4-1-2019

Can Measuring Levels of Serum Adhesion Proteins Replace the Ankle Brachial Index in the Fight Against Peripheral Artery Disease?

Mark K. Massey
University of the Pacific, eudaimonia333@gmail.com

Can Measuring Levels of Serum Adhesion Proteins Replace the Ankle Brachial Index in the Fight Against Peripheral Artery Disease?

By

Marc K. Massey

Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfilment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

April, 2019

Introduction

If you knew that you were going to have one of both of your legs amputated due to a preventable medical condition in the future, then any sane person would want to find a way of preventing such a disabling and life changing event. Currently peripheral artery disease (PAD) is a growing threat to health in modern times, which can lead to the situation mentioned above. Due to diet and lifestyle risk factors, PAD incidence has increased as the world has become more developed.[1] Mankind is unlikely to stop its march onward towards ever more developed states of living, which likely will mean even less healthy diets and more sedentary lifestyles in the years to come. With the trends as they are, with more than eight million Americans currently suffering from PAD and that number actively rising worldwide it is clear that something must be done.[2] While it is not currently agreed upon that PAD screening should be conducted in asymptomatic individuals, this is primarily due to the infeasibility of accurately conducting such screens. A secondary hurdle is that screening is something that is typically only conducted when there is an established methodology for preventing the progression of, or reversing the damage done by, the condition. With things as they are, it might seem that there is no hope for PAD screening, but a new age is dawning thanks to cutting-edge research.

The Pathophysiology of PAD

PAD is primarily caused by the progression and proliferation of atherosclerotic plaques formed by the collection of lipids in the intimal layer of arteries. The areas that are at greatest risk for this are places where the arteries are subjected to lots of stress and movement, and in places where they branch or curve and turbulent flow is created. Within these regions, the endothelial cells lining the arteries align differently. This hypothetically allows for damage to the

endothelial lining to be more likely in these sites than in other locations. Current atherosclerotic theory states that when an injury occurs to the endothelial cells, a complex cascade of expression and release of chemoattractants and adhesion proteins is started. These proteins then play a role in capturing and tethering platelets, lymphocytes, and monocytes that then accumulate at the damaged region. These lymphocytes and monocytes then migrate to the intimal layer of the vessel. Low density lipoproteins (LDL) then follow this migration and become oxidized. The monocytes differentiate to become macrophages and begin releasing proinflammatory substances and cytokines. The macrophages then phagocytize the LDL and become foam cells that proliferate along with smooth muscle, causing a thickening of the intimal layer. A fibrous cap then develops over the lesion leading to progressive stenosis, occlusion, and sometime thrombosis. The sequelae of this pathogenic process are claudication, ischemia, and even infarction of the affected tissue or limb.

Current PAD Screening

Currently screening is most commonly performed via ankle brachial index (ABI). ABI is a quick and cost-effective test that can be performed in the primary care setting.[3] Cost is a major determining factor in many aspects of health care and the methodology of PAD screening is no exception. While magnetic resonance angiography (MRA) is the undisputed gold standard for diagnosing the presence and severity of PAD, its cost is prohibitive. The national average is currently approximately $7,000 for imaging of the lower extremities.[4] While angiography with its many varied forms is agreed upon as the gold standard for confirming a diagnosis of PAD, its cost makes its use prohibitive except for in determining the extent of disease severity and

viability of revascularization. It is clear why ABI is the preferred screening method when you learn that it costs only a little more than $300 on average.[5]

ABI is a test that is performed by taking the systolic blood pressure in each of a patient's brachial arteries then taking the systolic blood pressure in both of the patient's dorsalis pedis and posterior tibial arteries. You then divide the higher of the two systolic values for each lower extremity by the highest systolic value obtained from the upper extremities. ABIs for each lower extremity can be calculated in this way. A normal ABI falls in the range of 1.0-1.4. Values above 1.4 are indicative of a noncompressible calcified vessel, values under 0.9 are diagnostic of PAD. In one study when an MRA showing 50% stenosis in pelvic or lower limb arteries was used as a reference standard for diagnosable PAD, ABI was found to have a sensitivity of 15% to 20% and a specificity of 99%.[6] Other studies have demonstrated the same high levels of specificity, yet have shown extremely variable levels of sensitivity ranging from 15% to 79%. A concerning fact is that the two groups with the lowest ABI sensitivity were found to be diabetics and the elderly.[7, 8]

