

Association between Cardiovascular Responses to Muscle Metaboreflex and Markers of Physical Fitness in Patients with Coronary Artery Disease

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Abstract

Background: The muscle metaboreflex regulates cardiovascular responses during exercise. In patients with coronary artery disease (CAD), this reflex primarily increases blood pressure via sympathetic-mediated vasoconstriction, thereby increasing peripheral vascular resistance (PVR) rather than enhancing stroke volume (SV). This response may result in early fatigue during physical exertion. However, the specific mediators of this response are unclear.

Objective: To investigate the association between cardiorespiratory and muscle fitness with cardiovascular responses to muscle metaboreflex activation in patients with CAD.

Methods: Twenty patients underwent an exercise test and a maximal voluntary contraction (MVC) test using handgrip strength. Hemodynamic variables were assessed using photoplethysmography during muscle metaboreflex activation via a post-exercise circulatory arrest (PECA) protocol. Changes (Δ) in mean arterial pressure (MAP), SV, and PVR at rest were used to assess the metaboreflex response.

Results: Participants (61.7 ± 8.0 years; 28.4 ± 3.9 kg/m²) had a mean $\text{VO}_{2\text{max}}$ of 31.96 ± 5.70 mL/kg/min, and a MVC of 90.5 ± 21.1 lbs. Metaboreflex activation significantly increased MAP ($+14.74 \pm 9.56$ mmHg, $p < 0.0001$) and PVR ($+0.13 \pm 0.07$ mmHg.s/mL, $p < 0.0001$), but not SV ($+1.91 \pm 5.54$ mL, $p = 0.13$). MVC was directly associated with ΔSV ($R = 0.54$ and $p = 0.01$), but not with ΔMAP ($R = 0.23$ and $p = 0.31$) or ΔPVR ($R = -0.10$ and $p = 0.65$). In multiple linear regression models adjusted for age and sex, ΔSV emerged as a predictor of MVC ($\beta = +1.37$ and $p = 0.03$). Conversely, no significant associations were found between $\text{VO}_{2\text{max}}$ and ΔSV ($R = 0.29$ and $p = 0.22$), ΔMAP ($R = 0.14$ and $p = 0.54$), or ΔPVR ($R = 0.05$ and $p = 0.83$).

Conclusions: These findings underscore the association between SV and muscle fitness during metaboreflex activation in patients with CAD.

Keywords: Cardiovascular Physiological Phenomena; Exercise Pressor Reflex; Exercise Tolerance; Myocardial Ischemia.

Introduction

Coronary artery disease (CAD), the most prevalent cardiovascular condition worldwide,¹ is characterized by myocardial ischemia, a reduction or interruption of coronary arterial blood flow to a specific region of the heart muscle, caused by progressive stenosis of the coronary arterial lumen, typically due to atheromatous plaque formation. This condition leads to a reduced supply of oxygen and nutrients to the heart cells and conduction system, potentially resulting in acute myocardial infarction.² Consequently, myocardium

damage may occur, leading to cardiac dysfunction and altered cardiovascular responses both at rest and during physical exercise.³

During exercise, the mechanisms controlling cardiovascular function must address two primary demands: 1) increasing the availability of oxygen to meet the needs of active muscles and ensure the clearance of metabolic byproducts through increased blood flow; and 2) regulating blood pressure to maintain adequate perfusion of vital organs without significant fluctuations.⁴⁻⁶ These adjustments are largely regulated by the autonomic nervous system, which employs neural control mechanisms such as the central command, baroreflex, and exercise pressor reflex or ergoreflex.⁷ Specifically, the exercise pressor reflex increases sympathetic activity through the activation of type III and IV muscle afferent fibers, which are sensitive to mechanical stimuli (mechanoreflex) and the accumulation of metabolites (metaboreflex).⁸⁻¹²

In healthy individuals, muscle metaboreflex activation mobilizes a functional reserve comprising four essential

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Central Illustration: Association between Cardiovascular Responses to Muscle Metaboreflex and Markers of Physical Fitness in Patients with Coronary Artery Disease

