

Strengthening Our Understanding of Muscle Metaboreflex Control in Patients with Coronary Artery Disease: (Dis)association Between Physical Fitness and Hemodynamic Responses

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Short Editorial referring to the article: Association between Cardiovascular Responses to Muscle Metaboreflex and Markers of Physical Fitness in Patients with Coronary Artery Disease

Ischemic Heart Disease remains a leading cause of mortality worldwide.¹ In addition to pharmacologic therapy and coronary revascularization, healthy lifestyle interventions such as diet and exercise are essential components of disease management.² Although exercise training is a Class I recommendation for patients with ischemic heart disease,³ physical exertion is not without risk in this population. Indeed, an exercise stress test is a well-established method for inducing myocardial ischemia. Furthermore, patients with ischemic heart disease often exhibit abnormal cardiovascular responses during exercise,⁴ which makes exercise prescription both challenging and potentially risky in this clinical population. Therefore, understanding the physiological mechanisms underlying the altered cardiovascular control at rest and during exercise, as well as the cardioprotective effects of exercise training in patients with ischemic heart disease,⁵ is critical for improving treatment strategies and optimizing disease management.

The cardiovascular responses to exercise are orchestrated by several integrative neural control mechanisms, including central command, the exercise pressor reflex, the arterial and cardiopulmonary baroreflexes, and the central and peripheral chemoreflexes. The exercise pressor reflex comprises group III and IV skeletal muscle afferents that discharge in response to mechanical deformation (i.e., muscle mechanoreflex) and the accumulation of metabolic by-products of muscle contraction (i.e., muscle metaboreflex).^{6,7} Inputs from group III/IV afferent fibers synapse within cardiovascular control areas in the brainstem that reflexively decrease parasympathetic and increase sympathetic nerve activity, leading to increased Heart Rate (HR), cardiac output, total peripheral resistance, and arterial blood pressure during exercise.^{6,7} It has been shown that the blood pressure responses to exercise and metaboreflex activation are directly associated with absolute muscle strength in young, healthy adults.^{8,9} Moreover, exercise training-induced improvements in cardiorespiratory fitness can

modulate metaboreflex control.¹⁰ Nevertheless, the extent to which the cardiovascular responses to muscle metaboreflex activation are related to markers of physical fitness in patients with Coronary Artery Disease (CAD) is currently unknown.

In a recent study published in the *International Journal of Cardiovascular Sciences*, Coelho et al.¹¹ sought to address this knowledge gap by studying 20 patients diagnosed with CAD at rest, during static handgrip exercise at 40% Maximum Voluntary Contraction (MVC), and Post-exercise Circulatory Occlusion (PECO) to isolate the muscle metaboreflex. Continuous beat-to-beat blood pressure and heart rate were measured via finger photoplethysmography. Stroke Volume (SV) was estimated using the Modellflow method, allowing the calculation of Peripheral Vascular Resistance (PVR). Cardiorespiratory fitness was determined as maximal oxygen consumption ($\dot{V}O_{2max}$) estimated during a treadmill exercise stress test, while muscle strength was defined by handgrip MVC. As expected, mean arterial pressure and PVR increased during static handgrip and remained partially elevated during PECO, whereas SV decreased during handgrip and returned to baseline levels during PECO. Notably, no relationships were observed between the cardiovascular responses to PECO and either cardiorespiratory ($\dot{V}O_{2max}$) or muscular (MVC) fitness, except for a moderate correlation ($r = 0.55$, $P = 0.01$) between changes in SV during PECO and MVC. This relationship remained significant after controlling for age and sex.

As with any human physiological research, several methodological aspects should be considered when interpreting the study's findings. Given the lack of a control group, it remains uncertain whether patients with CAD exhibit preserved or abnormal cardiovascular reactivity to exercise and PECO. Furthermore, whether these relationships (or lack thereof) would also be observed in age-matched healthy controls remains to be determined, which limits the clinical and physiological interpretability of the investigation. The authors also did not present the relationship analyses at rest or during static handgrip exercise, which could have provided a more comprehensive picture of the potential role of markers of physical fitness on the cardiovascular control among patients with CAP. For example, it would be informative to demonstrate whether the only relationship observed (i.e., between MVC and change in SV during PECO) remains significant and whether its strength would be similar, stronger, or weaker during static handgrip exercise. Such data could provide further insights into the interaction between muscle metaboreflex, mechanoreflex, and central command

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as potential modulators of the relationship between muscle strength and SV responses. Finally, beyond the well-established principle that correlation does not imply causation, another important aspect that readers should cautiously pay attention to while navigating through Coelho *et al.*¹¹ study is the authors' interpretations. Notably, the authors indicated that participants' MVC was treated as the dependent variable, whereas the cardiovascular responses to PECO were treated as independent variables. They further reported that one standard deviation in SV was associated with a 1.37 standard deviation increase in handgrip strength. However, the physiological plausibility of this interpretation warrants further discussion. It has been shown that muscle strength influences the cardiovascular responses to exercise and isolated muscle metaboreflex activation.^{8,9} In this context, Lee *et al.*¹² showed that reducing participants' MVC through exercise-induced muscle weakness significantly attenuated the blood pressure responses to metaboreflex activation. On the other hand, interventions that manipulate SV, such as postural changes¹³ or lower-body negative pressure,¹⁴

are unlikely to alter MVC. Therefore, readers are encouraged to exercise critical thinking when interpreting the findings of Coelho *et al.*¹¹

In summary, Coelho *et al.*¹¹ should be commended for studying a challenging clinical population. Their work represents an important step forward in advancing our understanding of muscle metaboreflex control in patients with CAD. Elucidating how markers of physical fitness influence the reflex cardiovascular control during exercise may ultimately enable safer and more personalized exercise prescriptions for this population. Future studies are required to confirm these findings and to underscore the mechanisms underlying cardiovascular (dis)regulation at rest and during exercise in patients with CAD.

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