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ORIGINAL ARTICLE

Arterial Stiffness is Related to Impaired Exercise Capacity in Patients With Coronary Artery Disease and History of Myocardial Infarction

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Background Augmented arterial stiffness and reduced cardiorespiratory fitness are associated with increased morbidity and mortality from coronary artery disease (CAD). The relationship between exercise capacity and arterial stiffness is independent of known influencing variables in CAD. This study aimed to analyse the interaction between exercise capacity, arterial stiffness and early vascular ageing in patients with CAD.

Methods This cross-sectional study included 96 CAD patients with myocardial infarction (55.9 ± 10.9 years, 81 men) referred to cardiac rehabilitation. Arterial stiffness was assessed using carotid-femoral pulse wave velocity (cf-PWV). Cardiopulmonary exercise test was performed to measure VO_2peak. Comparisons of VO_2peak across cf-PWV risk threshold values (high-risk cf-PWV $\geq$ 10 m/s) and tertile groups, and across cf-PWV threshold values and age groups (younger group<60 years) were performed. Correlation tests were used to study the association between pair of variables.

Results Patients with high-risk cf-PWV had lower VO_2peak than those with low-risk cf-PWV ($p < 0.001$). VO_2peak decreased across tertiles of cf-PWV, showing significantly lower values in the third tertile ($p < 0.001$). There were no differences in the VO_2peak between younger patients with high-risk cf-PWV and older patients irrespective of their cf-PWV values. VO_2peak showed an upward trend in younger patients with low-risk cf-PWV compared to their age-mates with high-risk cf-PWV ($p = 0.09$). VO_2peak was strongly and inversely correlated with cf-PWV ($r = -0.502$, $p < 0.001$).

Conclusions Arterial stiffening is associated with lower cardiorespiratory fitness in CAD patients with myocardial infarction. When its values are above risk threshold, exercise capacity is impaired regardless of the relationship between age and arterial stiffness.

Keywords Arterial stiffness • Exercise capacity • Vascular ageing • Coronary artery disease • Pulse wave velocity

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Introduction

Coronary artery disease (CAD) is the leading cause of mortality among cardiovascular diseases (CVD), accounting for around 20% of CVD deaths in Europe [1]. Although mortality rates have decreased over the past 25 years, almost 17 million European men (41% of all CVD) and just over 13 million European women (30% of all CVD) were living with CAD in 2015 [1]. This raised CAD morbidity has increased the demands on the health care system.

Arterial stiffness, a measure of the elastic properties of large arteries and wave reflection, has been recommended in the assessment of cardiovascular risk [2]. Arterial stiffening is characterised by adverse functional and structural changes within the vessel wall, including extracellular matrix degeneration, collagen deposition and cross-linking, elastin depletion and fragmentation, infiltration of vascular smooth muscle cells, macrophages and mononuclear cells, inflammation and endothelial dysfunction [3]. It reduces the cushioning function of the arterial system, leading to increased aortic systolic pressure and pulse pressure, and thereby increased left ventricular afterload and myocardial workload, left ventricular hypertrophy and myocardial oxygen demand [4]. In addition, the increased velocity of the forward pressure wave, which stems from aortic stiffening, promotes an earlier arrival of the reflected pressure wave during systole instead of diastole, resulting in reduced diastolic coronary perfusion pressure and myocardial oxygen delivery, in addition to increased systolic blood pressure and cardiac afterload [5]. Consequently, the mismatch between increased oxygen demand and reduced oxygen delivery may lead to increased predisposition of subendocardial myocardial fibres to ischaemia [6], which, together with atherosclerosis, may increase the risk of adverse cardiovascular events. Indeed, increased arterial stiffness is an independent predictive factor of cardiovascular events and mortality from CVD [7].