Patient Enrollment



Fitness Assessment



Hemodynamic Monitoring during Metaboreflex Activation Protocol



Data Analysis



The greater the increase in stroke volume in response to the muscular metaboreflex, the higher the handgrip strength



Reduced supply to active muscles, resulting from low increases in blood volume ejected per systole during strength exercise, may limit muscular performance in patients with CAD

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hemodynamic modulators: inotropism, chronotropism, cardiac preload, and cardiac afterload. These elements work together to facilitate increased blood pressure during physical exercise,^{6,13} depending on the intensity and type of exercise, and body position.¹⁴ However, when the capacity to recruit preload and inotropic reserves is limited, hemodynamic regulation relies more on afterload and vasoconstriction, leading to increased peripheral vascular resistance (PVR) to meet increased metabolic demands during exercise. This response seems to result from limitations in the ability to enhance both stroke volume (SV) and cardiac output (CO), which typically increase during muscle metaboreflex activation in healthy individuals, particularly when seated.¹⁴ The inability to increase SV leads to excessive elevations in PVR, thereby enhancing blood pressure.^{15,16}

This scenario appears to apply to patients with CAD, who exhibit heightened sympathetic-mediated vasoconstriction (increased PVR) at the expense of flow-mediated mechanisms (increased SV and CO) for adequate blood pressure increments in response to muscle metaboreflex activation.^{17,18} Theoretically, increased sympathetic-mediated vasoconstriction could limit blood flow to exercising muscles, reducing muscle perfusion and impairing the removal of exercise-induced metabolites.¹⁹ Consequently, exercise tolerance in patients with CAD may be compromised. Sustained elevation of PVR could contribute to early fatigue during exertion in these individuals, a symptom closely associated with CAD itself.²⁰

Given this context, there is a need to investigate the functioning of the muscle metaboreflex in patients with CAD,

particularly regarding how changes in the relative contributions of SV and PVR to blood pressure increases may affect overall strength and exercise endurance.¹⁶ Low exercise tolerance has significant clinical implications for patients with CAD, as higher levels of physical fitness are associated with improved quality of life and reduced mortality risk.^{21,22}

However, to date, there is insufficient evidence addressing the role of muscle metaboreflex in exercise tolerance among patients with CAD. Specifically, there is no information on how the muscle metaboreflex influences key aspects of physical fitness, such as strength and cardiorespiratory capacity, in individuals with this condition. Therefore, this study aimed to analyze the relationship between physical fitness and cardiovascular responses to muscle metaboreflex activation in patients with CAD. This investigation seeks to clarify whether the physical fitness of these patients correlates with variations in blood pressure, SV, and PVR during muscle metaboreflex activation. We hypothesized that the lower the cardiorespiratory and muscle fitness levels in patients with CAD, the lower the increase in SV during muscle metaboreflex activation, contrasting with a more substantial increase in PVR and blood pressure.

Methods

Participants

We enrolled 20 patients with CAD aged 40 to 75 years, who were participating in a cardiovascular rehabilitation

program. CAD was defined by the occurrence of any acute coronary syndrome, including ST and non-ST elevation myocardial infarction, and unstable angina (all defined by characteristic histories and electrocardiographic and cardiac enzyme abnormalities) or by the diagnosis of obstructive CAD based on coronary angiography (defined as $\geq 50\%$ stenosis of any epicardial coronary artery) in patients with stable angina. Exclusion criteria included heart failure, valvular heart disease, and active smoking. All participants provided informed written consent before participating in the study, which adhered to the principles of the Helsinki Declaration. The study protocol was approved by the institutional Ethics Review Board (CAAE 58415522.6.0000.5259).

Study design

This study employed a cross-sectional design conducted over two visits. During the first visit, eligible participants signed the informed consent form, and body mass and height were measured using a mechanical scale with a precision of 100g (Cambé, Rolândia, Brazil) and a stadiometer (Sanny, São Paulo, Brazil), respectively. Subsequently, maximal voluntary contraction (MVC) during handgrip was assessed in a seated position with 3 attempts (with a 3-minute interval between each attempt) using a hand dynamometer (Saehan®, SH5001, Masan, South Korea). Following this, the muscle metaboreflex activation protocol was conducted using the post-exercise circulatory arrest (PECA) method, during which cardiovascular variables were measured. During the second visit, patients underwent a treadmill exercise stress test to evaluate cardiorespiratory fitness. All volunteers were instructed not to consume food within 2 hours of the tests and to refrain from physical exercise, alcohol, or stimulants for up to 48 hours prior to the assessment protocol. Both visits occurred on weekday mornings (8–11 am) in a temperature-controlled environment (22–24°C, ~ 60% air humidity).

