how ruptured aneurysm patients were diagnosed in emergency wards and found that misdiagnosis or delayed diagnosis remained common—occurring in approximately every third patient that sought care for a ruptured aneurysm. Furthermore, misdiagnosis caused a median delay of 4.8 hours to surgical intervention compared with immediate (and correct) diagnosis in the emergency department. Somewhat surprisingly, misdiagnosis (and the subsequent delay to intervention) was not associated with increased mortality providing that a patient eventually underwent surgery. There were also no differences in the need for postoperative haemodialysis, days on ventilator, or length of hospital stay between misdiagnosed patients and correctly diagnosed patients.

However, an unpublished study reviewed outcomes both for surgical patients (misdiagnosed and correctly diagnosed) and for non-surgical patients.[14] It found that, overall, mortality was higher in patients who were misdiagnosed than in patients who were correctly diagnosed at the first assessment (74.6% vs. 62.9%; p=0.01). In an adjusted analysis, misdiagnosis remained an independent risk factor for mortality (odds ratio [OR] 1.83 [95% CI 1.13−2.96]; p=0.01).

The same study recorded the frequency of reported symptoms in ruptured aneurysm patients. As to be expected, abdominal pain (70%), back pain (43%) and syncope (36%) was common. However, nausea (23%) and vomiting (26%) were also frequently observed. Less than a third (31%) of all patients had a first recorded systolic blood pressure ≤90mmHg.

Conclusion

Misdiagnosis is common in patients seeking care for a ruptured aneurysm, and it is associated with an increased mortality. In an era in which there is substantial focus on the technical aspects of repairing ruptured aneurysms, the first assessment in the emergency department remains an important factor. A strengthened education about ruptured aneurysms directed at hospital staff and physicians who may encounter these aneurysms has the potential to reduce mortality.

Summary

- Misdiagnosis in the emergency department is common in patients with ruptured abdominal aortic aneurysms.

- Misdiagnosed patients have a substantially higher risk of dying from the ruptured aneurysm.

- Educational efforts directed to emergency department and staff might hold a potential to reduce the overall mortality in patients with ruptured abdominal aortic aneurysms.

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Peripheral arterial consensus

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Common femoral artery disease occlusion: The ostium of the profunda femoris artery should be treated with open surgery

JP Walsh and MT Menard

Introduction

The value of the profunda femoris artery in supplying distal perfusion in the setting of superficial femoral artery occlusion cannot be overstated. A study by Kruse *et al* used cadaveric lower extremities to demonstrate that the majority of collateral vessels supplying the distal lower extremity originate from the profunda (Figure 1).[1] This explains how an individual can maintain a viable, normally functioning lower extremity despite occlusion of the superficial femoral artery. Even in the presence of significant steno-occlusive disease of both the aortoiliac and femoropopliteal arterial segments, the profunda femoris circulation is often spared.[2] If present, atherosclerotic plaque of the profunda is generally limited to the short segment proximal to the first or second major branch point (Figure 2).[2]

In 1961, Morris and colleagues published "Surgical Importance of Profunda Femoris Artery".[3] This work describes how good, albeit not ideal, revascularisation of the lower extremity can be achieved by limiting the distal most extent of a bypass procedure to the femoral artery, so long as normal pulsatile flow is restored to the profunda femoris artery. Over the subsequent decade, interest in the profunda as
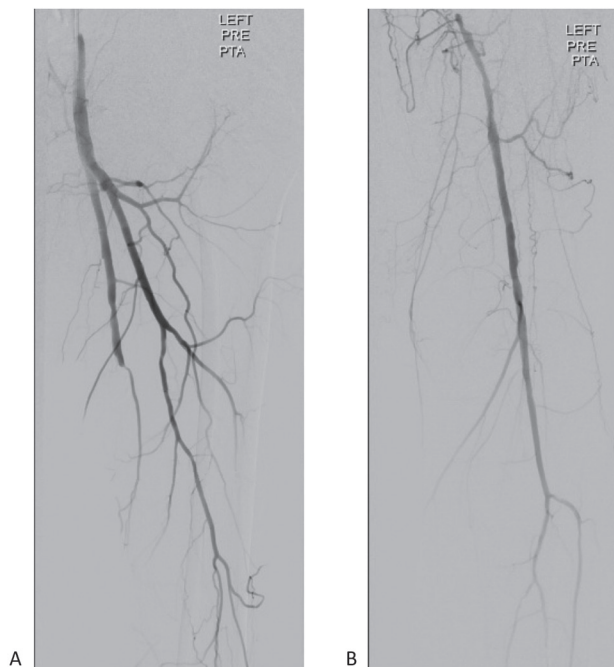

Figure 1: (A) Occluded superficial femoral artery with patent profunda femoris providing; (B) reconstitution of the popliteal artery through geniculate collaterals.
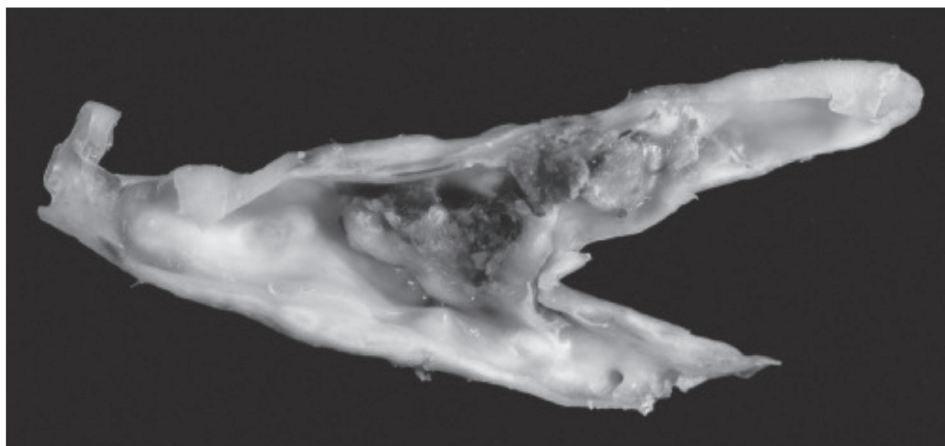
Figure 2. Atherosclerotic disease of the profunda femoris artery is generally limited to the short segment proximal to the first major branch point.

adequate runoff to support proximal aortofemoral and iliofemoral revascularisation in the setting of superficial femoral artery occlusion continued, with a surge in publications of small case series of patients.[4]

Use of profundaplasty as a standalone technique expanded rapidly in the 1970s, with the success of widely differing approaches described.[4] Berguer and colleagues emphasised the importance of extending a reconstruction at least as far as the first major branch point of the profunda.[5] Harper and Millar preferred to use only a short vein patch at the ostium.[6] Others described techniques including semi-closed endarterectomy, common femoral to profunda femoris arterial bypass, arterial flaps, and endarterectomy with and without patch angioplasty using vein or Dacron.[4] Regardless of the technique employed, short-term symptomatic improvement was achieved in most patients with claudication or mild rest pain, but isolated profundaplasty did not benefit those with severe rest pain or tissue loss.[4]

The 1980s ushered in the first reports of percutaneous transluminal balloon angioplasty of the profunda femoris artery as an alternative to open surgery.[7] With the evolution of endoluminal techniques, including stents, stent grafts, drug-coated balloons, drug eluting stents and atherectomy, the debate regarding the optimal management of atheromatous common femoral and profunda femoris artery disease has waged on.

The profunda femoris artery

Use of the profunda femoris as the outflow target of an inflow bypass graft in the setting of superficial femoral artery occlusion can improve the ankle-brachial-index (ABI) by upwards of 0.3 without any further distal revascularisation. Best results are achieved with a patent popliteal artery and a low profunda popliteal collateral index, in which profunda popliteal collateral index equals above-the-knee segmental pressure minus below-the-knee segmental pressure divided by above-the-knee segmental pressure (PPCI = AKSP - BKSP/AKSP). The profunda popliteal collateral index acts as a predictor of the haemodynamic potential of geniculate collaterals.[2]

Flow mechanics studies help to explain why unobstructed flow through the common femoral and profunda femoris arteries is the most important determinant
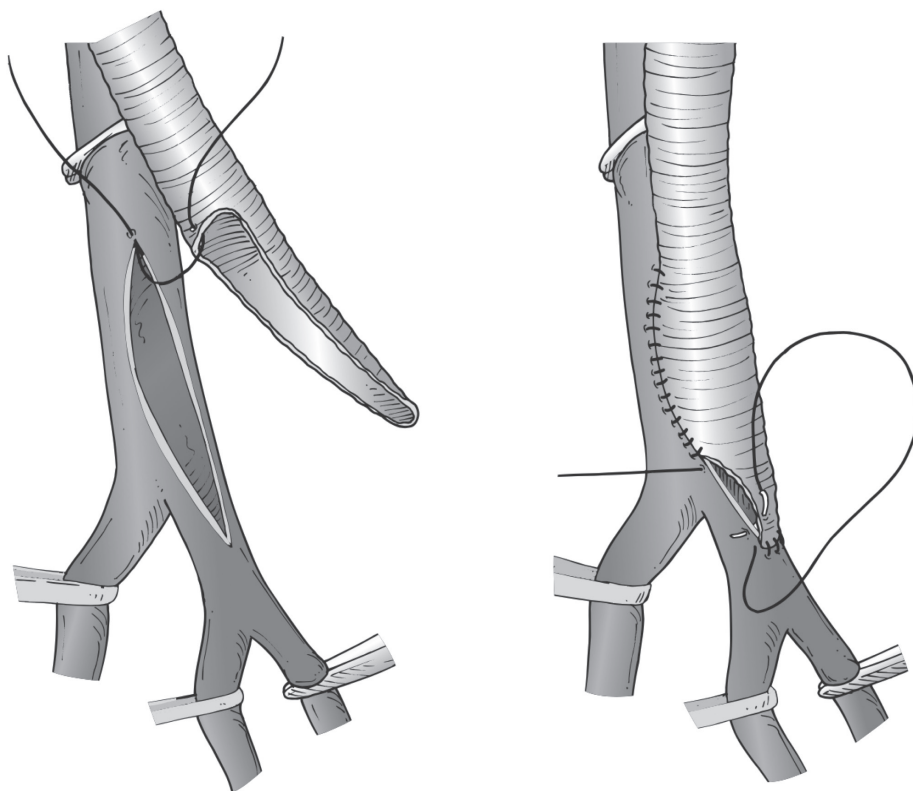
Figure 3: Extending the hood of the distal anastomosis onto the profunda femoris artery enhances outflow by overcoming the functional stenosis.

of lower extremity circulation. The superficial femoral artery is an artery of conduction, with a relatively constant cross-sectional area along its length. The profunda, however, is an artery of supply, rapidly increasing total cross-sectional area by branching into a large network of collaterals as it proceeds down the leg. As such, a widely patent profunda can overcome the cross-sectional area lost by an occluded superficial femoral artery and sustain patency of an inflow graft.[5]

It has been recommended by some authors that an aortofemoral bypass graft should always be extended to the profunda in the setting of superficial femoral artery occlusion, even in the absence of orificial profunda disease, as a "functional" stenosis is present in all patients based on calibre change at the bifurcation.[5] While this approach has not been universally adopted, it is common practice to extend the hood of the distal anastomosis over the origin of the profunda femoris artery to overcome this theoretical drop in outflow (Figure 3). In the setting of significant common femoral or profunda femoris origin atheromatous disease, an endarterectomy or profundaplasty is indicated.

Technique

The profunda femoris artery is exposed by distal extension of the dissection used to access the common femoral artery. In the setting of infection or significant scarring due to repeat groin exposures, a fresh tissue plane can be developed through a

lateral approach with medial retraction of the sartorius.[8] Because this procedure is generally performed for lower extremity ischaemia, every effort should be made to spare all collateral branches from both the common femoral and profunda femoris arteries to preserve perfusion.

Atherosclerotic plaque of the profunda can be underestimated by angiography, and so common and profunda femoris arteries should be palpated to gauge the degree of disease present.[8] Dissection should be continued along the anterior aspect of the profunda as necessary to ensure a soft clamp point is reached. In most cases, it is necessary to ligate the lateral femoral circumflex vein that courses deep to the superficial femoral artery and crosses anteriorly over the proximal profunda artery. The profunda orifice and extent of disease can be visually inspected after incision of the common femoral artery. The lumen can be further interrogated by assessing quality of back-bleeding and gentle insertion of sizing metal probes.[8] If isolated orifical plaque is present, it can be entirely removed by an eversion technique through the common femoral arteriotomy. If, however, the disease extends further beyond the orifice, extension of the arteriotomy onto the profunda may prove necessary. In this case, care should be taken to ensure the junction of the superficial and deep femoral arteries is not disrupted, as this segment is particularly prone to injury of the thin adventitial layer that remains following plaque removal. To avoid such difficulty in situations in which the common femoral artery distal to the profunda take-off and/or the proximal superficial femoral artery is being treated concomitantly, these authors favour using a separate arteriotomy beginning 1–2cm distal to the profunda take-off to address the profunda component.[8] Endarterectomy is then performed by developing the appropriate cleavage plane. While closure of the arteriotomy can be via primary closure, autogenous or synthetic patch, or by anastomosis with a graft limb, patch repair is associated with better long-term patency. In current practice, bovine pericardium is the most commonly used patch material and is the authors' patch of choice.

Evidence for views

Since its inception in the 1940s, femoral endarterectomy with or without patch angioplasty has been considered the gold-standard method of managing common femoral artery disease.[9] The importance of the profunda femoris artery was described by Morris *et al* in 1960 with a series of 102 patients amassed over a six-year period.[3] These patients, who had combined aortoiliac and femoropopliteal atherosclerotic disease, possessed certain factors precluding them from an aorta to femoral to popliteal revascularisation. As such, they underwent aortofemoral bypass with primary outflow via the profunda femoris artery. In this series, 40% of patients had return of palpable pedal pulses and 42% had non-palpable pulses but well perfused lower extremities free of claudication. Eighteen per cent of patients had less ideal outcomes, with 4% experiencing persistent postoperative claudication, 6% requiring subsequent femoropopliteal bypass, 4% ultimately proceeding to amputation, and 4% dying. This work, while demonstrating modest outcomes by today's standards, revealed that using the profunda femoris artery as outflow in the setting of an occluded superficial femoral artery was usually sufficient for supporting graft patency. Satisfactory perfusion was achieved in more than 80% of patients deemed unsuitable for further revascularisation efforts by the operating surgeon.

Ouriel and colleagues similarly recognised the value of the profunda when direct revascularisation to the common femoral artery was prohibitive.[2] In their report, a collection of 53 inflow procedures over a 15-year period were performed to the distal profunda femoris artery. The profunda was chosen as the outflow target due to occlusion of common and superficial femoral arteries (58%), reoperative groin (34%), or heavily diseased femoral vessels (8%). Patency rates were highly dependent on the inflow source, with aortoprofunda and femoroprofunda four-year patency rates of 96% and 100%, respectively compared with five-year patency of axillary profunda grafts of only 26%. Ankle brachial indices (ABI) rates were improved by a mean of 0.27+/-0.04 following revascularisation of the profunda, with improvement of symptoms in both claudicants and those with critical limb ischaemia. The most favourable symptomatic outcomes were achieved in patients with patent popliteal arteries (90% vs. 30% symptom improvement) and lower profundapopliteal collateral indexes (85% improvement with PPCI <0.25, 20% improvement with PPCI >0.25). This study illustrates the symptomatic benefits of isolated profunda revascularisation that can be achieved with proper anatomic selection.

While the utility and durability of common and profunda femoris artery revascularisation has long been established, more contemporary studies have investigated the safety of such open surgical procedures in the endovascular era. A 2008 study reviewed 65 elective common femoral endarterectomies over a four-year period at a single institution.[10] Technical success was achieved in 100% of cases, with symptomatic improvement in 98.5%. A major complication rate of 5%, a minor complication rate of 9%, and zero perioperative mortalities were observed. A retrospective National Surgical Quality Improvement Program database study looked at a total of 1,513 elective common femoral endarterectomy cases over the four-year period from 2007 to 2010.[11] Perioperative mortality rate was calculated at 1.5%, with functional non-independence prior to admission and dyspnoea at rest independent predictors of mortality on multivariate analysis. A perioperative complication rate of 7.9% was seen, with steroid use, diabetes, and obesity being multivariate predictors of morbidity. The majority of complications were categorised as minor, among them superficial surgical site infections, urinary tract infections, and deep venous thromboses, reinforcing the long-held view that surgical revascularisation is both durable and safe.

A similar Vascular Quality Initiative database study accrued 1,014 patients who had undergone endovascular intervention of the common and/or deep femoral arteries.[12] Interventions included angioplasty (76.6%), stenting (25%), stent grafting (2.3%) and atherectomy (19.4%). The perioperative mortality rate was 1.6%, with multivariate predictors of mortality being tissue loss, chronic obstructive pulmonary disease, end-stage renal disease, urgent rather than elective procedures and advanced age. Complications included access site haematoma (5.2%), arterial dissection (2.9%), distal embolisation (0.7%), access site stenosis or occlusion (0.5%) and arterial perforation (0.6%). Technical success was achieved in only 91% of interventions.

Taking these studies together, it would seem that endovascular and surgical interventions of the femoral artery have comparable morbidity and mortality, with higher technical success and primary patency of surgical revascularisation. This was again demonstrated by a single-centre cohort study of 100 patients out of Taipei.[13]

Femoral endarterectomy of 60 patients resulted in primary patency of 96.7% and 94.1% at one and two years, while endovascular intervention of 40 patients resulted in primary patency of 75% and 57.1%. Perioperative mortality and complication rates were similar between the two groups.

While there are no published randomised controlled trials comparing the two revascularisation techniques, a 2019 review of the literature explored the results of seven femoral endarterectomy studies and four endovascular studies.[14] This report noted that despite limited data, femoral endarterectomy has consistently demonstrated excellent technical success and long-term patency. Endovascular intervention of the common femoral artery was found to have lower primary patency and more frequent need for additional interventions than endarterectomy, but did have lower morbidity and mortality rates.

Conclusion

Based on the above stated literature, there is insufficient data to support endovascular management as the preferential treatment of common femoral and profunda femoris atherosclerotic disease. Unobstructed inflow to the common femoral and outflow via the profunda femoris artery is critical to perfusion of the lower extremity and as such, open surgical revascularisation, with its associated excellent technical success and durability, remains standard of care.

Summary

- The profunda femoris circulation is often spared in patients with significant aortoiliac and femoropopliteal atherosclerotic disease.

- The profunda femoris provides critically important collateral circulation to the lower leg in the setting of superficial femoral artery occlusion.

- Using profunda femoris artery as the distal target for inflow procedures results in excellent graft patency.

- Significant symptomatic improvement can be achieved through revascularisation of the profunda femoris artery when the popliteal artery is patent and the profunda-popliteal collateral index is low, despite superficial femoral artery occlusion.

- Endovascular intervention of the common femoral and profunda femoris arteries is safe and effective; however, primary patency and long-term durability are lower compared with open surgical revascularisation.

- Open revascularisation of the common femoral and profunda femoris arteries remains the standard of care given excellent technical success and durability and acceptable morbidity and mortality.

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Duplex findings of popliteal artery entrapment syndrome

F Burrows, M Crook and S Rogers

Introduction

Popliteal artery entrapment syndrome (PAES) is a rare vascular condition in which muscle or tendon variants cause extrinsic compression of the popliteal artery. This can restrict blood flow to the lower limb(s) leading to potential artery occlusion and damage.[1] The majority of cases are reported in men (60%), and the condition can either be anatomical or functional.[2–4]

Anatomical PAES can be caused by abnormal development of the popliteal fossa myofascial structure and/or embryological popliteal anatomy, and it can be combined with muscular hypertrophy. This unusual structural development can lead to extrinsic arterial compression.[5,6] Functional PAES affects mainly elite athletes such as cyclists, professional footballers and triathletes where over development of the gastrocnemius muscle head combined with, in some cases, an aberrant arterial path leads to arterial compression.[2]

Common symptomatic presentation of PAES includes calf or foot intermittent claudication during exercise that fully resolves at rest.[4,7] Neurological symptoms are variable but peroneal nerve dysfunction or nerve entrapment are usually not present.[8,9] Physical examinations may reveal decreased or absent pulses in the popliteal or crural/pedal arteries during forced dorsi- or plantar-flexion. Signs of decreased perfusion such as change in pallor, paresthesias and pain, may also be seen.[10,11] Weak or absent distal pulses during forced flexion manoeuvres present the main physical examination characteristics and can be corroborated by a reduction of >20mmHg on ankle-brachial pressure Index (ABPI) testing.[6,12]

There are various possible imaging modalities that can diagnose PAES, where magnetic resonance (MR) imaging is considered the gold-standard technique to determine anatomical PAES as it can highlight aberrant anatomy.[13,14] MR angiography is sensitive to popliteal artery compression or occlusion and flexion manoeuvres can be performed to elicit a symptomatic response.[13,15] MR angiography has also been suggested to provide an accurate diagnostic approach for PAES.[13,14] However, MR imaging and MR angiography are expensive, have long waiting lists for non-urgent referrals, and require patients to hold provocative positions (dorsi- and plantar-flexion) for long periods. Flexion manoeuvres used in MR scanning are often not forced, due to the length of time required to hold positions, meaning little resistance and muscular load is used.[16–18]

Ultrasound is non-invasive, cheap and readily available, but more importantly is dynamic. It can be used to show haemodynamic changes resulting from compression such as stenosis, occlusion, and an increase in peak systolic velocity (PSV), during dynamic forced/load manoeuvres of dorsi- and plantar-flexion. It is the process of eliciting contraction of the gastrocnemius muscle through forced loading that enables functional PAES to be detected.[19]

Because of the rarity and the many routes of referral to vascular surgery (sports medicine, physical therapy, general practice, and ortho-plastic surgery) PAES diagnosis is often protracted. Early diagnosis is optimal to prevent arterial damage and simple surgical exploration with fasciotomy, myotomy or fibrous band/muscle resection to release the artery could be sufficient to treat symptoms.[20] Other therapeutic options include thrombo-endarterectomy with venous patch arterioplasty for non-occlusive vascular injury and for occlusive arterial thrombosis, autologous bypass grafting may have superior results.[21,22] Ninety per cent of PAES patients who undergo surgical intervention, report significant improvement of symptoms with return to normal physical activity within three months.[23] Considering the elite athlete population and the cost associated with injury, short convalescence periods are a priority.

