HHS Public Access

Author manuscript

Circ Res. Author manuscript; available in PMC 2016 April 24.

Published in final edited form as:

Circ Res. 2015 April 24; 116(9): 1505–1508. doi:10.1161/CIRCRESAHA.115.306403.

A Compendium on Peripheral Arterial Disease

John P. Cooke[1] and **Zhen Chen**[2]

[1]Dept of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX, USA

[2]Division of Cardiology, University of California San Diego

The broad scope of PAD

Peripheral arterial disease (PAD) is usually taken to mean arterial occlusive disease due to arteriosclerosis, impeding the blood flow to the lower extremity. Of course, it is important to keep in mind that a broader definition of PAD would include all non-coronary arterial disease including carotid artery disease. Furthermore, there are many disorders that can cause arterial occlusive disease other than atherosclerosis although it is by far the most common. These disorders can be due to pathobiology intrinsic to the vessel wall, as in vasculitis, thromboangiitis obliterans, or fibromuscular dysplasia; or secondary to extrinsic pathology as in compression syndromes such as popliteal artery entrapment. Embolic disease (such as that due to atheroembolism from a diseased aorta, or cardiogenic thrombus) or dissection of the aorta, may cause occlusion of peripheral arteries. In addition, the broad scope of peripheral arterial diseases includes non-occlusive arterial disease, such as aneurysms, traumatic or congenital arteriovenous fistulas or malformations, and vascular tumors. However, for the purposes of this compendium, we focus on atherosclerotic arterial occlusive disease that impairs blood flow to the lower extremities.

Dying of neglect

Defined in this way, PAD is the most common disease that is most commonly overlooked. Although it is unusual for PAD to manifest in those under the age of 55, its prevalence increases sharply with age to affect about 8–10% of individuals over the age of 65, and about 20% of individuals over the age of 80 (1). Regrettably, most of these individuals are not diagnosed, as documented by in the PARTNERS screening study (2). As a consequence, individuals with PAD are less likely than those with coronary artery disease to receive optimal medical therapy. This is a tragic situation because optimal medical therapy saves life and limb. In their comprehensive and lucid review of medical therapy, **Creager and Bonaca** (3) point out that the aims are two-fold: to reduce cardiovascular morbidity and mortality, and to relieve symptoms and functional impairment associated with PAD. They detail how the use of statins, angiotensin converting enzyme inhibitors (ACEi), and anti-platelet agents substantially reduce cardiovascular morbidity and mortality in individuals with PAD. Furthermore, statins and ACEi, as well as cilostazol, can improve walking distance. As discussed by several of the authors, supervised exercise has the greatest

Corresponding author: John P. Cooke, M.D., Chair, Department of Cardiovascular Sciences, Houston Methodist Research Institute, 6670 Bertner Ave., Mail Stop: R10-South, Houston, Texas 77030, jpcooke@houstonmethodist.org.

efficacy of medical therapies to improve walking distance. Tobacco cessation is a mainstay of treatment, as it improves functional capacity, prevents the progression of disease, and reduces the risk of bypass failure (3).

Given that there is effective medical therapy, why is PAD underdiagnosed and untreated? As noted by **McDermott**, most individuals with PAD do not have the classic symptomatology of intermittent claudication as defined by as pain in the buttocks, thighs and/or calves that occurs during walking, relieved by standing still (4). Only 10–30% of PAD patients manifest these symptoms. They may be sedentary, and not aware of their limitations, or the patients (and physicians) attribute the leg pain to musculoskeletal disease or neuropathy that often co-exists in these elderly patients. Another cause of the poor recognition is suboptimal screening. It is not because screening procedures are highly technical or expensive. It is straightforward to make the diagnosis of PAD with simple equipment i.e., a blood pressure cuff and a hand-held Doppler. One measures the systolic pressure at the brachial, dorsalis pedis and posterior tibial arteries. The ankle-brachial index (ABI) for each leg is calculated by taking the higher of the two pressures taken at the ankle, and dividing it by the higher of the two brachial pressures. The normal ABI is 1.0–1.2 (the systolic pressure at the ankle can be slightly higher than the systolic pressure measured at the brachial artery in a healthy individual, due to pulse wave reflections). The diagnosis of PAD is made when the ABI ≤ 0.9.