Cardiorespiratory fitness assessment

Cardiorespiratory fitness was evaluated using a treadmill exercise test (Centurion 300, Brasília, Brazil) controlled by Ergo PC software (version 5.4.1.4, Brasília, Brazil), utilizing an individualized ramp protocol. To achieve maximal effort during the test, participants had to meet at least one of the following criteria: a) reach voluntary exhaustion; and/or b) attain 90% of the estimated maximal heart rate (HR) or exhibit no increase in heart rate despite an increase in speed. Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) was estimated using the FRIEND formula,²³ which has been validated for patients with CAD in a protocol-independent manner.²⁴

Handgrip maximal voluntary contraction

Muscle strength was evaluated using a maximal voluntary handgrip contraction test performed with a hydraulic hand dynamometer (Saehan®, SH5001, Masan, South Korea). Participants were seated with their elbows extended, and the dynamometer was secured on a table support. Each participant performed three attempts of 5 seconds each, with 3-minute intervals between attempts. The highest value was recorded as the result.

Muscle Metaboreflex Activation Protocol

Metaboreflex activation was performed using the PECA method, a widely applied, non-invasive, non-pharmacological approach.¹⁹ The PECA protocol lasted 12.5 minutes and consisted of the following phases: 5 minutes of rest; 90 seconds of isometric handgrip exercise (Saehan®, SH5001, Masan, South Korea) performed at 40% of MVC; 3 minutes of vascular occlusion; and 3 minutes of recovery. Vascular occlusion was achieved using a 92 x 10 cm nylon cuff placed around the proximal third of the exercised arm. The cuff was connected to a digital pneumatic cuff inflator (2000I simple, AAMED®, São Paulo, Brazil) and inflated to 200 mmHg 10 seconds before the end of the exercise phase, followed by deflation during the 3-minute recovery period. Throughout the protocol, volunteers remained seated and were instructed to avoid performing the Valsalva maneuver.

Cardiovascular variables assessment

The beat-to-beat blood pressure and heart rate were continuously and non-invasively monitored and recorded using digital photoplethysmography throughout the entire PECA protocol (Finometer, Finapres®, Amsterdam, Netherlands). Using BeatScope® software (Finapres®, Amsterdam, Netherlands), the Finometer employs the Modelflow method,²⁵ which calculates an aortic flow waveform from digital pressure obtained by a cuff placed around the middle finger. This method simulates a nonlinear three-element model of aortic input impedance. By integrating the computed aortic flow waveform for each heartbeat, it is possible to estimate left ventricular SV and, consequently, CO as the product of SV and HR.²⁶ PVR was calculated as the ratio of mean arterial pressure (MAP) to CO. For analysis, averages of the 5 minutes of rest and the 3 minutes of post-exercise vascular occlusion were used. Changes from rest to post-exercise vascular occlusion were calculated as responses to muscle metaboreflex activation (Δ).

Statistical analysis

A statistical power of 0.99 was achieved using post hoc analysis (GPower 3.1.9.4, Universität Kiel, Kiel, Germany) based on the sample size, predefined p value, and effect size ($f^2 = 1.95$) for the multiple linear regression model. Data normality was ratified by the Shapiro-Wilk test. Descriptive analyses of clinical variables, physical fitness, and cardiovascular variables included means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Cardiovascular responses during exercise and during the PECA protocol were analyzed using a repeated-measures one-way ANOVA, followed by Sidak's post hoc test for multiple comparisons. Pearson's correlation coefficients were calculated to determine the association between MVC, $\text{VO}_{2\text{max}}$, and changes (PECA – rest) in cardiovascular responses to muscle metaboreflex activation.

