

Review

Modern approaches and innovations in the diagnosis and treatment of peripheral vascular diseases

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1. Abstract

Amongst the three major vascular beds (coronary, cerebrovascular, and peripheral), peripheral vascular disease (PVD) has traditionally received the least attention, despite its growing global burden. The aging population has led to the increased prevalence of PVD, thereby increasing visibility to its various diagnostic and treatment modalities. In the past decade, research and development of innovations in the management of PVD has exploded. Modern advances in imaging, molecular technology, medical devices, and surgical techniques have reduced the morbidity and mortality of PVD. However, many challenges still remain due to the debilitating and progressive nature of this disease. In this article, we will introduce some common vascular diseases, the state of art in diagnosis and treatment, the limitations of modern technology, and our vision for this field over the next decade.

2. Introduction

Disease of the blood vessels, particularly diseases of the arteries, more commonly known as peripheral vascular disease (PVD), is one of the most prevalent cardiometabolic diseases. This occurs in nearly 200 million people worldwide, and is most commonly found in elderly patients, especially after the age of 65 years [1]. The incidence of PVD increases with age.

As the longevity of the population increases, PVD will continue to constitute a major problem. It is important to realize that the severity and the extent of vascular disease is influenced by several risk factors, including smoking, diabetes, chronic kidney disease, sedentary lifestyle, and obesity [2]. One of the more severe risk factors, type 2 diabetes (T2DM), affects more than 34 million Americans and causes severe PVD due to endothelial cell dysfunction

and inflammation. PVD in diabetic patients can lead to amputation, which occurs to nearly 130,000 American patients yearly. Such complications can be prevented through intensive insulin treatment and glycemic control [3].

The basic pathophysiology of peripheral vascular disease is atherosclerosis. The genesis, progression, and advances in management of atherosclerosis are described by other authors in this book. This section deals with the clinical aspect of atherosclerotic vascular disease, its impact on morbidity and mortality, and current management strategies. Enormous innovation has occurred in the last decade. Despite this, there is a need for more sophisticated therapies directed at prevention of this disease.

As is well known, atherosclerotic occlusion of the arterial system is a diffuse disease process affecting various vascular beds in the body, most notably in the coronary, cerebrovascular, and peripheral vascular systems. It is essential to understand that 1/3rd of patients presenting with vascular disease will have involvement of atherosclerosis in all three systems [2, 4]. In this section, we will discuss the standard of care of vascular disease of these systems and explore recent innovations in their diagnosis and treatment.

3. Peripheral arterial disease

Peripheral arterial disease (PAD) refers to the chronic occlusion of the infra-renal aorta and arteries of the lower extremities due to atherosclerosis. In the United States, approximately 6.5 million people aged 40 and older have PAD [5]. The classic symptom of PAD is intermittent claudication, which is pain or discomfort in the lower extremities upon physical exertion, like walking. While this may be overlooked as the result of aging or arthritis, if not recognized early and treated appropriately, claudication can lead to loss of limb or life [6]. It is now known that intermittent claudication is a marker of more generalized disease, as individuals with PAD are at a two to six times greater risk of myocardial infarction or stroke [7]. This warrants the initiation of lifestyle changes such as exercise therapy and smoking cessation, and medical therapy such as antiplatelet, anticoagulant, antihypertensive, lipid-lowering, and glycemic-control drugs [8].

3.1 Diagnosis

In the past, the only modality for diagnosing vascular disease was angiogram, which involves X-ray imaging performed simultaneously with injection of a contrast agent. The availability of the ankle brachial index, ultrasound, and Doppler ultrasound made it possible to diagnose vascular disease with reasonable accuracy in a non-invasive manner. Modern advancements in ultrasound technology had led to widespread use of duplex scan, which provides both a real-time image of the artery and velocity of blood flow (via spectral analysis). This technique has become the gold standard for diagnosing and following vascular disease due to its non-invasiveness and lack of harmful effect on

tissue, such as radiation [9]. Computed Tomography (CT) and magnetic resonance imaging (MRI) have emerged as the new diagnostic, more sophisticated, and non-invasive imaging modalities.

