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Characterizing the relationship between flow-mediated vasodilation and radial artery tonometry in peripheral artery disease

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ABSTRACT

Background: Arterial stiffness, measured by the augmentation index (AIX) from radial artery tonometry, and endothelial dysfunction, measured by brachial-artery flow-mediated vasodilation (FMD), have each been associated with increased risk of cardiovascular events. However, their interrelationship in peripheral artery disease (PAD) patients is poorly understood.

Materials and methods: In a cross-sectional analysis of 123 vascular surgery outpatients, the association between FMD and AIX was examined in controls with atherosclerotic risk factors ($n = 32$) and patients with PAD ($n = 91$). PAD was defined as claudication symptoms with an ankle-brachial index of <0.9 or a history of revascularization for symptomatic PAD. Controls had an ankle-brachial index ≥ 0.9 and no history of atherosclerotic vascular disease.

Results: Compared to controls, patients with PAD had lower FMD (6.3 ± 3.8 *versus* 8.4 ± 3.7, $P = 0.008$), while central AIX normalized to 75 beats per minute (25.5 ± 9.0 *versus* 19.3 ± 8.6, $P = 0.001$) and peripheral AIX (91.3 ± 14.5 *versus* 81.3 ± 11.4, $P = 0.001$) were higher. FMD was not significantly correlated with either central or peripheral AIX (central AIX: $P = 0.58$; peripheral AIX: $P = 0.89$) across the entire cohort, or in either the patients with PAD (central AIX: $P = 0.48$; peripheral AIX: $P = 0.23$) or controls (central AIX: $P = 0.43$; peripheral AIX: $P = 0.92$). In a multivariate model including FMD, higher AIX remained independently associated with PAD.

Conclusions: In an analysis of vascular surgery outpatients, no correlation between FMD and AIX was detected. Larger prospective studies are needed to determine whether the inclusion of both parameters improves predictive models for the early identification and potential risk stratification of PAD patients.

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Introduction

Peripheral artery disease (PAD), an atherosclerotic process of the peripheral arterial tree, is a significant public health concern due to its increasing worldwide prevalence and high economic burden for society.[1,2] In the United States, critical limb ischemia, the end-stage of PAD, accounts for over 300,000 inpatient admissions annually.[3] Additionally, affected individuals suffer from decreased quality of life and increased mortality.[4,5] Noninvasive measures of specific physiological processes play an important role in understanding the pathophysiology of PAD. They also have the potential to play a clinical role in the identification and risk stratification of individuals with PAD and the subsequent measurement of their response to treatment. Brachial artery flow-mediated vasodilation (FMD) for endothelial function and radial artery tonometry for arterial stiffness are two such measures.[6,7]

FMD involves a measurement of change in the brachial artery diameter in response to a hyperemic stimulus, which triggers endothelial cells to release nitric oxide (NO) and cause arterial dilation.[8] A higher FMD corresponds to better endothelial function, and two large meta-analyses have shown that cardiovascular disease (CVD) risk increases by approximately 10% for each 1% decrease in FMD.[9,10] Lower FMD has also been associated with increased risk of postoperative cardiovascular events after vascular surgery.[11] Despite concerns of using FMD in clinical practice due to labor intensiveness and reproducibility issues, standardization is improving its reliability.[12]

Arterial tonometry involves placing a small tonometer over a target artery to detect the underlying pulse waveforms, which are influenced by the stiffness of the arterial wall. Radial artery tonometry can be used to calculate a central and peripheral augmentation index (AIX), which refers to the ratio of the augmented pressure, resulting from wave reflections, to the pulse pressure, expressed as a percentage.[13] Tonometry at two arteries of a measured distance apart, most commonly the common carotid and femoral arteries, can be used to calculate the pulse wave velocity (PWV) through the central arteries, with higher velocity corresponding to greater arterial stiffness. AIX is an indirect measure of stiffness[14,15] and PWV is a direct measure.[16] Arterial stiffness is associated with adverse vascular outcomes and mortality,[17,18] while AIX specifically is also predictive of CVD risk.[19]

Although increased arterial stiffness and decreased endothelial function are associated with worse vascular outcomes, suggesting an inverse correlation, studies have not consistently shown a correlation between the two measures.[20-23] Furthermore, studies investigating the relationship between arterial stiffness and endothelial function in the PAD population are limited.[24] As these assessments become more widely utilized as measures of future risk, it is important to understand how they relate to each other and how they can be used together to improve accuracy. Additionally, FMD and AIX are measuring different vascular functions that could each play unique roles in increasing vascular risk. Understanding how arterial stiffness and endothelial function relate to predict outcomes in PAD is meaningful to understand how all of these factors can be prevented or treated. Therefore, the present study provides a robust data set to study the association between arterial stiffness, as measured by the AIX, and endothelial function, as measured by FMD, in the PAD population. Because both arterial stiffness and endothelial function are involved in the pathophysiology and outcomes of PAD, this study tests the hypothesis that there is an inverse correlation between FMD and AIX.

Materials and methods

Study participants

From February 2012 to September 2016, a cross-sectional sample of 123 veterans was enrolled from the San Francisco Veterans Affairs Medical Center outpatient vascular surgery clinic. Participants were identified as having PAD ($n = 91$) if they had an abnormal ankle-brachial index (ABI) (<0.9) plus symptoms of claudication or if they had a history of peripheral revascularization for symptomatic PAD. Controls ($n = 32$) had a normal ABI and no history of atherosclerotic vascular disease. To be eligible for inclusion in this study, all participants had to have complete radial artery tonometry and FMD data. All participants were aged at least 35 y, reflecting the population of veterans with PAD. Potential participants were excluded if they had a creatinine $\geq$2 mg/dL or a history of significant hepatic impairment (Child-Pugh $\geq$ B), nonvascular inflammatory disorders (e.g., requiring immunosuppressive medications), or other concurrent severe acute diseases. These exclusion criteria were used so that data from participants could be used for other studies on the role of inflammation in PAD.

Demographic information including age, sex, and race was recorded for all study participants. History of smoking was assessed, including pack years (defined as the number of years smoking multiplied by average number of packs per day), as well as history of major comorbidities including hypertension, hyperlipidemia, diabetes mellitus, or coronary artery disease. Measurements taken included body mass index, blood pressure at the brachial artery, and an ABI for each lower extremity using established techniques.[25] Participants completed the post-traumatic stress disorder (PTSD) checklist-civilian version and patient health questionnaire-9, with PTSD defined as a PTSD checklist $\geq$40[26] and depression defined as a score $\geq$10.[27] These mental health measures were included because FMD has been shown to be independently associated with PTSD.[28] Current use of the following medications was recorded: aspirin, angiotensin-converting enzyme inhibitor (ACE-inhibitor), beta-blocker, and statin. Finally, blood was obtained for laboratory assessment of high-sensitivity C-reactive protein (CRP), hemoglobin A1c, lipids (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein, and triglycerides), and estimated glomerular filtration rate (eGFR). The investigator-initiated protocol was approved by the University of California, San Francisco Committee on Human Research as well as the San Francisco Veterans Affairs Medical Center Research and Development Office with all participants giving informed written consent.