We investigated the role of triplex ultrasound on the effect of dynamic forced dorsi- and plantar-flexion manoeuvres in asymptomatic healthy controls, asymptomatic elite athletes and symptomatic patients. Our aim was to develop a diagnostic ultrasound based protocol for PAES.

Methods

Three groups of participants were recruited. Group one consisted of healthy individuals who did not exercise or who exercised less than three times a week; group two were elite athletes who exercised for at least one hour three to five times a week, and who ran >30k/m or cycled >250k/m per week; and group three were patients who were being investigated for symptomatic PAES. Symptomatic status was confirmed via the multidisciplinary team process. Patients who have previously been treated for PAES, prior lower limb vascular surgery, or were unable to perform vigorous exercise were excluded. Ethical approval was given from the National Research Ethics Committee (18/NW/0635) and all patients provided written consent.

Ultrasound Imaging

Triplex ultrasound scans were performed by an experienced, accredited clinical vascular scientist using a Mindray Resona 7 scanner (Mindray). A full bilateral arterial examination was performed on each patient with the abdominal arteries scanned via a 5–1MHz curvilinear ultrasound transducer. Arteries below the inguinal ligament were scanned using a 9–3MHz linear ultrasound transducer. Measurements of PSV and Doppler waveforms, in the proximal and distal vessels, were recorded. ABPI was calculated at rest using a sphygmomanometer (Accuson) and 8MHz continuous wave hand held Doppler (Life Dop, Summit Doppler 250Series). The brachial artery pressure was compared to the strongest signal from either the anterior or posterior tibial artery at the ankle, bilaterally. Post exercise ABPIs were also obtained following five minutes of vigorous calf raises or until the participant was unable to continue.

To assess for popliteal compression, provocative loading manoeuvres were undertaken with the patient in both erect (standing on a stool) and supine positions (lying on an examination couch) under direct ultrasound visualisation. Diameter (cm) and PSV (cm/s) measurements of the proximal and distal, right and left POPA at rest, during dorsi- and plantar-flexion were performed using a 9–3MHz linear probe. In the erect position, dorsi-flexion under load was elicited by hanging right/left heel off the edge of the stool, plantar-flexion was elicited by standing on tip toes. In the supine position, patients were laid prone with their feet hanging over the end of the examination couch. Dorsi- and plantar-flexion resistance was applied

by a second vascular scientist. In each position, diameter and PSV measurements were recorded for the proximal and distal popliteal artery. The largest change in diameter (cm) and PSV (cm/s) to determine location of maximal clinical change from rest was calculated.

Statistical analysis
Descriptive statistics including, means, standard deviations (SD), confidence intervals (CI) and ranges were calculated. An unpaired, two-tailed, independent Mann-Whitney t-test was performed to compare significance between groups using Graphpad Prism statistical software V8 (GraphPad software).

Results
Thirteen healthy controls (group one), 12 elite athletes (group two), and two symptomatic patients (group three) have been recruited at present. Mean ± SD and range were calculated for each group at rest and in flexion manoeuvres for both diameter and PSV. Full distal POPA compression was observed in the prone position during forced plantar-flexion in 70% of all study participants.

Changes in diameter

Group one
For mean diameter (cm) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone and erect positions, see Table 1. Mean diameter change ±SD in forced dorsi-flexion in the prone position was 0.03±0.12cm (95% CI -0.02–0.08); range = -0.27–0.41cm. In the erect position, mean diameter change ±SD was 0.03±0.09cm (95% CI -0.01–0.07); range = -0.19–0.22cm. Mean diameter change ±SD in forced plantar-flexion in the prone position was 0.36±0.18cm (95% CI 0.29–0.43); range = -0.05–0.57cm. In the erect position, mean diameter change ±SD was 0.04±0.12cm (95% CI -0.02–0.08); range= -0.17–0.26cm.

Group two
For mean diameter (cm) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone, and erect positions, see Table 1. Mean diameter change ±SD in forced dorsi-flexion while prone was 0.06±0.15cm (95% CI -0.01–0.12); range = -0.14–0.48cm. While in the erect position mean diameter change ±SD was 0.03±0.21cm (95% CI -0.12–0.06); range = -0.67–0.26cm. Mean diameter change ±SD in forced plantar-flexion while prone was 0.39±0.27cm (95% CI 0.27–0.50); range = -0.22–0.69cm. Mean diameter change ±SD in forced plantar-flexion in the erect position was -0.03±0.23cm (95% CI -0.13–0.07); range = -0.67–0.26cm.

Group three
For mean diameter (cm) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone and erect positions, see Table 1. Mean diameter change ±SD in forced dorsi-flexion while prone was 0.11±0.07 (95% CI -0.00–0.22) cm; range = -0.03–0.17cm. Mean diameter change ±SD in the erect position was 0.29±0.26cm (95% CI -0.12–0.7); range = -0.12–0.26cm. Mean diameter change ±SD in forced plantar-flexion while prone was 0.03±0.11cm (95% CI 0.14–0.19); range = -0.12–0.12cm. Mean diameter change ±SD in the erect position was 0.37±0.19cm (95% CI -0.06–0.68); range = -0.16–0.61cm.

		Rest		Dorsi-flexion		Plantar-flexion	
		Prone	Erect	Prone	Erect	Prone	Erect
Diameter (cm)	Group 1	0.47±0.07	0.51±0.06	0.46±0.11	0.49±0.08	0.06±0.15	0.41±0.13
	Group 2	0.57±0.08	0.56±0.09	0.64±0.06	0.67±0.08	0.19±0.29	0.52±0.13
	Group 3	0.52±0.12	0.54±0.10	0.39±0.06	0.48±0.18	0.00±0.00	0.10±0.13
PSV (cm/s)	Group 1	99.80±22.29	67.20±11.18	108.00±43.55	95.90±38.13	24.60±52.80	94.80±19.32
	Group 2	90.25±16.35	59.82±22.88	89.42±35.23	81.83±21.02	24.10±51.51	95.92±25.97
	Group 3	75.00±9.90	69.00±9.90	103.00±11.31	90.00±11.31	0.00±0.00	134.00±189.50

Table 1: Mean ± standard deviation (SD) diameter (cm) and PSV (cm/s) at rest, in dorsi- and plantar-flexion for groups one, two, and three respectively.

There was no significant difference observed the change in diameter between groups one and two in prone or erect dorsi-flexion or plantar-flexion (p=0.70; p=0.54; p=0.07; and p=0.39, respectively).

Changes in velocity

Group one
For mean PSV (cm/s) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone and erect positions, see Table 1. Mean PSV change ±SD in forced dorsi-flexion while prone was -5.90±47.56cm/s (95% CI -25.55–13.71); range =-124.00–71.00cm/s. Mean PSV change ±SD in the erect position was -40.19±42.27cm/s (95% CI -57.35– 23.04); range = -199.00–10.00cm/s. Mean PSV change ±SD in forced plantar-flexion while prone was 69.87±70.29cm/s (95% CI 41.48-98.26); range = -187.00–138.00. Mean PSV change ±SD in the erect position was 36.42±12.99cm/s (95%CI 9.66–63.18); range = -63.00–129.00cm/s.

Group two
For mean PSV (cm/s) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone and erect positions, see Table 1. Mean PSV change ±SD in forced dorsi-flexion while prone was -3.88±37.36cm/s (95%CI -19.65–11.90); range =-50.00– 105.00. Mean PSV change ±SD in the erect position was -33.18±28.79cm/s (95% CI -45.33– 21.02); range = -107.00–8.00. Mean PSV change ±SD in forced plantar-flexion while prone was 64.78±56.83cm/s (95% CI 40.79–88.78); range = -64.00–139.00cm/s. Mean PSV change ±SD in the erect position was -43.68±23.84cm/s (95% CI-53.75– -33.61); range = -107.00– -7.00cm/s.

Group three
For mean PSV (cm/s) change ±SD at rest, in dorsi-flexion and plantar-flexion in the prone and erect positions, see Table 1. Mean PSV change ±SD in

forced dorsi-flexion while prone was 3.50±41.32cm/s (95% CI -62.26–69.26); range = -29.00–59.00cm/s. Mean PSV change ±SD in the erect position was -24.00±11.20cm/s (95% CI -41.81- -6.19); range = -34.00 – -8.00cm/s. Mean PSV change ±SD in forced plantar-flexion while prone was 81.25±11.53cm/s (95% CI 62.90–99.60); range = 68.00–96.00. Mean PSV change ±SD in the erect position was -31.75±115.00cm/s (95% CI -214.70– 151.20); range = -192.00–62.00cm/s.

Between group comparisons
There was no significant difference in PSV change observed between groups one and two in prone or erect dorsi-flexion (p=0.49; p=0.62) nor in erect plantar-flexion (p=0.55). A significant difference in erect plantar-flexion was observed between group one and two (p<0.001).

Conclusion

The use of triplex ultrasound can be used to diagnose functional PAES in combination with MRI to determine aberrant anatomy. By comparing three different groups, our preliminary clinical findings indicate that a level of popliteal artery compression is normal within the asymptomatic population. We identified the greatest number of arterial compressions in the distal popliteal artery while prone during forced plantar-flexion. Therefore, ultrasound should be coupled with other imaging modalities and cannot be solely diagnostic. From our protocol, the proximal and distal popliteal artery should be investigated as approximately 8–17%
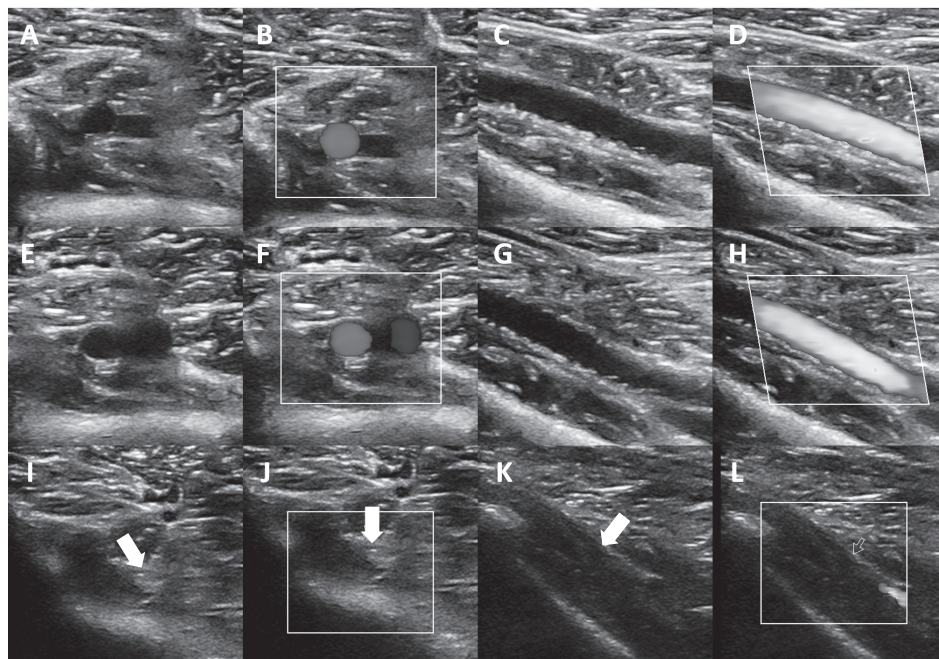
Figure 1: B-mode and colour Doppler ultrasound images taken of the distal popliteal artery in an asymptomatic elite athlete in transverse (TS) and longitudinal sections (LS) in the prone position. (A–B) TS image taken at rest; vessel widely patent. (C–D) LS image taken at rest; vessel widely patent. (E–F) TS image taken in forced dorsi-flexion; vessel widely patent. (G-H) LS image taken in forced dorsi-flexion; vessel widely patent. (I–J) TS image taken in forced plantar flexion; complete vessel compression noted. (K–L) LS image taken in forced plantar flexion; complete vessel compression noted. White arrows indicate location of complete artery compression.

of compression was observed in the proximal vessel while prone. Dorsi-flexion in the prone or erect position did not appear to elicit any functional compression. Functional compression was also not seen during plantar-flexion in the erect position.

Summary

- Compression of the popliteal seen by ultrasound should not be the sole diagnostic criteria for PAES. Popliteal artery compression exists in healthy, asymptomatic individuals, primarily in prone plantar-flexion.

- Triplex ultrasound imaging is ideal for functional PAES diagnosis, in addition to MR imaging for anatomical variants.

- A good ultrasound protocol should include proximal and distal popliteal artery measurements, in both forced flexion manoeuvres.

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Long-term survival with paclitaxel-coated devices— German insurance data

CA Behrendt

Introduction

In December 2018, Katsanos *et al* published a meta-analysis that aroused criticism concerning medical device safety issues and the validity of industry-sponsored randomised controlled trials. They reported a possible association between paclitaxel devices and increased long-term mortality for the management of femoropopliteal artery revascularisations; they used summary-level data from 28 randomised controlled trials that enrolled 4,663 patients (89% with intermittent claudication) with 12 different devices. Notably, only three out of these trials reported rates for three-year (or greater) mortality and most trials were underpowered.[1] The surprising results of this publication, together with the fact that some companies subsequently corrected the reporting of their trial data, led to a heated discussion that had a global impact.[2,3] As a result, regulators initiated extensive investigations and advised caution.[4] Additionally, ongoing trials such as BASIL-3 (Balloon vs. stenting in severe ischaemia of the Leg-3) and SWEDEPAD (Swedish drug elution trial in peripheral Arterial Disease) temporarily stopped their recruitment.

Overall, since December 2018, the vascular community, regulators, and industry have been discussing if there is a signal beyond the Katsanos meta-analysis.[5] Opponents of the meta-analysis raised several important concerns and emphasised methodological flaws, but the authors have defended their findings by presenting additional sensitivity analyses. Also, FDA confirmed—using patient-level survival data from pivotal randomised controlled trials—a higher mortality signal with paclitaxel. Meanwhile, researchers experienced in assessing real-world evidence have published large retrospective observational studies using patient-level data from the Society for Vascular Surgery Vascular Quality Initiative (VQI) registry, Medicare and Optum claims, US National Cardiovascular Data Registry (NCDR), and German health insurance claims (BARMER).[4,6–8]

In fact, the results of randomised controlled trials vs. those of observational studies in this area are diametrically opposed. There is a signal towards higher mortality for patients treated with paclitaxel devices vs. that for patients treated with standard therapies in summary-level data from randomised controlled trials, and a contrasting signal towards lower mortality among patients treated with paclitaxel devices in real-world data.[9]

The rise of paclitaxel pre 2018

Paclitaxel was derived from the Pacific yew's bark in the early 1960s, and its antitumor activity was first described in the late 1970s under the responsibility of the Susan

Horwitz´ laboratory at the Albert Einstein College of Medicine in New York City, USA. In 1992, this microtubule-stabilising drug was approved by the FDA for the treatment of ovarian cancer, and later for breast (1994) and lung cancer (1999), as well as Kaposi´s sarcoma.[10,11] Beginning at the turn of the millennium, various trials also showed the potential value of paclitaxel-eluting stents and paclitaxel-eluting balloons for coronary artery disease.[12–15] However, the superiority of sirolimus-eluting stents over paclitaxel-eluting stents led to paclitaxel being abandoned as the drug for coronary stents (N.B. everolimus is now used as the main drug for coronary stents); however, paclitaxel is still used for coronary drug-coated balloons.[15,16]

Nevertheless, for the treatment of peripheral arterial occlusive disease, paclitaxel remained the most promising agent for drug-coated devices; and its superiority (compared with uncoated devices) has been shown in multiple interventional studies (e.g., Zilver PTX, IN.PACT, THUNDER).[2, 17–19] Since 2009, around 15 paclitaxel-coated balloons and two paclitaxel-eluting stents have received the CE mark. Also, in 2012, the FDA approved the Zilver PTX as the first paclitaxel-eluting stent for the US market. Since then, three paclitaxel-coated balloons and one paclitaxel-eluting stent have subsequently gained FDA approval.

Paclitaxel-coated balloons and paclitaxel-eluting stents in societal guidelines

Following market approval, paclitaxel devices have been rapidly adopted as treatments for peripheral arterial disease. Also, societal guidelines have gradually accepted the inevitable.[20] In 2015, the Association of Scientific Medical Societies in Germany (AWMF) published guidelines for the diagnosis and treatment of peripheral arterial occlusive disease. The authors of these guidelines highlighted that, at mid-term follow-up, drug-eluting devices were associated with improved patency and lower reintervention rates. However, they also discussed the paucity of patient-oriented outcomes—such as walking distance, mortality, morbidity, quality of life, and amputations. They concluded that, mainly because of insufficient evidence, "the clinical relevance of drug-eluting devices could not be assessed satisfactorily" (expert consensus) but recommended their use in femoropopliteal artery disease "if restenosis or reintervention is crucial" (class of recommendation II, level of evidence B).[21] In the 2016 American Heart Association/American College of Cardiology (AHA/ACC) guidelines, the authors state that the "assessment of the appropriateness of specific endovascular techniques for specific lesions for the treatment of claudication is beyond the scope of this document". For both intermittent claudication and chronic limb-threatening ischaemia, a possible benefit of drug-eluting techniques was discussed. Again, the authors commented that these beneficial differences were mainly attributable to patency, restenosis, and repeat-revascularisation endpoints and that most studies were underpowered or did not examine patient-oriented outcomes, such as amputation (for chronic limb-threatening ischaemia), wound healing (for chronic limb-threatening ischaemia), walking function, or quality of life parameters.[22] The 2017 European Society for Cardiology/European Society for Vascular Surgery (ESC/ESVS) guidelines on the diagnosis and treatment of peripheral arterial diseases highlighted the available trial data showing better long-term patency of drug-eluting devices in femoropopliteal lesions. Accordingly, the authors recommended that the use of drug-coated balloons (class of recommendation IIB, level of evidence A) and drug-eluting stents (class of recommendation IIB, level of evidence B) be considered in short (<25cm) femoropopliteal lesions; they also said drug-coated balloons could be

considered for the treatment of in-stent restenosis (class of recommendation IIB, level of evidence B).[23] One year later, in 2018, the Society for Cardiovascular Angiography and Interventions (SCAI) consensus guidelines recommended paclitaxel devices as first-line endovascular treatment in the femoropopliteal artery (class of recommendation I, level of evidence A).[24] Finally, after the meta-analysis was published, the 2019 Global Vascular Guidelines on the management of chronic limb-threatening ischaemia included a statement on the safety of paclitaxel-eluting devices. The authors again highlighted the need for appropriately controlled prospective trials to determine the safety and efficacy of paclitaxel technologies, specifically in the chronic limb-threatening ischaemia population, with adequate long-term follow-up as an important research priority. However, since the first meta-analysis and corresponding guideline recommendations primarily were related to patients with intermittent claudication and to the treatment of femoropopliteal arteries, this discussion was beyond the scope of the Global Vascular Guidelines.[25]

The GermanVasc Paclitaxel Study

In the current retrospective observational study of health insurance claims data, we accessed longitudinal data from patients insured by the second-largest health insurance fund in Germany— BARMER (13.2% of Germany´s population). Among 9.4 million patients and 6.2 million hospitalisations, we included 37,914 patients (mean age 73.3 years; 48.8% female) who underwent an index intervention for symptomatic peripheral arterial occlusive disease between 1 January 2010 and 31 December 2018. To reach a more homogeneous sample, we excluded patients with prior interventions and major amputations. A look back until 2006 and a follow-up until 2019 was available for this study.

As subgroups were fundamentally different regarding relevant covariates, the cohort was stratified by chronic limb-threatening ischaemia vs. intermittent claudication and then by balloon vs. stent use. In the study, 21,546 propensity score matched patients were subsequently included in stratified analyses.

The rapid adoption of drug-eluting devices in Germany (unmatched cohort)

Until 2009, only 111 patients with drug-eluting stents and 138 patients with drug-coated balloons were identified in the BARMER cohort. The proportion of paclitaxel devices continuously increased from 3% for chronic limb-threatening ischaemia and 4% for intermittent claudication in 2010 to 39% and 48%, respectively, in 2018. The maximum increase was observed for stents when compared with balloons.[7] During the same period, the proportion of endovascular techniques among all revascularisations in patients with symptomatic peripheral arterial occlusive disease increased by 61%, and the disease-related annual costs per capita increased by 31%.[20]

All-cause mortality, amputation-free survival, and major cardiovascular events in matched cohorts

A total of 2,454 deaths occurred within five years of follow-up. The median follow-up was 983 days (interquartile range 412–1,777 days).[7] In patients with intermittent claudication, paclitaxel devices were associated with a significantly lower rate all-cause mortality at five years (9.4% vs. 10.5%; risk difference -1.12). The better survival with drug-eluting devices did not reach significance in Kaplan-Meier log rank test (p=0.07), but was confirmed by matched Cox-regression analyses in the balloon stratum
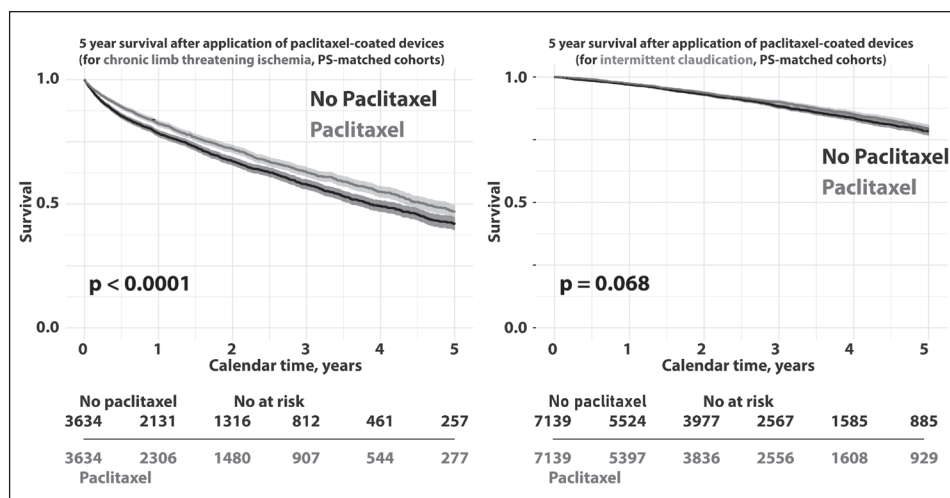
Figure 1: Kaplan-Meier curves for survival after treatment of chronic-limb-threatening ischaemia (left) and intermittent claudication (right) in propensity score matched cohorts. Figures include 95% Wald confidence intervals (CI) and log rank test (p value).

