Low Fitness and High Fatness: The “Double Whammy” on Vascular Health

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Background and Study Overview

Vascular aging is a complex, continuous process that involves alterations in the structural and functional properties of arteries¹. Specific to large arteries, vascular aging can broadly manifest as carotid and aortic luminal dilation, endothelial dysfunction, increases in carotid intima-media thickness, as well as central arterial stiffening¹. Importantly, increases in central arterial stiffness contribute to an augmentation of central blood pressure, via an early return of reflected waves from peripheral sites, as well as microcirculatory end-organ damage, via excess transmission of pressure pulsatility that may ultimately increase cardiovascular disease (CVD) risks¹. While there are likely several risk factors that may contribute to accelerated vascular aging and increased CVD risks, both reduced cardiorespiratory fitness (CRF)² and obesity³ are important risk factors that have been independently associated with central arterial stiffening. However, the interactive effects of CRF and obesity on vascular aging remain unclear. In this issue of *the Korean Journal of Sports Medicine*, Heffernan and Loprinzi⁴ sought to determine the joint association of CRF and obesity, quantified as the fatness-fitness index (FFI), on estimated pulse wave velocity (ePWV), pulse pressure, and the vascular overload index, all of which are indices of vascular aging that were derived from brachial blood pressure to inform overall vascular burden due to arterial stiffness and blood pressure pulsatility.

Using data from the 1999–2002 National Health and Nutrition Examination Surveys (NHANES) that included 8,080 adults (20–85 years of age), Heffernan and Loprinzi⁴ reported that higher FFI, calculated as the ratio of CRF to waist-to-height ratio (WHtR), was independently and inversely associated with ePWV, pulse pressure, and the vascular overload index based on weighted multivariable linear regression models. Importantly, these associations were maintained even after adjustment for demographic, behavioral, and traditional CVD risk factors. One important aspect of the present study was the evaluation of the interactive effects of CRF and obesity as a continuous variable, as opposed to a categorical approach, which provides insight into more subtle changes in fitness-fatness and the associated changes in measures of vascular aging. Furthermore, WHtR has been reported to be more predictive of central obesity than body mass index (BMI)^{5,6} and a better discriminator of CVD compared to other anthropometric indicators, including BMI and waist circumference⁷. Heffernan and Loprinzi⁴ concluded that maintaining higher CRF and lower body fat promotes healthy vascular aging, whereas the coexistence of lower CRF and high levels of obesity may accelerate vascular aging. Recently, Jae et al.⁸ reported that overweight/obesity and low levels of CRF were independently associated with the increased risk of sudden cardiac death in men; however, higher fitness appeared to attenuate this risk even in overweight/obese men. Collectively, these findings highlight the importance of improving CRF to attenuate the negative impact

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of obesity on vascular aging, which may ultimately confer a reduction in the risk of CVD events.

Sex Differences in Vascular Aging

An interesting observation from the work of Heffernan and Loprinzi⁴ that warrants further discussion is that females displayed an increased magnitude of association between FFI and ePWV, pulse pressure, and the vascular overload index compared to males. Although great strides have been made in recent years to address gaps in knowledge regarding sex-related differences in CVD risk, presentation, and outcomes, the understanding of the ‘how and why’ of sexual dimorphism in vascular aging remains limited. Males have a more pronounced display of vascular aging and CVD prevalence across the early and middle portions of the age spectrum, until the sixth and seventh decades at which point CVD prevalence in females becomes similar to or surpasses that of males⁹. Traditionally, this turning point is attributed to the withdrawal of endogenous sex steroids (i.e., estrogen) during the menopausal transition; however, a meta-analysis of observational studies (1966–2004) reported no convincing relation between postmenopausal status and CVD, particularly in females with a natural menopause¹⁰. Indeed, Heffernan and Loprinzi⁴ reported that the stronger association between FFI and vascular aging indices in females was maintained after controlling for age and other CVD risk factors. These data highlight potentially important implications for sex differences in vascular aging and CVD risk, whereby females see a greater positive impact of increased FFI and, conversely, potentially more detrimental effects of lower CRF and/or increasing obesity. The interactive effects of CRF and obesity may provide an important point of consideration when evaluating sex differences in the age-associated decrements in vascular aging and subsequent associations with mortality^{11,12}.

Experimental Considerations and Future Directions

Emerging evidence has identified FFI as a novel measure that is predictive of all-cause and CVD-specific mortality when the CRF component has been derived from estimated metabolic equivalents (METs) based on total duration of a symptom-limited maximal modified Balke graded exercise test^{13,14}. In the study

by Heffernan and Loprinzi⁴, FFI was calculated using CRF estimated from a sex-specific, nonexercise, prediction algorithm which generates METs. Additionally, physical activity status, a component of an algorithm for estimating CRF, was based on self-report questionnaires⁴, which may be more prone to recall or social desirability bias. Furthermore, a recent meta-analysis suggested that nonexercise estimated CRF may be less sensitive than objectively measured CRF from exercise testing in predicting all-cause and CVD mortality¹⁵. Thus, it is of great interest that future studies reassess the association between FFI and vascular aging using objectively measured physical activity (via accelerometry) or peak oxygen consumption from metabolic gas analysis during incremental exercise testing to volitional exhaustion to determine CRF.

Carotid-femoral PWV (cfPWV) is the gold standard, noninvasive method for the assessment of central arterial stiffness that has demonstrated an incremental predictive value for CVD events and all-cause mortality¹⁶. However, cfPWV requires specialized equipment and technical proficiency, thus limiting widespread incorporation into clinical practice¹⁶. In contrast, ePWV, which can estimate central arterial stiffness using age and mean blood pressure, has been shown to independently predict CVD events and all-cause mortality beyond traditional CVD risk factors^{17,18}. ePWV has also been independently associated with the risk of stroke¹⁹ and heart failure²⁰. Importantly, reductions in ePWV following antihypertensive treatment have been shown to confer better survival rates independently of systolic blood pressure reduction²¹, highlighting the clinical utility of ePWV as a simple tool to aid in CVD risk assessment and treatment. Thus, findings of an inverse association between ePWV and FFI in the study by Heffernan and Loprinzi⁴ provide important, new information that will hopefully pave the way for exciting future, large-scale, research to evaluate the interactive effects of CRF and obesity on central arterial stiffness for the prevention and treatment of CVD in clinical settings.

Another important future direction may focus on race and ethnic disparities in the joint association of CRF and obesity on vascular aging. Although Heffernan and Loprinzi⁴ statistically accounted for race and ethnicity in their statistical analyses, approximately 73% of the participants identified as Caucasian. Conversely, recent findings from the 2011–2018 NHANES have noted increasing,

age-adjusted, prevalence of obesity in U.S. adults (aged 20 years and older), particularly among the Hispanic, non-Hispanic Whites, and non-Hispanic Asian groups²². Given evidence of racial differences in central arterial stiffness^{23,24}, whether racial disparities modify the association of fitness-fatness interactions with vascular aging remains to be elucidated.

Conclusion

Heffernan and Loprinzi⁴ should be commended for their contribution, as findings from the current work have provided not only important insight regarding the interactive effects of fitness-fatness on vascular aging, but also raised questions to be explored in potential future research directions that may ultimately advance clinical care for the prevention and treatment of CVD.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Additional Contributions

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