Exercise capacity is also an important prognostic factor in patients with CAD. Among others, vascular properties are involved in the functional limitation of cardiac patients [8]. Increased arterial stiffness contributes to exercise-induced myocardial ischaemia [9], due to coronary perfusion insufficiency in response to the increased myocardial oxygen demand during exercise [10]. This may lead to impaired exercise tolerance and decreased cardiorespiratory fitness, a strong independent risk factor of all-cause and cardiovascular mortality in healthy adults and patients with CVD [11]. The inverse association between arterial stiffness and cardiorespiratory fitness has been demonstrated in young and older adults [12,13] and hypertensive middle-aged and elderly men [14]. Moreover, several studies have shown that age-related increases in arterial stiffness are attenuated in adults with higher cardiorespiratory fitness [15].

However, even though arterial stiffness is increased and cardiorespiratory fitness is reduced in patients with CAD, and both are associated with increased morbidity and mortality [16], the association between arterial stiffening and cardiorespiratory fitness in CAD patients is not entirely clear. Whether the association between exercise capacity and arterial stiffness is independent of known influencing variables in patients with cardiac disease including CAD has not yet been fully determined. Therefore, the aim of this study was to analyse the interaction between exercise capacity and arterial stiffness in patients with CAD.

Material and Methods

Participants

One-hundred patients aged 18 or over followed at the Cardiology Department of the Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal, due to an acute myocardial infarction, were consecutively recruited from February 2011 to July 2012 to this study. At the time of hospital discharge, a cardiologist explained the study details and asked all the patients with an acute myocardial infarction and complying with our inclusion/exclusion criteria to participate. Two hundred and fifty-six (256) patients were assessed for eligibility and 156 were excluded based on the following exclusion criteria: uncontrolled hypertension, uncontrolled cardiac arrhythmias, unstable angina pectoris, significant valvular disease, diagnosis of heart failure, uncontrolled metabolic disease, presence of pulmonary and renal co-morbidities. All patients were assessed one month after the acute event and before starting a cardiac rehabilitation program. Patients who agreed to participate provided written informed consent. The Hospital Ethics Committee granted ethical approval (reference 627/2010), all procedures were conducted according to the Declaration of Helsinki.

Procedures

Medical history, clinical data, medication and demographic data was abstracted from clinical files and confirmed with the patient. When invited to participate in the study, the examiner instructed the patients to avoid strenuous exercise, caffeinated products, and alcohol consumption for at least 24 hours and to not smoke or eat for at least 3 hours before evaluation. All the assessments were conducted in one morning.

Height, body mass and percentage of fat mass were evaluated with a stadiometer and a body composition analyzer (Tanita Inner Scan BC-522, Tokyo, Japan), respectively.

Daily physical activity was assessed during 7 consecutive days with an accelerometer (Actigraph GT1M, ActiGraph, LLC, Pensacola, FL, USA); a detailed description of physical activity assessment is provided in previous studies.

Exercise capacity was assessed during a maximal or symptom-limited treadmill exercise test using the modified Bruce protocol. Pulmonary gas exchange analysis was performed throughout the exercise protocol with an ergospirometry device (Cardiovit CS-200 Ergo Spiro; Schiller, Baar, Switzerland). VO_2 peak was defined as the highest VO_2 achieved by the patient during the test; values for VO_2 were indexed to body weight.

Arterial stiffness-related indexes were obtained by applanation tonometry with a system (Sphygmocor System, AtCor Medical, Sydney, NSW, Australia). Carotid femoral pulse wave velocity (cf-PWV), the gold standard for arterial stiffness measurements, was measured according to the recommendations [17]. All measurements were conducted by the same trained researcher. In brief, sequential and consecutive right carotid and femoral pressure waves were registered with parallel electrocardiogram recording. We measured the direct straight distance between the two measurement sites with a tape and then used 80% of this distance to determine the pulse wave travelled distance. cf-PWV was calculated as the distance travelled (in metres) by the pressure wave divided by the transit time in seconds. The mean of two measurements was taken for analysis; if the difference between the two measurements was >0.5 m/s, a third measurement was taken and the median value was used for analysis.