Multiple linear regression models were used to determine the association between MVC and $\text{VO}_{2\text{max}}$ (dependent variables) and cardiovascular responses to the muscle metaboreflex (independent variables), assuming normality of residuals and homoscedasticity. The angular coefficient (β),

representing the proportion of variance in the dependent variable explained by each model term, was calculated for changes in MAP, SV, and PVR in both unadjusted and age- and sex-adjusted models.

Data analysis was conducted using RStudio (version 2023.12.1, Massachusetts, USA) and GraphPad Prism 6.0 (GraphPad®, La Jolla, USA). A scatter plot and correlogram were created to visually depict the association between physical fitness variables and cardiovascular responses using the plot command and ggplot2 in the R Studio software (version 2023.12.1, Massachusetts, USA). Statistical significance was set at $P < 0.05$ for all analyses.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Sample characteristics

Table 1 presents the clinical characteristics of the sample. Fifty percent of the patients had a history of acute myocardial infarction, 80% had undergone coronary artery bypass surgery at least six months before inclusion in the study, 65% had diabetes, 100% had hypertension, and 65% had dyslipidemia. Additionally, 85% were classified as overweight or obese, and 25% were former smokers. Regarding medication use, all patients were taking aspirin and/or beta-blockers, statins, and either biguanides or sulfonylureas. Forty-five percent were prescribed diuretics, 10% were on antidepressants, and 20% were using other medications, such as those for gastrointestinal disorders.

Cardiovascular responses to muscle metaboreflex activation

Cardiovascular variables were continuously measured throughout the PECA protocol. Table 2 shows the mean values across each phase of the protocol, while Figure 1 illustrates the corresponding responses and changes during exercise and PECA compared to rest. Significant changes were observed during exercise, with increases in MAP ($p < 0.0001$; Figure 1 and Table 2) and PVR ($p = 0.0002$; Figure 1 and Table 2), accompanied by a reduction in SV ($p < 0.001$; Figure 1 and Table 2). During the vascular occlusion period (PECA), MAP and PVR remained elevated ($p < 0.0001$; Figure 1 and Table 2) relative to rest. In contrast, SV increased significantly from rest during recovery ($p = 0.01$; Table 2).

Association between physical fitness and cardiovascular responses

Figure 2 illustrates scatter plots and Pearson's correlation coefficients for the associations between physical fitness markers and cardiovascular responses to muscle metaboreflex activation. MVC correlated positively with Δ SV but not with Δ MAP and Δ PVR. VO_{2max} did not show significant correlations with any cardiovascular variables.

Table 1 – Characteristics of the study participants

	Participants
	(n = 20)
Men (n, %)	15 (75)
Age (y)	62 ± 8
Height (cm)	164 ± 9
Body mass (kg)	76.5 ± 12.7
Body mass index (Kg/m ²)	28.4 ± 5.1
MVC (lbs)	90.5 ± 21.1
VO_{2max} (ml/kg/min)	31.96 ± 5.7

Data expressed as mean (SD). MVC: maximal voluntary contraction; VO_{2max} : maximal oxygen consumption.

Table 2 – Mean ± standard deviation cardiovascular responses to muscle metaboreflex activation

	REST	EXERCISE	PECA	RECOVERY
MAP (mmHg)	97.1±9.5	119.9±14.8*	111.8±13.6*	98.0±9.7
SV (ml)	97.1±27.4	84.2±26.3*	99.0±27.3	102.2±30.4*
PVR (mmHg.s/ml)	0.98±0.30	1.43±0.71*	1.12±0.32*	0.96±0.28

MAP: mean arterial pressure; SV: stroke volume; PVR: peripheral vascular resistance; PECA: post-exercise circulatory arrest. * $p < 0.05$ vs. REST (one-way ANOVA).

To assess how the dependent variables (MVC and VO_{2max}) were influenced by changes in the independent variables (responses of MAP, SV, and PVR to muscle metaboreflex), both unadjusted and adjusted multiple linear regressions were performed, controlling for age and sex. Table 3 demonstrates a positive association between MVC and Δ SV in both the unadjusted and adjusted models ($p = 0.01$ and 0.03 , respectively). In both models, the adjusted R^2 coefficients were statistically significant ($p = 0.01$ and < 0.001 , respectively). After adjusting for age and sex, the model indicated that an increase of one standard deviation in SV is associated with a 1.37 standard deviation increase in handgrip strength, assuming all other variables remain constant. No associations were found between VO_{2max} and cardiovascular responses to muscle metaboreflex activation (Figure 2), although the adjusted R^2 coefficient in the model adjusted for age and sex was statistically significant ($p < 0.01$; Table 3).

