Circulatory and Ventilatory Power: Characterization in Patients with Coronary Artery Disease

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Abstract

Background: Circulatory power (CP) and ventilatory power (VP) are indices that have been used for the clinical evaluation of patients with heart failure; however, no study has evaluated these indices in patients with coronary artery disease (CAD) without heart failure.

Objective: To characterize both indices in patients with CAD compared with healthy controls.

Methods: Eighty-seven men [CAD group = 42 subjects and healthy control group (CG) = 45 subjects] aged 40–65 years were included. Cardiopulmonary exercise testing was performed on a treadmill and the following parameters were measured: 1) peak oxygen consumption (VO_2), 2) peak heart rate (HR), 3) peak blood pressure (BP), 4) peak rate-pressure product (peak systolic HR x peak BP), 5) peak oxygen pulse (peak VO_2/peak HR), 6) oxygen uptake efficiency (OUES), 7) carbon dioxide production efficiency (minute ventilation/carbon dioxide production slope), 8) CP (peak VO_2 x peak systolic BP) and 9) VP (peak systolic BP/carbon dioxide production efficiency).

Results: The CAD group had significantly lower values for peak VO_2 ($p < 0.001$), peak HR ($p < 0.001$), peak systolic BP ($p < 0.001$), peak rate-pressure product ($p < 0.001$), peak oxygen pulse ($p = 0.008$), OUES ($p < 0.001$), CP ($p < 0.001$), and VP ($p < 0.001$) and significantly higher values for peak diastolic BP ($p = 0.004$) and carbon dioxide production efficiency ($p < 0.001$) compared with CG. Stepwise regression analysis showed that CP was influenced by group ($R^2 = 0.44$, $p < 0.001$) and VP was influenced by both group and number of vessels with stenosis after treatment (interaction effects: $R^2 = 0.46$, $p < 0.001$).

Conclusion: The indices CP and VP were lower in men with CAD than healthy controls. (Arq Bras Cardiol. 2015; 104(6):476-486)

Keywords: Exercise; Oxygen Uptake; Cardiopulmonary Exercise; Cardiovascular Disease, Adults.

Introduction

Cardiopulmonary exercise testing (CPX) is considered the gold standard for evaluating the response to aerobic exertion in patients with cardiovascular diseases to determine the physiological mechanisms of exercise intolerance[1]. Some indices, such as peak oxygen consumption (VO_2), carbon dioxide production eficiency derived from the linear relationship between minute ventilation (VE) and carbon dioxide production (VCO_2) (VE/VCO_2 slope)[2] and oxygen uptake efficiency (OUES), derived from the linear relationship between VO_2 and VE[3,4], have been used to assess healthy subjects[2,4], patients with heart failure[5-8] and with other forms of heart disease[9], such as coronary artery disease (CAD)[10,11]. Circulatory power (CP) is a less frequently assessed variable obtained from CPX and calculated as the product of peak VO_2 and peak systolic blood pressure (BP). CP has shown some potential for clinical utility[12-15] and has been proposed as a surrogate for cardiac power. This index has also been shown to be an independent predictor of mortality, with a lower CP portending a worse prognosis[12,14,15]. More recently, Forman et al. (2012)[16] introduced and evaluated the prognostic use of a novel index, named ventilatory power (VP), which was calculated by dividing peak systolic BP by the VE/VCO_2 slope. According to the authors, better prognosis is reflected by a higher VP value, i.e., greater systolic BP and/or lower VE/VCO_2 slope.

While these variables have been assessed in heart failure cohorts, we are unaware of any previous study that evaluated the CP and VP indices in CAD patients without heart failure who were managed using standard medication, angioplasty or coronary artery bypass graft (CABG) surgery. Thus, the purpose of this study was to test the hypothesis that both CP and VP would be significantly lower in these CAD patients

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compared with healthy controls; therefore, could provide another potentially valuable measure of cardiopulmonary function in these patients.

Methods

This is an observational, cross-sectional, comparative study.

Participants

Men between 40–65 years of age were allocated to two groups: 1) patients with CAD confirmed by cardiac catheterization (CAD-G) and without heart failure and 2) an apparently healthy control group (CG). Subjects in CAD-G were recruited through a local hospital (hemodynamic section) and CG subjects were identified from a registry database in our laboratory and contacted to determine interest. Subjects were invited to participate in this study between June 2008 and April 2013. The inclusion criteria for CAD-G were: 1) CAD patients with or without myocardial infarction (1 month to 3 years since the event) optimally managed using current standard pharmacologic regimens and potentially: a) mechanical or chemical reperfusion and/or b) CABG surgery (6 months to 3 years post-surgery) and 2) preserved left ventricular function with an ejection fraction > 50%. Inclusion criteria for CG were: 1) apparently healthy based on clinical examination and 2) no use of prescription medications. The exclusion criteria for both groups were: 1) body mass index (BMI) ≥ 30 kg/m^2, 2) use of tobacco, 3) habitual drinking or illegal drug use, 4) orthopedic limitations, 5) neurological disease, 6) diabetes, 7) uncontrolled systemic arterial hypertension, 8) functional capacity ≤ 4 metabolic equivalents, 9) lung diseases, 10) inappropriate behavior of BP to exertion, 11) malignant ventricular arrhythmia, 12) atrial fibrillation, 13) complex ectopic ventricular beats, 14) supraventricular or sinus tachycardia, 15) 2º and 3º atrioventricular block, 16) fixed frequency pacemaker, and 17) participation in a regular exercise program in the last 6 months. This study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki (1975). Written informed consent was obtained from each individual before the initiation of the study.

