Association between baseline cardiovascular mechanics and exercise capacity in patients with coronary artery disease

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Abstract

Objective: Functional capacity is one of the cardinal determinants of morbidity and mortality in patients with coronary artery disease (CAD). We hypothesized that baseline cardiovascular mechanics, including cardiac systolic and diastolic functions, arterial mechanics, and ventriculo-arterial interaction, may play a role in predicting exercise capacity in patients with CAD.

Methods: Fifty consecutive patients with CAD who were referred to cardiac rehabilitation were prospectively included in the study. Patients with non-sinus rhythms or severe valvular disease were excluded. Full left ventricular pressure–volume loops were constructed and arterial mechanics was evaluated using echocardiographic and tonometric measurements. Cardiopulmonary exercise tests were performed to measure exercise capacity.

Results: Fifty patients were enrolled in the study. Ventriculo-arterial coupling showed a moderate correlation with peak oxygen consumption (VO_2) (r=0.410, p=0.04) in patients with reduced left ventricular ejection fraction (LVEF). Only left ventricular volume at 15 mm Hg (r=0.514, p<0.01) in diastolic parameters (stiffness constant, p=0.75; ventricular compliance, p=0.17) and arterial compliance (r=0.467, p=0.01) in arterial parameters [arterial elastance, p=0.27; systemic vascular resistance, p=0.45; augmentation pressure, p=0.85; augmentation index (AIx), p=0.63; heart rate-corrected AIx, p=0.68] emerged as significant factors correlated with peak VO_2 in patients with normal LVEF.

Conclusion: Comprehensive evaluation of resting cardiovascular mechanics can give clues about exercise-recruited reserves of the cardiovascular system. Optimization of ventriculo-arterial coupling in patients with reduced LVEF and arterial compliance in patients with normal LVEF should be the main target in patients with CAD and limited functional capacity. *(Anatol J Cardiol 2016; 16: 608-14)*

Keywords: arterial compliance, cardiopulmonary exercise test, coronary artery disease, functional capacity, pressure–volume loop

Introduction

Functional capacity is one of the cardinal determinants of morbidity and mortality in patients with coronary artery disease (CAD) (1). Although coronary anatomy and left ventricular ejection fraction (LVEF) have been the main parameters of focus, the cause of functional limitation in patients with CAD is not necessarily limited to systolic, diastolic, or chronotropic characteristics of the heart and may also include vascular properties and other non-cardiovascular elements (2). For elucidating the underlying cause of functional limitation in a particular patient, one must be able to quantitatively assess all these factors.

Unfortunately, patients with functional limitation are generally assessed with non-stress tests that (a) are usually insensitive to reserves of the cardiovascular system and (b) almost completely ignore extra-cardiac parameters or the interaction between these parameters and the heart (3). Analysis of the pressure–volume (PV) loop and arterial wave propagation may theoretically overcome some of the abovementioned limitations, which can give load-independent measures of left ventricular contractility, complete diastolic PV relationship, ventriculo-arterial coupling, arterial stiffness, and pulsatile load. Recently, with the introduction of non-invasive, single-beat solutions and availability of arterial tonometry, it has become possible to assess all these parameters non-invasively (4, 5).

However, no study till date has used a comprehensive cardiovascular mechanics approach to seek the determinants of exercise capacity in patients with CAD. A limited number of stud-

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ies in patients with isolated CAD and extrapolations from heart failure cohorts with both reduced and preserved LVEF indicate that arterial compliance (6) and left ventricular systolic (7, 8) and diastolic functions (9–12) may be correlated with exercise capacity. However, these studies did not evaluate the whole set of cardiovascular mechanics and most of them only focused on one subgroup of patients with CAD, either with normal or abnormal LVEF.

We hypothesized that a comprehensive cardiovascular mechanics approach to patients with CAD with normal or abnormal LVEF may provide important insights into functional capacity limitation.

Methods

Study design

The study was conducted at Hospital Lariboisiere, a tertiary center for cardiac rehabilitation. The study included consecutive outpatients with functional capacity limitation and those with recent revascularization procedure who were referred to our laboratory for cardiac rehabilitation. Patients with non-sinus rhythms or severe valvular disease were excluded. Twenty-five patients with abnormal LVEF (<55%; Group I) and 25 patients with normal LVEF (≥55%; Group II) were included. The patients were under optimized, stable treatment, and medications were not withdrawn for the study. All patients gave their informed consent. The study was approved by the Local Ethics Committee. Routine blood chemistry was measured at the core laboratory of the hospital. Transthoracic echocardiography and arterial tonometry were performed just before the cardiopulmonary exercise test (CPET).