While the ABI and Doppler ultrasound has allowed for the non-invasive diagnosis of PAD, several limitations exist. A proportion of patients with PAD may not present with classical symptoms and thus may be inadequately screened/diagnosed. Furthermore, ABI measurements are unreliable in patients with diabetes and end-stage renal failure, due to medial sclerosis of the arteries. Recent studies in novel, adjunctive diagnostic tools have been performed. Infrared thermography (IT) has been used to evaluate skin temperature, which is altered depending on changes in blood flow. Some studies have shown its ability to detect temperature differences in the feet of patients with PAD and provide additional information regarding foot circulation and subclinical infections [10, 11]. Enhancements in photoplethysmography, used clinically today as a pulse oximeter, has been another promising avenue for the non-invasive imaging of PAD. Created by engineers at Rice University, the PulseCam combines photoplethysmography with a camera to create a three-dimensional spatial-temporal map of blood perfusion over a large skin surface area. Lab experiments have shown a greater reliability and sensitivity in detecting blood flow occlusion compared to conventional pulse oximeters and IT technology [12].

3.2 Treatment

Historically, direct surgical reconstruction was the only way to restore circulation to the affected extremity, either through removal of the plaque (endarterectomy) or bypassing the diseased segment. History was made in 1977 when Andrea Gruntzig demonstrated to the world that stenosed coronary arteries could be made patent by balloon dilation (known as angioplasty) [13]. Percutaneous transluminal angioplasty and stenting are now the initial treatment to open arterial occlusion and restore blood flow. Numerous other endovascular technologies, such as orbital atherectomy and drug-coated balloon/stents also exist. This minimally invasive technique, performed under local anesthesia, permits quick recovery and return to daily activities.

Depending on the length and severity of blockage, a significant number of patients will still need surgical reconstruction like bypass surgery. The earliest bypass grafts were autogenous vessels such as the human saphenous vein. The next arterial conduits developed were synthetic grafts, made from Dacron and Teflon. The human saphenous vein remains the gold standard for lower extremity bypass procedures. However, saphenous veins may be unavailable to harvest or are structurally inadequate in certain patients. Similarly, synthetic grafts, both Dacron and Teflon, have risk of infection and dismal patency rates due to low flow and small size of lower extremity vessels [14, 15]. There is a great need for a conduit similar to the saphenous vein.

The future remains bright, as tremendous work is being done to create a human bioengineered acellular blood vessel. Our hope for an ideal conduit is one that is biologically inert, non-thrombogenic, durable, long-lasting and can be easily retrieved off-the-shelf. A recently published phase II clinical study showcased the implantation of human acellular blood vessels (HAV) in femoropopliteal bypass surgery in 20 patients with occlusions of the superficial femoral artery (SFA). The HAVs were made from cadaveric human vascular smooth muscle grown on a degradable polymer scaffold that were later decellularized. Over a 2-year period, there were no structural failures or direct graft infections, and a 24-month patency rate of 58% [16].

The boundaries of endovascular treatment have also been pushed through the development of an entirely percutaneous femoropopliteal bypass to treat challenging PAD. This is done through endovascular deployment of stent grafts through a nearby transvenous route to bypass arterial lesions. In a 1-year safety and effectiveness multicenter study, this novel bypass system was implanted in 78 patients with chronic total occlusions or severe calcification of the SFA. There was a procedural success rate of 96% and the 1-year primary patency rate was 81%. 1-year stent thrombosis was seen in 16.5% of patients. This technology ultimately benefits those with significant PAD that are unable to tolerate bypass surgery [17].

At a fundamental level, there is question whether endovascular or open surgery is superior. The sole landmark study comparing the efficacy of these two methods is the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial in 2005. Performed across 27 hospitals for 5 years, the study compared 228 patients that underwent surgical bypass, and 224 patients that underwent angioplasty. This study showed no difference in 30-day mortality between the two arms. However, the surgical bypass group has significantly higher rates of morbidity, such as wound complications, infections, or cardiovascular events. Furthermore, endovascular treatments had a higher rate of re-interventions compared to surgical bypass [18]. That being said, numerous advancements have been made in endovascular technology today. We look forward to future studies that seek to compare the clinical efficacy of all these modern technological advancements versus open bypass surgery.