Clinical examination

Prior to study initiation, all subjects underwent a clinical evaluation to characterize their clinical status. The evaluation comprised: 1) clinical cardiac examination; 2) resting ECG (Ecafix TC 500, São Paulo, São Paulo, Brazil); 3) maximal standard exercise test on a treadmill (DIGISTRESS Vega, Digitronica, Belo Horizonte, Minas Gerais, Brazil); and 4) laboratory measurements: glycemia, hemoglobin, lipid profile, urea, creatinine, and uric acid. Subjects discontinued pharmacological prior to the exercise test, which was conducted by a physician using the Bruce protocol[17] in accordance with the American Thoracic Society recommendations[1], Symptoms of dyspnea and leg fatigue were assessed using the modified Borg scale[18] and all subjects were asked about the occurrence of angina at each stage of the exercise protocol.. After a minimum resting period of 48 h, all eligible subjects performed CPX.

Cardiopulmonary exercise testing (CPX)

On the same day as CPX, the maximal walking velocity on a treadmill (Master ATL, Inbramed, Porto Alegre, Rio Grande do Sul, Brazil) was determined for all subjects. The starting treadmill speed was set at 3.0 km/h without elevation, with subsequent 0.5 km/h increases in speed every 30 s. At this point, the speed was increased or decreased by 0.1 km/h until the subjects reached a maximal comfortable walking cadence without running[19]. After determining the maximal walking velocity, symptom-limited CPX was performed using a calibrated ventilatory expired gas unit (CPX-D, Medical Graphics, Saint Paul, Minnesota, United States) according to a ramping protocol: 1) 1 min at rest; 2) an incremental phase, beginning at an initial speed of 0.8 km/h until maximal walking velocity was reached; 3) 0.5% increase in incline grade every 15 s; 4) 1 min of active recovery at 3.0 km/h; and 5) 5 min of passive recovery. Ventilatory expired gases were collected breath-by-breath and calculated as moving means after every eight respiratory cycles (Breeze Suite 6.4.1, Medical Graphics, Saint Paul, Minnesota, United States)[19,20]. The criteria for test termination were based on current exercise guidelines[21,22].

Throughout CPX, ECG (12 simultaneous leads) and heart rate (HR) were monitored and registered (WinCardio, Micromed, Brasilia, Distrito Federal, Brazil). Delta of HR was expressed as peak HR minus HR at rest and the predicted maximum HR was calculated as 220 minus age in years. The BP was measured at rest, every 2 min during the test and throughout recovery (BD, São Paulo, São Paulo, Brazil). Perceived exertion (symptoms of dyspnea and leg fatigue) was assessed using the modified Borg scale[18] and all subjects were asked about the occurrence of angina and symptoms at each stage of the exercise protocol, according to current exercise guidelines[21,22].

Peak VO_2 and peak respiratory exchange ratio (RER) (defined as the ratio between VCO_2 and VO_2) were expressed as the highest averaged values observed during the last 30 s of exercise[19,23]. The VE/VCO_2 slope and the OUES were calculated from the initiation of exercise to peak[16,22]. The VE/VCO_2 slope was obtained by analyzing the linear relationship between VE and VCO_2, with VE on the y-axis and VCO_2 on the x-axis[2]. The OUES was obtained by analyzing the linear relationship between VO_2 and VE, with VO_2 on the y-axis and the log-transformation of VE on the x-axis[3,4]. Other variables were calculated: 1) peak rate-pressure product (RPP) = product of peak systolic BP and peak HR; 2) peak oxygen pulse = peak VO_2 divided by the peak HR; 3) CP = product of peak VO_2 and peak systolic BP[12] and 4) VP = peak systolic BP divided by the VE/VCO_2 slope[16].

Statistical analysis

Based on a pilot study using VP and CP as endpoints (CAD-G = 5 individuals; CG = 5 individuals), a sample size for the current study that would provide sufficient statistical power ($\beta = 0.8$) to detect an important difference ($\alpha = 0.05$) was estimated to be 12 and 21 subjects (VP and CP, respectively) in each group (GPower software package, version 3.1.6, Kiel, Schleswig–Holstein, Germany). The Kolmogorov–Smirnov test was used to investigate the data distribution. Continuous

quantitative variables were expressed as mean ± standard deviation (SD) and categorical variables as absolute values and percentages. Subjective data (dyspnea and leg fatigue) were expressed as median ± [minimum − maximum]. The unpaired Student's *t*-test was used to compare the continuous quantitative variables between CAD-G and CG. Fisher's exact test was used to compare the categorical variables between groups and the situations after versus before treatment. Stepwise regression analysis was performed to determine the possible influence of group, medications, risk factors (hypertension and dyslipidemia) and number of vessels with stenosis after treatment on the main studied variables (HR, BP, VO_2, VE/VCO_2 slope, CP and VP). One-way ANOVA (followed by Tukey's post-hoc test) was performed after subdividing CAD-G according to the type of event and treatment to assess possible differences between subgroups. Pearson correlation analysis was applied to determine the relationships between CP or VP and peak VO_2, OUES, RPP and oxygen pulse. The probability of type 1 error occurrence was established at 5% for all tests ($p < 0.05$). SPSS (version 17.0, SPSS Inc., Chicago, Illinois, United States) was used to perform the statistical analysis.