(hazard ratio 0.87, 95% CI 0.76-0.99) while no statistically significant difference was observed in the stent stratum. For amputation-free survival and major cardiovascular events following treatment of patients with intermittent claudication, no benefit with paclitaxel devices was observed.

In patients with chronic limb-threatening ischaemia, a significantly lower all-cause mortality was seen in patients treated with paclitaxel devices at five years (31.8% vs. 35.8%; risk difference -4.02). The better survival was confirmed by Kaplan-Meier log rank test (p<0.001) and by matched Cox regression analyses in both the balloon (hazard ratio 0.82, 95% CI 0.74-0.91) and stent stratum (hazard ratio 0.84, 95% CI 0.73-0.96). There was also a benefit in terms of amputation-free survival and major cardiovascular events with both balloons (hazard ratio 0.85, 95% CI 0.78-0.91) and stents (hazard ratio 0.82, 95% CI 0.77-0.88).

Conclusion

The GermanVasc study on drug-eluting devices in femoropopliteal artery revascularisations used longitudinal patient-level data to evaluate outcomes after five years of follow-up. Better survival was observed in patients receiving drug-coated balloons for intermittent claudication. Furthermore, better survival, amputation-free survival, and lower rates of cardiovascular events were observed with both drug-eluting stents and drug-coated balloons in patients with chronic limb-threatening ischaemia. Although this study used robust and commonly accepted methods, the problem of residual confounding remains unsolved. As patients who received drug-eluting devices were fundamentally different (in terms of baseline characteristics) from those who did not in the unmatched cohort, the possibility that unmeasured confounding may partly explain the findings should be considered. It is important to further develop ways to ensure high quality in observational studies.

Both the VASCUNET committee of the European Society for Vascular Surgery and the International Consortium of Vascular Registries may be able to help in developing commonly accepted standards for studies using real-world data from

registries and administrative databases.[26] Regulators and policymakers may take real-world evidence into consideration when discussing adverse events in underpowered randomised controlled trials.[6] Against that backdrop, the complex question of how to measure quality in the healthcare of patients with peripheral occlusive artery disease remains largely unsolved, especially concerning relevant patient-reported outcomes.[27,28]

Finally, while the ongoing discussion has primarily considered above-the-knee revascularisations for intermittent claudication, Katsanos *et al* recently published a systematic review and meta-analysis evaluating paclitaxel devices for the management of below-the knee lesions in patients with chronic limb-threatening ischaemia. They reported a similar mortality signal with these devices as they had with their first meta-analysis.[29] These new findings will most likely extend the ongoing discussion. It is certainly advisable to start another adequately powered and industry-independent randomised controlled trial involving proper endpoints in the longer-term follow-up. However, using a rather conservative power estimation, at least 7,000 patients would be necessary, and it will take a long time until the results will become available. This emphasises the underlying dilemma: valid data from randomised controlled trials are not always available and real-world evidence is available but still not commonly accepted as high-level evidence.

Summary

- Since the first paclitaxel devices were CE marked in 2009 and gained FDA approval in 2012, approximately 20 different devices are now available and (until December 2018) were increasingly being used.

- A systematic review and meta-analysis of summary-level data from randomised controlled trials found an association between paclitaxel devices and increased all-cause mortality in patients undergoing femoropopliteal artery revascularisations, which led to an ongoing heated discussion and a global stagnation of the application of the devices.

- The results from randomised controlled trials vs. observational studies in this field remain diametrically opposed. There is a signal towards higher mortality for paclitaxel devices vs. control therapies in summary-level data from randomised controlled trials, and a contrasting signal towards lower mortality among the paclitaxel exposed in real-world data. However, most randomised controlled trials were underpowered and most of the observational studies were limited by a short follow-up.

- The current study, outlined in this chapter, on paclitaxel devices in femoropopliteal artery revascularisations used longitudinal patient-level data to prove an association between drug-eluting devices and improved outcomes after five years of follow-up.

- Adequately powered prospective trials with long-term follow-up are needed to validly answer what is "real" behind the evidence from randomised controlled trials and observational studies.

- The aspect of quality of care in peripheral arterial occlusive disease treatment remains under represented in the literature.

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First-in-man study on the clinical use of a sirolimus-coated balloon in infrainguinal peripheral arterial disease

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Introduction

There is an abundance of data to show the superiority of drug-coated balloons and drug-eluting stents over plain balloon angioplasty in terms of long-term angiographic (primary patency rate, late lumen loss) and clinical results (target lesion revascularisation and device-related events).[1,2] The European Society of Cardiology (Level A evidence) and the Society for Cardiovascular Angiography and Interventions (Level 1A evidence) have both recommended that drug coated balloons should be used as the first-line endovascular treatment for a wide range of femoropopliteal indications in peripheral vascular disease.[3,4]

Concerns over paclitaxel

Various medical therapies related to percutaneous angioplasty aimed at preventing restenosis have been described in literature, but only the local delivery of the drug paclitaxel has so far been shown to improve the longevity of interventions for peripheral arterial disease; therefore, paclitaxel has been the mainstay of drug-coated balloons. The volume of data accumulated from randomised controlled trials and registries on the superiority of paclitaxel devices have been so convincing that they have led to a rapid worldwide adoption of paclitaxel devices as the gold-standard treatment for peripheral arterial disease.

However, recent data suggest long-term safety concerns with paclitaxel devices. Katsanos *et al* released, in December 2018, a systematic review and study-level meta-analysis, which reported a late all-cause mortality signal for patients in the paclitaxel-coated balloon and paclitaxel-eluting stent arms of randomised clinical trials.[5] The results of pooled data from 28 randomised controlled trials of paclitaxel-eluting technologies (24 studies on drug-coated balloons and four on drug-eluting stents) used in 4,663 patients showed that all-cause death at two years (reported in 12 randomised controlled trials) was significantly higher following the application of paclitaxel-coated devices (risk ratio [RR] 1.68, 95% confidence interval [CI] 1.15 to 2.47). Similarly, all-cause death up to five years (reported in three studies: one with four years' and two with five years' follow-up) was significantly higher in the paclitaxel devices arm (pooled RR 1.93, 95% CI 1.27 to 2.93). Meta-regression showed a significant relationship between

exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; p<0.001).

Given that paclitaxel eluting devices have already been used in thousands patients worldwide since their introduction into the peripheral endovascular arena over 10 years ago, these results have sent shockwaves across the international vascular community and healthcare regulatory authorities. The FDA swiftly published the first provisional warning in January 2019 on paclitaxel use. A second update was issued in March 2019, closely followed by safety notices released by Health Products Regulatory Authority (HPRA) in Ireland and Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in France.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) released a stronger statement on this issue in June 2019—their independent paclitaxel expert advisory group recommended withholding the use of paclitaxel coated/eluting devices from routine clinical use in patients with intermittent claudication "as the potential mortality risk generally outweighs the benefits" but noted that the devices may still be used in patients with critical limb ischaemia providing there is appropriate informed patient consent and an enhanced patient follow-up with adverse event reporting protocols. This resonated with similar advisories from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM, Germany). On the other end of the spectrum, the Federal Agency for Medicines and Health Products of Belgium issued an outright ban in July 2019 on the use of paclitaxel device—"do not use paclitaxel drug-coated balloon or drug eluting stents as a preferred treatment for intermittent claudication until further notice".

The final FDA update in August 2019, after a public meeting of the Circulatory System Devices Panel, concluded that for most patients, consideration of "alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents would provide a more favourable risk-benefit profile in light of currently available information. For individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel device outweigh the adherent potential risks of late mortality". As such, any decision to employ paclitaxel devices should be made only following complete disclosure of all potential adverse outcomes to patients in whom their use is clearly indicated.

Numerous arguments have been put forth to oppose the Katsanos meta-analysis. The increased mortality should be interpreted with caution given the multiple limitations in the available data. These limitations included pooling of studies of different paclitaxel devices that were not intended to be combined, lack of standardisation of trial endpoints that precluded meaningful data comparison, lack of patient-level outcomes, and a paucity of long-term follow-up data for a substantial proportion of the included trials (100% at 12 months, 43% at two years, and only 10% at four to five years).[6–12] Furthermore, there is no clear identified pathophysiological plausible mechanism for the late deaths.

Notwithstanding the above considerations, the general consensus is that the Katsanos paper was based on robust statistical analyses. Despite the limitations of the available data, the cautionary warnings that been issued by major healthcare regulatory authorities across the world are hardly surprising given their sole aim is to protect patient safety. Therefore, erring on the side of caution is prudent under these circumstances.

Sirolimus as an alternative

In the past year, the worldwide use of paclitaxel has dramatically reduced and if the current trend continues, paclitaxel devices may be ultimately consigned to the past. If this happens with no alternatives for antirestenotic therapies, the outlook for the vascular community would be bleak. Many vascular specialists perceive plain balloon angioplasty and bare metal stents to be basic technologies with poor outcomes. Reverting to using solely these for the management of peripheral arterial disease without other effective adjunctive treatments would be a major regression.

Sirolimus is a potent antiproliferative agent that prevents activation of smooth muscle cells after vascular injury. It places the cell, reversibly, into the G0 resting phase (cytostatic), whereas paclitaxel acts late in the cell reproductive cycle, interfering with microtubule formation during cell division, leading to cell death (apoptosis). Unlike paclitaxel, sirolimus has beneficial, potent anti-inflammatory effects and a broader therapeutic range. Its effects have been well-studied in similar realms of the coronary circulation, where sirolimus-eluting stents have been shown to be safe and more effective than paclitaxel devices. The drug is generally perceived by cardiologists as superior to paclitaxel because of lower restenosis rates in the coronary bed following sirolimus-eluting vs. paclitaxel-eluting stents.

Historically, packaging sirolimus onto a balloon platform that can be directly delivered to the vessel wall in an adequate quantity to inhibit neointimal hyperplasia has been difficult. Sirolimus has poor bioavailability compared to paclitaxel. Sirolimus in its natural state has slow tissue absorption, necessitating the use of a co-solvent to enhance tissue uptake. The sirolimus molecule also deactivates quickly when delivered into aqueous media, and first attempts to use the agent on a drug eluting stent in the superficial femoral artery have shown marginal or no benefit.

The emergence of nanotechnology has, however, enabled the application of sirolimus to the peripheral circulation. Preclinical animal model testing using novel phospholipid-encapsulated sirolimus nanocarriers coated on balloon-only catheters demonstrated efficient transfer of sirolimus to all layers of the vessel wall, achieving high tissue concentration of drugs that persisted for days after application. This has formed the foundation for the use of sirolimus in peripheral arterial disease.[13]

These early preclinical successes have been translated into the clinical arena within the cardiology field. The 12-month clinical outcomes of the novel MagicTouch sirolimus-coated balloon (Concept Medical) for the treatment of *de novo* coronary artery lesions and in-stent restenosis have been recently reported in the Nanolute Registry.[14] MagicTouch uses novel nanotechnology in which sirolimus is encapsulated in phospoholipid nanocarriers before being coated onto the surface of the balloon. Procedural success rate was high at 99.7% with bailout stenting required in only 6.6% lesions. Despite high rates of diabetes (47%), the overall device-related adverse cardiac events and target lesion revascularisation rates were low at 4.2% and 3.6%, respectively, at one year. The first direct comparison between paclitaxel- and sirolimus-coated balloons for the treatment of in-stent restenosis in the coronary bed were performed by Ali et al.[15] They found that sirolimus was non-inferior to paclitaxel in this setting, and the two devices provided equivalent six-month angiographic performance.

Figure 1A: Chronic total occlusions of anterior tibial artery, dorsalis pedis artery and posterior tibial artery.
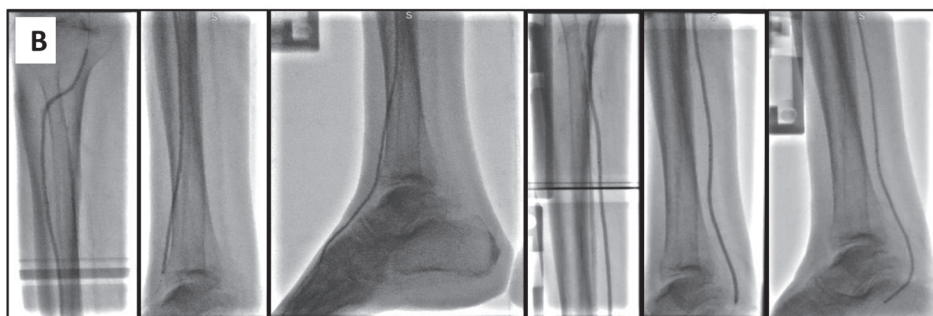
Figure 1B: Plain balloon angioplasties of anterior tibial artery, dorsalis pedis artery and posterior tibial artery using 2.5mm and 3mm diameter non-compliant balloons.

XTOSI study on sirolimus-coated balloon for peripheral arterial disease

The XTOSI first-in-man study of the MagicTouch sirolimus-coated balloon is an ongoing registry to investigate the safety and efficacy of this sirolimus-coated balloon in the treatment of both femoropopliteal and below-the-knee arterial lesions. It is a prospective, premarket, non-randomised, all comers single-arm trial. Target enrolment of 50 patients have been completed. The primary outcome was six-month primary patency defined by duplex peak systolic velocity ratio of <2.4.
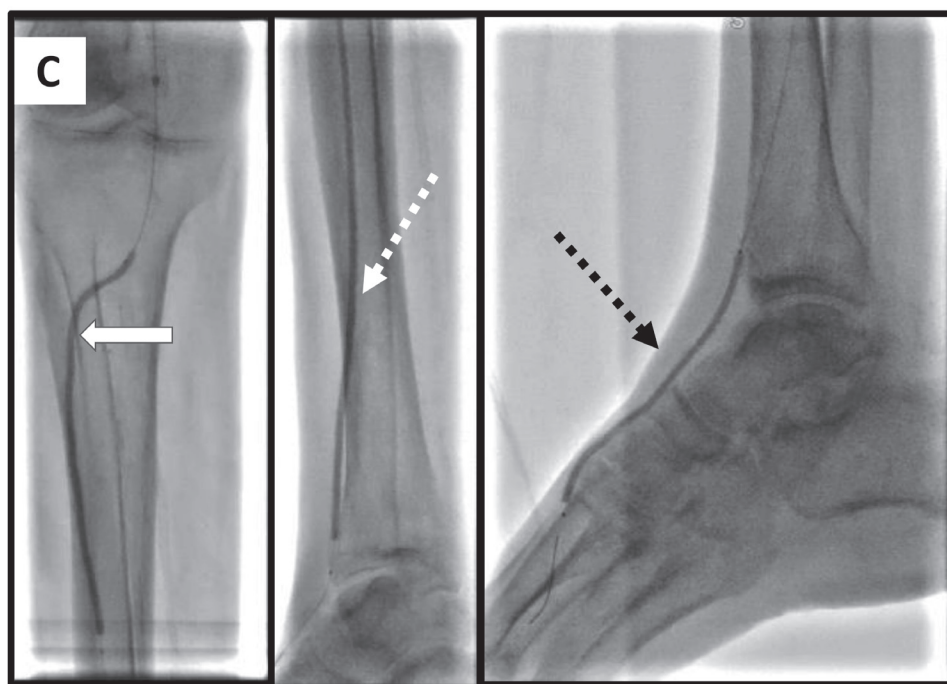
Figure 1C: Application of MagicTouch Sirolimus coated balloons onto anterior tibial artery (3mmX150mm, solid white arrow; and 3mmX150mm, dashed white arrow) and dorsalis pedis artery (2.5mmX100mm, dashed black arrow).
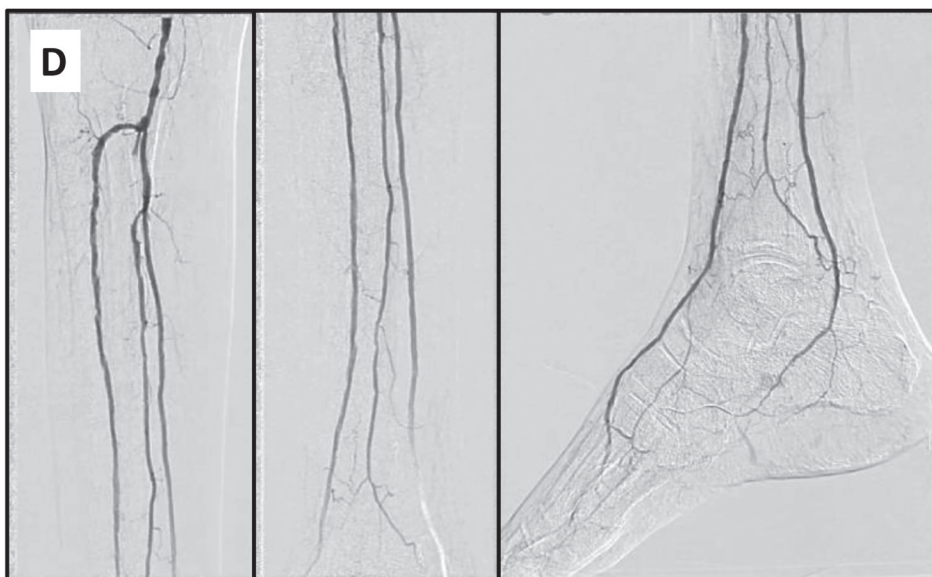
Figure 1D: Satisfactory flow via anterior tibial artery and posterior tibial artery to the foot with no evidence of distal embolisation or "slow flow" phenomenon.

XTOSI patients were a high risk cohort in which 90% had diabetes, 22% were on renal dialysis, 26% had previous myocardial infarction, and 80% had American Society of Anesthesiologists (ASA) scores of three or four. The vast majority of indication for angioplasty was for critical limb ischaemia (92% had Rutherford scores of 5 or 6; and 52% had Wound, Ischemia, and foot Infection

[WIfI] scores of four or more). The majority of application of MagicTouch sirolimus-coated balloon was onto below-the-knee arteries (62%).

The six-month interim data for 40 patients are available. Overall primary patency at six months was 80%. Subset analyses showed six-month primary patency for femoropopliteal and below-the-knee arteries of 88% and 74% respectively. The six-month freedom from target lesion revascularisation for the whole cohort, femoropopliteal and below-the-knee arteries were 89%, 94% and 84% respectively. Safety endpoint which was defined as composite of absence of 30-day mortality, 30-day major limb amputation and six-month target lesion revascularisation was 85%. The six-month amputation-free survival and limb salvage rate were 87.5% and 97.5% respectively.

There was no reported distal embolisation or "slow flow phenomenon" after application of sirolimus-coated balloon in the below-the-knee vessels. An advantage of the MagicTouch sirolimus-coated balloon is the absence of flaking of the sirolimus drug or carrier from the balloon. Figure 1 demonstrates the successful application of MagicTouch sirolimus-coated balloon in below-the-knee and dorsalis pedis arteries with no untoward effects of distal shedding.

The MagicTouch sirolimus-coated balloon was granted Breakthrough Device Designation by the FDA in August 2019 for the treatment of below-the-knee disease. In October 2019, it received CE mark certification for the treatment of peripheral arterial disease.

Conclusion

Sirolimus-coated balloons may offer a new alternative for drug eluting technologies in the treatment of peripheral vascular disease with promising results from initial studies. The XTOSI first-in-man study showed promising efficacy and safety for the use of MagicTouch sirolimus coated balloon for both femoropopliteal and below-the-knee disease. Level one data in a larger population are urgently needed and plans are underway for randomised controlled trials of MagicTouch sirolimus-coated balloons vs. plain balloon angioplasty for both femoropopliteal and below-the-knee disease (FUTURE SFA and FUTURE BTK randomised controlled trials).

Summary

- Paclitaxel devices are effective in preventing restenosis in femoropopliteal arterial disease.

- However, the Katsanos meta analyses showed increased long-term mortality in the paclitaxel-eluting devices arm at two years and five years.

- Major health regulatory bodies including FDA and UK MHRA have issued warnings related to the use of paclitaxel devices.

- Sirolimus is an alternative antiproliferative agent with potentially better safety and efficacy profile.

- Novel nanotechnology has enabled the effective delivery of sirolimus into vessel walls via sirolimus-coated balloons.

- XTOSI study interim analyses have shown promising data on the efficacy and safety of MagicTouch sirolimus-coated balloon for both femoropopliteal and below-the-knee indications in peripheral arterial disease.

- Level 1 data in a larger population for the efficacy and safety of sirolimus-coated balloon in peripheral arterial disease are urgently needed.

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National variation in the incidence of major amputation in diabetes

W Jeffcoate

Introduction

In 2001, a study showed that there was an eight-fold variation in the incidence of major amputation in people with diabetes in the US Medicare population; another study showed that this variation persisted, unchanged, 10 years later.[1,2] Additionally, a 2012 study indicated a 10-fold variation in the incidence of major amputation between different primary care trusts in England (UK).[3] Although the overall incidence of major amputation in England has fallen by some 10% since 2012, the extent of variation has decreased only marginally—to seven-fold (between care commissioning groups) even after adjusting for gender and ethnicity data.[4] This means that despite benefitting from a centrally funded national health service, a patient with diabetes may be eight times more likely to lose their leg if they live in one part of England than a patient who lives in another part of England.