Statistical Analysis

Statistical analysis was carried out with IBM SPSS software 23.0 (SPSS Inc., Armonk, NY, USA). Data are presented as means ± SD or median (25–75th percentile), as appropriate. Pearson and Spearman's bivariate correlation test was used to analyse the association between two variables. Continuous variables with non-normal distribution (cf-PWV, augmentation index adjusted to 75 bpm and moderate to vigorous physical activity) were transformed to their square root before statistical analysis, but for clarity reasons they were presented in their original scale. The cut-off value of 10 m/s was used for cf-PWV, above which there is an increased risk for cardiovascular events [18]. Comparisons of cardiorespiratory fitness across cf-PWV threshold values and tertile groups were performed through the Student's independent t-test and one-way ANOVA, respectively. Comparisons of cardiorespiratory values across cf-PWV risk threshold values and age groups (ageing x cf-PWV risk threshold) were performed through the general linear model. When a significant ageing x cf-PWV risk threshold interaction was observed, post hoc analysis was performed to ascertain the differences between groups. Ageing groups were divided in younger (< 60 years of age) and older adults (≥60 years of age) for the purpose of analysis. Statistical significance was set at $p < 0.05$ for all tests.

Results

Patient's characteristics are shown in Table 1. One patient was excluded from the study because he was diagnosed with heart failure after recruitment, and three patients were not included in the analysis since cf-PWV analysis was not possible in these patients. A total of 96 patients were analysed. There were no differences between males and females in cf-PWV (9.3 ± 2.4 vs. 9.6 ± 2.2 m/s). Also, no differences were found in cf-PWV between patients with diabetes, hypertension and obesity and those without these cardiovascular risk factors.

Table 1 Patient's characteristics.

Age (years)	55.9 (10.9)
Male	81 (84.4%)
Weight (kg)	75.3 (10.3)
BMI (kg/m^2)	27.1 (3.2)
Type 2 diabetes	22 (22.9%)
Currently smoking	47 (49%)
Hypertension	90 (93.8%)
Anterior MI	39 (40.6%)
One vessel	77 (80.2%)
Two vessels	18 (18.8%)
PTCA	86 (89.6%)
CABG	4 (4.2%)
ACEi	87 (90.6%)
Beta blockers	91 (94.8%)
Statins	86 (89.6%)
Angiotensin II antagonists	1 (1.1%)
Nitrates	11 (11.5%)
Diuretics	8 (8.3%)
Calcium channel blockers	6 (6.3)
LVEF (%)	53.7 (8.3)
VO_2peak (mlO_2.kg^{-1}.min^{-1})	27.1 (3.2)
cf-PWV (m/s)	8.7 (7.7-10.7)

Data are mean (SD), number (%) or median (interquartile range). Criteria for: diabetes are based on fasting blood glucose level >125 mg/dL or current treatment with insulin or oral antidiabetic agents; hypertension are based on seated blood pressure >140/90 mm Hg or antihypertensive treatment; obesity are based on body mass index ≥30 kg/m2.
Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; BMI, body mass index; cf-PWV, carotid-femoral pulse wave velocity; CABG, coronary artery bypass grafting; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

No differences in demographic characteristics of the patients were found across tertiles of cf-PWV, except for age (Table 2). Cardiorespiratory fitness decreased across tertiles of cf-PWV (Figure 1). VO_2peak in the third tertile was significantly lower compared with the second and first tertiles (23.3 ± 4.9 vs. 28.3 ± 5.5 and 31.3 ± 6.8 mlO_2.kg^{-1}.min^{-1}, $p < 0.001$). No significant differences were found in VO_2peak between first and second tertiles ($p = 0.13$). Differences remained statistically significant after adjustment for age, gender, traditional cardiovascular risk factors, including hypertension, total time spent in physical activity and time spent in moderate to vigorous physical activity ($p < 0.05$). Thirty (30) patients (31.3%) presented cf-PWV values over the high-risk threshold of 10 m/s, among which 8 (8%) were younger adults whereas 22 (29%) belonged to the older adults group. Patients with high-risk cf-PWV were older compared with those with low-risk cf-PWV (< 10 m/s) (64.0 ± 8.6 vs. 51.9 ± 9.7 years, $p < 0.001$). In addition, patients with baseline high-risk cf-PWV also had significantly lower VO_2 peak than those with low-risk cf-PWV (23.0 ± 4.7 vs. 29.8 ± 6.2 mlO_2.kg^{-1}.min^{-1}, $p < 0.001$, Figure 2); differences remained

Table 2 Characteristics of patients across the tertile groups of cf-PWV.