Echocardiography

Two-dimensional images and flow and tissue Doppler recordings were obtained for all patients using a transthoracic Doppler echocardiograph with a 3.5-MHz transducer (GE Vivid I or 7, Horten, Norway). Left ventricular volumes were calculated by modified Simpson's biplane method from the apical 4-chamber and 2-chamber views. Doppler recordings were obtained in the apical 4-chamber view by positioning the sample volume at the tips of the mitral leaflets. The sample volume was positioned at the medial mitral annulus in the apical 4-chamber view to measure early diastolic tissue Doppler velocity (E'). The diameter of the inferior vena cava and its percent change during inspiration were measured in the subcostal view for estimation of right atrial pressure (13). Systemic vascular resistance (SVR) was estimated as [(mean tonometric aortic pressure – right atrial pressure)/cardiac output] x 80 and expressed as dyne.s.cm^{-5}. Total arterial compliance (C_a) was calculated using the decay time method (14). The left ventricular diastolic PV relationship, diastolic stiffness constant (ß), diastolic volume corresponding to 15 mm Hg (V_{15}), and ventricular compliance (C_{vent}) were calculated as described previously (5).

Arterial tonometry

Radial pulse wave was recorded at rest by applanation tonometry (SphygmoCor Px PWA System, AtCor Medical, West Ryde, Australia) on the left radial artery and central aortic pressure wave was calculated by dedicated software using the wave transfer function. The SphygmoCor device provides a quality index that represents the reproducibility of the waveform. Only measures with a quality index of ≥80 were included in this study. Augmentation pressure was calculated as aortic systolic blood pressure minus the pressure at the first peak shoulder of the aortic pulse wave. Then, augmentation index (AIx) was defined as augmentation pressure divided by pulse pressure. AIx was corrected for a heart rate of 75 bpm using an inverse regression of 4.8% for each 10-bpm increment, as recommended by the manufacturer, and expressed as AIx@75. The modified single-beat method was used to estimate end-systolic elastance (E_{es}) (4). Arterial elastance (E_a) was estimated by dividing end-systolic pressure by the stroke volume (15). Ventriculo-arterial coupling was calculated by the E_{es}/E_a ratio. Zero intercept of the end-systolic PV relationship (V_0) was projected from E_{es}, end-systolic volume, and end-systolic aortic pressure.

Full left ventricular PV loops were constructed using echocardiographic and tonometric measurements as defined previously (4, 5). The cardiovascular mechanics parameters were grouped into 4 different subcategories as follows (Fig. 1): (a) systolic parameters (LVEF, E_{es}, and V_0), (b) diastolic parameters (V_{15}, ß, and C_{vent}), (c) vascular parameters [E_a, SVR, C_a, and wave reflection parameters (AP, AIx, and AIx@75)], and (d) ventriculo-arterial coupling (E_{es}/E_a).

CPET

CPET was performed on a bicycle ergometer with 10 W/min workload increments up to exhaustion (peak respiratory exchange ratio: >1.1) (16). Respiratory gas analysis involved use of an Oxycon Pro Jaeger (San Diego, CA, USA). VO_2, CO_2 production (VCO_2), and ventilation (V_E) were measured on a breath-by-breath basis. The percent predicted peak VO_2 was calculated as peak VO_2 divided by the maximal predicted peak VO_2 according to the values reported by Wasserman et al. (17). The anaerobic threshold was measured by classical methods (18). The V_E/VCO_2 slope was calculated by automatic linear regression fitting with the breath-by-breath values obtained during the entire exercise test from initiation to peak.