Results

Of a total of 97 apparently healthy subjects, we excluded 52 subjects aged < 40 or > 65 years. Forty-five subjects were contacted and recruited for CG. In relation to CAD-G, 54 subjects were recruited; however, 12 were excluded after clinical examination because of BMI ≥ 30 kg/m² (n = 2), use of tobacco (n = 2), chronic obstructive pulmonary disease (n = 2), presence of cardiac arrhythmias (n = 2), uncontrolled systemic arterial hypertension (n = 1), restenosis after mechanical reperfusion (n = 2), and inability to perform the maximal standard exercise test (n = 1). Thus, our sample consisted of 87 men (45 in CG and 42 in CAD-G). It is important to emphasize that a preliminary analysis (one-way ANOVA) was performed by dividing CAD-G into subgroups according to the type event and treatment. There were no significant differences between subgroups pertinent to any of the studied variables; thus, we pooled the data of all patients in CAD-G.

The characteristics of CAD-G and CG are presented in Table 1. No significant difference was found between groups with regard to age ($p = 0.087$), height ($p = 0.318$), weight ($p = 0.165$), and BMI ($p = 0.222$). In relation to the clinical data of CAD-G before treatment, most patients had two vessels with stenosis (33%), and considering only the 41 subjects with stenosis, the vessel most affected was the anterior descending artery (78%). After treatment, most patients had one-vessel stenosis (48%), and considering only the 29 subjects with stenosis, the vessel most affected was the left circumflex artery (45%). Most subjects in CAD-G (76%) previously suffered a myocardial infarction and had been managed in the following ways: 1) only with standard medication (2%), 2) angioplasty (60%), and 3) CABG (14%). The remaining subjects in the experimental group had CAD with no previous myocardial infarction (24%) and had been managed with: 1) medication only (5%), 2) angioplasty (7%), and 3) CABG (12%) (Table 1). Of the 42 subjects in CAD-G, 15 had a past smoking history and none was diabetic; furthermore, 38 subjects were diagnosed with systemic arterial hypertension and 39 with dyslipidemia; both risk factors were managed pharmacologically. Of the 45 subjects in CG, three had a past smoking history and none had a diagnosis of diabetes, systemic arterial hypertension or dyslipidemia. None of the CG subjects used any prescribed medication (Table 1).

Table 2 shows the comparison between groups in relation to peak variables obtained during the maximal standard exercise test that preceded CPX. CAD-G had significantly lower values for HR ($p < 0.001$) and systolic BP ($p = 0.012$) compared with CG. In addition, CAD-G had significantly higher values for diastolic BP ($p = 0.016$) and symptoms of dyspnea and leg fatigue ($p < 0.001$ and $p = 0.008$, respectively) compared with CG. Furthermore, the occurrence of angina (reported by the patients) was present in only 5% of CAD-G (n = 2), whereas it was not present in any subjects in CG. ECG recordings revealed that 7% of CAD-G (n = 3) presented ST segment depression < 2 mm and 5% (n = 2) presented ST segment depression ≥ 2 mm; there was no abnormality in ECG in CG (Table 2).

During CPX, the maximum walking velocity obtained was significantly lower in CAD-G (6.2 ± 0.4 km/h, range: 5–7 km/h) than CG (7.1 ± 0.7 km/h, range: 6–8 km/h in CG) ($p < 0.001$); however, there were no significant differences with respect to maximum grade obtained between groups: 12.8 ± 4.9 % (range: 3.5–22 %) in CAD-G and 11.6 ± 5.6% (range: 1.5–21 %) in CG ($p = 0.311$). Key CPX variables and aerobic functional classification according to American Heart Association (AHA) guidelines[24] for CAD-G and CG are presented in Table 3. There were no significant differences in HR and BP between groups during rest. During peak effort, CAD-G had significantly lower values for VO_2 ($p < 0.001$), HR ($p < 0.001$), % of predicted maximum HR ($p < 0.001$), delta of HR ($p < 0.001$), systolic BP ($p < 0.001$), RPP ($p < 0.001$), oxygen pulse ($p = 0.008$), OUES ($p < 0.001$), CP ($p < 0.001$), and VP ($p < 0.001$) compared with CG. In addition, during peak effort, CAD-G had significantly higher values for diastolic BP ($p < 0.001$), the VE/VCO_2 slope ($p = 0.004$), symptoms of dyspnea and leg fatigue ($p = 0.008$ and $p < 0.001$, respectively) compared with CG. Furthermore, angina (reported by the patients) occurred only in 2% of CAD-G (n = 1) and was not present in any subjects in CG. There were no ECG abnormalities in either group (CAD-G and CG) during CPX (Table 3). With regard to the aerobic functional classification according to AHA guidelines[24], Table 3 shows that the majority of patients of CAD-G had a weak aerobic classification (53%), while in CG slightly more than half of subjects had a regular level of aerobic classification (53%).