Discussion

Our study aimed to investigate the relationship between cardiovascular responses to muscle metaboreflex activation

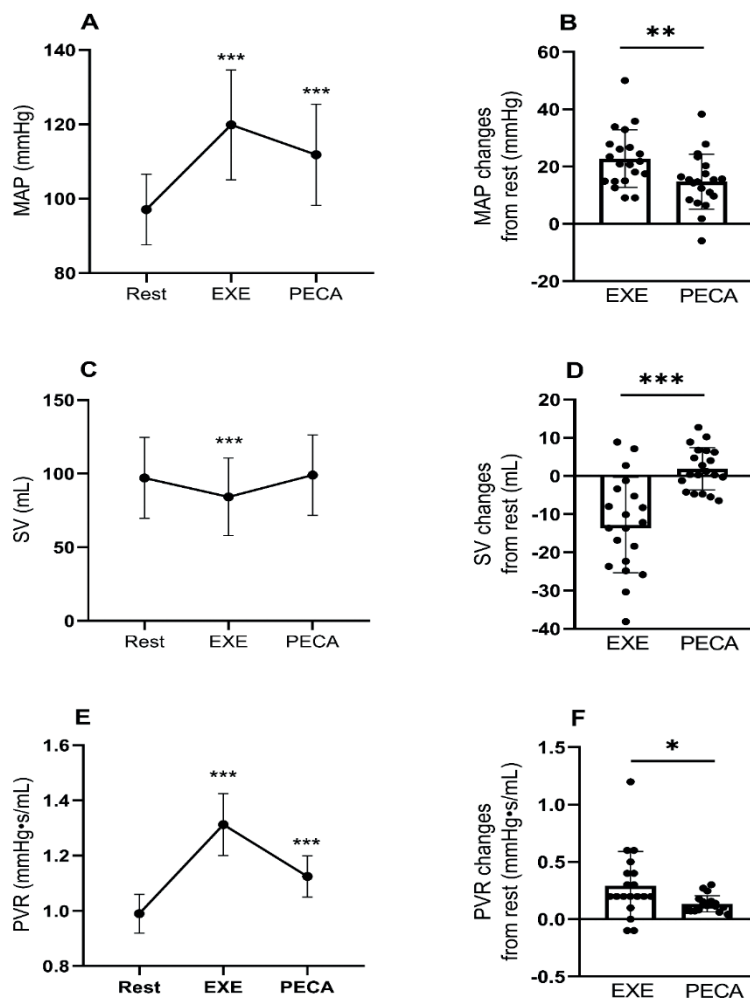


Figure 1 – Mean responses (A, C, and E) and changes from rest (B, D, and F) for mean arterial pressure (MAP), stroke volume (SV), and peripheral vascular resistance (PVR) during handgrip exercise (EXE) and post-exercise circulatory arrest (PECA). * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ vs. rest.

and both muscle and cardiorespiratory physical fitness in patients with CAD. As shown in the Central illustration, a key finding was that changes in SV during muscle metaboreflex activation were positively associated with maximal handgrip strength. These findings suggest that reduced oxygen and nutrients delivered to active muscles, resulting from low increases in blood volume ejected per systole during strength exercise, may limit muscle performance in patients with CAD. However, handgrip MVC is a brief effort, lasting only a few seconds, and primarily relies on the ATP-CP energy system, with minimal dependence on blood supply. Therefore, future investigations, including assessments of blood flow and muscle oxygenation, would be valuable in this regard.