The Case Against ABI

There are further arguments against the use of ABI in addition to its relatively cumbersome and time-consuming nature. One such reason is that the test itself has an 80%-85% chance of giving a false positive result.[9] This is one of the reasons that many are shying away from PAD screening because without greater reliability and ease of testing the risk of causing untoward physical and psychological harm is too great. Further reason comes from the fact that due to unknown physiologic factors there is variability in ABI results for different races.[10]

Unfortunately, ABI is also often performed and interpreted improperly.[5] A reality in modern healthcare is that time is the enemy of the clinician and sometimes of proper patient care as well. One study cited a lack of time as being the deciding factor for purposely performing ABIs incorrectly.[11] This admission speaks volumes when you consider that the average ABI when properly preformed takes on average only five minutes.[12]

If taking an extra five minutes is enough for clinicians to deem a test too cumbersome to be properly performed then regardless of the test's innate value to patient care, it is essentially worthless. It would seem that there must be a better way. The good news is that, thanks to cellular adhesion proteins, the answer may be as simple as adding a few more items to the patient's lab orders.

The Role of Cellular Adhesion Proteins

Endothelial dysfunction has been noted as playing a key role in the development of atherosclerotic disease.[13] Many plasma markers of endothelial function have been identified and are actively being studied for their potential role in PAD screening. One promising feature of these plasma markers is that some have been shown to be significantly associated with PAD in high risk populations such as African Americans and Hemodialysis patients.[14, 15] One of these markers, thrombomodulin (TM) is an endothelial glycoprotein that has a role in the protein C anticoagulant pathway. Interestingly, the plasma concentration of TM reflects the level of endothelial damage, which is logical when one learns that TM has been identified as a marker of

microvascular endothelial damage.[16, 17, 18] Unsurprisingly, this was able to be substantiated in a 2016 study conducted by Tokyo Medical and Dental University.[19]

Another marker being studied is P-selectin, which is involved in the bonding of endothelial cells and the activation, rolling, and attachment of leukocytes.[20] In a comprehensive study involving over 2,000 participants P-selectin was found to be significantly associated with the development of PAD. Not only that, it was also significantly associated with both prevalent and incidental PAD, in addition to progression from normal ABI to an ABI less than 0.9.[1] Taking these correlations one step further P-selectin also has been found to accelerate atherosclerotic plaque progression.[21] Could perhaps the future of PAD screening lie in the measurement of serum concentrations of one or more of these cell adhesion proteins?

How Cellular Adhesion Proteins Change the Game

While it may be difficult with the current amount of research data to definitively prove that either ABI or cellular adhesion plasma markers are a superior modality for PAD screening in terms of sensitivity and specificity, what certainly can be determined is that any easy and cost effective test like ABI that is not utilized, is inferior to a modality that can offer comparable results and is more likely to be used regularly. As the popular sports aphorism goes, "You miss 100% of the shots that you don't take." This can easily be applied to the screening of patients. If a test is deemed to be time consuming then it won't be used in the primary care setting.

It is a well agreed upon fact that longer patient visits yield better results for patient outcomes as they allow for more elements of care to be considered and integrated into the

treatment plan.[22] Clinicians and their clinical teams have an innate sense of this and work within the constraints of the modern day healthcare system to bring as much benefit as possible to the patient. What this means is trimming the fat and eliminating any part of the visit that is seen by a team member as being unnecessary. The consultation with the provider cannot be cut and is prioritized over all other parts of the visit. One thing that is often cut from the visits of the patients most in need of PAD screening is ABI testing.[12] In order to ensure that patients are screened for PAD, one potential answer is to have the screening performed when the patient isn't at their primary care provider's office.