Stepwise regression analysis was performed to determine the possible influence of group, medications, risk factors (hypertension and dyslipidemia), and number of vessels with stenosis after treatment on CPX variables of interest. We found that none of the variables were affected by risk factors. However, the following influences were determined: 1) peak VO_2 was influenced by group and medications (interaction effects: $R^2 = 0.46$, β of group = 0.95 and β of medications = −0.35, $p < 0.001$); 2) peak systolic BP was influenced only by medications ($R^2 = 0.11$, β = 0.34, $p < 0.001$); 3) the

Table 1 – Characteristics of CAD-G and CG

	CAD-G (n = 42)		CG (n = 45)	p value
Age, years	54.3 ± 6.6		53.9 ± 6.4	0.087
Anthropometry				
Height, m	1.70 ± 0.07		1.73 ± 0.13	0.318
Weight, kg	79.0 ± 12.3		76.9 ± 9.9	0.165
Body mass index, kg/m^2	27 ± 3.9		26 ± 5.9	0.222
Cardiac function				
LVEF, %	63.9 ± 7.1		-	-
Vessels with stenosis, n (%)	**Before treatment (n = 42)**	**After treatment (n = 42)**		
Without stenosis	1 (2)	13 (31)	-	< 0.001
One diseased vessel	10 (24)	20 (48)	-	0.039
Two diseased vessels	14 (33)	6 (14)	-	0.071
Three diseased vessels	8 (19)	3 (7)	-	0.194
Multivessel (> 3 diseased vessels)	9 (22)	0	-	0.002
Location of stenosis (> 50%), n (%)	**Before treatment (n = 41)**	**After treatment (n = 29)**		
Anterior descending artery	32 (78)	8 (28)	-	< 0.001
Left circumflex artery	26 (63)	13 (45)	-	0.147
Right coronary artery	24 (58)	10 (34)	-	0.056
Diagonal arteries	8 (19)	6 (21)	-	1.000
Marginal arteries	4 (10)	1 (3)	-	0.394
CAD characteristics, n (%)				
With myocardial infarction				
Treated only with medication	1 (2)		-	-
Treated with angioplasty	25 (60)		-	-
Treated with CABG	6 (14)		-	-
Without myocardial infarction				
Treated only with medication	2 (5)		-	-
Treated with angioplasty	3 (7)		-	-
Treated with CABG	5 (12)		-	-
Risk factors, n (%)				
History of smoking	15 (36)		3 (7)	< 0.001
Diabetes	0		0	-
Arterial hypertension	38 (90)		0	< 0.001
Dyslipidemia	39 (93)		0	< 0.001
Medications, n (%)				
Beta-blocker	37 (88)		-	-
ACE inhibitor	24 (57)		-	-
Diuretic	12 (29)		-	-
Lipid-lowering	39 (93)		-	-
Antiplatelet/ anticoagulant	42 (100)		-	-

Data are presented as mean ± SD or absolute values (%).
CAD-G: coronary arterial disease group; CG: control group, n: number of individuals; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; (-): not applicable; ACE: angiotensin converting enzyme. Unpaired Student's t-test and Fisher's exact test.

Table 2 – Peak variables obtained during maximal standard exercise testing for clinical evaluation in CAD-G and CG

	CAD-G (n = 42)	CG (n = 45)	p value
HR, bpm	144.9 ± 20.0	169.9 ± 19.1	< 0.001
Systolic BP, mmHg	175.7 ± 26.5	189.5 ± 22.3	0.012
Diastolic BP, mmHg	91.3 ± 11.8	85.0 ± 11.2	0.016
Symptoms of dyspnea (0–10)	7.0 [2 - 10]	4.0 [2 - 6]	< 0.001
Leg fatigue (0–10)	6.0 [0 - 10]	4.5 [2 - 5]	0.008
Angina, n (%)	2 (5)	0	0.230
ST segment depression < 2 mm, n (%)	3 (7)	0	0.108
ST segment depression ≥ 2 mm, n (%)	2 (5)	0	0.230

Data are presented as mean ± SD, median [minimum - maximum] or absolute values (%).
CAD-G: coronary artery disease group; CG: control group; n: number of subjects; HR: heart rate; BP: blood pressure. Unpaired Student's t-test and Fisher's exact test.

VE/VCO_2 slope was influenced only by group ($R^2 = 0.08$, $\beta = 0.30$, $p < 0.001$); 4) CP was influenced only by group ($R^2 = 0.44$, $\beta = 0.67$, $p < 0.001$); and 5) VP was influenced by group and number of vessels with stenosis after treatment (interaction effects: $R^2 = 0.46$, β of group = 0.62 and β of number of vessels with stenosis after treatment = −0.30, $p < 0.001$).