As well as being an operation that is associated with marked reduction of life expectancy, major amputation is obviously life changing. Therefore, variation in the incidence major amputation to the degree seen in England is likely to reflect considerable inconsistencies in the quality of healthcare delivery. All those responsible—whether administrators or clinicians—should be required to review the causes of this variation and to seek to eliminate it as quickly as possible. Such variation would not be tolerated in any other branch of medicine—for example, cancer, stroke or heart disease.

Cautions required in interpretation of amputation data

The usefulness of major amputation as an outcome measure in diabetes

The incidence of major amputation is a flawed but, nevertheless, valuable measure of the disease outcome in diabetes. This contrasts with the measure of "lower extremity amputation", which combines both major (above the ankle) and minor amputations; lower extremity amputation is of limited value except as a measure of cost burden to healthcare providers.

The principal advantage of using major amputation is that data are routinely, and relatively reliably, collected as part of hospital activity statistics in many countries. The limitations are mainly concerned with the variable documentation of diabetes in discharge data and where national diabetes databases exist, these may be limited to those who receive diabetes-specific treatments and will not include those managed by diet alone. Other limitations relate to the general failure to

distinguish between primary surgery and reoperation, and to the exact site of the operation not being recorded.

Choice of denominator

The incidence of major amputation must be expressed in terms of the relevant population with diabetes, and this is not possible where there is no nationwide or whole population healthcare delivery network with the necessary data. If it is expressed in terms of the total population, any variation will include that which results from the differences in diabetes prevalence.

For similar reasons, amputation data in diabetes should ideally be adjusted for ethnicity (as they are in the data published annually in the Diabetic Foot Profiles of Public Health England). This is because amputation in diabetes is nearly always preceded by ulceration and the incidence of foot ulcers is known to vary between racial groups—being relatively low in South Asian populations with diabetes, for example, when compared with Caucasian races. The impact of ethnicity can, however, be more complex in countries that lack a health service that is free to all at the point of delivery because it can be confounded by the coincident impact of social deprivation and, hence, of variable access to effective healthcare. A fuller summary of the problems encountered in the interpretation of the results of amputation incidence can be found elsewhere.[5]

Status of major amputation as a measure of ulcer outcome in diabetes

The main weakness, however, associated with using major amputation as a measure of outcome of foot disease in diabetes relates to the fact that amputation is just an operation. As such, it reflects not only the effect of the disease but is influenced by other clinical circumstances and by decisions made by both the surgical team and by the patient and their family. Operations and other treatment choices are not usually used to define clinical outcomes in other conditions: mastectomy is not used to define the outcome of breast cancer and nor is colectomy used for colon cancer.

The incidence of major amputation

The incidence of major amputation related to diabetes in England

The median annual incidence of major amputation in patients with diabetes is currently 8.2 per 10,000 (annualised data from 2015 to 2018). This is lower than that reported in many other countries, and it is also far lower than that reported from regions in England 25 years ago. In the mid-1990s, the incidence of major amputation was as high as 31.1 per 10,000 in Middlesbrough (UK) and 41.4 in Ipswich.[6,7]

Data from the National Diabetes Foot Care Audit of England and Wales has recently reported that of 24,200 foot ulcers referred for specialist assessment between April 2015 and March 2018, 385 major amputations were undertaken within six months (representing just 1.6% of all referrals).[8] When the data are divided into those with less or more severe ulcers at the time of first assessment, the incidence major amputation within six months were 0.7% and 2.7% respectively.

The National Diabetes Foot Care Audit has also shown that the quicker the referral for expert assessment of any new ulcer episode (as recommended is NICE

guidance), the less likely is the ulcer to be severe, the higher in the incidence of healing within 12 weeks, and the lower are the incidences of both hospital admission and of major amputation.

Modelling to document the relative contribution of patient and ulcer factors or variation in clinical outcome in England and Wales

Data from up to 29,000 ulcers registered with the National Diabetes Foot Care Audit have also now been used to explore factors statistically linked to different clinical outcomes: healing and being ulcer-free within 12 weeks, occurrence of major amputation, and/or death within six months. While more detailed results of modelling are documented elsewhere, the findings were as follows:[8]

Being alive and ulcer-free at 12 weeks

A statistical link was observed between 12 separate variables. Of these, the strongest associations with adverse outcome were with the presence of peripheral arterial disease and with ulcer depth, but the overall model strength was only weak.

Occurrence of major amputation within six months

Nine separate variables were linked with major amputation and of these, the relationship was strongest with peripheral arterial disease and with ulcer area. The overall model strength was reasonable but more close to strong.

Death within six months

Nine variables also had consistent associations with mortality and of these the relationship was strongest with age and with pre-existing heart failure (both details of the person rather than the ulcer). The overall model was more strong.

Although the strength of these models were moderate to strong, they suggest nevertheless that factors other than those identified contributed to the variation that was observed between different providers and localities. One of these may be the quality of glucose control in the years preceding amputation. It emerged in multivariate analysis as the dominant risk factor for major amputation in a recent report on complications by the parent National Diabetes Audit.[9]

Other factors that contribute to variation in outcome

There are four strands of circumstantial evidence that suggest that of other potential determinants of the outcome of ulcer management (and hence of variation in the incidence of major amputation). It is probable that some relate not so much to details of the patient or their ulcer but more to the process of care delivery.

Feedback from well-performing centres

The opinion of the 10 best performing services identified by the National Diabetes Foot Care Audit was sought on the factors that were central to effective care. All 10 reported that the key to outstanding performance lay in the structure of the care pathway (enabling prompt expert assessment of all newly presenting ulcers) and in the close integration of services provided by different healthcare specialists.

Variation in patterns of clinical decision making

A study conducted two decades ago explored possible explanations for the varying incidences of major amputation in four centres in England that had participated in the multinational Global Lower Extremity Amputation Study. This follow-up study suggested that one factor that could have contributed to the high incidence was the personal opinion of surgeons at participating centres regarding indications for amputation.[10]

Far stronger evidence for the existence of differing professional attitudes to the need for amputation comes from the work of Holman and colleagues[3] and more recently from Barron and colleagues at Public Health England (data presented at Diabetes UK 2019). Both these groups demonstrated strong direct statistical associations between higher incidence of major amputation in diabetes and both (a) higher incidence of minor amputation in diabetes and (b) higher incidence of major amputation in people without diabetes. These findings strongly suggest that the threshold for undertaking amputation varies significantly from centre to centre.

Geographical clustering of high amputation and low amputation locations in the USA

The study that explored the variation in incidence of major amputation in the USA 10 years ago demonstrated significant clustering of localities with either low or high incidences of major amputation.[2] The authors speculated that this clustering might reflect geographical variation in professional attitudes towards best practice acquired during postgraduate education of specialists in training.

Major improvements following the introduction of new care pathways

The fourth, and the possibly most convincing, strand of evidence relates to the outcome of action taken by centres in England that were identified as having a very high incidence of major amputation 25 years ago. One of these (Middlesbrough) had reported an incidence of major amputation of 31.1 per 10,000 people with diabetes in the Global Lower Extremity Amputation study previously cited. This group responded by establishing a dedicated multidisciplinary service for the management foot ulcers in diabetes and urged all community staff to refer every new ulcer at the earliest opportunity. Despite the fact that the spectrum of treatments available was largely unchanged, the incidence of major amputation at this centre fell dramatically from 31.1 to 7.6 per 10,000 people with diabetes within five years.[6] This initiative was mirrored by a very similar, but an independent, study conducted in Ipswich at exactly the same time and which demonstrated a fall in incidence of major amputation from 41.4 per 10,000 (cited earlier) to 6.7 per 10,000 within five years and thereafter maintained.[7] These two remarkable studies illustrate the potentially enormous benefit achievable by facilitating the delivery of a prompt and truly multidisciplinary service for all newly presenting foot ulcers. Similar improvements accompanying the efficient delivery in integrated care have been reported more recently from the West Country (UK).[11]

Conclusion

Although the evidence is indirect and far from scientifically proven, it is highly likely that the current wide variation that persists in the incidence of major amputation in England and the USA could be explained by aspects of professional

performance—whether in the effectiveness of routine diabetes care, in the structure of care pathways, in the varying times to referral for expert assessment or in the varying opinions of individual professionals on aspects of best management.

Observations on variation in incidence of major amputation in diabetes were one of the main triggers of the potentially important, albeit probably time-limited, injection of "transformation funding" by NHS England three years ago. A large number of services (but by no means all) embraced this scheme but it is still too early to know whether the investment will be associated with tangible improvements and if so, whether they will be maintained. Nevertheless, that this initiative was considered necessary signals the recognition that a "sea change" is required to improve a situation that should have been resolved a decade ago.

The author thanks both Naomi Holman and Emma Barron for their work in first highlighting the variation which exists in major amputation across England.

Summary

- The available evidence suggests that the incidence of major amputation varies by as much as seven times even in countries, such as the UK, that have a nationalised health service.

- Variation of such order would not be tolerated in the management of cancer, stroke or cardiac diseases and should not be tolerated any longer in (or by) people with diabetes.

- The extent of the variation is as clear as any single measure can be and it can only be concluded that the quality of care being delivered in some localities is unacceptably low.

- The fact that such variation has persisted in England for more than 10 years since it was first publicised is an indication of startling failure by those responsible for the design and delivery of care.

- There is much circumstantial evidence that persisting variation reflects differing structures of care, the possible impact of differing professional opinion and the need for more effective integration of care between the multiple professional groups involved.

- If the incidence of major amputation across England was reduced to below the current median, the number of limbs lost because of diabetes each year would be reduced by one-third, from approximately 3,000 to 2,000.

- And while these arguments are largely based on data from England, the need for urgent review is clearly of equal importance in other parts of the UK as well as in other countries.

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Current era outcomes of prosthetic bypass grafting to below-the-knee targets

SL Blackwood and MT Menard

Introduction

Infrainguinal open surgical bypass remains the gold-standard treatment for lifestyle-limiting claudication and critical limb ischaemia. It has long been established that autogenous venous conduit confers the best results for below-the-knee bypass grafts.[1] However, prosthetic bypass grafts have been shown to function as viable bypass conduits to tibial targets when sufficient venous conduit is unavailable. In recent decades, long-term patency rates of prosthetic grafting have increased as patient selection, perioperative medical management, smoking cessation programmes, and graft surveillance have all improved. Even with routine use of preoperative duplex ultrasound, up to one third of patients are found to have no suitable autologous veins. Common reasons for either the greater saphenous vein or alternative venous conduits to be unavailable or unusable include post-phlebitic scarring, varicose vein disease, prior harvest for lower extremity or coronary artery bypass, chronic leg oedema, and the need to preserve veins for dialysis access. In such situations, prosthetic conduits can be an appropriate and successful option for lower extremity surgical revascularisation, even for targets distal to the popliteal artery. Recognising that autologous vein remains superior and tibial and pedal endovascular techniques are becoming increasingly popular, this chapter will evaluate both historic and current outcomes of prosthetic bypass grafts to below-the-knee targets.

General overview

Synthetic grafts have excellent patency when used as conduits for large diameter vessels. For example, five-year primary and secondary patency rates of 85% and 92% have, respectively, been reported for aortobifemoral grafts undertaken for occlusive disease.[2] Early cumulative patency and limb salvage rates of femoral to above-the-knee popliteal synthetic grafts approach those of autologous single segment great saphenous vein, long known to be the most efficacious conduit available. When the great saphenous vein is not available, upper extremity veins, short saphenous vein, or composite vein are all excellent and proven alternatives. McPhee *et al* have shown that for critical limb ischaemia when a single segment of great saphenous vein is not present, similar patency (near 50% at five years) and limb salvage rates (80–90% at five years) can be achieved between prosthetic and composite vein grafted to the below-the-knee popliteal artery or tibioperoneal trunk.[3] In their study, the rate of anticoagulant use was higher for those patients receiving prosthetic grafts, and their results were more favourable than historic

reports of prosthetic grafting to the below-the-knee popliteal region, where one- and three-year patency rates closer to 40% and 30%, respectively, are more typical.[1]

The issue of when best to use prosthetic grafts and what results can be expected when doing so in the lower extremity is influenced by numerous factors, which can make direct head-to-head comparisons between graft conduits challenging. Nevertheless, there is now a robust library of evidence that reflects advances in prosthetic materials, adjuvant medical therapy and overall clinical practice.

Indication for surgical intervention

The two predominant indications for surgical reconstruction are lifestyle limiting claudication and critical limb ischaemia, the latter defined by rest pain or a non-healing wound. Historically, the long-term outcomes of open surgical bypass are significantly better for patients with claudication than with critical limb ischaemia. In a study by Whittemore *et al* of 300 infrainguinal polytetrafluoroethylene (PTFE) bypasses, cumulative patency rates were notably better at five years for claudicants
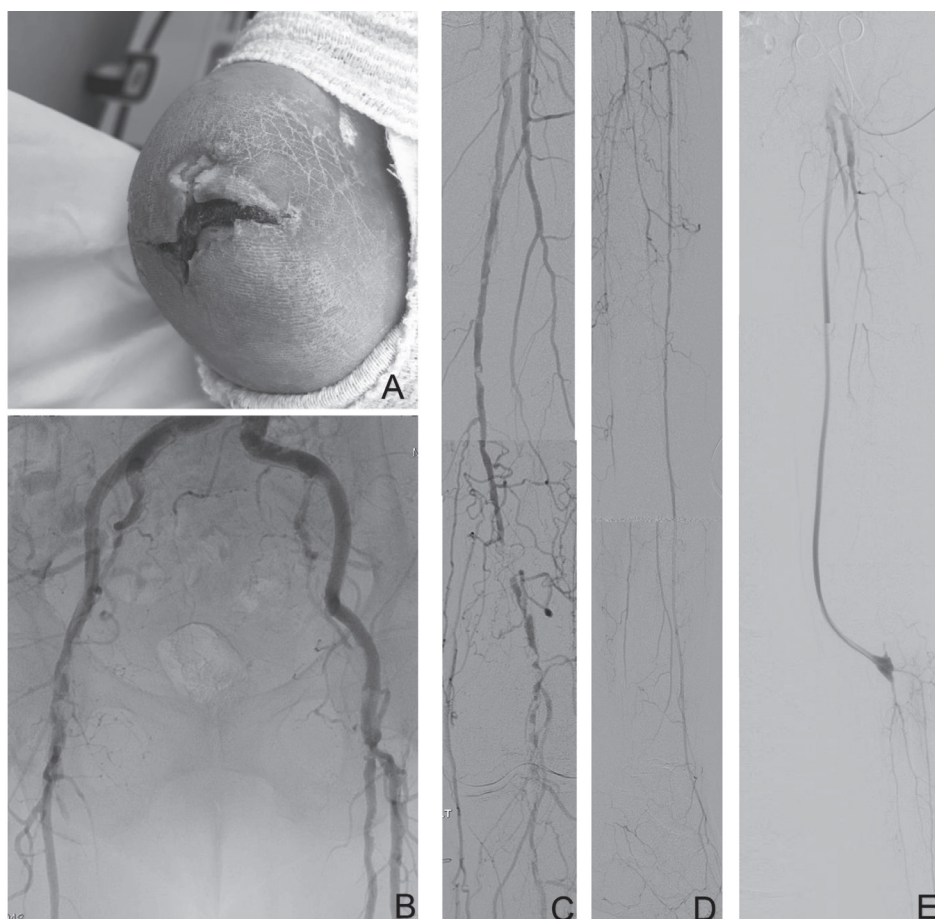
Figure 1: An 85-year-old woman with a gangrenous left heel ulcer, severe rest pain, short-distance claudication and poor-quality venous conduit. Her rest pain and claudication resolved and heel ulcer healed following tibioperoneal trunk endarterectomy and femoral-to-tibioperoneal trunk bypass with Distaflo prosthetic conduit (BD). (A) Heel ulcer. (B–D) Preoperative angiography indicating preserved Inflow and diseased femoropopliteal and tibial arteries. (E) Intraoperative completion angiogram.

(n=85; 57%) compared to those who underwent surgery for limb salvage (n=215; 24%).[4] Recent studies continue to illuminate the comparatively poor long-term success of bypasses to tibial and below-the-knee popliteal sites, with only a third of the bypasses remaining free from intervention or thrombosis at three years.

Choice of graft material

Over the years, different synthetic options have been used, with patterns of use primarily dictated by surgeon preference. The two main prosthetic graft materials are polyethylene terephthalate (PET or Dacron) and PTFE, both of which have been favourably modified over time. While PTFE has become the most commonly used bypass graft material for infrainguinal reconstruction, some surgeons prefer the flexibility of Dacron; there is no evidence to show that one graft outperforms the other in this anatomic location. One representative study, a multicentre prospective randomised trial evaluating Dacron and PTFE grafts in the above-the-knee popliteal artery, found no difference in three-year primary or secondary patency rates (primary patency rate, 62% ±14.4 for Dacron; 57%±15.5 for PTFE).[5]

The three main types of Dacron conduit used for infrainguinal reconstruction include a standard woven polyester version, heparin-bonded Dacron and a more recently available externally-supported ringed Dacron outer graft fused to an internal heparin-bonded expanded PTFE graft. The most widely used contemporary prosthetic graft is the Propaten PFTE graft (Gore), which incorporates a layer of heparin bonded to the inner lumen. Available either supported or unsupported by rings, it represents a significant advance over the prior iterations of PTFE. A recent study of 252 limbs undergoing bypass to either the above- or below-the-knee popliteal artery showed improved primary patency at up to five years with Propaten compared to standard, non-heparin bonded PTFE grafts.[6] A competing PTFE option, the Distaflo (BD) graft, is lined with carbon and has an engineered distal cuff that obviates the need for a distal anastomotic vein cuff. Three cases using the Distaflo graft are shown in Figures 1 and 2.
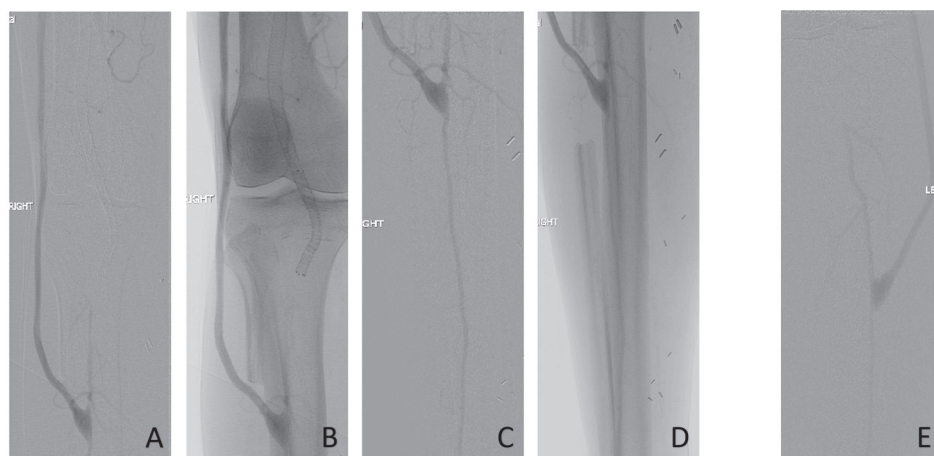
Figure 2: A 67-year-old man with severe comorbid disease and status post prior failed right leg femoropopliteal stenting and failed bilateral bypass grafting with saphenous vein, with bilateral recurrent tissue loss. Symptoms resolved with staged right and then left profunda-peroneal grafting with Bard Distaflo prosthetic conduit, via a lateral approach following partial fibulectomy. Completion angiogram on the (A–D) right and (E) leg graft on the left. Graft patent at four years. Note prior failed stents in image B and fibulectomy in images B and D.

Use of a vein cuff

Adjunctive distal anastomotic vein cuffs have shown utility in improving patency rates of prosthetic bypass grafts, particularly in the setting of distal tibial targets. A wide range of cuff configurations, some as simple as a patch and others more creative and complex, have been devised and championed over the years.[7–10] Despite the advantages shown in a number of reports, a recent Cochrane review found no difference in patency or limb salvage when comparing bypass grafts with or without vein cuffs in the below-the-knee popliteal segment. Notably, the level of evidence was rated as weak, largely because of the lack of standardisation in reported results, small sample size comparisons, and the paucity of high-quality trial data in general.[11] In one study of 352 patients with critical limb ischaemia who underwent either femoral to popliteal (n=202) or femoral-to-distal (n=150) bypass with PTFE prosthetic, neither cohort derived any benefit in primary or secondary patency or limb salvage with the addition a vein cuff.[12] In a propensity matched, multi-institutional cohort analysis of 264 patients using the Vascular Surgery Group of New England database, combined with our prospectively maintained institutional registry, we found the use of a distal vein adjunct was protective in prosthetic bypass surgery against major adverse limb events.[13] Patients receiving a vein cuff were more likely to have a distal tibial target and be discharged on anticoagulation, highlighting their clinical and anatomic complexity. A smaller report comparing 112 patients undergoing tibial bypass found comparable one-year primary patency of single segment saphenous vein (n=50) to heparin-bonded ePTFE grafts (n=62) with an adjunctive vein cuff (86% vs. 75%, respectively).[14] While more recent results show promise with regard to generally improving efficacy with prosthetic grafts, the majority of studies are limited by small sample size and longer-term durability continues to favour vein bypass.