Statistical analysis

Baseline characteristics were summarized using standard descriptive statistics. Continuous variables were analyzed by the Shapiro–Wilk test for normality assumption in both groups, and normally distributed continuous variables were analyzed by independent samples t-test. The comparisons between groups were made using Fisher's exact test or chi-square test for categorical data as appropriate. Pearson's correlation analysis was used to explore the relationship between the change in peak VO_2 and

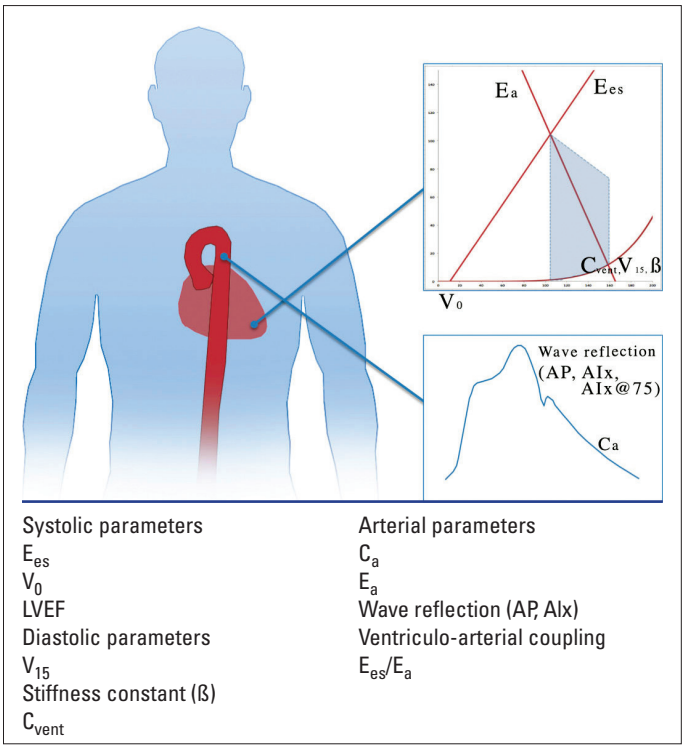

Figure 1. Baseline cardiovascular mechanics parameters used in the study. Cardiac parameters were obtained from constructed pressure–volume (PV) loop. Systolic parameters were defined as follows: end-systolic elastance (E_{es}), which is the slope of the end-systolic PV relationship; V_0, which is the zero intercept of E_{es}; LVEF, left ventricular ejection fraction, which can be deduced from the PV width divided by the PV width plus V_0. Diastolic parameters are V_{15} (volume corresponding to 15 mm Hg on the diastolic PV relationship curve), stiffness constant (estimated from the diastolic PV curve by the equation EDP=α. $EDV^{ß}$), and ventricular compliance (C_{vent}; ventricular volume divided by diastolic pressure). Arterial parameters were obtained from tonometric measurements. These parameters are follows: arterial compliance (C_a from the diastolic decay curve), arterial elastance (E_a), augmentation pressure (AP; systolic blood pressure minus the pressure at the first peak shoulder of the aortic pulse wave), augmentation index (AIx; AP divided by pulse pressure), and augmentation index at a heart rate of 75 beats per minute (AIx@75). Lastly, ventriculo-arterial coupling is defined as E_{es} divided by E_a.

systolic, diastolic, and arterial parameters. These relationships were corrected for the observed differences in the baseline characteristics [systolic and diastolic blood pressure, baseline brain-type natriuretic peptide (BNP) levels, estimated glomerular filtration rate, and aldosterone blocker use] with partial correlation analysis. All analyses were computed using Statistical Package for Social Sciences software (SPSS Version 21; IBM Corporation, Armonk, New York, USA).

Results

Patients

All 50 patients completed the study. There were no procedure-related adverse events during the study. The baseline characteristics were summarized in Table 1.