A more plausible interpretation is that the observed association reflects underlying integrative mechanisms linking cardiovascular and muscle function in CAD patients. For instance, individuals with more effectively preserved central

hemodynamic responses during metaboreflex activation may also have greater muscle quality or neuromuscular efficiency, which are determinants of strength. In this context, SV response might serve as an indirect marker rather than a mechanistic determinant of muscle strength. Studies in healthy individuals show that occluding blood flow to muscles significantly reduces time to exhaustion and strength, underscoring the crucial role of blood flow in ATP production and clearance of metabolic byproducts.²⁷ Despite this, no studies have investigated the relationship between muscle fitness and muscle metaboreflex in CAD patients or healthy individuals.

Therefore, our findings contribute to current knowledge by demonstrating that muscle fitness, as measured by handgrip strength, is strongly associated with SV responses to the muscle metaboreflex in patients with CAD. Future investigations incorporating measures of muscle mass,

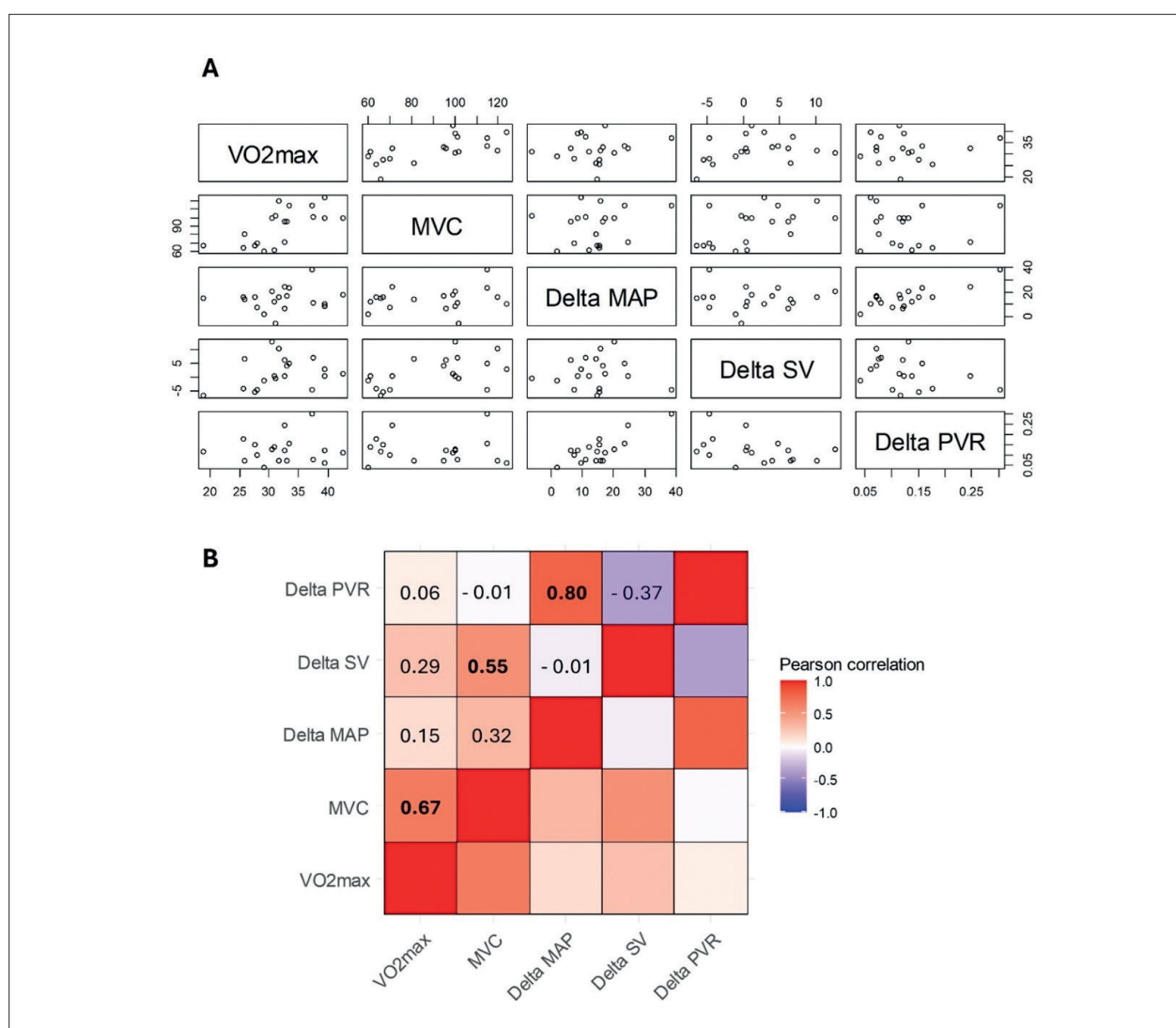


Figure 2 – Correlation plot (A) and correlogram (B) between physical fitness and cardiovascular responses to muscle metaboreflex. In Panel B, shades of red indicate an increasingly positive correlation coefficient. Correlation coefficients in bold are statistically significant.

neuromuscular activation, and peripheral hemodynamics may help disentangle the mechanisms underlying this association. In theory, if physical training adaptations enhance SV responses to metaboreflex activation, this could translate into broader benefits for cardiovascular and muscle fitness in patients with CAD. However, the current design does not allow for causal inference, and further longitudinal studies are required to determine whether training-induced changes in muscle metaboreflex responses are associated with improvements in muscle or cardiorespiratory fitness in patients with CAD. In other clinical conditions, there is disagreement about the role of physical training in cardiovascular responses during activation of the muscle metaboreflex. Some authors observed a reduction in MAP and PVR, or an increase in SV and muscle blood flow.²⁸⁻³⁰ In contrast, others failed to identify any cardiovascular adaptations related to the muscle metaboreflex induced by physical training.³¹⁻³³ Furthermore, no studies have