Creation of a distal arteriovenous fistula

End-stage renal disease or long-standing diabetes can lead to progressive occlusive disease of the small vessels of the foot and result in a so called "desert foot". The hallmark of such extreme distal disease is one in which there are no identifiable vessels below the ankle and loss of the arcuate plantar arch. Many surgeons believe this anatomic pattern, which renders patients at higher risk for postoperative graft thrombosis due to a lack of sufficient arterial runoff, is growing in prevalence. Some authors have advocated that the creation of an arteriovenous fistula distal to a high-risk venous or prosthetic bypass graft as an adjunctive technique to enhance outflow leads to better graft patency and limb salvage.[7,10] Decreasing the compliance mismatch between the stiff graft material and the target artery and the overall compliance will, in theory, favourably alter distal anastomotic shear stress and resultant intimal hyperplasia formation. Using the vein fistula as a cuff to create a more patulous distal anastomosis can further mitigate the impact of any intimal hyperplasia that does develop. Paty *et al* prefer to construct the arteriovenous fistula with the vena comitans 5–10cm downstream of the distal anastomosis to recruit the outflow of the intervening arterial segment side branches.[15] With such efforts, primary patency rates for prosthetic grafts to infrapopliteal targets have improved from 30% to 48% at two years in one study and to near 60% at three years in other reports.[7,9,10]

Use of antithrombotic therapy

The benefits of antiplatelet therapy in reducing the risk of stroke, myocardial infarction and overall cardiovascular mortality in peripheral arterial disease patients are well demonstrated. Defining optimal antiplatelet and anticoagulation therapy following vein or prosthetic lower extremity grafting, on the other hand, has long been an elusive goal. The Dutch bypass oral anticoagulants or aspirin study suggested that vein bypasses fare better with oral anticoagulation while prosthetic grafts have better results with antiplatelet therapy.[15] An older randomised controlled trial comparing no treatment to dual antiplatelet therapy (DAPT) in both venous and prosthetic infrapopliteal grafts found improved patency rates (85% vs. 53%) in the prosthetic group with DAPT.[16] The CASPAR study found similar results with DAPT, though at the cost of an increased risk of non-severe bleeding.[17] One group demonstrated that with appropriate antithrombotic adjunctive therapy, short-term patency, limb salvage and mortality rates following prosthetic grafting to below-the-knee targets can approach that of single segment greater saphenous vein.[18] With the relatively recent introduction of several novel anticoagulants, it is anticipated that patency may improve further.[18,19] In particular, the results of the Voyager trial are eagerly awaited, as they may further elucidate the potential benefit of rivaroxaban following open or endovascular intervention for symptomatic peripheral arterial disease.[18]

Postoperative surveillance programme

Bypass graft surveillance remains an important component of the long-term success of any limb salvage effort. Appropriately timed surveillance can identify preocclusive stenotic lesions and prompt revision of a threatened graft, leading to improved primary-assisted and cumulative patency. Accenting this point, while primary patency rates have remained relatively stable through the years, cumulative patency rates have risen in the contemporary period due to graft surveillance, early reintervention, and the use of antithrombotic therapy.[19]

Conclusion

Looking at our own unpublished retrospective experience with femorotibial prosthetic bypass, we compared 35 Distaflo and 27 Propaten grafts placed between 2007 and 2017 for critical limb ischaemia. The three-year primary patency in the Propaten group was significantly better at 76% than the 48% seen with Distaflo (p=0.04). Limb salvage at three years was equivalent in both groups (75% Propaten vs 73% Distaflo, p=0.433). These results are promising and demonstrate that limb salvage and relatively good patency can be achieved in patients who need operative bypass to distal targets but are without adequate autogenous conduit.

Summary

- Synthetic bypass grafts should be considered for limb salvage even to distal tibial targets if the great saphenous vein is unavailable, as some patients may only need short-term patency to heal ulcers or surgical wounds.

- There is currently no published evidence to suggest that one prosthetic graft conduit when used below-the-knee is superior.

- Adjunctive vein cuffs or distal arteriovenous fistulas may improve primary and secondary patency rates in PTFE grafts to below-the-knee targets.

- Patients with prosthetic tibial bypass grafts should be considered for DAPT as the risk of major bleeding is low and this regimen improves graft patency.

- The use of duplex ultrasound for graft surveillance and appropriate revision of threatened grafts is recommended given improved cumulative patency.

- The role of optimal anticoagulation following prosthetic lower extremity grafting has yet to be fully defined and awaits further high-quality randomised control trial data.

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Perfusion as a new concept to predict outcome after revascularisation in limb ischaemia

JA Reekers and KMB Huntjens

Introduction

A patient with chronic ischaemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease is how we today define patients who should be treated with revascularisation. But after revascularisation it is often difficult to make a reliable prediction about the final clinical outcome of such an endovascular revascularisation procedure for chronic limb-threatening ischaemia (CLTI). The reason for that is both insufficient clinical science during the last decades (studies that have been conducted with variable inclusion criteria, analysing patients with mild and severe ischaemia in one study) and the emphasis on non-clinical proxy endpoints.[1–2] Another important reason is the current lack of focus on understanding the mechanism and physiology of CLTI. Also the subjective observation ("eye balling") that angiography shows a better "image" after the procedure is not always a guarantee for a good clinical outcome. There have, however, been promising attempts to overcome this problem and to develop a prediction model based on a combination of independent risk factors (wound extent, degree of ischemia, and extent of foot infection), such as the Society for Vascular Surgeons (SVS) Wound, Ischaemia, and Foot infection (WIfI) classification system.[3] Although the original WIfI classification and recent modifications have shown very promising results, it also contains a subjective parameter, like the degree of ischaemia.[4] Ischaemia is not a disease by itself but rather a manifestation of an underlying disease(s); it is a container concept, as there can be various causes for ischaemia and these can be either external (inflow obstruction), self-contained, or be a summation of various aetiologies, like in diabetic foot disease.

This lack of focus on the various causes for ischaemia is manifested by the mantra that increasing the blood flow to the foot is always the best solution for the problem of CLTI. Everything we do today to treat CLTI is based on this mantra of opening vessels to improve the flow to the foot. There are, however, ample examples which show that flow improvement is not always the solution and, moreover, flow improvement is sometimes not needed to treat CLTI. Of all diabetic CLTI patients who undergo a successful endovascular or bypass revascularisation, >20% will still undergo major amputation within 12 months.[5–7] In >50% off all amputations, the revascularisation is still patent at the time of amputation.[6] This amputation percentage has not decreased over the last decade despite major advantages in percutaneous revascularisation technologies.[8–9]

Small artery disease, as recently recognised by Ferraresi, is a good example that improving inflow is not the optimal treatment for CLTI.[10] Another example that vessel obstruction is not always the cause for ischaemia is non-obstructive coronary artery disease, which is now recognised as a new entity causing ischaemia of the myocardium without any inflow obstruction.[11] These are only two examples that inflow obstruction is not always be the most important cause of CLTI. There are more well-known other causes for tissue ischaemia, such as diabetic microangiopathy, anaemia, hypovolemia and dehydration. The absence of a good and objective definition of ischaemia is one of the main reasons why there is no multifactorial thinking about ischaemia. The old consensus definition, based on ankle-brachial index, pressures, TcPO2, has already, for decades, been proved not to match with clinical reality.[12–13] Patients outside the consensus guideline sometimes need urgent revascularisation while other patients, with the same ischaemia, could experience good wound healing without any revascularisation (and without amputation).[14–16] The term "chronic limb-threatening ischaemia" was recently introduced to underline the fact that ischaemia is a continuum. CLTI is a clinical syndrome defined by the presence of peripheral arterial disease in combination with rest pain, gangrene, or a lower limb ulceration for more than two weeks' duration. Venous, traumatic, embolic, and non-atherosclerotic aetiologies are excluded.[17] Because peripheral arterial disease is hereby defined as the only cause for limb ischaemia, it was converted in daily practice by a simple new definition of ischaemia—CLTI is equal to shortage of blood(flow). This new definition is the main cause for our current thinking about CLTI, in which revascularisation is the holy grail, leading to the current emphasis on revascularisation and patency. True figures about clinical failure of revascularisation in real CLTI are hidden by the opportunistic and propagandistic way we perform science about CLTI today.[2]

It is time for a better and more physiological definition of limb ischaemia. Also the term "limb-threatening" has no meaning because we can only know how limb-threatening the disease was in retrospect, and then only if we do not treat the patient at all. The new definition of CLTI suggests that a limb will be lost if we do nothing, which is often not the case.[14–16] In cardiology, the definition of ischaemia is clearer as it is called "cardiac ischaemia". Cardiologists recognise acute ischaemia, which is myocardial infarction based on an acute occlusion, and intermittent ischaemia, which is angina pectoris. Therefore, talking about "limb ischaemia" would be more clear. This limb ischaemia can be intermittent or permanent. Permanent ischaemia can be with or without tissue loss. Intermittent ischaemia and permanent ischaemia are two different diseases, only 5% of the patients with intermittent ischaemia progress to having permanent ischaemia. Therefore, comparing treatment outcomes of both groups in one study design is a scientific flaw. Limb ischaemia is a more inclusive and a more physiological definition that also recognises that the primary cause for limb ischaemia is not the shortage of blood(flow) but a shortage of oxygen in the tissue. Decrease of blood inflow is the most encountered and recognised macrovascular reasons for ischaemia, but there are many other aetiologies that can lead to permanent tissue ischaemia. The following aetiologies have all been recognised as causing tissue ischaemia: decreased nitric oxide production; increased peroxynitrite production; increased platelet activation; increased leucocyte adhesion; microvascular thrombosis; precapillary arteriole collapse; and impaired oxygen exchange. The best method, therefore, to

measure limb ischaemia would be a direct measurement of oxygen in the tissue, and not, as is currently done, in the skin. There are some interesting developments in this direction, but we have to wait and see how this will develop.[18]

To understand and guide our endovascular revascularisation procedures, we also need new and more physiological parameters to guide us. First, we need more information about how to make a decision, during the procedure, about how many vessels and which vessels need to be opened to obtain a good clinical result. Opening more vessels will take more time and will increase the risk for complications. If one vessel revascularisation is enough, this will be beneficial for the patient. Secondly, we need to be able to predict if revascularisation will have a good clinical result. If a poor clinical outcome is to be expected despite optimal angiographic revascularisation, the consequence could be that any reintervention might be in vain. This would protect the patient from a redundant and unnecessary reintervention

Tissue perfusion

Definitions:
- Perfusion (P) = the total amount of blood (Vb) in a volume of tissue (Vt) during a defined period of time (t). P=Vb/Vt.t.
- Macrocirculation = the circulation of blood in the arteries to the tissue of the organs.
- Microcirculation = the total of all the arterioles (well innervated and 10–100µm in diameter), capillaries (not innervated and 5–8µm in diameter) and post-capillary venules in the tissue. At the level of the capillaries oxygen is transported to the tissue (muscle) cells by diffusion, to be transformed into energy by the mitochondria (ATP).
- Perfusion angiography = the technique to image and to analyse the tissue perfusion in a defined area of tissue during a defined period of time. This technique has been described previously.[19–20] A meticulous acquisition protocol should be followed.
- Smart perfusion (newer version of the 2D-perfusion software) or 2D-perfusion software = the software algorithm to analyse the perfusion angiography data.

A simple description of the basic physiological mechanisms to protect tissue from shortage of oxygen

In reality, the mechanisms for protection of tissue from ischaemia are much more complex than described in this chapter but to understand and to use perfusion angiography these basic physiological principles are sufficient. Under normal physiological circumstance, any shortage of oxygen in the tissue (ischaemia) will set off two mechanisms to increase the inflow of blood (oxygen) to the microcirculation.

Vasodilatation of the macrocirculation
This is triggered by the production locally of nitro oxide, which will result in vasodilatation and, thereby, increase in inflow. The magnitude in which vessels dilate is dependent on the conditions of the vessel wall, but it is assumed

that during permanent ischaemia, there is maximal macrovessel dilation to optimise inflow.

Secondly lowering of the peripheral resistance (opening of the arterioles) to increase the inflow to the microcirculation. Lowering of the peripheral resistance by dilation of the arterioles (precapillary sphincters) is party done by nitro oxide. But there is also another mechanism that controls the arterioles, and that is through the alpha-receptors and the sympathetic nerve. This system is directed by local vessel-wall pressure distention and the central nervous system.[21–23] This is a complex system, not fully understood. How much the arterioles will dilate in permanent limb ischaemia is probably different in every patient.

What does perfusion angiography measure?

The blood flow through the foot consists of four territories.

- Flow through the macrocirculation, which are the inflow vessels. Only the larger macrocirculation vessels are depicted on angiography. This macrocirculation is <10% of the total flow through the foot.
- Flow through the microcirculation to allow oxygen exchange. The capillary territory is very large and contains about 80% of the total blood flow through the foot. The flow is slow and the pressure in the capillaries is low and regulated by the precapillary sphincters. This is the same as peripheral resistance (Figure 1).
- If all the macrocirculation inflow to the limb would be transported through the capillaries, this would lead to very high capillary pressure with permanent capillary damage.
- To keep the balance between the total inflow and the minimal capillary flow, in rest, there is a mechanism of precapillary shunting through the so called through-fare channels. This are passive shunts. The surplus of inflow, in a normal and resting situation, is shunted directly to the veins. These shunts
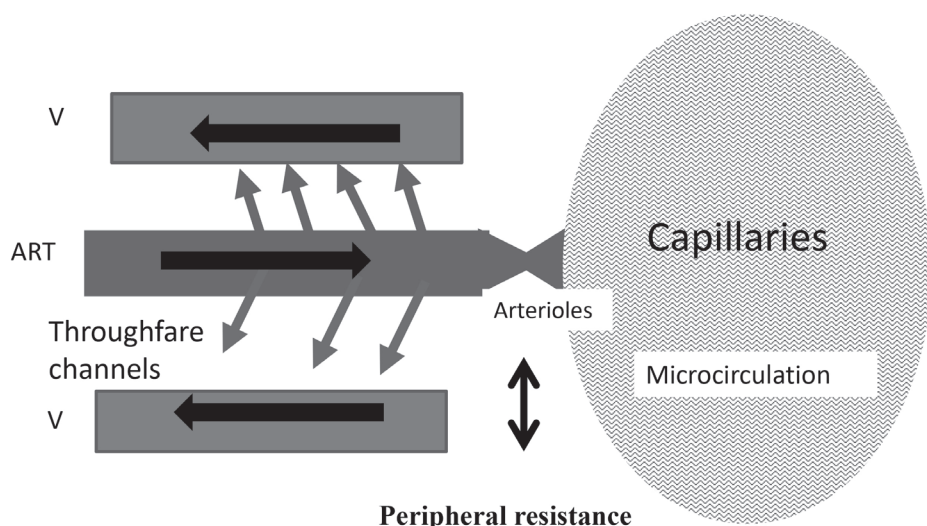

Figure 1: The final flow through the microcirculation is determined by the arterioles. These are also called the precapillary sphincters. With high peripheral resistance (normal non-ischaemic situation), the surplus of blood is shunted back through the throughfare channels (which are passive arteriovenous shunts).

exist at all levels of the limb muscles and also in the foot. These shunts are needed because there is no mechanism to reduce the flow, determined by the cardiac output, to a leg. The arteriovenous shunts are like a passive pressure valve to prevent congestion/oedema. These shunts also add to the total flow as measured with perfusion angiography. How much they contribute is unknown cardiac output, to a leg. The arteriovenous shunts are like a passive pressure valve to prevent congestion/oedema. In rest, supine and under non-ischaemic conditions, the peripheral resistance will also not change to regulate blood flow. These shunts also add to the total flow as measured with perfusion angiography. How much they contribute is unknown.

- There is outflow in the venules and the veins of the foot which adds about 10% to the measured perfusion.

Therefore, if you measure tissue perfusion in a region of interest in a supine position with perfusion angiography, you measure a summation of all four vascular territories (macro-microcirculation-shunting and venous flow).

The contribution of each vascular territory, in the perfusion image, is different depending on the physiological situation and demands. In permanent limb ischaemia, the macrovessels are dilated and the peripheral resistance is lowered, and, normally, the increase in inflow will result in better microcirculation perfusion and a better oxygenation (territories one, two, and four). Because the microcirculation is 80% of the vascular flow volume in the foot, the increase in perfusion of the foot measured with perfusion angiography during CLTI is foremost a representation of a real increase in tissue perfusion.

The question to be solved is how much increase in perfusion after revascularisation in patients with permanent limb ischaemia is needed to predict a good clinical outcome. From a pilot study, a more than 20% increase in perfusion will
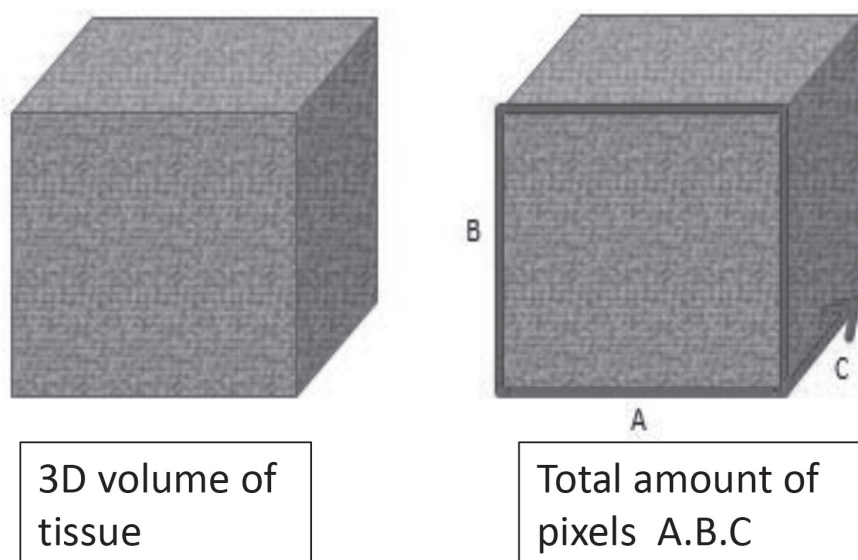

3D volume of tissue

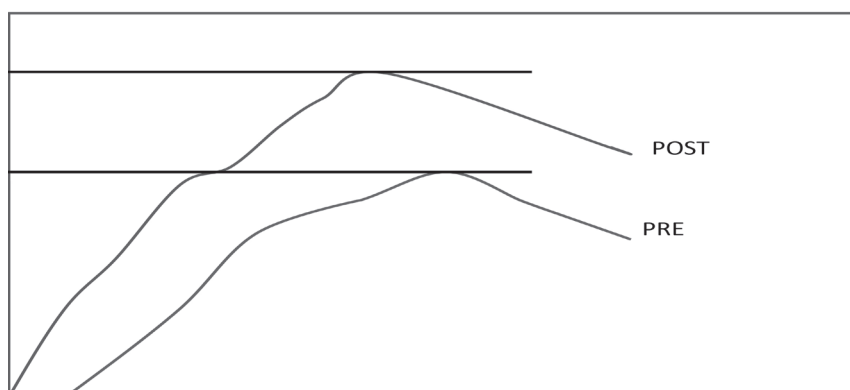Total amount of pixels A.B.C

Figure 2

Figure 3: The inflow velocity (earlier arrival time) is increased post intervention and, therefore, the contrast detection in the fixed region of interest which makes the curve, starts earlier. The pre flow is slower and the contrast detection starts three seconds later. During analysis, you have to correct for this as the pre curve will contain three seconds of empty frames and, therefore, the perfusion will be artificially lower.
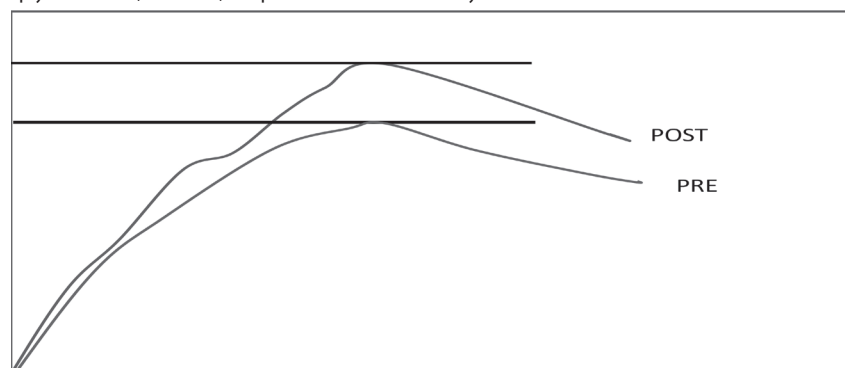

Figure 4: If you correct for that the acquisition times for both, post and pre will be the same and both curves give a more realistic representation of the perfusion because the time of acquisition is now the same.

probably have a positive effect in terms of improving two scales on the Rutherford classification (unpublished data).

Measuring the same acquisition pre- and post-intervention

Perfusion is the maximum blood volume (contrast) in a 3D tissue volume/time. Because 3D acquisition is not possible, we measure with perfusion angiography with a surrogate parameter: the 2D density/time that is the density in all the pixels in the 3D tissue volume (A,B,C) within a fixed acquisition time (Figure 2). The 2D measurement is only valid when the whole foot is diseased, such as in atherosclerosis or diabetic microangiopathy. It is not valid in case of a single vessel embolic occlusion.