Figure 1 illustrates a significant correlation between both CP and VP and peak VO_2, considering the subjects by aerobic functional classification according to AHA guidelines[24]. For better visualization of Figure 1, only those with a weak (n = 22) and regular level of classification (n = 14) in CAD-G and only those with regular (n = 24) and good level of classification (n = 15) in CG were included in the statistical analysis and presented in this figure. With respect to CP, there was a strong positive correlation with peak VO_2 (Figure 1A, $r = 0.91$, $p < 0.001$), while VP showed a moderate positive correlation with peak VO_2 (Figure 1B, $r = 0.43$, $p < 0.001$). Figure 2 illustrates the significant correlations between CP and VP and other CPX indices (OUES, RPP, and oxygen pulse), considering the entire study cohort. CP exhibited a strong positive correlation with OUES (Figure 2A, $r = 0.75$, $p < 0.001$) and peak RPP (Figure 2C, $r = 0.74$, $p < 0.001$) and moderate positive correlation with peak oxygen pulse (Figure 2E, $r = 0.59$, $p < 0.001$); with regard to VP there was a moderate positive correlation with OUES (Figure 2B, $r = 0.55$, $p < 0.001$), peak RPP (Figure 2D, $r = 0.58$, $p < 0.001$) and peak oxygen pulse (Figure 2F, $r = 0.55$, $p < 0.001$).

Discussion

The main findings from this study were: 1) CAD patients without heart failure under current standard pharmacologic regimens, angioplasty, or surgical management had lower CP and VP values compared with CG; 2) the indices CP and VP correlated positively with VO_2 according to aerobic functional classification as per AHA guidelines[24]; and 3) the response of CPX and the metabolic, ventilator, and cardiovascular variables demonstrated lower functional capacity and poorer exercise response in subjects with CAD.

To the best of our knowledge, this is the first study to introduce CP and VP indices in the functional evaluation of subjects with CAD without heart failure compared with apparently healthy controls. Thus, our findings have a potential clinical relevance given that these indices may be used to assess the functional significance of the disease process. The potential advantage of CP and VP indices is that both are simple and noninvasive and synergistically combine singular indices related to cardiopulmonary integrity and health.

Sample characteristics

As listed in Table 1, the groups did not differ in terms of age; this is an important consideration as it is known that aging affects peak VO_2 [25,26]. In addition, we did not include obese individuals because they present with abnormal exercise responses unique to body habitus, which could have confounded our results[27,28]. We included patients with controlled systemic arterial hypertension and controlled dyslipidemia in CAD-G; however, we observed (using stepwise regression analysis) that these factors did not influence the CPX response.

Cardiopulmonary exercise testing (CPX)

CP and VP were lower in CAD-G than in CG; the same observation was applicable to the following peak variables obtained during CPX: VO_2, HR, % of predicted maximum HR, delta of HR, systolic BP, RPP, oxygen pulse, and OUES. Moreover, higher values of peak diastolic BP and the VE/VCO_2 slope were found in CAD-G. Pharmacologic management, such as angiotensin-converting enzyme inhibitors, diuretics, and particularly beta-blockers, may contribute to the exercise response because CAD-G presented with lower values of peak systolic BP, peak HR, and peak VO_2 in relation to CG during CPX. In addition, during the maximal standard exercise test performed with suspended pharmacological therapy, CAD-G presented with a higher peak HR (approximately 7%) than CPX, in which the subjects were undergoing pharmacological therapy. Although these medications may have influenced our results, they are considered standard of care therapy for these patients[29,30], and beta-blocker withdrawal can increase the risk of heart events[31]. Because VO_2 is present in the formula of CP and BP is present in the formula of CP and VP, it is important to consider that medications

Table 3 – Variables obtained during cardiopulmonary exercise testing and aerobic functional classification according to AHA guidelines in CAD-G and CG

	CAD-G (n = 42)	CG (n = 45)	p value
Rest			
HR, bpm	65.9 ± 11	69.7 ± 11	0.110
Systolic BP, mmHg	120.7 ± 10.7	117.4 ± 18.7	0.298
Diastolic BP, mmHg	82.6 ± 7.6	79.7 ± 9.6	0.103
Peak			
VO_2, ml.kg^{-1}.min^{-1}	22.9 ± 4.8	32.7 ± 6.6	< 0.001
RER	1.11 ± 0.07	1.12 ± 0.08	0.738
HR, bpm	135.4 ± 22.2	165.0 ± 18.7	< 0.001
% of predicted maximum HR	81.8 ± 13.4	97.7 ± 9.9	< 0.001
Delta of HR, bpm	52.7 ± 23.1	85.2 ± 20.7	< 0.001
Systolic BP, mmHg	169.8 ± 24.6	186.1 ± 19.8	< 0.001
Diastolic BP, mmHg	88.3 ± 9.9	80.1 ± 10.7	< 0.001
RPP, mmHg.bpm	23052 ± 4889	30713 ± 4800	< 0.001
Oxygen pulse, mL/beat	13.5 ± 2.9	15.4 ± 3.8	0.008
VE/VCO_2 slope	31.6 ± 5.2	28.6 ± 4.4	0.004
OUES	1963 ± 449.7	2555 ± 552	< 0.001
CP, mmHg.ml.kg^{-1}.min^{-1}	3902 ± 1016	6099 ± 1403	< 0.001
VP, mmHg	5.5 ± 1.2	6.6 ± 1.3	< 0.001
Symptoms of dyspnea (0–10)	6.0 [4 - 8]	4.5 [2 - 5]	0.008
Leg fatigue (0–10)	7.0 [4 - 9]	4.5 [2 - 6]	< 0.001
Angina, n (%)	1 (2)	0	0.230
ST segment depression < 2 mm, n (%)	0	0	-
ST segment depression ≥ 2 mm, n (%)	0	0	-
Aerobic functional classification, n (%)			
Very weak	6 (14)	1 (2)	0.052
Weak	22 (53)	3 (7)	< 0.001
Regular	14 (33)	24 (53)	0.083
Good	0	15 (33)	< 0.001
Excellent	0	2 (5)	0.494