	Tertile 1 (*n* = 32)	Tertile 2 (*n* = 32)	Tertile 3 (*n* = 32)	P-value
Age (years)	46.9 (7.8)	56.8 (9.0)[a]	63.9 (8.5)[a,b]	<0.0001
Men	28 (87.5%)	28 (87.5%)	25 (78.1%)	0.491
Weight (kg)	77.6 (11.3)	73.4 (8.9)	74.9 (10.3)	0.250
BMI (kg/m^2)	27.2 (3.8)	26.8 (2.8)	27.3 (3.0)	0.775
Diabetes	4 (12.5%)	8 (25.8%)	10 (31.3%)	0.188
Hypertension	30 (93.8%)	29 (93.5%)	31 (96.9%)	0.801
Smokers	21 (65.6%)	21 (65.6%)	11 (34.4%)	0.011
Obesity	8 (25.0%)	11 (35.5%)	11 (40.6%)	0.403
1 vessel disease	26 (81.3%)	27 (87.1%)	24 (75.0%)	0.472
2 vessels disease	6 (18.8%)	4 (12.9%)	8 (25.0%)	0.472
PTCA	30 (93.8%)	27 (87.1%)	29 (90.6%)	0.666
CABG	0 (0.0%)	1 (3.2%)	3 (9.4%)	0.166
Statins	27 (84.4%)	30 (96.8%)	29 (90.6%)	0.244
ACEi	29 (90.6%)	27 (87.1%)	31 (96.9%)	0.366
ARA	0 (0.0%)	1 (3.2%)	0 (0.0%)	0.352
Nitrates	4 (12.5%)	4 (12.9%)	3 (9.4%)	0.891
Diuretics	2 (6.3%)	3 (9.7%)	3 (9.4%)	0.852
CCB	2 (6.3%)	2 (6.5%)	2 (6.3%)	0.999
Total PA (min/week)	1,855.7 (914.8)	1,704.8 (762.7)	1,832.6 (829.0)	0.757
Light PA (min/week)	1,593.6 (818.9)	1,520.1 (691.9)	1,667.4 (772.9)	0.765
MVPA (min/week)	231 (72.0–386.0)	167 (86.0–232.5)	91 (31.5–269.5)	0.056
cf-PWV (m/s)	7.25 (7.1–7.7)	8.7 (8.4–9.1)[a]	11.5 (10.7–13.6)[a,c]	<0.0001

Data are mean (SD), number (%) or median (interquartile range). Criteria for: diabetes are based on fasting blood glucose level >125 mg/dL or current treatment with insulin or oral antidiabetic agents; hypertension are based on seated blood pressure >140/90 mm Hg or antihypertensive treatment; obesity are based on body mass index ≥30 kg/m2.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; BMI, body mass index; ARA, angiotensin-II receptor antagonists; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; cf-PWV, carotid-femoral pulse wave velocity; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MV; moderate to vigorous; PA, physical activity; PTCA, percutaneous transluminal coronary angioplasty.

[a]Significantly different than tertile 1, $p < 0.001$.

[b]Significantly different than tertile 2, $p = 0.004$.

[c]Significantly different than tertile 2, $p < 0.001$.

statistically significant after adjusting for age, as well as gender, cardiovascular risk factors, and medication. We then analysed the effect of age and cf-PWV on cardiorespiratory fitness (Figure 3). Younger patients with low-risk cf-PWV showed significantly higher values of VO_2peak than the older counterparts with high-risk cf-PWV ($p < 0.05$). There was also a tendency for younger patients with low-risk cf-PWV to show higher cardiorespiratory fitness than younger patients with high-risk cf-PWV (30.8 ± 6.4 vs. 25.5 ± 5.5 mLO_2.kg^{-1}.min^{-1}, $p = 0.09$). However, there were no differences between the younger patients with high-risk cf-PWV and the groups of older patients with low-risk and high-risk cf-PWV (25.5 ± 5.5 vs. 26.8 ± 4.6 vs. 22.2 ± 4.1 mLO_2.kg^{-1}.min^{-1}, $p > 0.05$). Additionally, cf-PWV was strongly associated with age ($r = 0.675$, $p < 0.001$, Figure 4a) and VO_2peak was strongly and inversely correlated with cf-PWV ($r = -0.502$, $p < 0.001$, Figure 4b), systolic blood pressure and augmentation index adjusted to 75 bpm (Aix@75) ($r = -0.474$, $p < 0.05$). In multivariate analysis, only age, Aix@75 and cf-PWV remained as significant predictors of VO_2peak (adjusted $r2 = 0.399$, $p < 0.001$)