If we keep A, B and C the same (same angulation and fixed distance of the tube and detector), keep the inflow volume the same and keep the acquisition time (both starting at the same moment of perfusion) the same, during the pre- and post-intervention acquisition, we can calculate the difference in tissue perfusion pre- and post-intervention for several parameters. Wash-in time, peak density and width are the best reproducible parameters. To keep the acquisition time, the same pre- and post-intervention, the contrast inflow in the tissue should start at the same time (Figure 3 and Figure 4).
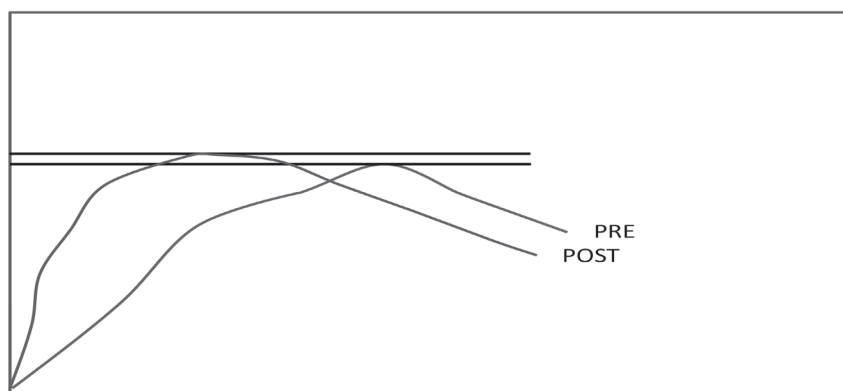
Figure 5: Shortening of the wash in time will be seen as an earlier peak. This represents a faster flow through the tissue. However, if the peak is the same pre and post, this faster flow has probably not led to a better tissue perfusion.
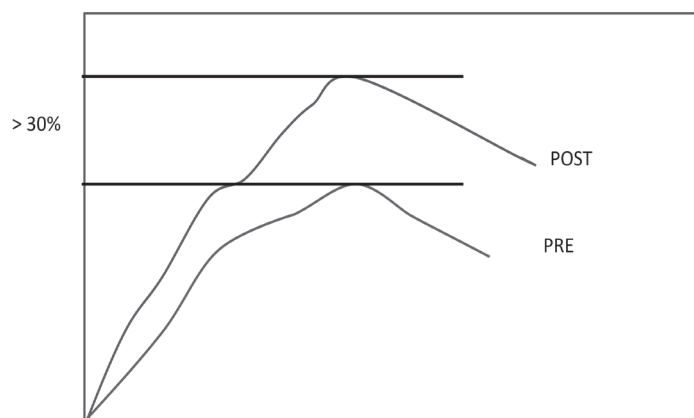
Figure 6: Both curves reach the peak at the same time, this means that the flow velocity is not increased. Moving of the post curve to the left indicates a bigger flow-volume. The total tissue perfusion has increased by 30%. In case of permanent limb ischaemia, this is probably mostly microcirculation flow.
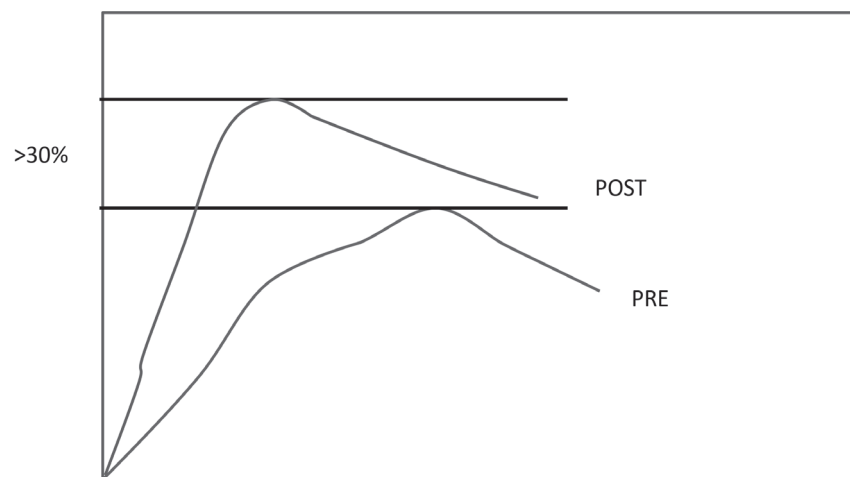
Figure 7: The flow velocity is increased. (The peak post is reached earlier than the peak pre). Thirty per cent increase in tissue perfusion (30% higher peak) and faster flow.
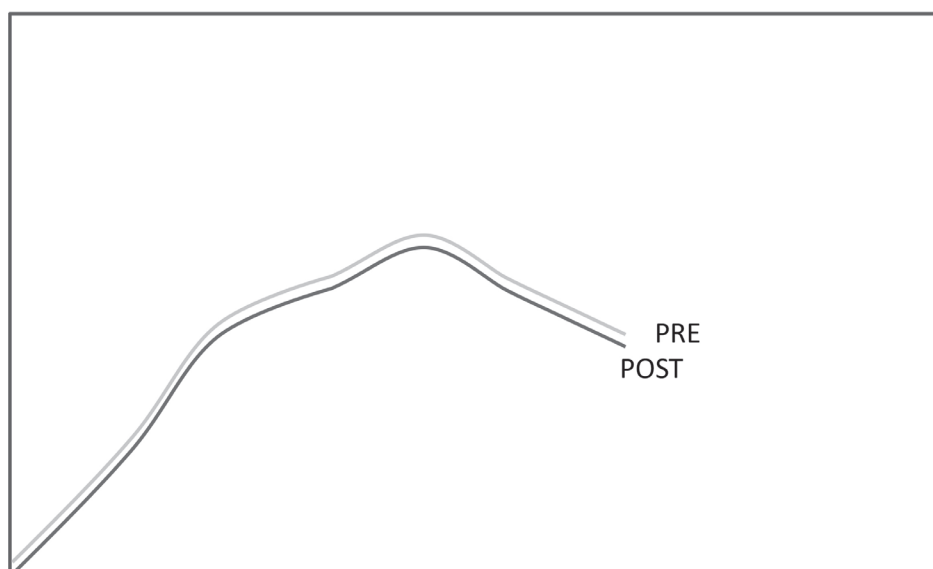
Figure 8: The inflow volume post intervention is not increased. The flow velocity is not increased. (The peak pre and post is reached at the same time). No increase in tissue perfusion. This predicts early amputation within 12 months with an almost 100% certainty.[23]

Faster flow does not mean better tissue perfusion because all this increase in flow can be shunted through the through-fare channels and will never reach the microcirculation. This can theoretically be seen in small artery disease.[10]

Peak density

How to read the perfusion angiography curves

There are only a minimal number of standard curves possible in permanent ischaemia (Figures 5,6,7).

Acquisition protocol

This has been described before.[19–20] Perfusion angiography needs a very meticulous protocol and acquisition of the perfusion data. Any deviation, even small changes, will lead to false perfusion data. The contrast density has to be high for perfusion angiography to obtain valid perfusion curves. That is why perfusion angiography cannot be used in acute ischaemia due to obstructive (no-flow) emboli. Movement artefacts will make the acquisition data useless for interpretation. The use of a dedicated footrest, to minimise movement of the foot, is, therefore, mandatory.

Analysis protocol

Like with the acquisition protocol, the analysis needs to follow fixed guidelines. The colour images hold no information only the curves derived from these images contain perfusion information. Any deviation from the recommended analysis protocol will make the perfusion data unreliable.

Conclusion

Perfusion angiography using the 2D or smart perfusion software is a new and promising tool for better understanding 0the effects and results of peripheral revascularisation in patients with permanent limb ischaemia. Perfusion angiography could play an important role during revascularisation procedures to determine the endpoint for the procedure ("have we done enough?") and to predict the clinical outcome. Combination perfusion data with other scoring systems for outcome, such as the WifI classification, could be another step forward in predicting outcome.

This new tool still needs validation and well-conducted studies to prove the effectiveness of the technique are necessary. It is, however, mandatory that all these studies follow the same protocols and analysis. A central coordination of perfusion studies is, therefore, a prerequisite for the success of this new technology. For questions about the technique or for help starting a perfusion study, please contact: perfusion@jimreekers.amsterdam.

Summary

- "Limb ischaemia", which can be intermittent or permanent, may be better terminology than CLTI.

- Perfusion angiography using the 2D or smart perfusion software is a new and promising tool for evaluating peripheral revascularisation in patients with permanent limb ischaemia.

- Studies to validated perfusion angiography are required, but these studies need to follow the same protocols and analysis.

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Silent coronary ischaemia in patients undergoing peripheral vascular surgery

D Krievins, E Zellans, G Latkovskis and CK Zarins

Introduction

Patients undergoing peripheral vascular surgery have an increased risk of postoperative death and myocardial infarction due to coronary artery disease. Functionally significant coronary artery disease is frequently unrecognised because patients are limited in their ability to walk and often have no cardiac symptoms. Clinical practice guidelines recommend no systematic preoperative cardiac testing of vascular surgery patients as prospective trials have shown no benefit from preoperative coronary revascularisation, and preoperative testing is unlikely to alter patient management.[1,2] Thus, most patients undergo peripheral vascular surgery without specific knowledge regarding the presence or absence of functionally significant coronary disease with 3% postoperative mortality and 25–50% five year mortality.[3-5]

Non-invasive diagnosis of lesion-specific coronary ischaemia

A new non-invasive cardiac diagnostic test, coronary computed tomography-derived fractional flow reserve (FFR_{CT}) can reliably identify ischaemia-producing coronary stenosis in chest pain patients. The FFR_{CT} test is based on anatomic information provided by coronary CT angiography with mathematical modelling of coronary blood flow and computational analysis of fractional flow reserve values throughout the coronary tree.[6] A 3D colour-coded map of FFR_{CT} values provides a unified anatomic-functional assessment of coronary artery disease, which readily identifies ischaemia-producing coronary lesions. Prospective clinical trials have shown good correlation of computed FFR_{CT} to invasively measured FFR, with accurate differentiation of patients with coronary ischaemia from those with non-functional coronary lesions.[7] The clinical usefulness of FFR_{CT} analysis for stable chest pain patients is well documented and FFR_{CT} analysis has been shown to be equivalent to coronary angiography for heart team decision-making in patients with multivessel coronary disease.[8-10,11] The value of FFR_{CT} analysis in patients with peripheral vascular disease is not yet defined.

Silent coronary ischaemia in patients with critical limb-threatening ischaemia

In a small study, 54 consecutive patients with critical limb-threatening ischaemia and no clinical evidence of coronary artery disease underwent preoperative cardiac evaluation with coronary CT angiography and FFR_{CT}. Asymptomatic (silent)

44% Single vessel ischemia

0.87
0.85
LCX
RCA
0.73
LAD

61 yo female diabetic with nonhealing toe ulcer

56% Multivessel ischemia

RCA
0.92
LCX
0.77
0.84
0.64
0.72
0.86
0.72
0.85
0.59
0.65
0.66
LAD

75 yo man with ischemic rest pain
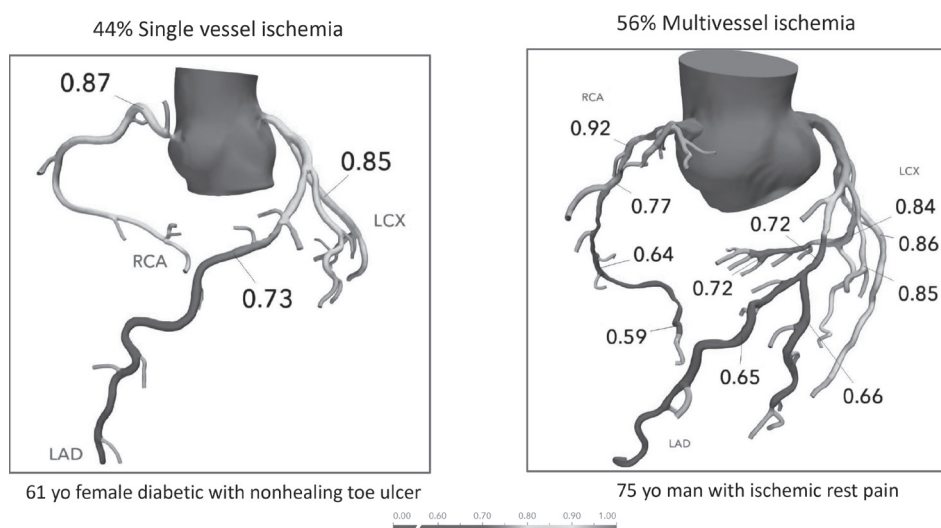
0.00   0.60   0.70   0.80   0.90   1.00

Figure 1: Silent coronary ischaemia in 68% of patients.

ischaemia-producing coronary stenosis was found in 69% of patients, with severe coronary ischaemia (FFR$_{CT}$ ≤0.70) in 43%.[12] The high prevalence of silent ischaemia was unexpected, since none of the patients had chest pain symptoms and this prompted the question of whether the knowledge that a patient had silent ischaemia could modify patient management to improve outcome.

Can preoperative diagnosis of silent coronary ischaemia reduce postoperative death/myocardial infarction?

We conducted a study to determine whether preoperative diagnosis of silent coronary ischaemia using FFR$_{CT}$ could modify patient management and reduce postoperative death and myocardial infarction in patients with no cardiac symptoms needing elective lower extremity revascularisation. Patients in a prospective, open-label study of preoperative cardiac testing with coronary CT angiography and computed FFR$_{CT}$ analysis were compared to a control group of patients with no cardiac symptoms who underwent peripheral vascular surgery with standard preoperative cardiac evaluation during the year prior to starting the prospective study. Study patients (n=135) were similar to controls (n=135) with regard to age (65±8 vs. 66±8 years), gender (79% vs. 81% male), comorbidities, medications, preoperative ankle-brachial index, indications for surgery (critical limb-threatening ischaemia in 86% vs. 82%) and type of surgery performed.[13]

Study patients

All patients were cleared for elective vascular surgery following standard preoperative cardiac evaluation, including resting electrocardiography. After signing informed consent, patients underwent standard coronary CT angiography with beta-blockade for heart rate control and sublingual nitroglycerin for coronary vasodilation.[14] CT angiography image datasets were sent via secure web-based interface for FFR$_{CT}$ analysis (HeartFlow). Results of FFR$_{CT}$ analysis were available to treating physicians within 24 hours and patient management was guided by a multidisciplinary vascular team comprised of vascular surgery, anaesthesiology,

cardiology and cardiac surgery. Coronary CT angiography in 135 study patients revealed extensive coronary calcification (mean Agatston score 1156±1026) with ≥50% stenosis in 70% and left main stenosis in 7% of patients. FFR_{CT} analysis could not be done in nine patients due to poor CT angiography image quality (motion or misregistration). FFR_{CT} analysis in 126 patients revealed ischaemia-producing coronary stenosis (FFR_{CT} ≤0.80) in one or more vessels in 68% of patients; severe ischaemia (FFR_{CT} ≤0.75) was present in 53% of patients. Representative examples of patients with single vessel or multivessel ischaemia are shown in Figure 1. After risk-benefit consideration, 130 patients (96%) underwent peripheral vascular surgery as planned, in accord with guidelines with cardiac anaesthesia and close patient monitoring.[4,14] Vascular surgery was postponed in five patients: one patient had coronary revascularisation with vascular surgery three months later and four had medical therapy with vascular surgery cancelled. There were no postoperative deaths. One patient had myocardial infarction on postoperative day three and was
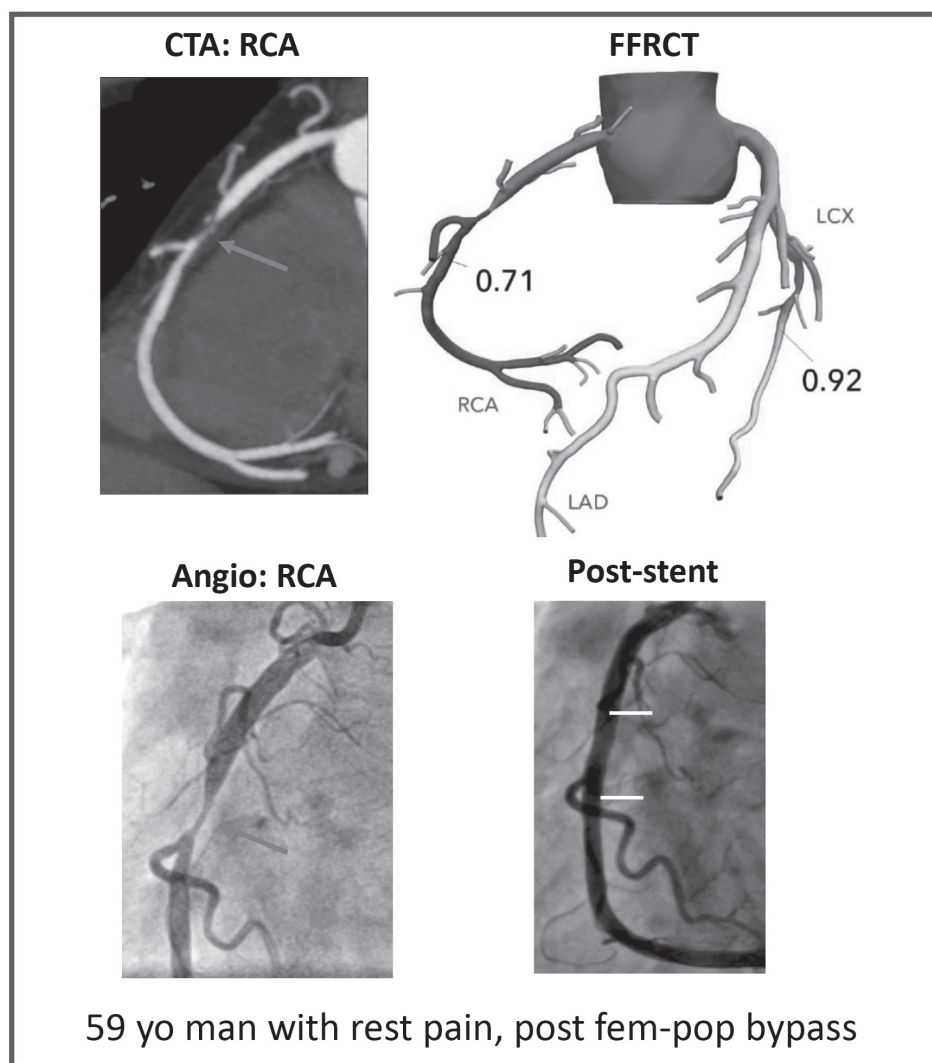

59 yo man with rest pain, post fem-pop bypass

Figure 2

CTA: severe calcification Agatston score 3353

RCA

LM and LAD

FFRCT

0.73

RCA

0.80

0.69

0.63

0.76

0.63

0.75

LCX

0.67

0.68

LAD

FFR$_{CT}$

occlusion 0.00 0.60 0.70 0.80 0.90 1.00

MAY BE FUNCTIONALLY   MAY NOT BE

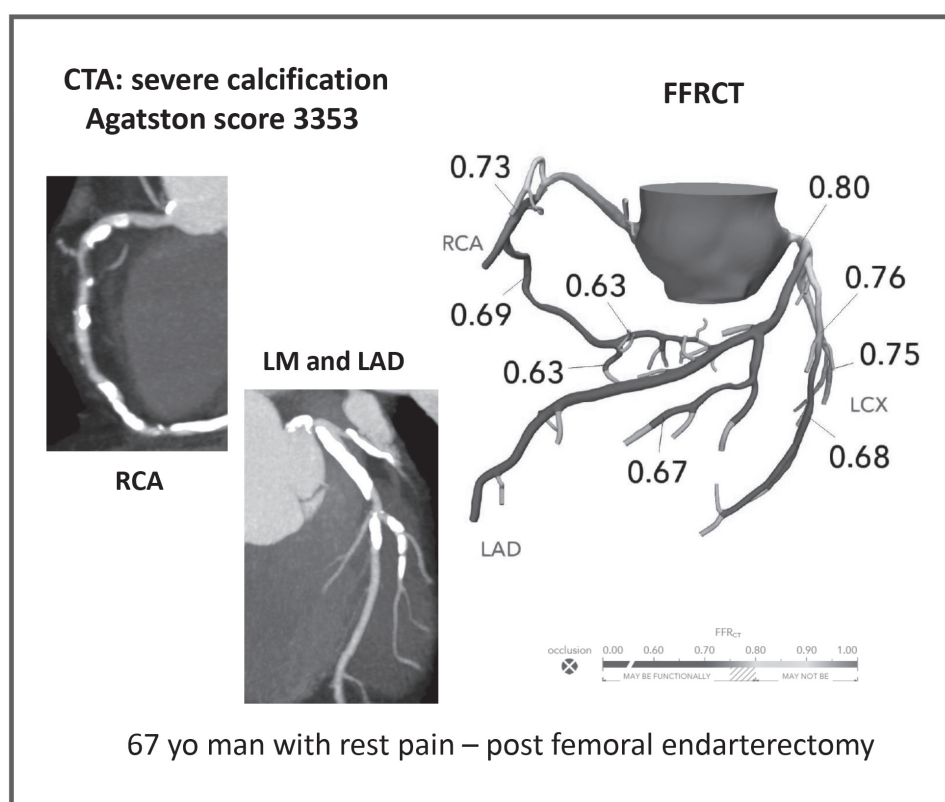**67 yo man with rest pain – post femoral endarterectomy**

Figure 3

successfully treated with urgent percutaneous coronary intervention. This patient had no FFR$_{CT}$ analysis due to poor CT angiography image quality.

Control patients

All patients were cleared for elective vascular surgery following standard preoperative cardiac evaluation and resting electrocardiography. Vascular surgery was performed in all 135 patients in accord with guideline directed care.[15] During the postoperative period, seven patients had myocardial infarction, with five cardiac deaths. One patient with myocardial infarction had successful urgent coronary revascularisation with percutaneous coronary intervention.

Postoperative patient management

All patients in both groups were treated with optimal guideline-directed medical therapy, including statins, antihypertensives, antiplatelets/anticoagulants, glycaemic control and risk factor control. Additionally, study patients with silent coronary ischaemia were evaluated for postoperative coronary angiography and selective coronary revascularisation. Coronary angiography was performed in 75 patients one—three months after recovery from surgery with coronary revascularisation in 54 patients (40% of patients in the study). Percutaneous coronary intervention was performed in 47 patients with coronary artery bypass grafting in seven patients. An example of postoperative percutaneous coronary intervention is shown in Figure 2. An example of postoperative coronary artery bypass grafting is shown in Figure 3.

No postoperative coronary angiography or elective coronary revascularisation was performed in control patients.

Patient outcomes

At 30 days, compared to control patients, study patients had a lower rate of death (0% vs. 3.7%) and myocardial infarction (0.7% vs. 5.2%) but these differences were not statistically significant (p=0.06 and p=0.07). At one year, compared to control patients, study patients had a lower rate of death (0.7% vs. 4.4%; p=0.04) and myocardial infarction (2.2% vs. 8.1%; p=0.03). Kaplan-Meier survival analysis revealed improved one-year survival in study patients compared to control (p=0.018).

Results

This study showed that patients with no cardiac history or symptoms have a high prevalence (68%) of unsuspected, silent coronary ischaemia. Nonetheless, clinically-indicated peripheral vascular surgery was safely performed in most patients using cardiac anaesthesia and close patient monitoring. Knowledge of the presence or absence of, and extent of silent coronary ischaemia allowed risk-stratification of patients and enabled their management by a multidisciplinary vascular team. Patients with multisite arterial ischaemia were managed with staged peripheral and coronary revascularisation, resulting in improved one-year survival compared to historical control patients with standard preoperative cardiac evaluation and care.

