JACC: ADVANCES VOL. 2, NO. 5, 2023

EDITORIAL COMMENT

Arterial Stiffness

A Noninvasive Biomarker for Pathological Aging*

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Explorers like Juan Ponce de León were on a quest to discover the Fountain of Youth to find a remedy for aging as early as the 16th century. Now, centuries later, advancements in scientific knowledge have resulted in an increase in the average life expectancy by a few decades in the developed world, but the fountain of youth remains undiscovered. The growing aging population is affected by a myriad of geriatric syndromes, which include cognitive impairment, frailty, disability, and sarcopenia. Studying the development of these syndromes can elucidate the mechanisms by which pathological aging occurs, which is a step towards finding interventions to halt it.

One geriatric syndrome that affects older adults is physical frailty, which is defined as "increased vulnerability resulting from age-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday acute stress is compromised."[1] It is associated with poor outcomes including disability, cognitive impairment, hospitalization, and major adverse cardiovascular events.[2] The highest prevalence of frailty is among older patients with cardiovascular disease (CVD), and a bidirectional relationship between the 2 has been proposed. Cellular and molecular drivers of CVD like inflammation, oxidative stress, and metabolic dysfunction have also been linked with the development and progression of frailty.[3]

Aging is associated with arterial stiffness due to increased collagen deposition and elastin depletion.[4] This results in an increase in the pulse wave velocity (PWV), a measure of central arterial stiffness. Hence, the PWV is a biomarker that can be measured noninvasively and provides information about the geometric and elastic properties of the arterial tree. PWV has been found to be strongly associated with the development of CVD and has been identified as a noninvasive biomarker that can be used to identify patients who have subclinical atherosclerotic disease.[5]

In this issue of *JACC: Advances*, Álvarez-Bustos et al[6] report a study on the association between PWV, frailty, disability, and mortality in community-dwelling older adults. This study included 978 subjects without diabetes mellitus (DM) who participated in the Toledo Study of Healthy Aging, a prospective cohort study of community-dwelling adults over 65 years of age residing in Toledo, Spain. PWV was measured as the distance traveled by the pulse wave from the carotid to the femoral artery in meters, divided by the time interval in seconds. Frailty status was assessed using the frailty phenotype and the Frailty Trait Scale-5, similar tools with subjective and objective measurements (grip strength, walking speed, activity level) used to detect physical frailty.

Álvarez-Bustos et al show that on cross-sectional analysis, PWV was associated with frailty, whether measured by the frailty phenotype (OR: 1.77 [95% CI: 1.53-2.04]; $P < 0.001$) or the Frailty Trait Scale-5 (OR: 1.61 [95% CI: 1.33-1.94]; $P < 0.001$), above a cutoff point of 11.5 m/s, whereas below this cutoff, PWV was not associated with frailty or disability, however age was. On longitudinal analysis, PWV >10 m/s was associated with incident frailty (OR: 1.36 [95% CI: 1.12-1.65]; $P < 0.01$), whereas below this cutoff, PWV was not associated with incident frailty, but age was. Furthermore, PWV >12.5 increased the risk of incident disability (OR: 1.35 [95% CI: 1.14-1.59]; $P < 0.05$)

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

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ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100436

and resulted in worsening disability (OR: 1.28 [95% CI: 1.10-1.50] $P < 0.05$), regardless of baseline frailty status. PWV >11.0 m/s was an independent significant predictor of death (HR: 1.37 [95% CI: 1.19-1.58]; $P < 0.005$). Below this threshold, age was significantly associated with mortality (HR: 1.05 [95% CI: 1.01-1.10]; $P < 0.05$). Álvarez-Bustos et al used multiple adjusted models to assess the effect of variables on outcomes; however, the results remained significant despite adjusting for factors like systolic blood pressure, smoking, and polypharmacy.

Elucidation of the pathophysiological mechanisms of frailty development is important, as the development of frailty reflects pathologic aging and predisposes to poor outcomes. Orkaby et al[7] had shown that in cross-sectional analysis, higher PWV values were associated with higher mean levels of frailty; however, Álvarez-Bustos et al have added evidence of a causal mechanism by showing that arterial stiffness is associated with incident frailty and onset and progression of disability. These findings suggest that arterial stiffness is one pathophysiologic mechanism whereby frailty develops and progresses. Inflammation, oxidative stress, and hormonal imbalance at the cellular level lead to remodeling of the arterial walls, leading to macrovascular stiffness, which leads to decreased blood flow to the musculoskeletal system at a microvascular level.

Prior studies have shown that arterial stiffness is associated with sarcopenia.[8] The investigators suggest that the mechanism by which frailty and disability occur may be due to poor muscular perfusion, which impacts the availability of nutrients needed for muscle function. The PWV is a biomarker that can be easily measured using a noninvasive technique in cardiovascular practices and may be used to identify patients with subclinical CVD who are at risk for frailty development. This provides an opportunity for interventions that may halt the development of pathological aging. A recent randomized controlled trial has shown exercise training can reduce arterial stiffness; however, the mean baseline PWV of the older adult population being studied was 7 to 8 m/s.[9] Interventions need to be studied in older adults with higher PWV to see if arterial stiffness can be reduced once it reaches levels as high as 10 m/s and whether that reduction has meaningful long-term benefits like preventing the development of frailty and disability. These interventions should not be limited to diet and exercise, as the development of vascular stiffness involves reductions in nitric oxide, increased activity of the renin-angiotensin-aldosterone system, increased activity of proteases, and collagen deposition, all of which can be pharmaceutical targets.[4] The finding that when PWV is below a threshold (11.5 m/s), age, not PWV, is associated with frailty suggests that there are pathways other than vascular dysfunction that also lead to frailty, and those should also be further explored.

This study has several limitations that limit its applicability to cardiovascular practice. Many patients with CVD have DM, and this study excluded patients with DM. Additionally, this study is on a very specific population of Toledo, Spain. The cutoff values in this study are probably not applicable to other ethnicities, ie, African Americans, as a prior study has shown that average PWV is higher in postpubertal Brazilian Blacks when compared to non-Blacks.[10] Additionally, as the investigators point out, those with DM develop poor outcomes at higher thresholds of PWV. This study needs to be reproduced in different populations to increase its applicability to clinical practice in different areas of the world.

In conclusion, Álvarez-Bustos et al[6] demonstrate that arterial stiffness is associated with frailty, disability, and mortality. This provides evidence that the mechanistic factors leading to frailty development include arterial remodeling. Future studies are needed to determine the threshold of PWV that is associated with frailty and disability in different populations. Additionally, further data on interventions is needed to see whether PWV is modifiable at those thresholds and whether reduction of PWV in the elderly results in clinically meaningful outcomes. If so, we may be on the verge of discovering the fountain of youth that Ponce de León died searching for.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS arterial stiffness, cardiovascular ageing, frailty, geriatric cardiology, pulse wave velocity