Data are presented as mean ± SD, median [minimum - maximum] or absolute values (%).
CPX: cardiopulmonary exercise testing; AHA: American Heart Association; CAD-G: coronary artery disease group; CG: control group; n: number of subjects; HR: heart rate; BP: blood pressure; VO_2: oxygen uptake; RER: respiratory exchange ratio; % of predicted maximum HR: % of 220 minus age; Delta of HR peak HR minus HR at rest; RPP: rate-pressure product; VE/VCO_2 slope: linear relation between minute ventilation, and carbon dioxide production; OUES: linear relationship between oxygen uptake and minute ventilation, CP: circulatory power; VP: ventilatory power. Unpaired Student's t-test and Fisher's exact test.

influenced peak VO_2 and peak systolic BP (as indicated by stepwise regression analysis), but did not influence CP and VP. Furthermore, the group influenced peak VO_2, the VE/VCO_2 slope, CP, and VP, while the number of vessels with stenosis after treatment influenced the VP. Thus, we believe that the lower values of CP and VP observed during CPX in CAD-G are related to standard medications, level of aerobic capacity and characteristics of CAD and that the reduction of VP in this population may also be related to number of vessels with stenosis after treatment.

One way to quantify exercise performance is by measuring peak VO_2. In the present study the lower values of this variable observed in CAD-G reinforce the role of CAD in a worse CPX response[10], which was also directly related to the ventilatory inefficiency observed in this group (higher VE/VCO_2 slope and lower OUES). High values of the VE/VCO_2 slope are often related to a worsening pulmonary hemodynamic profile and increased chemoreceptor and ergoreceptor activation, as well as decreased autonomic modulation and cardiovascular function[7]. Lower OUES

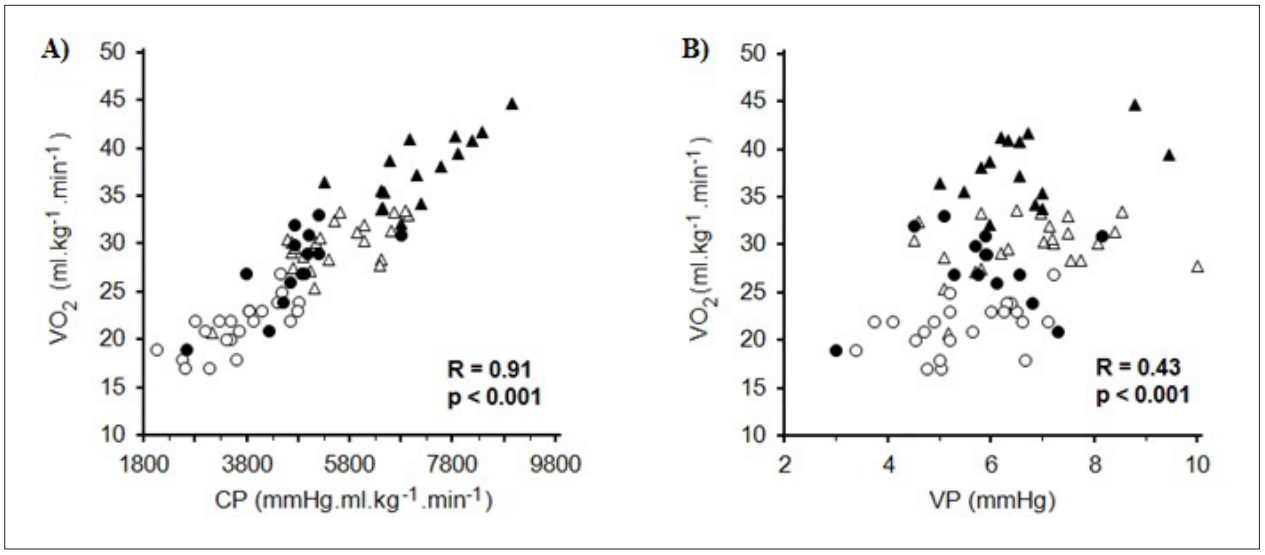

Figure 1 – *Circulatory power (CP) and ventilatory power (VP) correlated with oxygen uptake (VO_2) by aerobic functional classification according to American Heart Association guidelines. Legend: (o) coronary artery disease group (CAD-G) with weak functional classification, (•) CAD-G with regular functional classification, (Δ) control group (CG) with regular functional classification and (▲) CG with good functional classification. Pearson correlation analysis.*

values indicate that the extraction and utilization of oxygen is impaired because this variable is strongly correlated to VO_2 [3,4,10]. Furthermore, we observed in the present study that RPP and oxygen pulse were lower in CAD-G at peak CPX. RPP has been used as a relevant parameter in evaluating ventricular function, and high values at peak exercise are most likely related to good ventricular function and no ischemia[32,33]. In addition, the oxygen pulse indicates the amount of oxygen consumed per heart beat, which reflects the efficiency of the cardiovascular system and may provide prognostic information in patients with CAD[34,35].