Discussion

The main finding of the present study indicates that cardiorespiratory fitness is inversely associated with arterial stiffness in CAD patients who have suffered an acute myocardial infarction. In addition, patients with lower arterial stiffness showed higher cardiorespiratory fitness whereas patients with high-risk arterial stiffness values (i.e., cf-PWV ≥ 10 m/s) showed lower cardiorespiratory fitness. Finally, despite the association between ageing and arterial stiffness, there were no differences in cardiorespiratory fitness between younger patients with arterial stiffness values above risk threshold and older patients irrespective of arterial stiffness.

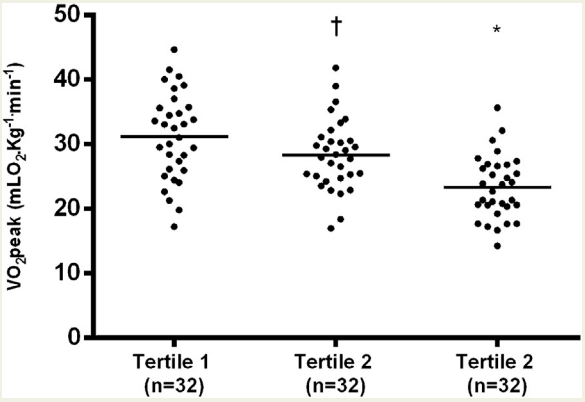

Figure 1 Values of VO_2peak across tertiles of cf-PWV. * Significantly lower than tertile 2, $p < 0.001$; † Significantly lower than tertile 1, $p < 0.01$.
Abbreviations: cf-PWV, carotid-femoral pulse wave velocity.

Association Between Cardiorespiratory Fitness and Arterial Stiffness

Several studies have shown an inverse association between arterial stiffness and cardiorespiratory fitness, however most of them were conducted in healthy subjects [13,19] and those with the largest samples were limited to young adults [19]. Decreased cardiorespiratory fitness is a strong and independent predictor of all-cause and cardiovascular mortality, myocardial infarction and downstream revascularisation in patients with CAD [20]. On the other hand, arterial stiffness is elevated and predicts ischaemic threshold in these patients [21]. It has been demonstrated that large artery stiffness is correlated with shorter time to myocardial ischaemia during exercise treadmill testing in patients with CAD [21]. Likewise, another study assessed the correlation between VO_2 peak during symptom-limited cardiopulmonary exercise testing and PWV measured through an oscillometric method in patients with CAD, and showed that patients with high arterial stiffness (PWV values above median) have shorter time to myocardial ischaemia and lower VO_2peak [22]. The results from the present study confirm and extend these previous observations by showing, for the first time in patients following myocardial infarction, that VO_2peak is lower in those with greater arterial stiffness independent of traditional cardiovascular risk factors. A number of reasons have been postulated to explain the relationship between arterial stiffness and cardiorespiratory stiffness, one of which is reduced coronary perfusion due to arterial stiffening, which predisposes patients to myocardial ischaemia and reduced exercise tolerance. Arterial stiffening also increases cardiac afterload and consequently myocardial oxygen demand, which may contribute to reduced cardiac output during peak exercise and thereby reduced cardiorespiratory fitness [6]. In addition, there is evidence that central arterial stiffness is inversely associated with absolute and relative muscle strength, which may also contribute to decreased exercise tolerance in these patients [23].

