JACC: ASIA VOL. 3, NO. 2, 2023

EDITORIAL COMMENT

Arterial Stiffness as a Prognostic Marker for Peripheral Artery Disease Risk

Clinical Relevance and Considerations*

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Peripheral artery disease (PAD) is an atherosclerotic disease characterized by narrowing of the peripheral arteries and reduced blood flow in the lower limbs.[1] It is estimated that more than 200 million people report having minor-to-severe symptoms of PAD worldwide.[2] Symptoms often include claudication (leg pain during walking) and foot ulcers, which can potentially require leg amputation.[3] Atherosclerosis is defined by the accumulation of plaques within peripheral vessels and is thought to be initiated by factors such as sedentariness, smoking, obesity, diabetes, hypertension, and aging.[4] These factors can damage the elastic properties of the artery, ultimately leading to abnormal arterial wall thickness, stiffness, and increased vascular resistance and blood pressure.[4] The most used clinical diagnostic method for PAD is the ankle-brachial index (ABI), which assesses the systolic blood pressure differences between the ankle and brachial arteries. Although blood pressure changes in the local vascular beds are the most sensitive manifestation for atherosclerosis formation, growing evidence suggests that arterial stiffness (AS) is independently associated with PAD, even when adjusting for several atherosclerotic risk factors. The most commonly used assessment of AS is pulse wave velocity (PWV),[5] which quantifies the speed of an arterial pressure wave as it travels through the arterial network. Changes in AS have been recognized as one of the earliest manifestations of vascular dysfunction and the formation of atherosclerotic lesions.[5-7] Unfortunately, current diagnostic methods for PAD do not include AS measurements, and there is a growing body of evidence that suggests examining the combined effect of AS and blood pressure on the incidence of PAD. In the current issue of *JACC: Asia,* Wu et al[8] investigated the clinical importance and practical usefulness of the combined assessment of AS and blood pressure for the risk stratification in PAD.

A total of 8,960 participants were enrolled in this study and completed a baseline evaluation between 2008 and 2018 and followed up until the incident of PAD or the end of 2019. Resting blood pressure was measured from the seated position and used to determine status of hypertension. Brachial-ankle PWV (baPWV), an indicator of systemic AS, was measured in the supine position. Participants were divided into four main groups based on AS and blood pressure status, with an additional layer of grouping based on the measurement severity. Results from this study indicate that the highest incidence rate of PAD was associated with severe AS, regardless of hypertension or blood pressure. Additionally, when adjusting for all participant characteristics, the grouping for participants who were nonhypertensive and had severe AS (baPWV >1,800 cm/s) had a greater risk score for developing PAD (2.286) than those with hypertension and moderately elevated AS (baPWV >1,400 cm/s) (1.887). Collectively, these results show a significant association between AS and the onset of PAD, regardless of blood pressure status, and provide valuable insight for potential early diagnosis and targeted therapies.

EXPERIMENTAL CONSIDERATIONS AND FUTURE DIRECTION

Wu et al[8] provide valuable insight for the predictive potential of AS on risk for development of PAD,

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.03.001

regardless of hypertension status. However, additional factors pertaining to the development of AS and hypertension must be considered in future studies. For instance, natural aging alone is considered a key non-modifiable independent risk factor for the development of both AS and hypertension.[1,5] It may be important to consider monitoring changes in AS and blood pressure over time throughout the natural aging process, most particularly in the absence of PAD and other vascular diseases (ie, healthy aging vs PAD). Additionally, incorporating lower limb arterial duplex ultrasound and computed tomography angiogram with PWVs and blood pressure assessments in future work may enhance risk stratification assessments for PAD.

Increases in baPWV by as little as 100 cm/s are linked to a >10% increase in risk for cardiovascular events and cardiovascular mortality.[9] Even though baPWV is a well-validated and convenient method to assess systemic AS, future work should differentiate the PWV of specific arterial segments in these risk stratifications. Adding assessments of central (carotid-femoral) and lower extremity (femoral-ankle)[10,11] PWV may give additional insight regarding both the systemic and limb-specific impact of potential PAD manifestation on the arterial network. This is important to consider, as several pathologies can contribute to structural changes within the arterial system in patients with PAD, such as endothelial cell damage, smooth muscle proliferation, microvascular calcification, and arterial stenosis.[12-16] In this case, including central and lower limb specific PWV assessments in future longitudinal studies may provide more specific insight regarding AS and incidence of PAD.

Additionally, Wu et al[8] comprehensively assessed several common cardiometabolic risk biomarkers, such as blood glucose, triglycerides, and cholesterol panels, which were included as covariates in their analyses. However, we and others have contributed to a growing body of evidence suggesting that disturbances in other molecular such as oxidative stress/antioxidant molecules, inflammatory adipokines and cytokines, and endothelial-derived vasoactive metabolites may play an important role in vascular remodeling and AS for patients with PAD.[3-5,13,17-19] Furthermore, others have reported elevated proinflammatory molecules and disturbances within the vascular nitric oxide system in this population, which can negatively affect vascular homeostatic regulation.[18,19]

CONCLUSIONS

The present work by Wu et al[8] provides valuable insight for predicting the occurrence of PAD beyond the typical contribution of hypertension. The outcome of this observational study reveals that elevations in AS coincide with increased risk for developing PAD, regardless of an individual's blood pressure status. Investigations building off this work should consider including additional measurements for AS (central and peripheral PWVs) and exploring the potential contribution of molecular factors to elevations in AS. Collectively, these investigations stand to provide valuable information for earlier detection of risks for vascular disease manifestation, which may enable clinicians to provide timely and more efficacious prognosis in disease development of PAD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS arterial stiffness, blood pressure, brachial-ankle pulse wave velocity, hypertension, peripheral arterial disease