Another interesting and novel finding of this study was that subjects with a lower peak VO_2 presented with lower indices CP and VP that correlated with the aerobic functional classification according to AHA guidelines[24]. A recent prospective study[36] that evaluated the associations between exercise test parameters and all-cause mortality in patients without previous cardiovascular disease showed that poor exercise tolerance (determined by the observed duration of exercise in relation to the predicted duration) is associated with greater mortality risk. In our cross-sectional comparative study we observed that CP and VP positively correlated (strong and moderate correlation, respectively) with aerobic functional classification evaluated by peak VO_2.

Cohen-Solal et al. (2002)[12] longitudinally evaluated (mean follow-up 25 ± 10 months) 175 heart failure patients who were subjected to an incremental CPX. Their study showed that CP was predictive of prognosis and that the combination of VO_2 and systolic BP (through the CP index) strengthens the prognostic value of CPX, particularly in subjects with low peak VO_2 and peak BP. Similar to the previous report, Forman et al. (2012)[16] evaluated the prognostic use of VP in a longitudinal study (mean follow-up 4 years) with 875 heart failure patients submitted to CPX. The authors showed that VP was independently predictive of cardiac events compared with standard CPX indices (i.e., peak VO_2 and the VE/VCO_2 slope); furthermore, in a multivariate analysis, combined CP and VP provided even better prognostic discrimination. Although traditional variables obtained by CPX, such as VO_2, systolic BP, and the VE/VCO_2 slope, reflect the aerobic capacity, hemodynamic control and carbon dioxide production eficiency efficiency, respectively, CP and VP are indices that combine these variables. VP, as an index that combines systemic hemodynamics with carbon dioxide production efficiency during exercise, and CP as an index that combines central and peripheral components of cardiac stroke work, appear to both portend important information regarding disease severity and prognosis[12,16,37].

Recently, Borghi-Silva el al (2014)[37] assessed the relationship between VP and key measures obtained using Doppler echocardiography in patients with heart failure and reduced ejection fraction; their results showed that lower values of VP translate into a very unfavorable phenotype characterized by a lower peak VO_2 and cardiac output response. The current study is a cross-sectional analysis with the goal of characterizing these indices in a CAD cohort under current standard pharmacologic regimens, angioplasty, or surgical management without heart failure. Our findings demonstrate that CP and VP are abnormal in CAD patients compared with healthy controls, and are related not only to standard medication but also to the level of aerobic capacity and characteristics of CAD; moreover, VP is related to the number of vessels with stenosis after treatment. Future work is needed to determine the prognostic utility of CP and VP in patients with CAD and establish whether both indices perform similarly to what has been found in patients with heart failure[12,14,16].

Study limitations

This investigation is characterized by an initial exploration of CP and VP indices in males with CAD; however, it has some limitations. First, although the literature[12,16,37]