It is not inconceivable that one day we may move beyond endovascular or surgical treatment for bypassing vessels. Even with modern advances in revascularization, a significant proportion fail, leading to amputations or even death. We imagine a future where proliferation of existing blood vessels can be stimulated through enhancing the production of angiogenesis factors in ischemic areas, termed “therapeutic angiogenesis”. One of the earliest works was conducted by Isner *et al.* [19], who applied human plasmid encoding vascular endothelial growth factor (VEGF) to the coating of an angioplasty balloon, facilitating intra-

arterial gene transfer to the distal popliteal artery in a single patient. This technique showed an increase in collateral vessel formation. Unfortunately, many later-stage clinical trials have not led to clinical impact in limb salvage and amputation, due to difficulties in route of delivery and unsuccessful gene transfer [20]. There has been considerable interest in the intramuscular injection of mesenchymal stem cells from bone marrow aspirate to promote limb salvage in patients with critical limb ischemia. The largest and most recent clinical trial to date is “The safety and efficacy study of autologous concentrated bone marrow aspiration (cBMA) for critical limb ischemia trial”, otherwise known as the MOBILE study. Unfortunately, recent results do not show a significant difference in amputations rates and pain at one-year between the stem cell treated and control group. However, new studies involving more potent progenitor cells and a multi-modal approach involving electroceutical dressing are currently being investigated [21, 22]. While we are in the early stages of this treatment modality, we remain optimistic that therapeutic angiogenesis may one day be an adjuvant therapy to revascularization procedures.

4. Cerebrovascular disease and carotid artery disease

Stroke, the sudden interruption of blood supply to the brain, is the 5th leading cause of death in the United States, with over 795,000 people in the US experiencing a stroke annually [23]. Nearly 18–25% of all ischemic strokes can be attributable to extracranial disease, particularly in the carotid artery [24]. Carotid artery stenosis refers to the narrowing of the carotid artery, most frequently due to atherosclerosis causing buildup of a plaque within the artery. Embolization of this plaque may result transient ischemic attack and stroke, leading to motor and sensory deficit, and even painless, temporary, monocular blindness (amaurosis fugax). Many patients may also present asymptotically. The risk factors for carotid artery stenosis are the same as PAD, such as hypertension, hyperlipidemia, sedentary lifestyle, smoking, age, and male sex.

4.1 Diagnosis

The most commonly used, least invasive, and inexpensive diagnostic modality for carotid artery stenosis is the Doppler ultrasound, which detects arterial wall morphology and blood flow velocity. These findings can calculate the percentage stenosis of the lumen, which in combination with the presence of symptoms, dictates the course of treatment [25].

However, the degree of stenosis may not accurately assess the occurrence of stroke. Advances in ultrasound, CT, MRI, and PET have allowed for the detection of additional biomarkers based on plaque composition to determine plaque vulnerability, a better predictor of stroke occurrence. For example, high risk plaque fea-

tures such as intraplaque hemorrhage, lipid rich necrotic core (LRNC), thin/ruptured fibrous cap, and large plaque thickness were associated with an increased risk of stroke in asymptomatic patients [26]. Similarly, in patients with symptomatic carotid stenosis, intraplaque hemorrhage has been identified as a strong link to future ischemic stroke [27]. MRI has been the superior technique in detecting features of plaque vulnerability in terms of reproducibility. Most recently, studies have shown the potential of positron emission tomography (PET) and molecular imaging (e.g., iron oxide contrast agents) in quantifying the accumulation of inflammatory cells as a biomarker for plaque vulnerability [28].

We envision a future where such novel imaging techniques can quickly identify the different biomarkers of plaque vulnerability and calculate the percentage risk of stroke development regardless of percent stenosis or presence of symptoms. This will guide clinical decision making to better identify which patients are in need of medical versus surgical management, saving healthcare dollars and increasing life expectancy.

4.2 Treatment

The first endarterectomy was performed in 1947 by Portuguese surgeon Cid Dos Santos, who removed an occluding plaque from the femoral artery. This technique would later be applied by DeBakey and Eastcott to the carotid artery, giving birth to the carotid endarterectomy (CEA). Refinements in CEA would make it one of the most widely studied and performed surgical procedure [29]. Years later, carotid artery angioplasty and stenting would also be introduced as an alternative procedure.