The ABI is a very useful screening approach that should be adopted in all medical practices that care for older adults. Indeed, the American Heart Association and American College of Cardiology have published guidelines recommending that individuals at risk have an ABI screening performed (5). Diabetics or smokers over the age of 55, and anyone over the age of 65, should have an ABI performed to detect undiagnosed PAD. *The purpose of routine screening is not to identify patients for endovascular interventions. It is to identify individuals who are at greater risk for cardiovascular morbidity and mortality, so that they can get the proper medical treatment.* Regrettably, the US Preventive Services Task Force has claimed that more evidence is required before ABI screening can be recommended. This assessment is delaying the widespread implementation of ABI screening as well as the diagnosis and proper medical therapy for many US citizens.

Risky business

Criqui and Aboyans are leading authorities on the epidemiology of PAD, and team up in this compendium to provide an elegant review of the risk factors determining the incidence and prevalence of PAD. Of course, the usual suspects play a role in atherosclerosis affecting the lower extremities, including tobacco, diabetes mellitus, age, dyslipidemia and hypertension (2). However, in this regard there are some curious differences between PAD and the other major arterial diseases i.e., the coronary and carotid vessels. Tobacco exposure is a risk factor for all three, but seems to be a stronger determinant of PAD. This preferential effect on the limb vessels is unexplained, but one clue comes from the surprising observation that nicotine receptors are expressed by blood vessels (6). These nicotinic acetylcholine receptors mediate a number of vascular processes related to atherosclerosis, including neovascularization of atherosclerotic plaque and proliferation of vascular smooth

muscle cells (7). The nicotinic receptors appear to be widespread in the vasculature, but is it possible that these receptors are differentially active in peripheral vessels? Of interest, **Leeper and Khullo** point out that one of the genetic variants that increases the risk of PAD is in a gene encoding a nicotinic acetylcholine receptor (8).

Diabetes mellitus is also a very strong risk factor for PAD. Furthermore, patients with more severe disease (critical limb ischemia) are likely to be diabetic. Intriguingly, the arterial occlusive disease incurred by diabetic patients in their peripheral as well as their coronary arteries tends to be more diffuse and with greater distal extent, by comparison to non-diabetics (2). In addition, diabetics often have more vascular calcification, sometimes extending to the digital arteries of the toes. The mechanisms underlying this propensity for distal and diffuse disease, with greater calcification, is not fully explained, but may be in part due mesenchymal stem cells activated in the vessel wall by inflammatory and metabolic signals.

Another unexplained finding is the increased risk of PAD in African-Americans, even after accounting for ethnic differences in the burden of risk factors (2). It is possible that unconventional risk factors, such as social stress or walkability of the urban environment could be involved. Other unconventional risk factors considered by Criqui and Aboyans include oral health or history of infectious disease, both of which are related to the intriguing new research front regarding the effects of the microbiome on the progression of atherosclerosis.

Epidemiological studies that employed questionnaires lack sensitivity as most patients with PAD do not have classical symptoms of intermittent claudication. Those epidemiological studies that use the ABI provide more accurate reflection of the incidence or prevalence of PAD. However, even the traditional ABI under-reports PAD. Some lesions which may be hemodynamically significant during exercise, may not cause a pressure gradient at rest. Furthermore, the traditional method for expressing the ABI (i.e. using the highest of the ankle pressures) may miss single vessel disease at the ankle. When the lowest of the ankle pressures is used, the number of patients classified as having PAD doubled in a large cohort of patients undergoing coronary angiography (9). On long-term follow up, the additional patients detected using this alternative ABI had greater mortality than those patients who were classified as not having PAD by either ABI method. Thus the alternative ABI method identifies more patients that are at risk for cardiovascular mortality. Accordingly, there is reason to re-examine the methodology for the ABI calculation. An alternative approach for screening would be to develop a blood test for detecting patients with PAD (10). However, the current biomarkers currently do not have the sensitivity or specificity to replace the ABI measurement.

Stepping forward

Hiatt and colleagues have contributed greatly to our understanding of the pathobiology of PAD, and elucidate these mechanisms in this compendium. It is clear from their work and the studies of **Mary McDermott** that the functional limitation of PAD patients is multifactorial (4, 11). Although the impaired perfusion may be primary, secondary changes

in the skeletal muscle, including mitochondrial dysfunction, denervation and replacement of myocytes with fibrofatty tissue contribute. Other concomitant conditions that may exacerbate the vascular impairment and functional limitations include oxidative stress, inflammation, endothelial vasodilator dysfunction, increased blood viscosity and hypercoagulation. The contribution of these other mechanisms may explain why limb hemodynamics are not predictive of the patient's performance on a treadmill test (12). Attention to other mechanism that impair functional capacity could lead to new therapeutic avenues. In the meantime, given its established efficacy to improve walking distance, the authors recommend supervised exercise training. Exercise has beneficial effects on the lipoprotein profile, resting blood pressure and heart rate, insulin sensitivity, neurohormonal activity, and endothelial elaboration of vasoprotective factors (13). Whereas exercise training is effective at improving functional capacity, it is not known if an exercise training program can reduce mortality in PAD patients. However, it is noteworthy that in PAD patients, functional capacity is a stronger predictor of mortality than are the classical risk factors (14). Finally, it is worth noting that many patients with PAD tend to be sedentary individuals. Whether this is cause or effect has recently been addressed by a study revealing that recalled lifetime recreational activity is a positively correlated to ABI (15). Thus, it appears that a lifetime of sedentary behavior increases the risk for PAD.