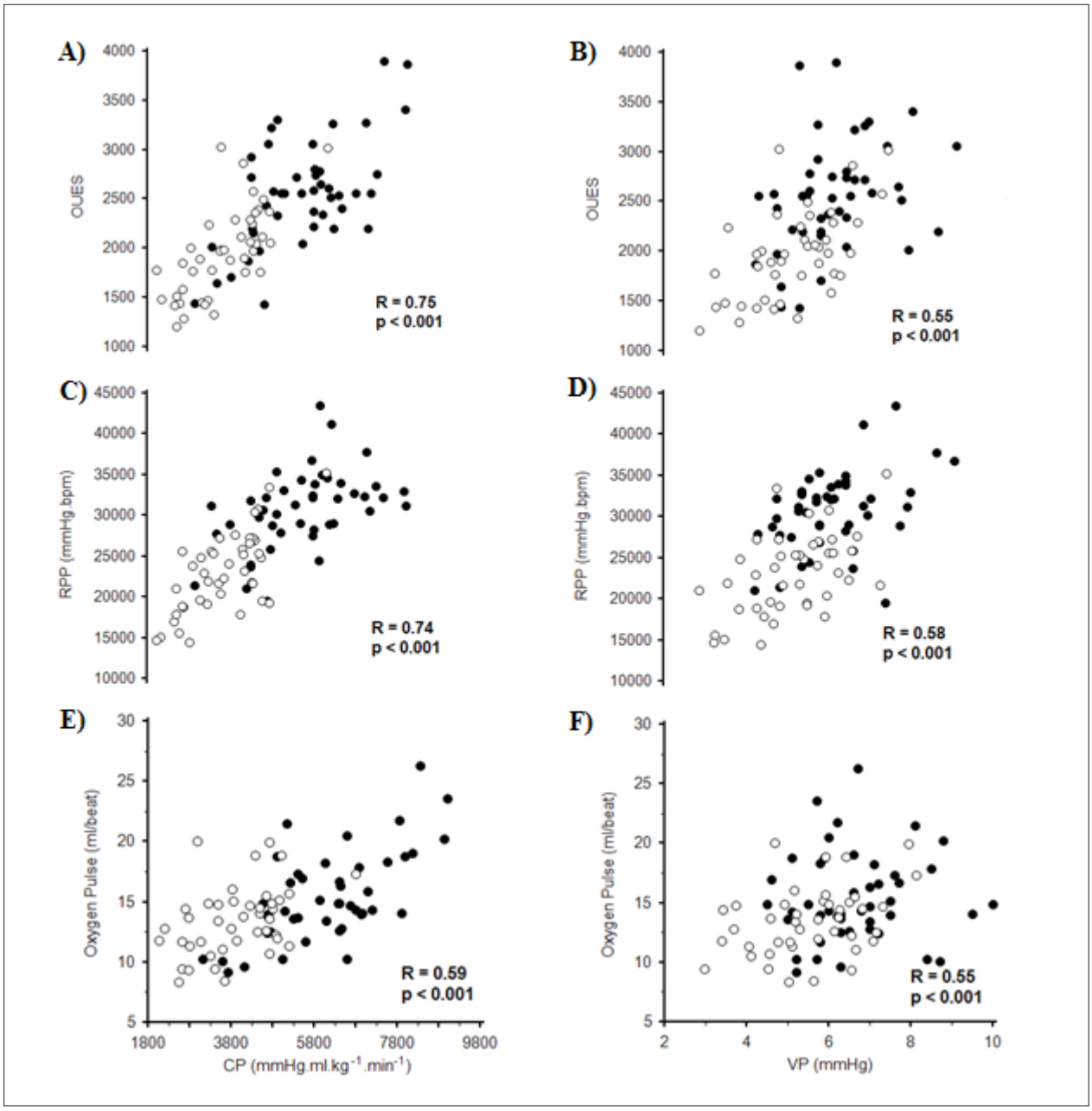

Figure 2 – *Circulatory power (CP) and ventilatory power (VP) correlated with OUES, RPP and oxygen pulse. Legend: (o) coronary arterial disease group (CAD-G), (•) control group (CG), OUES linear relationship between oxygen uptake and minute ventilation, RPP rate-pressure product. Pearson correlation analysis.*

indicates that CP and VP appear to be important prognostic markers in patients with heart failure, the cross-sectional nature and relatively small sample size of the current study did not allow us to expand upon prognostic utility. Therefore, additional prospective evaluations in this population are needed to determine the usefulness of these indices as prognostic markers. In relation to cardiac function, the CAD group was characterized only by left ventricular ejection fraction because 50% of patients were evaluated by ventriculography and 50% by echocardiogram. Women were not included in this study because the selected age could include both women with regular menstrual cycle (with and without use of contraceptives) and women in the postmenopausal stage (with and without use of hormone replacement therapy) and these differences could influence our results[38,39]. Although the pharmacologic management of systemic arterial hypertension by angiotensin converting enzyme inhibitors, diuretics, and particularly beta-blockers may have influenced the behavior of CP and VP (as well as of other indices obtained from CPX), medication cessation is not possible because it is mandatory therapy for some patients. Future studies including a control group of systemic

arterial hypertension patients without CAD (with similar pharmacologic management to our study) could eliminate the possible influence of medications on studied variables.

Conclusions

The CP and VP indices were lower in men with CAD, without heart failure, and under current standard pharmacologic regimens, angioplasty, or surgical management than healthy controls, demonstrating a poorer cardiopulmonary function in this population. Our results suggest that both CP and VP may hold value as screening tools in assessing the functional significance of disease, exercise tolerance, and may consequently assist in the prescription of physical training in this population when used individually or complementarily to other indices currently attained by CPX. In fact, a multivariate approach including indices related to both central and peripheral function would likely provide a more comprehensive evaluation of exertional physiology. Future investigations are needed to evaluate if lower CP and VP values are due only to the CAD or to the use of standard pharmacologic regimens, as well as to verify the prognostic value of these indices in this patient population.

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Author contributions

Conception and design of the research:Castello-Simões V, Catai AM. Acquisition of data:Castello-Simões V, Minatel V, Karsten M, Simões RP, Perseguini NM, Milan JC, Neves LMT. Analysis and interpretation of the data: Castello-Simões V, Minatel V, Karsten M, Simões RP, Perseguini NM, Milan JC, Arena R, Neves LMT, Catai AM. Statistical analysis: Castello-Simões V, Minatel V, Karsten M, Simões RP, Neves LMT, Borghi-Silva A. Obtaining financing: Castello-Simões V, Karsten M, Perseguini NM, Catai AM. Writing of the manuscript:Castello-Simões V, Karsten M, Simões RP, Catai AM. Critical revision of the manuscript for intellectual content: Castello-Simões V, Simões RP, Arena R, Borghi-Silva A, Catai AM.

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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