There are few options for when this encounter could happen then without creating another separate visit. One place that must be visited in the course of the normal patient care is the lab. This required stop offers an excellent place for screening tests to be incorporated. A blood draw takes only seconds longer to perform if it is for five tubes of blood to be drawn versus two. By taking advantage of this fact the actual testing involved in screening for PAD can be moved out of the general practitioner's office. All a provider need do in that case would be to add an order for the cell adhesion proteins that are associated with PAD to the lab slip.

The Future of PAD Screening

Another benefit of adopting this screening method is that the cost per patient for the lab test comes out to only $12.98.[23] Based on information from a Health Service Research study and the Health Cost Institute it can be extrapolated that the average ABI which takes five minutes on average to complete in a primary care PA or NP office costs $30.05 based solely on the time it takes.[24, 25] This of course doesn't factor in the cost of the personnel and equipment required to

perform the test which is why the actual figure as mentioned is $300 on average. The math speaks for itself. Measuring soluble P-selectin has been shown by multiple large scale studies to be an effective method for assessing the presence and progression of PAD and offers a reasonable alternative to a test modality that no longer seems to offer the most logical solution to screening patients.[1, 14] The current literature offers droves of evidence for the move towards utilizing soluble plasma markers for such a purpose, though there is of course as in any burgeoning new field room for further research. The possibilities for the future of these markers is bright as they have even been identified as targets for future therapeutic agents to reverse or stop the advance of PAD.

References:

1. Wassel CL, Berardi C, Pankow JS, et al. Soluble P-selectin predicts lower extremity peripheral artery disease incidence and change in the ankle brachial index: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2015;239(2):405-411. doi:10.1016/j.atherosclerosis.2015.01.022.

2. Rosamond W, Flegal K, Furie K et al. Heart disease and stroke statistics: 2008 update—a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117(4):e25–e146

3. Lau JF, Weinberg MD, Olin JW. Peripheral artery disease. I. Clinical evaluation and noninvasive diagnosis. Nat Rev Cardiol2011;8(7):405–418.

4. MRI of Lower Extremity Cost and Procedure Comparison. NewChoiceHealth.com. https://www.newchoicehealth.com/procedures/mri-of-lower-extremity. Accessed Dec 10, 2018.

5. How Much Does an Ankle-Brachial Index Test Cost Near Me? MDsave. https://www.mdsave.com/procedures/ankle-brachial-index-test/d784fcc5. Accessed Dec 10, 2018.

6. Wikström, Johan, et al. "Lower Extremity Artery Stenosis Distribution in an Unselected Elderly Population and Its Relation to a Reduced Ankle-Brachial Index." Journal of Vascular Surgery, vol. 50, no. 2, 2009, pp. 330–334., doi:10.1016/j.jvs.2009.03.008.

7. Xu D, Li J, Zou L, et al. Sensitivity and specificity of the ankle—brachial index to diagnose peripheral artery disease: a structured review. Vascular Medicine. 2010;15(5):361-369. doi:10.1177/1358863x10378376.

8. Wikström J, Hansen T, Johansson L, Lind L, Ahlström H. Ankle brachial index <0.9 underestimates the prevalence of peripheral artery occlusive disease assessed with whole-body magnetic resonance angiography in the elderly. Acta Radiologica. 2008;49(2):143-149. doi:10.1080/02841850701732957.

9. United States Preventive Services Task Force. USPSTF Recommendation: Screening for PAD and CVD Risk Assessment With the ABI. JAMA. https://jamanetwork.com/journals/jama/fullarticle/2687361. Published July 10, 2018. Accessed October 21, 2018.