investigated the relationship between these adaptations and muscle and cardiorespiratory fitness.

Our data demonstrated that isometric handgrip exercise at 40% MVC induced hemodynamic changes compared with rest. Similarly, TOSKA (2010) reported significant increases in MAP and peripheral vasoconstriction, along with a decrease in SV, during 2 minutes of isometric handgrip exercise at 40% of MVC, assessed using photoplethysmography and Doppler ultrasonography, respectively.³⁴ This reduction in SV can be attributed to the increase in HR, which shortens ventricular filling time and consequently reduces SV.² Furthermore, increased afterload due to sympathetically mediated peripheral vasoconstriction reduces venous return and further contributes to the decrease in SV.¹⁵

In contrast, our findings differ from those of MAGNANI et al. (2018), who observed unchanged SV during handgrip exercise compared to rest in patients with CAD, despite

Table 3 – Association between physical fitness variables and cardiovascular responses to muscle metaboreflex activation

Cardiovascular responses	VO _{2max} (ml/kg/min)					
	Unadjusted			Adjusted [§]		
	β (95% CI)	p	Adjusted R ²	β (95% CI)	p	Adjusted R ²
ΔMAP (mmHg)	0.12 (-0.31 to +0.56)	0.54		0.00 (-0.26 to +0.28)	0.93	
ΔSV (ml)	+0.30 (-0.24 to +0.84)	0.25	-0.06	+0.32 (-0.05 to +0.71)	0.08	0.61
ΔPVR (mmHg.s/ml)	-2.08 (-19.64 to +15.45)	0.80		+2.09 (-9.00 to +13.18)	0.69	
Cardiovascular responses	MVC (lbs)					
	Unadjusted			Adjusted [§]		
	β (95% CI)	p	Adjusted R ²	β (95% CI)	p	Adjusted R ²
ΔMAP (mmHg)	+1.19 (-0.001 to +2.39)	0.05		+0.80 (-0.12 to +1.72)	0.08	
ΔSV (ml)	+1.95 (+0.47 to +3.43)	0.01	0.36	+1.37 (+0.08 to +2.66)	0.03	0.64
ΔPVR (mmHg.s/ml)	-46.24 (-95.93 to +3.44)	0.06		-28.41 (-67.33 to +10.51)	0.13	

Estimates and coefficients in bold are statistically significant. [§]Model adjusted for age and sex. MAP: mean arterial pressure; SV: stroke volume; PVR: peripheral vascular resistance; MVC: maximal voluntary contraction (multiple linear regression, adjusted and unadjusted model for age and sex).