Limitations

This study is limited by the fact that the prospective study lacked a concurrent control group. Comparisons of outcomes relative to a retrospective control group should be viewed with caution. Although the two patient study groups were similar and patients were cared for by the same group of vascular surgeons, anaesthesiologists, cardiologists and cardiac surgeons using the same techniques in two consecutive time frames, there were significant differences in patient management. Knowledge of the presence of silent ischaemia in study patients resulted in postponement of scheduled vascular surgery in five patients, and the extent to which this, rather than multidisciplinary patient management, accounted for the reduction in postoperative cardiac events is unknown. Furthermore, due to the limited number of patients, short follow-up period and lack of concurrent control patients, the benefit of postoperative coronary revascularisation is uncertain. However, the favourable results showing improved one year survival in this study demonstrates the feasibility of FFR_{CT} analysis and its potential value in the preoperative coronary assessment of peripheral vascular surgery patients. Results shown here should be viewed as hypothesis-generating and suggest the need for future prospective controlled trials.

Discussion

This study demonstrates the potential value of preoperative non-invasive cardiac evaluation using coronary CT angiography and FFR_{CT} in patients undergoing elective peripheral vascular surgery compared to the current standard of care. Despite extensive coronary calcification, FFR_{CT} analysis was successfully performed
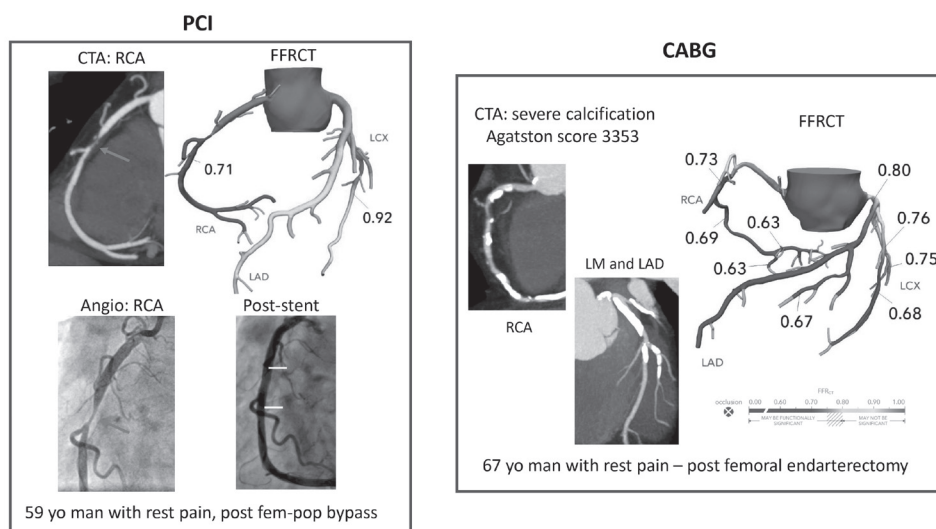
Figure 4: Selective coronary revascularisation (one to three months postop).

in 93% of patients. The finding of unsuspected, silent coronary ischaemia did not result in cancellation of needed vascular surgery, which was performed safely in almost all patients using cardiac anaesthesia, close patient monitoring and best medical therapy. However, the identification of high-risk patients with silent ischaemia enabled multidisciplinary vascular team care of patients as strongly recommended by 2017 ESC/ESVS guidelines.[2]

Results of FFR_{CT} analysis resulted in early cardiology involvement in patients with silent ischaemia, shared and coordinated decision making and vascular team guidance on timing of staged peripheral and coronary revascularisation. In this study all patients presented with symptomatic peripheral artery disease, with 86% having critical limb-threatening ischaemia needing revascularisation, which was performed in almost all patients despite the presence of coronary ischaemia. It should be noted that elective coronary revascularisation was performed after vascular surgery, with the objective of relieving significant coronary ischaemia in order to improve long-term survival. This strategy is in stark contrast to prospective, randomised trials in vascular surgery patients which have focused on determining the value of coronary revascularisation before vascular surgery to improve survival.[1] Failure of these trials to demonstrate a benefit in long-term survival accounts for current guideline recommendations against systematic preoperative cardiac evaluation of vascular surgery patients.[2] While some may question the need for coronary revascularisation after vascular surgery, since the patient has already survived the stress of vascular surgery, our strategy of post-vascular surgery coronary revascularisation based on FFR_{CT} evidence of lesion-specific coronary ischaemia is consistent with the results of prospective randomised trials showing that coronary revascularisation is superior to medical therapy in reducing death and myocardial infarction in coronary artery disease patients with coronary ischaemia by invasive fractional flow reserve ≤0.80.[15,16] The subset of patients with silent coronary ischaemia who were treated medically in the prospective, randomised FAME 2 trial had a significantly higher rate of death/myocardial infarction at five years compared to symptomatic patients, leading the authors to conclude that in-patients with haemodynamically significant stenosis,

fractional flow reserve-guided revascularisation should be considered even in the absence of symptoms.[17] Favourable results in this preliminary study suggest the need for prospective, controlled trials to determine the role of systematic preoperative evaluation of patients using FFR_{CT} with selective coronary revascularisation of patients with significant coronary ischaemia to improve long-term survival.

Conclusion

Patients undergoing peripheral vascular surgery have a high prevalence of unsuspected, silent coronary ischaemia. Preoperative diagnosis using CT angiography and FFR_{CT} can help guide a multidisciplinary team approach to high-risk patients with staged peripheral and coronary revascularisation to reduce postoperative death and myocardial infarction, and improve survival. Prospective, controlled trials are needed to further evaluate the role of CT angiography and FFR_{CT} in the diagnosis and treatment of patients undergoing peripheral vascular surgery.

Summary

- Coronary artery disease is primary cause of early and late death in peripheral arterial disease patients.

- Coronary artery disease is often unrecognised due to lack of symptoms and lack of ischaemia testing.

- New non-invasive test allows diagnosis of ischaemia-producing coronary stenosis.

- Systematic preoperative testing reveals high prevalence of silent coronary ischaemia.

- Despite presence of silent ischaemia, vascular surgery may be performed safely in most patients.

- Selective postoperative coronary revascularisation of coronary ischaemia resulted in fewer deaths and myocardial infarctions and improved one year survival compared to historical controls.

- Prospective clinical trials are needed to assess role of FFR_{CT} in cardiac evaluation of peripheral arterial disease patients.

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Critical limb ischaemia is being underdiagnosed and undertreated

JC van den Berg, on behalf of the CLI Global Society

Introduction

Over the last few decades, peripheral arterial disease has become one of the most rapidly growing diseases, with an incidence that exceeds ischaemic heart disease, cancer, and other disease states.[1] It affects 4 million people in the UK and 27 million people in Europe and North America. The majority of patients with peripheral arterial disease remain asymptomatic, and only around 10% of patients will have a progression to end-stage disease—so-called critical limb ischaemia.[2]

In symptomatic patients, the proportion of those with critical limb ischaemia can be as high as 43.5%.[3] Together with the increased risk for cardiovascular morbidity that is associated with peripheral arterial disease, critical limb ischaemia poses a threat to the life and limb of the patient, with a five-year mortality rate of 60% that is only surpassed by lung cancer.[4]

Despite major progress in revascularisation techniques for critical limb ischaemia, amputation and mortality rates have not been significantly reduced.[5] Overall, outcomes like death and myocardial infarction, as well as those related to limb and functional status, remain worse in critical limb ischaemia patients than in any other group of patients with atherosclerotic cardiovascular disease.[6]

Timely identification and referral for treatment of critical limb ischaemia are often delayed because community practitioners poorly recognise the disease entity.[7] As a consequence, the low recognition of prevalence, morbidity and mortality often results in underdiagnosis and undertreatment. Underdiagnosis and undertreatment of critical limb ischaemia contribute to the lack of improvement in clinical outcome, and both will be discussed in this chapter.

The problem of underdiagnosis

Overall patient perception of peripheral arterial disease remains low, despite attempts to raise public health awareness and education regarding its prevalence. In addition to this, lack of physician knowledge and failure to identify critical limb ischaemia, together with limited access to care and absence of knowledge on the current status of revascularisation techniques, contribute to the problem. Particularly in critical limb ischaemia, an arterial cause of the threatened limb remains unrecognised in a large percentage of patients, and this may influence patient outcomes negatively. For example, in a patient presenting with a wound that is considered to be primarily neuropathic in origin, arterial testing may not be performed and this may delay the diagnosis of a concomitant arterial problem. As a consequence, this may increase the risk of major amputation because of either

wound extension or development of systemic infection.[6] Furthermore, if arterial aetiology is not identified, optimal medical care (e.g. counselling for smoking cessation, antiplatelet therapy, and use of angiotensin-converting enzyme inhibitors and statins) will not be initiated.[6]

The presence and severity of peripheral arterial disease can easily be determined with an ankle-brachial index measurement, and this test is still considered to be more useful and reliable as a screening tool than other more sophisticated tests such as transcutaneous oxygen pressure measurement (in the general non-diabetic population).[7] Despite the low threshold for non-invasive testing (related to its wide availability and low cost), studies of Medicare beneficiaries have demonstrated that only 60% of patients have some type of physiologic testing performed in the two years prior to a (non-traumatic) amputation.[8] By following a circumscribed protocol that includes foot and pulse examination, combined with Doppler evaluation, up to 70% of major limb amputations can be avoided.[3] Also another study showed that early recognition of tissue loss and referral to a vascular specialist may lead to improved limb salvage.[9] It has also been reported that ischaemic rest pain, erroneously, is oftentimes considered more urgent than tissue loss, despite the far worse prognosis in the latter.[9]

Despite the existence of various (international) guidelines, well-established clinical pathways that could assist primary care physicians to identify and rapidly refer critical limb ischaemia patients are not widely available. This may lead to delayed treatment and loss of limbs. Although guidelines from various societies recommend that all patients with a diagnosis of critical limb ischaemia should undergo an imaging study (computed tomography, magnetic resonance or digital subtraction angiography), one study showed that only a quarter of patients undergo angiography.[10] A recent analysis of a large, public health insurance database in Germany—including 41,882 patients—found that 44% of amputees with critical limb ischaemia had not undergone a (diagnostic) angiography in the hospital prior to their amputation. The number of patients without angiography or a revascularisation attempt during the index hospitalisation, or the two years before, was slightly lower when a 24-month timeframe prior to the amputation was taken into account. However, it was still only 37%.[5]

If angiography is performed to evaluate the options for endovascular or surgical revascularisation, the risk of major amputation may be 90% lower.[10] For this reason, no amputation should be performed without angiography except for those cases in which systemic infection (sepsis) warrants urgent primary amputation.[6]

The issue of undertreatment

The treatment of critical limb ischaemia is influenced by a lot of factors that include physician experience, geographic influences, type of healthcare delivery system as well as socioeconomic factors.[9] Regional variation in the numbers of revascularisation procedures and major amputation risks exist, and it has been shown that hospital referral regions with increased rates of revascularisation have correspondingly lower rates of major amputation.[11] Undertreatment is not only related to the revascularisation itself, but also to the institution of medical therapy. Non-surgical interventions are an essential part of the treatment: since patients with critical limb ischaemia typically have multiple systemic comorbidities in addition to their extensive atherosclerosis, it is of utmost importance to optimally

control diabetes, hypertension and hyperlipidaemia by optimising medical therapy. In addition to this analgesia, local wound care, pressure relief and prevention and treatment of infection should be provided.[12] By doing so the risk of cardiovascular complications, major amputation and mortality can be reduced significantly.[6] Patients with diabetes mellitus and end-stage renal disease are particular at risk for amputation because they present with foot lesions that preclude limb salvage and have anatomical challenges (severe calcification) respectively. Unfortunately, less than one-third of patients with critical limb ischaemia receive optimal medical therapy.[13]

Treatment with (surgical or endovascular) revascularisation is oftentimes not considered as initial therapy. Major amputation as primary treatment is still performed in up to 8.5% of patients that present with critical limb ischaemia, with 30% of these patients only presenting with Rutherford category 4 or 5.[14] Major amputation doubles the risk of death over the next year.

A similar trend was seen in the already mentioned German insurance database, which demonstrated that only 45% of patients with Rutherford Category 4–6 who underwent an amputation had an attempt to revascularisation, with an additional 7% who underwent angiography and/or revascularisation in the two years before the index hospitalisation that led to the amputation.[5] When looking at this database in more detail, we can note that the frequencies of diagnostic angiographies and (any) revascularisation was significantly decreased in patients with higher Rutherford categories (that probably needed intervention most). In patients with Rutherford category 1–3, angiography was performed in 58.2% of cases, while this number was 58.4%, 51.6% and 47.9%, respectively, in patients with Rutherford category 4, 5, and 6. Revascularisation (any form) was performed in 75.3% of patients with Rutherford category 1–3 and in 71.3% of those with Rutherford category 4. For patients with Rutherford category 5 and 6, these figures were 50.9% and 49.2% of cases respectively (with a highly statistical significant difference).

Similarly, a wide variation in lower extremity amputation rates and the intensity of peripheral vascular interventions is seen across the USA. This finding suggests that there is differential recognition and treatment of critical limb ischaemia across regions, even when differences in disease prevalence are taken into account.[15] Revascularisation should always be considered among all patients with critical limb ischaemia, even in severe and advanced tissue loss (with the exception of patients presenting with septicaemia). Consultation of a vascular specialist (as part of a multidisciplinary team) is necessary to identify patients where revascularisation is deemed not necessary or unlikely to preserve the limb.[6] It has been demonstrated in recent studies that limb salvage can be achieved in most cases, even those with extensive Rutherford category 6, by limiting the amputation to a minor amputation of digit or single ray.

After revascularisation, close and frequent follow-up is necessary—keeping the toe-and-flow principle as proposed by Rogers *et al* in mind—to monitor progression of wound healing and to intervene early in cases where wound healing slows down.[16] It has been demonstrated in several studies that this approach improves the care of diabetic patients with critical limb ischaemia and improves limb salvage.[17]

These findings emphasise that there is still a lot of room for improvement of care for critical limb ischaemia patients. This care should be preferably provided in a specialised centre that can offer a multidisciplinary approach. In order to ensure

easily accessible care, the patient can be followed at a basic care or intermediate level (locally). In case more specialised care is needed (e.g. endovascular revascularisation), there should be a low threshold to refer the patient to a centre of excellence (3 tier approach).[16]

Conclusion

Most current guidelines underline the lack of data regarding the treatment and outcomes of patients with critical limb ischaemia, despite the increase in prevalence of the disease, and future research should focus on reducing this gap in knowledge.

To further reduce limb loss in patients with critical limb ischaemia and reduce underdiagnosis and undertreatment, patient awareness should be increased by educational programmes. Additionally, primary care physicians should be educated not only in timely recognition of critical limb ischaemia, but also should be informed about modern revascularisation options. The threshold to refer to specialised centres should be as low as possible, and upon referral, a multidiscliplinary critical limb ischaemia team should be available to optimise management of these patients.

Summary

- Despite major progress in revascularisation techniques for critical limb ischaemia, amputation and mortality rates have not been significantly reduced.

- Timely identification and referral for treatment of critical limb ischaemia are often delayed because community practitioners poorly recognise the disease entity. As a consequence, the low recognition of prevalence, morbidity and mortality often results in underdiagnosis and undertreatment.

- If angiography is performed to evaluate the options for endovascular or surgical revascularisation, the risk of major amputation may be 90% lower.

- Revascularisation should always be considered among all patients with critical limb ischaemia, even in severe and advanced tissue loss.

- To further reduce limb loss in patients with critical limb ischaemia and reduce underdiagnosis and undertreatment, patient awareness should be increased by educational programmes.

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Endothermal heat-induced thrombosis and treatment

M Sadek and L Kabnick

Introduction

Endothermal ablation techniques, such as endovenous laser ablation (EVLA) and radiofrequency ablation, are the standard for the treatment of patients with clinically significant superficial truncal vein reflux. Histologically, the appearance of the treated vein reflects a combination of endothelial injury, thrombosis, fibrosis, and eventual vein occlusion. The thrombus that forms may propagate into the respective deep vein junction, thereby defined as an endothermal heat induced thrombosis (EHIT).[1] Earlier reports used the term of deep vein thrombosis (DVT) but without clear characterisation of the pathology being evaluated, and this generated variability in reporting and treatment.[2–4]

EHIT classification system

Kabnick created a classification system for EHIT to standardise the concept across the literature and clinical practice.[1] The Kabnick classification for EHIT is based on the extent of propagation of thrombus into the respective deep vein lumen as identified by duplex ultrasound in the erect position.

The Kabnick EHIT Classification scheme is as follows:
- EHIT 1: Up to and including the respective deep vein junction
- EHIT 2: Propagation into the respective deep vein but comprising <50% of the deep vein lumen
- EHIT 3: Propagation into the respective deep vein but comprising >50% of the deep vein lumen
- EHIT 4: Occlusive deep vein thrombus, contiguous with the treated truncal vein.

The incidence of EHIT ranges from 0% to 16%, again much of the variability resulting from inconsistencies in the early literature.[5,6] Regardless of its natural history, EHIT remains poorly defined—particularly when one evaluates the subgroups within the EHIT classification. Additionally, the natural history is further complicated by considering the truncal vein that is being treated. The most common forms of EHIT are propagation into the common femoral vein following treatment of the great saphenous vein, propagation into the popliteal vein following treatment of the small saphenous vein. Earlier timed duplex ultrasound would identify a greater number cases of EHIT because most have been shown to resolve within two weeks.

At present, there are no randomised controlled trials delineating the appropriate treatment for EHIT. The recommendations are based on case series, extrapolation

from the DVT literature, and mostly on expert opinion taking into account the risk-benefit ratio associated with treatment vs. observation.[7]

Our current recommendations for the treatment of EHIT are as follows:

- EHIT 1: No treatment and no subsequent duplex ultrasound evaluation
- EHIT 2: No treatment or low-dose aspirin. The treatment should be limited to resolution of the entity as determined by subsequent duplex ultrasound.
- EHIT 3: The benefit of anticoagulation may outweigh the risk and low molecular weight heparin is suggested. Direct oral anticoagulants may be considered
- EHIT 4 (occlusive DVT): Therapeutic anticoagulation as would be recommended in the CHEST guidelines for the treatment of a provoked acute DVT.[8]

Conclusion

These are our guidelines and practice may vary from practitioner to practitioner.[9,10] It is unlikely that a randomised controlled trial will be powered adequately to allow for a formal evaluation of this entity.[11]

For the treatment of chronic venous insufficiency, the initiation of endothermal ablation (now the gold-standard treatment) has resulted in significant improvements to safety and efficacy. It also resulted in the recognition of the post-procedural entity known as EHIT. The Kabnick classification scheme was developed in order to standardise reporting and treatment. Treatment with anticoagulation is generally reserved for EHIT 3 or EHIT 4. Lastly, the clinical relevance of EHIT is still being debated, and this is consequential given the cost associated with post-procedural screening ultrasound.[12]

Summary

- The EHIT classification system was created to standardise the concept across the literature and clinical practice.

- Treatment with anticoagulation is generally reserved for patients with EHIT 3, or EHIT 4.

- The clinical relevance of EHIT is still being debated.

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The role of compression following treatment of varicose veins

R Bootun, TRA Lane and AH Davies

Introduction

The management of varicose veins has changed drastically over the past 20 years with the introduction of newer technologies. However, a common practice that has remained almost untouched is the application of compression following varicose veins treatment. A survey of the members of the Vascular Society of Great Britain and Ireland found that the use of this post-treatment approach was still quite prevalent, with practitioners using four different combinations of compression modalities after endothermal ablation and seven following foam sclerotherapy.[1]

The evidence for the use of compression post-intervention is reviewed in this chapter to understand the role it plays following varicose vein treatment. El-Sheikha *et al* (2015) previously conducted a systematic review on the use of compression following varicose vein treatment and found that there was insufficient evidence to guide treatment.[2]

Effect of compression post-treatment

The National Institute for Health and Care Excellence (NICE) published guidelines regarding the management of varicose veins in 2013.[3] A hierarchy of treatment was described, whereby the first line treatment was deemed to be endothermal ablation, followed by foam sclerotherapy (second line) and surgery (third line).

A number of investigators have evaluated the use of compression following varicose veins treatment and have looked at a multitude of potential outcomes to identify the benefit of this practice.[4–14] The effect of compression following each modality is discussed below.

Endothermal ablation

Bakker *et al* (2013) reported on a randomised controlled trial comparing the use of short (two days) and long duration (seven days) of compression stockings following endovenous laser ablation (EVLA).[9] They found that there was a statistically significant difference in the quality of life and pain scores at one week in favour of longer duration compression stockings. No such differences were noted at two days and at six weeks. Elderman *et al* (2014) similarly also noted a small, but significant, difference in the degree of pain experienced by patients in the first week following randomisation to wearing class 2 compression stockings.[10] Furthermore, significantly more patients in the no compression group required additional analgesia for pain. There was a statistically significant difference noted in

patient satisfaction on day two and six months in the group wearing compression stockings. However, no differences were observed in the quality of life, time to return to normal activity, leg circumference, or complication rates.

Similarly, Ye *et al* (2016) conducted a randomised controlled trial comparing the use of compression with no compression following endovenous laser ablation (EVLA).[11] After wearing an elastic bandage for the first night, the compression group was provided with stockings to wear for two weeks while the no compression group were provided with none. The pain score was better in the compression group at one week, but there were no significant differences observed at 24 hours and two weeks. Additionally, the improvement in the quality of life, time to return to activities and bruising was similar.

However, this finding was not replicated in other studies. Indeed, Ayo *et al* (2016) looked into the effect of compression following endothermal ablation (EVLA and radiofrequency ablation).[12] Patients were assigned to wear compression stockings for seven days, or no compression. No differences in pain and post-operative bruising were found between the two groups, and the venous clinical severity scores (VCSS) and quality of life were also similar.

Krasznai *et al* (2016) compared the effect of post-treatment compression following radiofrequency ablation and found that there was no difference in leg oedema between those wearing compression for four hours compared to 72 hours.[13] Patients in the shorter duration group experienced significantly fewer complications as well, but there was no difference in the pain scores or time to normal activity.