10. Singh S, Bailey KR, Kullo IJ. Ethnic differences in Ankle Brachial Index are Present in Middle Aged Individuals without Peripheral Arterial Disease. International Journal of Cardiology. January 2013:228-233. doi:10.1016/j.ijcard.2011.05.068.

11. Davies JH, Kenkre J, Williams EM. Current utility of the ankle-brachial index (ABI) in general practice: implications for its use in cardiovascular disease screening. BMC Fam Pract. 2014;15:69. Published 2014 Apr 17. doi:10.1186/1471-2296-15-69

12. Pearson T, Kukulka G, Ur Z. Ankle brachial index measurement in primary care setting: how long does it take? Current neurology and neuroscience reports. https://www.ncbi.nlm.nih.gov/pubmed/19864988. Published November 2009. Accessed November 21, 2018.

13. Vita JA. Endothelial function. Circulation. 2011;124: e906–e912. pmid:22184047

14. Berardi C, Wassel CL, Decker PA, et al. Elevated Levels of Adhesion Proteins Are Associated With Low Ankle–Brachial Index: Multi-Ethnic Study of Atherosclerosis. Angiology. 2016;68(4):322-329. doi:10.1177/0003319716659178.

15. Cheng C, Chen Y, Shu K, Chang H, Chou M. Higher serum levels of soluble intracellular cell adhesion molecule-1 and soluble vascular cell adhesion molecule predict peripheral artery disease in haemodialysis patients. Nephrology. 2012;17(8):718-724. doi:10.1111/j.1440-1797.2012.01654.x.

16. Blann AD, Seigneur M, Steiner M, Boisseau MR, McCollum CN. Circulating endothelial cell markers in peripheral vascular disease: relationship to the location and extent of atherosclerotic disease. Eur J Clin Invest. 1997;27: 916–921. pmid:9395787

17. Salomaa V, Matei C, Aleksic N, Sansores-Garcia L, Folsom AR, Juneja H, et al. Cross-sectional association of soluble thrombomodulin with mild peripheral artery disease; the ARIC study. Atherosclerosis. 2001;157: 309–314. pmid:11472730

18. Sernau T, Wilhelm C, Seyfert U, Gabath S, Henkels M, Amiral J, et al. Thrombomodulin is a marker of microvascular, but not for macrovascular endothelial cell damage. Vasa. 1995;24: 347–353. pmid:8533445

19. Igari K, Kudo T, Toyofuku T, Inoue Y. The Relationship between Endothelial Dysfunction and Endothelial Cell Markers in Peripheral Arterial Disease. Plos One. 2016;11(11). doi:10.1371/journal.pone.0166840.

20. Afshar-Kharghan V, Thiagarajan P. Leukocyte adhesion and thrombosis. Current neurology and neuroscience reports. https://www.ncbi.nlm.nih.gov/pubmed/16319685. Published January 2006. Accessed November 26, 2018.

21. Woollard KJ, Lumsden NG, Andrews KL, et al. Raised Soluble P-Selectin Moderately Accelerates Atherosclerotic Plaque Progression. PLoS ONE. 2014;9(5). doi:10.1371/journal.pone.0097422.

22. Wilson A, Childs S. The relationship between consultation length, process and outcomes in general practice: a systematic review. British Journal of General Practice. https://bjgp.org/content/52/485/1012/tab-pdf. Published December 1, 2002. Accessed November 26, 2018.

23. Human P-Selectin/CD62P Quantikine ELISA Kit. RnD Systems. https://www.rndsystems.com/products/human-p-selectin-cd62p-quantikine-elisa-kit_dpse00. Accessed December 9, 2018.

24. Trends In Primary Care Visits. Trends In Primary Care Visits - HCCI. https://www.healthcostinstitute.org/research/publications/hcci-research/entry/trends-in-primary-care-visits. Accessed April 2, 2019.

25. Tai-Seale M, Mcguire TG, Zhang W. Time Allocation in Primary Care Office Visits. Health Services Research. 2007;42(5):1871-1894. doi:10.1111/j.1475-6773.2006.00689.x.