an increase in MAP. This discrepancy may be due to methodological differences. Unlike our protocol and that of TOSKA (2010), the authors used dynamic handgrip exercise for 3 minutes at 30% of MVC. Protocols involving isometric exercises of moderate to high intensity are generally preferred over dynamic, low-intensity exercises in activating the muscle metaboreflex, as continuous compression of blood vessels is more likely to induce metabolite accumulation.^{19,35}

The PECA protocol is widely used in various clinical conditions to elicit cardiovascular responses during muscle metaboreflex activation, without interference from central command and mechanoreflex.^{19,36,37} In our study, post-exercise vascular restriction successfully maintained MAP and PVR elevated compared to rest (+14.7 mmHg and +0.13 mmHg.sec/mL, respectively), without changes in SV. These cardiovascular responses align with previous findings indicating that increased cardiac afterload, but not preload, elevates MAP due to muscle metaboreflex activation in CAD patients.^{17,18} This suggests the efficacy of our protocol in activating the muscle metaboreflex. In contrast to PVR, we observed considerable interindividual variability in SV responses to muscle metaboreflex activation (standard deviation ±5.54 mL). This underscores the need for further investigation into how different patterns of SV responses (increases or decreases) correlate with physical fitness measures in this population. The relatively low variability in PVR may explain the lack of observed relationships with this outcome, as potential interactions may not be readily apparent in a less variable group.

Our hypothesis was partially confirmed – maximal handgrip strength was associated with changes in SV in response to the metaboreflex, whereas VO_{2max} was not. Oxygen supply to working muscles is a critical factor

influencing cardiorespiratory fitness.³⁸ However, endurance performance is also influenced by additional factors such as the oxygen extraction capacity of skeletal muscle, as well as age and sex.³⁹⁻⁴¹ Our multiple linear regression analysis further supports this premise, revealing that the adjusted R² increased significantly when age and sex were included in the prediction model for VO_{2max}.

Our study has both limitations and strengths. The main limitation includes the absence of a cardiopulmonary exercise test, which would have allowed direct measurement of VO_{2max} and minimized potential errors in estimating cardiorespiratory fitness. Although the VO_{2max} estimate obtained using the FRIEND equation showed no statistical difference compared with direct gas analysis²³ and has been validated in patients with CAD²⁴, this remains a methodological constraint. Another important limitation is the lack of a control group without CAD, which restricts the interpretation of our findings to within-group changes in these specific patients. Moreover, the study relied solely on correlational data from a relatively small sample, which limits statistical power and precludes more definite mechanistic or clinical conclusions. Additionally, handgrip exercise to assess muscle strength is noteworthy. Future studies could benefit from exercises involving larger muscle groups not related to the PECA protocol, offering deeper insights into the relationship between muscle strength and cardiovascular responses to the muscle metaboreflex. Furthermore, while finger photoplethysmography was employed to evaluate PVR, more direct methods should be considered for future investigations to assess peripheral vasoconstriction more accurately.

On the other hand, our study is the first to explore the association between cardiovascular responses to the muscle metaboreflex and markers of physical fitness, which holds

clinical implications for patients with CAD.^{21,22} In our adjusted multiple linear regression model, we found that the change in SV during muscle metaboreflex activation predicted maximal handgrip strength, even after adjusting for sex and age, key confounders in this context.

Conclusions

This study is the first to examine the association between cardiovascular responses to muscle metaboreflex activation and physical fitness markers in patients with CAD. Our findings highlight the potential role of SV in moderating muscle fitness in this population and underscore the need for further research into the mechanisms underlying this relationship, particularly in larger and more diverse populations.

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Author Contributions

Conception and design of the research: Coelho VCO, Borges J; Acquisition of data: Coelho VCO, Gama GS, Costa CLF; Analysis and interpretation of the data and Statistical analysis: Coelho VCO, Gama GS, Costa CLF, Borges J; Obtaining financing: Borges J; Writing of the manuscript: Coelho VCO; Critical revision of the manuscript for content: Gama GS, Costa CLF, Rangel MVS, Borges J.

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Potential conflict of interest

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

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Study association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Pedro Ernesto under the protocol number CAAE 58415522.6.0000.5259. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Data Availability Statement

All datasets supporting the results of this study are available upon request from the corresponding author [Juliana Borges].

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