Today, the mainstays of carotid artery stenosis treatment involve carotid endarterectomy (CEA), or carotid artery stenting (CAS). These procedures are typically done in patients with severe symptomatic stenosis, although consideration may also be given to asymptomatic patients with high grade stenosis. CAS is seen as an alternative to CEA in patients at increased risk for surgery or unfavorable neck anatomy, but recent studies have reported CAS to have higher perioperative stroke risk due to aortic arch and carotid lesion manipulation [30]. While the introduction of embolic protection devices to prevent distal plaque embolization to the brain has improved the complication rates of CAS, the risk still remains. Ongoing trials continue to compare the true efficacy of both techniques.

The development of transcarotid artery revascularization (TCAR) and flow reversal has allowed for completion of CAS with reduced risk of embolic stroke. In this procedure, two incisions are made to access the proximal common carotid artery (CCA) and common femoral vein (CFV). The two sites are externally connected to a flow controller, which establishes flow reversal from the CCA to CFV so that any embolic matter is diverted away from the brain. TCAR has seen high technical success rates

and a lower in-hospital stroke/transient ischemic attack rate compared to the traditional trans-femoral carotid stenting. However, studies comparing its safety efficacy compared to CEA remain to be completed [31].

However, once an ischemic stroke has occurred due to embolus, what treatment options exist? For decades, the standard therapy was initiation of intravenous thrombolytic therapy (alteplase) within 4.5 hours of symptom onset [32]. Recently, endovascular mechanical thrombectomy has emerged as the standard of care for large-vessel occlusion of anterior cerebral circulation within 24 hours of neurologic baseline. The two current techniques are stent retriever thrombectomy (temporary deployment of a stent within the clot) and aspiration thrombectomy (suction at the clot interface). A combined technique, known as Solubra, has been recently developed [33].

Advances in imaging technologies, like diffusion and perfusion MRI (DWI/PWI), has allowed the stroke interventionalist to identify patients who will have the best outcomes from endovascular thrombectomy. DWI estimates the rate of water diffusion into tissue and can detect ischemic brain tissue within several minutes from arterial occlusion onset. PWI detects areas of decreased perfusion and quantifies perfusion parameters like mean transit time and cerebral blood flow. Together, these techniques identify brain tissue that is irreversibly damaged (infarct core) or can undergo reperfusion (penumbra), allowing for individualized stroke treatment.

Despite all the advances in imaging and thrombolysis, treatment modalities are limited by a strict time window. The time window for intravenous thrombolytic therapy is <4.5 hours and for intra-arterial mechanical therapies <8 hours; any time beyond this results in permanently lost brain tissue [34]. There are resource-limited settings where patients may live too far from a medical institution to receive timely stroke therapy. Thus, is it possible to enhance the ischemic tolerance of brain tissue, thereby prolonging the stroke treatment window? Several approaches have been attempted. Metalloproteinase inhibitors, like minocycline and cilastazol, have been seen to preserve the integrity of the blood brain barrier and expand the time window by several hours [35, 36]. Additionally, granulocyte colony stimulating factor (G-CSF) has promoted neovascularization within ischemic regions in rat studies [37]. Lastly, use of therapeutic hypothermia and antioxidants (vitamin C) have been seen to neutralize free radical formation in ischemic brain parenchyma, providing neuroprotection [38]. We envision a future where medications can expand the therapeutic window, increasing the number of patients eligible to be saved by thrombolytic techniques.

5. Abdominal aortic aneurysms

Abdominal aortic aneurysm (AAA) refers to the focal dilation of the abdominal aortic to more than 1.5 times a normal, adjacent segment. AAAs are most common in elderly white males (age >50) and smokers, with over 200,000 people in the US diagnosed each year [39]. The pathophysiology of AAA is multifactorial. Inflammatory processes weaken the cellular structure of the arterial wall, causing extracellular matrix (ECM) degradation and smooth muscle cell apoptosis. The mechanical stress of pulsatile blood flow expands the weakened wall vessels, causing aneurysmal dilation. While most cases of AAA are asymptomatic, symptomatic patients will present with abdomen or back pain, hypotension, or a pulsatile mass. Some aneurysms may expand to a rapid degree, increasing the risk of AAA rupture; this has a 100% mortality if not surgically repaired. The most important risk factor for AAA is smoking; others include advanced age, male sex, and atherosclerosis.