In 2019, Pihlaja *et al* described another randomised controlled trial comparing the use of compression following radiofrequency ablation (tributaries treated with foam sclerotherapy) and found no difference in the pain scores.[14] Rates of phlebitis was similar as was the time to normal activity and quality of life at six months. The compression group had less pigmentation though.

Most of these randomised controlled trials (except for Pihlaja *et al)* did not include patients having tributary treatment, so that it is not possible to derive any evidence as to whether compression is advantageous in this group of patients. Occlusion rates also appear to be unaffected by the use of compression (all treated veins occluded) and the incidence of deep vein thrombosis (DVT) was low (one popliteal vein thrombosis in the study by Pihlaja *et al*).[9,14]

Recently, further evidence has emerged from another randomised controlled trial comparing the use of compression and no compression after 24 hours of bandaging.[15] The primary outcome measure was the pain score over the first 10 postoperative days and patients were reviewed at two weeks and six months. Two hundred and six patients were randomised, 49% of them in the compression group. The mean age was 49.7 years, and 51.4% of the recruited patients were males. Baseline clinical etiological [aetiology] anatomical pathophysiological (CEAP) class was similar between the two groups. The median time to stop wearing compression stockings was seven days. In the compression group, the median pain score using a visual analogue scale (VAS) was significantly lower on days two to five when compared to the no compression group. Patients having phlebectomies and receiving compression stockings had significantly better pain scores on days one to three, day five and day seven. The median VCSS was better in the no compression group at baseline, but there were no significant differences by the six-month point. Despite general improvement from baseline, there were no discernible differences between

the generic- and disease-specific quality of life at two weeks and six months. For both groups, time to resume normal activities and to return to work was similar at two days and three days, respectively. Complete saphenous vein occlusion was found in 87.5% of patients in the compression group, compared to 92.1% of patients in the no compression group (p=0.121). Patients having endothermal ablation with concurrent phlebectomies had more incidence of ecchymosis, but this was not significant (12.5% vs. 2.6%; p=0.127). There was one below-the-knee DVT noted in a patient from the no compression group.

Foam sclerotherapy

Researchers have also looked into the effect of compression after foam sclerotherapy. Hamel-Desnos *et al* (2010) compared the use of class 2 compression stockings for three weeks to no compression and did not register a difference in the amount of pain experienced.[7] There were similar rates of phlebitis, induration, bruising and usage of analgesia. There were two DVTs recorded in the compression group. Although the compression stockings were meant to be worn for three weeks, only 40% managed to achieve this with the main reason for non-compliance being discomfort and tightness.

For their part, O'Hare *et al* (2010) evaluated the use of bandages for 24 hours or five days followed by thromboembolic deterrent stockings for two weeks following foam sclerotherapy.[8] Again, no differences in pain were shown, with similar quality of life improvement and pigmentation rates. Treatment was equally effective in both groups in both these trials.

A randomised controlled trial is currently underway at Imperial College London comparing the use of compression and no compression stockings and, hopefully, will be able to shed some light as regards the benefits of this intervention post-foam sclerotherapy.[16]

Surgery

Following saphenofemoral junction ligation and stripping of the great saphenous vein, Biswas *et al* (2007) randomised patients to receiving one week or three weeks of thromboembolic deterrent stockings.[5] The pain score was significantly better in the three-week group at one week. More patients from the one-week group also required more analgesia. There were no major differences with regards to complication rates, including bruising, between the two groups and time to return to normal activities was also similar.

Another randomised controlled trial investigated the use of class 2 compression stockings for four weeks against elastic bandaging for three days only and failed to detect any significant differences in the degree of pain.[6] A small, but significant improvement in oedema from baseline was shown in the longer compression group, but there was no difference with the shorter duration group. Those receiving bandaging for three days had a more rapid recovery.

Raraty *et al* (1999) compared the use of short-stretch bandage (Panelast) for one week with crepe bandage followed by thromboembolic deterrent stockings for six weeks and demonstrated a significant difference in the pain scores on day one only in the short-stretch bandage group.[4] There were no differences in analgesia use or time to resume activities.

Non-thermal ablation

Non-thermal, non-tumescent (NTNT) ablative methods have been available for past few years, and the use of compression is dependent on the modality used. Following cyanoacrylate adhesive injection, patients routinely have a simple bandage applied at the puncture site only.[17,18] Further compression is deemed not to be necessary as the vein wall is not perforated during ablation.[17] Even though not puncturing the vein either, mechano-chemical ablation (MOCA) usually requires the application of compression stockings after treatment.[19,20]

So far, no published trials have compared the use of compression following an NTNT, although there is an ongoing trial currently assessing the effects of compression following MOCA.[21]

Systematic reviews and meta-analysis

In their systematic review, El-Sheikha *et al* (2015) highlighted the heterogeneity prevalent in the studies looking at the effect of compression following varicose vein treatment.[2] These included differences in the intervention being evaluated, the type and duration of compression used, as well as the outcome measures being looked at. In effect, these discrepancies also precluded any attempts at conducting a meta-analysis and meant that there was insufficient evidence available to offer guidance regarding best practice.

Al Shakarchi *et al* (2018) reviewed the use of compression after endothermal ablation and included three more trials than El-Sheikha's study.[22] The authors found a single study demonstrating a better pain score after wearing compression stockings for seven days, but, in all studies, longer duration of compression did not offer any additional benefits in terms of recovery time, leg swelling, bruising or complications. They concluded that wearing compression for an extended period was probably unnecessary and recommended that stockings not be used for longer than 48 hours.

Discussion

A review of the evidence does indicate that, at present, it is unclear whether wearing compression following varicose vein treatment is advantageous.

The NICE guidelines also found no robust evidence to suggest that compression post-treatment offered any additional benefit.[3] As a result, in those cases where it was being provided, the recommendation from the NICE guidelines was to offer compression stockings/hosiery for no longer than seven days. Because of this lack of evidence, one of the research recommendations was to evaluate the clinical and cost effectiveness of this particular intervention.

A joint clinical practice guideline from the American Venous Forum, Society of Vascular Surgery, American College of Phlebology, Society for Vascular Medicine and International Union of Phlebology for the use of compression following invasive treatment for varicose veins has also recently been published.[23] Following endothermal ablation, foam sclerotherapy or stripping of the saphenous veins, the guidelines recommend using compression (elastic stockings or wraps) with the duration of this intervention based on best clinical judgement. These are, however, only weak recommendations with the level of evidence being either moderate or low/very low quality. The guidelines also suggest using pressure above 20mmHg

following radiofrequency ablation/EVLA or surgery, but again, the evidence is rather weak.

Conclusion

The use of compression following interventional treatment for varicose veins remains a controversial subject despite numerous trials investigating this post-treatment approach. This is also not helped by the heterogeneity in study designs and outcome measures evaluated in the studies. So far though, there appears to be a trend emerging towards lower intensity of pain experienced by patients offered compression, especially in the few days following treatment, but with no associated advantages in the longer term. As such, and with the absence of obvious harm brought about by this intervention, it would appear a reasonable compromise to offer compression for at least seven days as suggested by the NICE guidelines until more robust evidence becomes available.

Summary

- The use of compression following varicose vein intervention is common, but the practice is quite variable.

- There is currently no robust evidence that compression following endothermal ablation is definitely superior, although lately, there has been emerging evidence that there might be a lesser degree of pain in those wearing compression.

- There is limited evidence that compression following surgery might be beneficial in terms of pain, but no other major differences have been noted.

- There does not appear to be significant differences in those using compression following foam sclerotherapy.

- There is no evidence of any benefit of compression following non-thermal treatment

- Systematic reviews have not convincingly demonstrated that post-intervention compression is better.

- NICE guidelines recommend using compression for no more than seven days after varicose vein treatment (if being used).

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Which patients with venous leg ulceration should undergo proximal deep imaging?

M Nortley, A Wigham and E Wilton

Introduction

Chronic venous insufficiency affects about 7–9% of the population.[1] Its prevalence increases with age and progression of chronic venous disease is associated with a family history of varicose veins and with a history of deep vein thrombosis (DVT).[2] Venous leg ulcers are the most severe manifestation of chronic venous disease and the result of elevated ambulatory venous pressure within the lower limb and venous hypertension. This can be caused by either deep or superficial venous reflux or venous outflow obstruction. Causes of venous reflux include valvular incompetence (deep venous incompetence and superficial venous reflux/varicose veins) and calf pump failure. In the deep veins, thrombosis may cause valvular damage (reflux) or scarring and chronic obstruction. Other causes of chronic venous obstruction include congenital abnormalities, May-Thurner Syndrome (compression of the left iliac vein by the left common iliac artery), and external compression by a pelvic mass or primary malignancy. Obstruction from secondary venous disease and venous reflux including post-thrombotic syndrome are associated with a much more rapid progression of chronic venous disease and a higher rate of venous ulceration, as compared to primary venous disease.[3]

Venous disease is the most common cause of leg ulceration in the UK, accounting for 60–80% of cases. Its prevalence is an estimated 0.1–0.3% in the UK.[4] Reflux in the superficial veins is seen in approximately 80% of limbs with venous ulceration.5 Isolated superficial venous reflux occurs in approximately 45–50% of cases of venous ulceration or in combination with deep venous reflux (30–40%).[5,6] Approximately 5–10% of patients with venous ulcers have diseased deep-venous systems only.

An estimated 1% of total health costs in the Western world result from the therapy costs of chronic leg ulcers. Venous leg ulceration, therefore, places a significant burden on healthcare expenditure with cost estimations of £941.1 million in 2012/2013. For any one individual, the mean NHS cost of wound care per annum was an estimated £7,600 per venous leg ulcer. However, the cost of managing an unhealed venous leg ulcer was 4.5 times more at £13,500.[7]

NHS organisations are currently reviewing their care provision for lower limb wounds, including ensuring they use an evidence-based leg ulcer pathway. As part of that, prompt and appropriate investigation of venous leg ulcers is paramount.

Post-thrombotic syndrome

Post-thrombotic syndrome is a long-term complication of DVT. It affects between 30% and 50% of patients with DVT. The syndrome is characterised by chronic pain, swelling, oedema, venous ectasia, skin induration, venous claudication and ulceration, with the latter developing in 5% to 10% of cases.[8,9] It has a significant impact on quality of life. Most patients who develop post-thrombotic syndrome become symptomatic within two years from the acute episode, and up to 10% of patients develop venous ulceration over a 10-year period.[10,11]

Symptoms include pain (especially related to exertion), cramps, heaviness, paraesthesia, and pruritus in the affected limb. The characteristic signs include affected limb oedema, telangiectasia, venous ectasia, skin hyper-pigmentation, skin induration (lipodermatosclerosis) and, eventually, skin ulceration.

Various clinical scales have been developed to help diagnose post-thrombotic syndrome. The Villalta scale, the venous clinical severity score and scoring schemes based on the clinical etiology [aetiology] anatomic pathophysiologic (CEAP classification) system.[12] The Villalta scale grades the severity of five symptoms (pain, cramps, heaviness, pruritus, and paraesthesia) and six signs (oedema, skin induration, hyperpigmentation, venous ectasia, redness, and pain on calf compression) from 0 to 3. A total score of ≥5–14 indicates a mild-to-moderate case, and a score ≥15 or presence of a venous ulcer indicates a severe case.

The risk of developing post-thrombotic syndrome is increased if there is incomplete resolution of symptoms at one month, a proximal (iliofemoral) DVT, previous ipsilateral DVT, high body mass index (BMI), effectiveness of oral anticoagulation and residual DVT identified on duplex ultrasound after anticoagulation treatment has been instigated.[13,14]

Clinical evaluation

For a leg ulcer to be classified as a venous leg ulcer, there needs to be clinical manifestations consistent with chronic venous disease. Clinical evaluation should differentiate primary, secondary, or congenital venous problems and establish the presence or absence of venous reflux, obstruction, or both. A thorough medical history should be performed to identify symptoms potentially related to venous disease, including extremity pain, aching, throbbing, cramps, heaviness, itching, tiredness and fatigue. Venous symptoms are usually exacerbated by limb dependency and relieved by rest or elevation. Medical history should also include risk factor assessment for venous disease, including age, BMI, prior venous thromboembolism, family history of venous thromboembolism, family history of varicose veins, episodes of superficial thrombophlebitis, spontaneous venous bleeding, prior use of compression therapy, prior venous operative interventions, the presence of other systemic diseases associated with leg ulceration, a history of intravenous drug use and other possible associated medical factors that may contribute to non-healing leg wounds (e.g. concomitant arterial disease or diabetes).

Physical examination for signs of venous disease should include inspection for telangiectasia, varicose veins, oedema, chronic venous skin changes (skin discoloration/haemosiderin deposition, inflammation, eczema, hyperpigmentation, malleolar flair, corona phlebectatica, atrophie blanche and lipodermatosclerosis) and the presence of a healed or active ulcer. An arterial examination of the lower limbs should also be carried out.

Venous duplex ultrasound

Venous duplex imaging is the most common technique used to confirm the diagnosis of chronic venous insufficiency. It combines B-mode imaging of the deep and superficial veins with pulsed Doppler assessment of flow direction with provocative manoeuvres. The presence of venous obstruction because of chronic deep vein thrombosis or venous stenosis may be directly visualised or inferred from alteration in spontaneous flow characteristics. Comprehensive venous duplex ultrasound evaluates for both venous obstruction/DVT and deep/superficial venous reflux. A reflux time of >0.5 seconds for superficial veins and 1.0 second for deep veins is typically used to diagnose the presence of reflux.[15] A longer duration of reflux implies more severe disease but does not correlate well with clinical manifestations.

Venous outflow obstruction has been underappreciated as a cause of venous hypertension and associated venous disease because of lack of a non-invasive screening study that reliably identifies the problem. Venous duplex ultrasound of the femoral vein may provide indirect evidence of outflow obstruction with non-phasic flow in computed tomography (CT) venography, non-phasic flow during Valsalva manoeuvre, low or no velocity augmentation, presence of collaterals and reverse flow in the ipsilateral internal iliac vein. Phasic flow, however, may be present even with obstruction.

Direct duplex ultrasound can show venous diameter stenosis. A velocity ratio of 2.5 has also been shown to distinguish between stenoses over and under 50% angiographic diameter reduction, and patients with clinically relevant stenosis >50% have been identified with statistical significance.[16] Luminal changes may also show thrombus or synechiae in the lumen.

For improved diagnostic accuracy, patients with a venous leg ulcer and suspected thrombotic or non-thrombotic venous outflow obstruction should undergo additional cross-sectional imaging CT venography or MR venography.

Magnetic resonance venography

Magnetic resonance (MR) venography provides a good overview of chronic venous changes in the leg, pelvis, and abdomen. Intraluminal changes, external compression, extent of occlusive disease, collateral pathways, and/or flow redistribution can all be visualised. Dynamic imaging can also show inflow and outflow of the pelvic vasculature. The main advantage over CT is the lack of ionising radiation, which is desirable in younger patients and when serial investigations are required.

Computed tomography venography

CT venography is widely available in many centres. It allows post thrombotic stenotic change to be identified, as well as collaterals and will identify external compression. Intraluminal changes have been described but, are inferior to MR venography.[17] Features of post-thrombotic scarring, including reduced vein diameter, luminal obliteration, residual thrombus, development of fibrotic bands and superficial collateral veins can all be identified. No flow related information is possible. A disadvantage of CT venography is exposure to high levels of ionising radiation.

MR/CT venography imaging should be performed from upper thigh to diaphragm. Despite drawbacks of each imaging modality, when contemplating deep venous reconstruction, cross-sectional imaging should be considered for
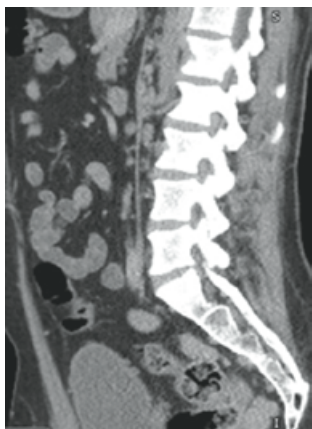
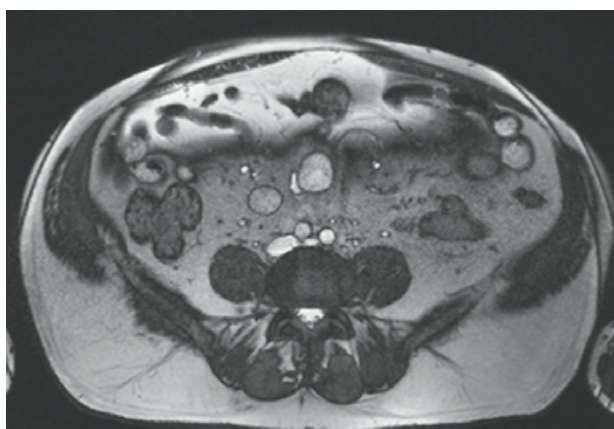**Figure 1:** CT venogram demonstrating chronic IVC occlusion.

Figure 2: MR venogram demonstrating May Thurner Syndrome—compression of left common iliac vein by the right common iliac artery.

preoperative planning and to compliment intraoperative imaging tools, including intravascular ultrasound and contrast venography.

Direct catheter venography

Direct catheter venography can/should be performed in all patients in whom common femoral vein disease is identified and there are concerns regarding adequacy of inflow. It is also used to confirm the diagnosis of venous outflow obstruction. It provides information on venous inflow, locations of venous stenosis, and provides a road map for interventional planning including access.
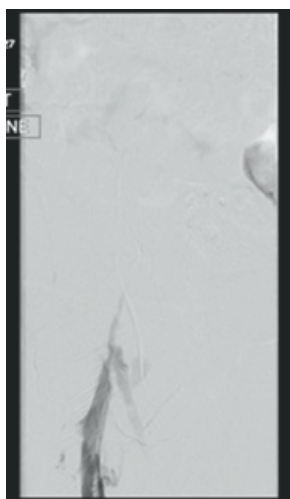

Figure 3a: Direct catheter venography demonstrating iliac vein occlusion with good femoral vein and profunda vein inflow.
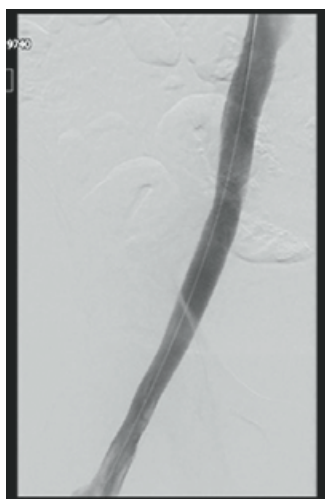

Figure 3a: Direct catheter venography demonstrating iliac vein occlusion with good femoral vein and profunda vein inflow.

Intravascular ultrasound

Intravascular ultrasound (IVUS) can be used to further characterise suspected venous abnormalities identified on venography and is particularly useful prior to consideration of proximal venous stenting (common femoral vein to inferior vena cava). IVUS consists of a miniaturized ultrasound probe fixed to an intravascular catheter and provides a 360-degree 2D greyscale ultrasound image of lumen and vessel wall structures. Using key landmarks (usually the profunda vein) and venous branches, venous abnormalities can be characterised in more detail. IVUS is able to give real-time information such as the presence of external compression, acute and chronic thrombus, fibrosis, mural wall thickening and trabeculations.

Conclusion

The clinician should have a high index of suspicion for proximal venous outflow obstruction in any patient with a venous leg ulcer and symptoms or signs of post-thrombotic syndrome. Wider education of healthcare professionals will prompt further investigation for potential venous disease. Patients with underlying proximal deep venous obstruction/stenosis may benefit from treatment with IVC/iliac venous stenting, if they have symptoms and signs of significant chronic venous insufficiency. There is increasing evidence to support iliac/IVC stenting for chronic central venous outflow obstruction in patients with symptomatic CVI due to proximal venous disease—in particular, a reduction in pain (86–94%), swelling (66–89%) and improvement of ulcer healing (58–89%).[18]

Patients should meet the criteria for intervention before investigations are commenced. It is vital that the patient is able to be compliant with a full anticoagulation regimen and is fully informed on the follow up schedule and potential need for reintervention.

There is still significant controversy and debate about the order and manner by which patients with significant CVI and iliocaval obstruction associated with severe reflux of the superficial venous system should be treated.[19] Long-term outcomes for endovenous intervention are awaited. CVI and chronic venous ulceration remain a significant burden on healthcare systems worldwide. Increased education amongst
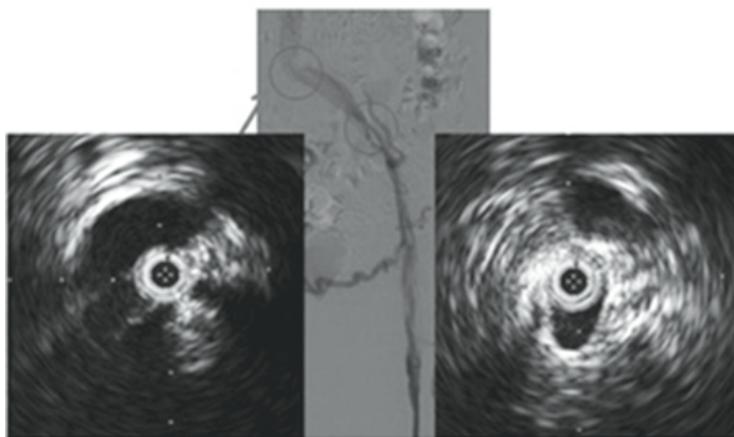

Figure 4: Assessment of venous stenoses

medical professionals to identify cases of CVI that warrant further investigation will be key to reducing that burden.

Summary

- Venous disease is the most common cause for leg ulcers in the UK.

- Post-thrombotic syndrome develops in 30–50% of patients with acute DVT.

- 10% of patients with post-thrombotic syndrome will develop venous leg ulceration over a 10-year period.

- A thorough history is required to identify those patients who may benefit from further venous investigation.

- A high index of suspicion for proximal venous disease is required when assessing patients with venous leg ulceration.

- Imaging modalities include venous duplex ultrasound, magnetic resonance venography, computer tomography venography, direct catheter venography and intravascular ultrasound.

- Patients should meet the criteria for intervention before investigations are commenced—specifically compliance with an anticoagulation regimen.

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