Nature versus nurture

Of course, there must be genetic factors that contribute to the risk of developing PAD. However, the search for genetic determinants has not been as successful for PAD as it has for coronary artery disease. Given the heterogeneity of PAD and the strong environmental influences **Kullo and Leeper** suggest approaches that may yield more insight s into hereditary mechanisms of disease (8). Large collaborative meta-analyses of from genome-wide association studies are ongoing. Another approach is to employ large DNA repositories tied to electronic medical records. Also, it will be useful to study more homogenous subsets of individuals with PAD, stratified by risk factors and location of disease. In addition, novel insights might be gained by studying arterial diseases that have stronger genetic determinants and which share some biological processes with atherosclerosis (such as the abnormal proliferation of vascular smooth muscle cells in fibromuscular dysplasia and in atherosclerosis). In addition, in families with a strong predisposition to PAD, whole genome/exome sequencing has uncovered new candidates, such as variants of NT5E (involved in adenosine metabolism) and IN080D (involved in chromatin remodeling). The authors propose that, since it is difficult to obtain vascular tissue, one might perform RNA-seq studies of circulating cells that might report on inflammatory or coagulation processes that may contribute to PAD. However, such indirect assessments may be surpassed by with the new technology of induced pluripotency. For example, one may harvest easily accessed tissue from patients e.g., skin fibroblasts, and generated from these cells induced pluripotent stem cells (iPSCs) using the Yamanaka approach. Subsequently, the iPSCs can be differentiated into cells that are less easily obtained from the patient, such as endothelial cells (16). These iPSC-derived cells permit the study of "disease-in-a-dish" and are accelerating our discovery of new pathobiological insights and therapeutic approaches (17).

Finally, the authors link nature and nurture by discussing the role of epigenetics in vascular disease. Epigenetics is the study of factors that can alter gene expression by modifying DNA, altering the chromatin structure that is physically associated with DNA, or modulating the RNA transcripts of the DNA. Non-coding RNAs such as microRNAs (miRs), regulate multiple vascular functions. For example, miR-92a has been characterized as an important modulator of angiogenesis, NO-dependent vasodilation, and endothelial innate immune response and inflammation (18,19). Powerful new techniques such as ChIP-Seq are permitting rapid profiling of chromatin modifications that influence gene activity. Using such techniques, environmental factors such as tobacco have been found to alter the epigenetic state (8). Relevant to this discussion is the recent observation that inflammatory signaling has global effects on chromatin structure, which can increase the open probability state of the epigenome (20). In this state, cells have greater epigenetic plasticity and as a consequence, greater phenotypic fluidity. Indeed, the generation of iPSCs from somatic cells requires activation of inflammatory signaling. Furthermore, in this state of epigenetic plasticity, somatic cells have the capacity to transdifferentiate into other somatic cells (21). This phenomenon of ‘transflammation’ may underlie pathological processes involved in atherosclerosis such as endothelial-to-mesenchyme transition, but it may also be therapeutically modulated.

Vascular regeneration

The ability to generate iPSC-derived vascular cells might open a new chapter in stem cell and angiogenic therapies for vascular disease (22). To be sure, this field needs new approaches as the early promise of these regenerative therapies has not been met. **Cooke and Losordo** provide an overview of the scientific foundation for PAD regenerative therapy, and the clinical results to date (23). Although it is clear from the pre-clinical studies that angiogenesis and arteriogenesis can be manipulated by a variety of cytokines and progenitor cells, something has been lost in the translation to clinical studies. Although some phase I and II studies of these regenerative therapies have been encouraging, the definitive phase III studies have been negative. This may be due to deficiencies in the commonly used murine hindlimb ischemia model. In this model, the limb ischemia is surgically induced, and is really a model of acute ischemia. The authors suggest that results may be more predictive if an animal model of chronic arterial occlusive disease in the setting of cardiovascular risk factors was employed. Such a model might also be more useful in addressing unanswered questions related to the dose, duration of treatment, and delivery method to be utilized. Although a successful phase III study is yet to be reported, there is a Phase III study underway of plasmid DNA encoding hepatocyte growth factor for intramuscular injection, as well as phase II studies of a variety of progenitor cells for PAD (23).