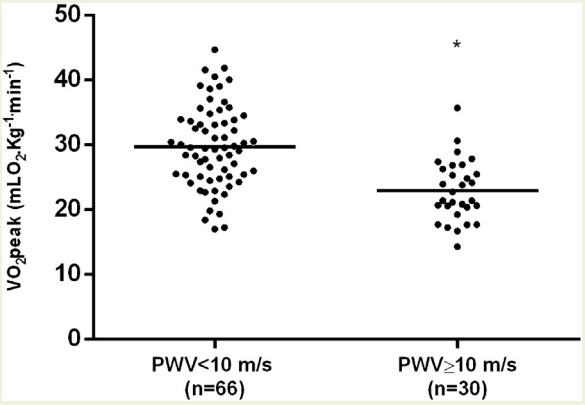

Figure 2 VO_2peak in CAD patients with high-risk and low-risk cf-PWV. * Significantly lower than CAD patients with low-risk cf-PWV, $p < 0.001$.
Abbreviations: cf-PWV, carotid-femoral pulse wave velocity; CAD, coronary artery disease.

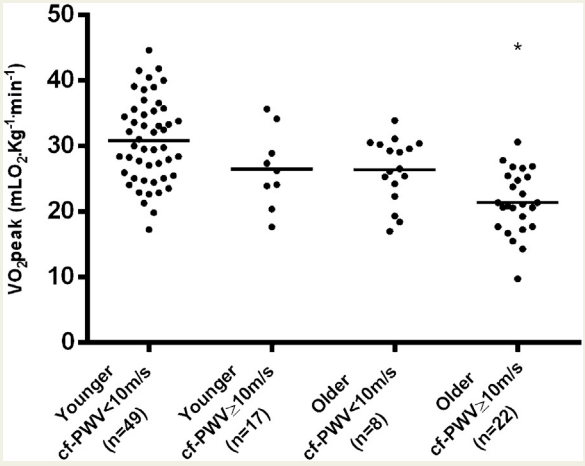

Figure 3 VO_2peak in younger and older CAD patients with high-risk cf-PWV (≥10 m/s) and low-risk cf-PWV (<10 m/s). * Significantly lower than younger patients with low-risk cf-PWV, $p < 0.05$.
Abbreviations: cf-PWV, carotid-femoral pulse wave velocity; CAD, coronary artery disease.

Ageing, Arterial Damage and Cardiorespiratory Fitness

Like many previous studies, arterial stiffness was associated with ageing, with one third of the patients in our study showing signs of increased cardiovascular risk related with arterial stiffening. The prevalence of patients with high-risk arterial stiffness in our study is higher than that reported by a previous study, but similar when age groups are considered [24]. In contrast to this work, which studied the distribution of pulse wave velocity in randomly sampled population