5.1 Diagnosis

The best initial and non-invasive diagnostic tool for AAA is the ultrasound. It is used to quickly assess for the presence and size of an AAA in asymptomatic patients. It also has excellent utility as a screening device. However, ultrasound lacks the ability to detect leaks or involvement of branching arteries. CT with IV contrast is the modality of choice to confirm AAA and provides these additional details, alongside its location and any presence of thrombus.

5.2 Treatment

Surgery is indicated for AAAs if there is rapid aneurysm growth (>1 cm/year), size larger than 5.5 cm, or rupture. The first open abdominal aortic aneurysm resection with graft replacement Charles Dubost in 1951 [40]. This involved isolation of the abdominal aorta, aneurysm resection, and replacement with a synthetic aortic graft. 40 years later, endovascular aneurysm repair (EVAR) was introduced, allowing for introduction of an aortic graft in the dilated aorta through a tiny incision in the femoral artery. Today, AAAs can be treated with both approaches, although the rates of EVAR now exceed open surgery today. This is attributed to studies documenting reduced perioperative and 30-day mortality of EVAR compared to open surgery.

Unfortunately, many patients cannot undergo EVAR due to anatomical challenges in the proximal aortic neck, the area of the aortic inferior to the renal arteries and superior to the aneurysm sac [41]. These may include a shorter aortic neck, neck angulation, and presence of thrombus/calcification. Such challenges impact proper stent placement and can lead to an endoleak, where blood flows outside the lumen of the graft and into the aneurysm sac. Sophisticated CT technology has allowed aortic grafts to be custom made for each patient with fenestrations that

align with orifices of celiac, superior mesenteric, and renal arteries. This procedure, called fenestrated endovascular aortic aneurysm repair (FEVAR), has enabled treatment of even the most complex aneurysm with endovascular technique.

Today, the only method to prevent AAA formation and expansion is lifestyle changes, such as smoking cessation, blood pressure control, and aerobic activity. However, the cause of AAA formation is still unknown and remain widely debated, although several mechanisms have been proposed. Key contributing molecular factors that have been studied are matrix metalloproteinases (MMP), angiotensin II, reactive oxygen species (ROS), and infiltration of inflammatory cells [42]. Additionally, patients with Ehlers-Danlos and Marfan syndrome, genetic connective tissue disorders, have a higher risk of AAA formation due to mutations in collagen and fibrillin respectively. Understanding the various molecular mechanisms of arterial wall weakening may allow us to one day prevent the breakdown of collagen and fibrillin through medical therapies. Doxycycline was once touted as a potential therapeutic to reduce AAA expansion through inhibition of MMPs. However, clinical studies have shown no significant reduction in aneurysm growth [43]. Recent studies on statin use have shown a lower AAA growth and rupture rate through atherosclerosis stabilization and of reduction MMP expression [44].

There remains no strong clinical recommendation for medical therapy use in preventing AAA formation and expansions. Fortunately, we are still seeing the development and testing of novel techniques in animal. Kurashiki *et al.* [45] recently developed a peptide vaccine against angiotensin II has prevented AAA expansion through inhibition of macrophage and MMP and TNF α in rats. Furthermore, injection of stem cells within the aortic lumen has also shown AAA prevention in rodent models through modifying vascular smooth muscle cells to effectively secrete ECM components [46]. We remain optimistic for a future where medical therapy can be the mainstay for treatment and prevention of AAA.

6. Aortic dissection

Aortic dissection (AD) is the most common acute catastrophe involving the human aorta. AD refers to a tear in the inner layer of the aorta (intima), allowing blood to flow in between the layers of the arterial wall. If unrecognized and untreated, mortality is 2% per hour. This is one of the most lethal disease, nearly 50% of patients die within 24 hours [47]. The most common cause of aortic dissection is hypertension, although certain connective tissue disorders like Marfan's and Ehlers-Danlos are also contributors in younger patients. Surgery and endovascular techniques are available to treat aortic dissections now.