When to intervene

When should the patient with PAD have surgery or endovascular intervention? Clearly, when a patient suffers from critical limb ischemia (with pain in the foot at rest, a non-healing leg ulcer or gangrene), or in the setting of an acutely ischemic limb, an interventional approach must be considered. However, the answer is less clear for the patient with intermittent claudication. The question is addressed from different perspectives by

several authors in the compendium. **Bonaca and Creager** describe the trials that have compared the symptomatic and functional benefits of medical therapy versus endovascular approaches. The CLEVER study examined the benefits of optimal medical therapy (OMT), OMT + exercise training, and OMT + endovascular stenting in patients with aorto-iliac disease. In brief, OMT + exercise training was superior for the primary endpoint of walking distance on a treadmill, whereas the secondary endpoint of quality-of-life was somewhat better for OMT + endovascular stenting. In the ERASE trial, patients with intermittent claudication due to aorto-iliac or superficial femoral artery disease were treated with supervised exercise training ± endovascular stenting. Those patients that were also stented had a significantly better result (in walking distance and quality of life) that was sustained to 12 months. Thus selected patients with intermittent claudication, not responding sufficiently to medical therapy, may benefit from a more interventional approach, combined with optimal medical therapy.

In those patients requiring a more invasive approach, the endovascular approach is often preferred over surgery because of the decreased morbidity of most endovascular procedures by comparison to open procedures. **Kinlay and Thukkani** provide a thoughtful discussion of the decision process and approaches required for endovascular treatment, which is nicely complemented by the analysis of the surgical approach by **Conte and Vartanian** (24,25).

Together, these articles illustrate the complexity of these decisions, which require a comprehensive assessment of the patient's current medical regiment, their functional status, the anatomic pattern of disease, and the comorbid conditions. A variety of pre-procedural imaging methods and physiological tests can provide valuable information that modifies the approach. In general, patients with focal and discrete lesions, particularly when the disease is more proximal (ilio-femoral), respond well to endovascular intervention. When the anatomic disease is more advanced patterns (e.g. extensive and diffuse lesions, long chronic total occlusions, or concomitant aneurysms) a surgical approach is generally preferred. In some complex patients, a hybrid approach, combining catheter-based and open techniques, is preferred. That being said, the domain of endovascular intervention continues to expand with the advent of new technology that improves endovascular results such as drug-eluting or covered stents, and drug-eluting balloons. Whatever the intervention, post-procedural pharmacotherapy is needed to minimize failure of the procedure (e.g. thrombosis). Once the patient leaves the hospital, what should be the intensity and method of surveillance to detect and correct early recurrence of disease before the conduit becomes occluded? These and other topics are cogently discussed. Although the field of vascular intervention has radically changed in the past few decades, the pace of change is likely to continue with the adoption of such exciting new technologies as 3-D imaging with robotic manipulation of endovascular devices, and with the development of tissue engineered vascular grafts.

To conclude, much is afoot in the world of PAD. We appreciate the opportunity to bring attention to a disease that is too often overlooked. The good news is that there are robust methods to detect the disease, to fully characterize the severity of the disease by imaging and functional testing, to substantially alleviate symptoms and improve functional capacity, and to prevent death and disability. We thank our co-authors for their commitment to this

work and to the field of vascular medicine, and we hope that the readers enjoy our Compendium.

Acknowledgments

Funding: This work was supported in part by NIH funding to JPC (U01 HL100397, U01 HL099997, 1UM1 HL113456, and 1R01 EY02060901) and to ZC (K99HL122368)