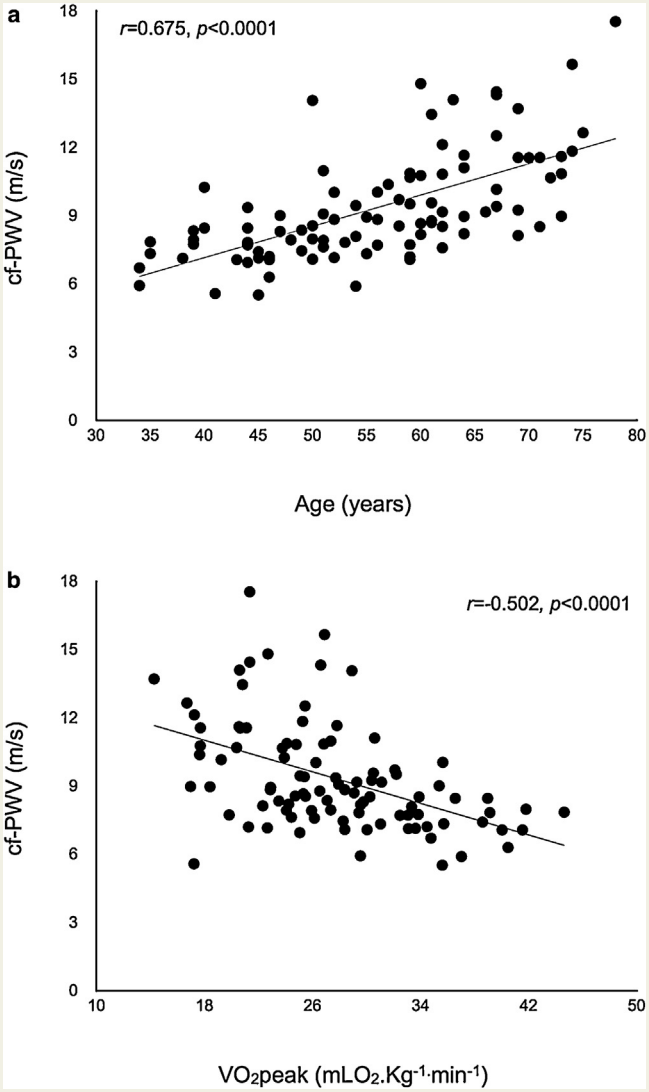

Figure 4 Association of cf-PWV with age (Figure 4a) and VO_2peak (Figure 4b).
Abbreviations: cf-PWV, carotid-femoral pulse wave velocity.

dwellers, we included an older population of CAD patients, which may have raised the overall prevalence of patients with high-risk arterial stiffness. In addition, we showed, for the first time, that patients with a high-risk cf-PWV have lower cardiorespiratory fitness, even after controlling for age, the presence of cardiovascular risk factors and medication. Notably, the younger patients in the high-risk group showed similar cardiorespiratory fitness compared to both groups of the older patients, indicating that increased arterial stiffness may compromise aerobic capacity and predispose younger patients with a history of myocardial infarction to secondary cardiovascular events and mortality. The role of increased cf-PWV as an independent risk marker for cardiovascular events and total mortality has been confirmed in a recent large meta-analysis, especially in middle-aged compared with older adults [25], suggesting that increased arterial stiffness in younger patients represents a differential biological vascular ageing process as compared to older ones [26]. This differential effect also suggests that the association between arterial stiffness, atherosclerosis and cardiorespiratory fitness is complex and not merely incidental. The process of vascular ageing is characterised by a number of adverse changes within the vascular wall that are involved both in atherosclerosis and arterial stiffening, including endothelial dysfunction, oxidative stress and low-grade vascular inflammation [27]. This may impair vasodilation and coronary artery oxygen delivery [6]. It has been demonstrated by several studies that increased arterial stiffness is related with impaired coronary blood flow reserve in CAD patients, even in fully revascularised patients [28]. Changes in arterial properties also increase left ventricular afterload requiring the left ventricle to generate additional useless energy, thereby increasing myocardial oxygen demand, which further reduces coronary flow reserve and increases predisposition

to ischaemia [29]. Arterial stiffness together with impaired coronary microcirculation and epicardial coronary stenosis deteriorate myocardial function, which can partially explain the deterioration found in cardiorespiratory fitness [7]. Moreover, higher aortic PWV is related to the prevalence, severity and composition of atherosclerotic plaques, in particular with intraplaque haemorrhage [30]. The presence of greater and more vulnerable atherosclerotic plaques may be related to the greater epidemiological risk of cardiovascular events and mortality observed in younger adults. Thus, assessment of arterial stiffness and cardiorespiratory fitness may be paramount for identifying CAD patients, especially the younger ones, at high risk of cardiovascular morbidity and mortality. In these cases, participation in cardiac rehabilitation programs can be important to reduce arterial stiffness and contribute to a better prognosis [31].

Limitations

The present study has a few limitations. Although this is, to the best of our knowledge, the largest study to date that assessed the relationship between arterial stiffness and cardiorespiratory fitness in CAD patients with a history of myocardial infarction, the sample size and the retrospective nature of the analysis precluded a balanced distribution of patients according to arterial stiffness and age groups. On the other hand, both arterial stiffness and cardiorespiratory fitness were assessed through gold-standard measures. Thus, future prospective studies are warranted to confirm these findings

Conclusions

In conclusion, arterial stiffening is associated with lower cardiorespiratory fitness in CAD patients and history of myocardial infarction, particularly in middle-aged adults.

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