6.1 Diagnosis

For AD, CT angiography (CTA) is the gold standard for detecting AD and may show a dissection flap or aortic dilation. Magnetic resonance imaging may also be used in patients with contraindications to CTA. In emergency situations where a patient is unstable, transesophageal echocardiography can be rapidly performed.

Biomarkers have also been helpful in the diagnosis of AD. Levels of D-dimer, the product of fibrin degradation after fibrinolysis of a thrombus, has been shown to have high sensitivity and moderate specificity for diagnosing AD. Clinically, a negative D-dimer test has been most valuable as a marker to rule out AD or differentiate from myocardial infarction (Cui). Other markers being studied include smooth muscle myosin heavy chain, MMP-9, and elastin degradation products [48].

Novel imaging techniques like flow MRI can detect flow velocity, as well as the amount and distribution of wall shear stress in the aorta. Elevated wall shear stress has been associated with degeneration of connective tissue fibers of the ECM of the thoracic aorta, increasing susceptibility to dilation and/or dissection [49]. Additionally, positron emission tomography (PET) with 18-fluoro-2-deoxyglucose (FDG) has been used to identify the presence of macrophages and other inflammatory cells in the aortic wall. One study reported FDG uptake to be associated with a decrease in collagen and vascular smooth muscle cells of the aorta [50]. Such techniques may become common place in the future to pre-emptively treat aortas at risk for aneurysm or dissection.

6.2 Treatment

The treatment of AD depends on the anatomic location of dissection. In ADs affecting the ascending aorta, urgent open surgery is recommended. Uncomplicated ADs limited to the descending aorta are treated with blood pressure and pain control medications. Complications such as end-organ ischemia, rupture, and continuing pain and hypertension despite medical therapy prompts endovascular treatment.

Endovascular repair for descending ADs was first introduced in 1999 due to the risk associated with open surgical repair. There are several techniques used today, including fenestration of the dissection flap, stent graft placement, or a combination of the two. Branched endografts are also custom made to fit within the branches of the aorta.

Similar to AAA, the only true preventative strategies for AD are lifestyle management changes like blood pressure control and smoking cessations. Aortic dilation is also monitored through imaging techniques like ultrasound, with prophylactic surgery recommended for greater than 5.5 cm. Patients with connective tissue diseases like Marfan syndrome require even more frequent screening and lower threshold for prophylactic surgery.

7. Conclusions

Peripheral vascular disease remains a major global burden with significant health and socioeconomic consequences. PVD is a systemic atherosclerotic process, leading to feared complications such as loss of limb, stroke, and death. Major innovations in the detection and management of PVD has arisen in the past decade. Improvements in ultrasound, CT, MRI, and PET has led to detailed visualizations of human vasculature and enabled the prediction of at-risk patients, allowing for appropriate treatment in a timely fashion. An increasing number of vascular procedures are moving towards minimally invasive endovascular techniques, leading to faster patient recovery. Advances in tissue engineering and graft development has created more effective and durable vascular conduits that can be customized to each patient. Additionally, numerous medical therapies are being developed that target key points of the molecular pathogenesis of various vascular diseases. As the advances mentioned in this article are brought into clinical practice, the management of PVD will ultimately move towards prevention and early treatment. Furthermore, any advances in the clinical management of other cardiometabolic diseases will only serve to enhance the treatment of PVD.

8. Author contributions

RS contributed to PVD and Cerebrovascular and Carotid disease sections; SB contributed to Aortic Diseases –Abdominal Aortic Aneurysms and Aortic Dissection.

9. Ethics approval and consent to participate

Not applicable.

10. Acknowledgment

Not applicable.

11. Funding

This research received no external funding.

12. Conflict of interest

The authors declare no conflict of interest.

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Keywords: Review; Peripheral vascular disease; Carotid stenosis; Peripheral arterial disease; Stroke; Abdominal aortic aneurysm; Aortic dissection; Atherosclerosis

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