References

1. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001 Sep 19; 286(11):1317–24. [PubMed: 11560536]
2. Criqui M, Aboyans V. Epidemiology of Peripheral Artery Disease. CIRCRES. 2015
3. Creager M, Bonaca MP. Pharmacological Treatment and Current Management of Peripheral Artery Disease. CIRCRES. 2015
4. McDermott M. Lower Extremity Manifestations of Peripheral Artery Disease: The Pathophysiologic and functional implications of Leg Ischemia. CIRCRES. 2015
5. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, Golzarian J, Gornik HL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE, American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Apr 9; 61(14):1555–70. [PubMed: 23473760]
6. Heeschen C, Jang J, Hoai-Ky V, Kaji S, Yang P, Hu RS, Cooke JP. Nicotine is an agent of angiogenesis. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med. 2001 Jul; 7(7):833–9. [PubMed: 11433349]
7. Lee J, Cooke JP. The role of nicotine in the pathogenesis of atherosclerosis. Atherosclerosis. 2011 Apr; 215(2):281–3. [PubMed: 21345436]
8. Kullo I, Leeper N. The Genetic Basis of Peripheral Arterial Disease: Current Knowledge, Challenges and Future Directions. CIRCRES. 2015
9. Nead KT, Cooke JP, Olin JW, Leeper NJ. Alternative ankle-brachial index method identifies additional at-risk individuals. J Am Coll Cardiol. 2013 Aug 6; 62(6):553–9. [PubMed: 23707317]
10. Wilson AM, Cooke JP. Biomarkers in peripheral arterial disease. J Am Coll Cardiol. 2010 May 11; 55(19):2017–23. [PubMed: 20447524]
11. Hiatt W, Armstrong E, Larson C, Brass E. Peripheral Artery Disease: Pathogenesis of the Limb Manifestations and Exercise Limitations in Peripheral Artery Disease. CIRCRES. 2015
12. Szuba A, Oka RK, Harada R, Cooke JP. Limb hemodynamics are not predictive of functional capacity in patients with PAD. Vasc Med. 2006 Nov; 11(3):155–63. [PubMed: 17288121]
13. Chiu JJ. pathophysiological basis and clinical perspectives. Physiol Rev. 2011 Jan; 91(1):327–87. [PubMed: 21248169]
14. Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, Caceres RD, Cooke JP. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. J Vasc Surg. 2013 Mar; 57(3):728–33. [PubMed: 23044259]
15. Wilson AM, Sadrzadeh-Rafie AH, Myers J, Assimes T, Nead KT, Higgins M, Gabriel A, Olin J, Cooke JP. Low lifetime recreational activity is a risk factor for peripheral arterial disease. J Vasc Surg. 2011 Aug; 54(2):427–32. [PubMed: 21664093]
16. Rufaihah AJ, Huang NF, Jame S, Lee J, Nguyen HN, Byers B, De A, Okogbaa JN, Rollins M, Reijo-Pera R, Gambhir SS, Cooke JP. Endothelial cells derived from human IPSCs increase capillary density and improve perfusion in a mouse model of peripheral arterial disease. Arteriosclerosis, Thrombosis and Vascular Biology. 2011 Nov; 31(11):e72–9.

17. Volz KS, Miljan E, Khoo A, Cooke JP. Development of pluripotent stem cells for vascular therapy. Vascul Pharmacol. 2012 May-Jun;56(5–6):288–96. [PubMed: 22387745]

18. Chen Z, Wen L, Martin M, Hsu CY, Fang L, Lin FM, Lin TY, Geary MJ, Geary GG, Zhao Y, Johnson DA, Chen JW, Lin SJ, Chien S, Huang HD, Miller YI, Huang PH, Shyy JY. Oxidative Stress Activates Endothelial Innate Immunity via Sterol Regulatory Element Binding Protein 2 (SREBP2) Transactivation of MicroRNA-92a. Circulation. 2015 Epub 2014 Dec 30.

19. Bonauer A, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, Burchfield J, Fox H, Doebele C, Ohtani K, Chavakis E, Potente M, Tjwa M, Urbich C, Zeiher AM, Dimmeler S. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. Science. 2009

20. Lee J, Sayed N, Hunter A, Au KF, Wong WH, Mocarski E, Reijo Pera R, Cooke JP. Activation of innate immunity is required for efficient nuclear reprogramming. Cell. 2012 Oct 26; 151(3):547–58. [PubMed: 23101625]

21. Sayed N, Wong WT, Ospino F, Meng S, Lee J, Jha A, Dexheimer P, Aronow BJ, Cooke JP. Transdifferentiation of human fibroblasts to endothelial cells: role of innate immunity. Circulation. 2015 Jan 20; 131(3):300–9. [PubMed: 25359165]

22. Leeper NJ, Hunter AL, Cooke JP. Stem cell therapy for vascular regeneration: Adult, embryonic and induced pluripotent stem cells. Circulation. 2010; 122:517–526. [PubMed: 20679581]

23. Cooke JP, Losordo DW. Modulating the vascular response to limb ischemia: angiogenic and cell therapies. CIRCRES. 2015

24. Kinlay S, Thukkani A. Endovascular Intervention for PAD. CIRCRES. 2015

25. Conte M, Vartanian S. Surgical Intervention for PAD. CIRCRES. 2015