Table 1. Patient characteristics*

	All n=50	Group I (n=25)	Group II (n=25)	P†
Demographic characteristics				
Age, years	57±10	56±10	56±10	0.61
Male	44 (88)	22 (88)	22 (88)	1.00
White	48 (96)	23 (92)	25 (100)	0.49
Medical history				
Hypertension	39 (58)	13 (52)	16 (64)	0.39
Dyslipidemia	50 (100)	25 (100)	25 (100)	1.00
Diabetes	12 (24)	5 (20)	7 (28)	0.74
Tobacco use	32 (64)	17 (68)	15 (60)	0.55
Prior CABG	8 (16)	3 (12)	5 (20)	0.70‡
Prior MI	38 (80)	22 (88)	18 (72)	0.28
NYHA functional class				
I	17 (34)	7 (28)	10 (40)	0.16
II	19 (38)	8 (32)	11 (44)	
III	14 (28)	10 (40)	4 (16)	
Extent of CAD				
1-vessel disease	13 (31)	7 (30)	6(33)	0.98
2-vessel disease	14 (34)	8 (35)	6 (33)	
3-vessel disease	14 (34)	8 (35)	6 (33)	
Clinical measurements				
Weight, kg	81±15	81±13	82±16	0.81
Height, cm	172±7	172±7	172±6	0.67
BMI, kg/m^2	27±4	27±3	27±5	0.90
Systolic blood pressure, mm Hg	116±19	110±15	121±20	0.04
Diastolic blood pressure, mm Hg	71±10	67±10	75±9	<0.01
Heart rate, beats.min^{-1}	64±10	66±11	62±8	0.17
BNP, pg/mL	234±280	373±337	101±104	<0.01
eGFR, mL/min	91±27	81±23	101±28	<0.01
Hb, g/dL	13±1	13±1	13±1	0.94
Treatment				
ACE-I/ARB	44 (88)	24 (96)	20 (80)	0.18
Beta-blockers	45 (90)	23 (92)	22 (88)	1.00
Diuretics	12 (24)	9 (36)	3 (12)	0.09‡
Aldosterone blockers	14 (28)	11 (44)	3 (12)	0.02‡
Statins	50 (100)	25 (100)	25 (100)	1.00
Digoxin	0 (0)	0 (0)	0 (0)	1.00
Nitrates	5 (10)	1 (4)	4 (16)	0.34‡

*Values are presented as mean±standard deviation or n (%). Continuous variables were compared using independent samples t-test. The comparisons of proportions were made using the chi-square test unless stated. ‡Fischer's exact test; †P indicates the difference between 2 groups
ACE-I - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blocker; BMI - body mass index; BNP - brain-type natriuretic peptide; CABG - coronary artery by-pass grafting; CAD - coronary artery disease; eGFR - estimated glomerular filtration rate (Cockcroft-Gault formula); Hgb - hemoglobin; LVEF - left ventricular ejection fraction; MI - myocardial infarction; NYHA - New York Heart Association

Table 2. Comparison of CPET variables

Parameter	All	Group I	Group II	*P*
Peak VO_2, $mL.kg^{-1}.min^{-1}$	17.9±4.5	16.9±4.6	18.8±4.3	0.14
Percent predicted VO_2	67±15	62±17	72±11	0.02
πO_2, $mL\ O_2.kg^{-1}.beat^{-1}$	12.5±2.9	11.7±3.2	13.3±2.5	0.68
Peak workload, Watts	103±34	96±36	109±31	0.18
Workload at AT, Watts	55±26	49±24	61±27	0.11
AT, $mL.kg^{-1}.min^{-1}$	11.2±4.1	10.1±3.9	12.3±4.0	0.05
Percent predicted AT,	43±17	37±16	48±16	0.02
V_E/V_{CO2}	35±9	39±8	31±8	<0.01

AT - anaerobic threshold; Circ Pw - circulatory power; CPET - cardiopulmonary exercise test; V_{CO2} - the volume of exhaled carbondioxide in a minute; V_E - total volume of exhaled air; V_{O2} - the volume of inhaled oxygen in a minute; πO_2 - Oxygen pulse
P indicates the difference between 2 groups, calculated using independent samples t test

CPET parameters

A comparison of CPET results between the groups is given in Table 2. In summary, the patients in Group II showed slightly better overall exercise performance than the patients in Group I, but this difference did not reach statistical significance. However, when the percent predicted peak VO_2 was analyzed, the patients in Group II showed significantly higher values than the patients in Group I. In addition, the anaerobic threshold, percent predicted anaerobic threshold, and V_E/VCO_2 values were significantly better in Group II. None of the test results showed electrocardiographic signs of ischemia.

Differences in cardiovascular mechanics between the groups

The differences in cardiovascular mechanics are summarized in Table 3. Given that the groups had been divided according to LVEF, all systolic parameters were significantly higher in Group II, as expected. With regard to diastolic parameters, only V_{15} showed a significant difference between the groups. No arterial parameter showed a meaningful difference. Ventriculo-arterial coupling showed a higher power output profile in Group II, whereas it showed a more energetic efficiency profile in Group I.

Determinants of peak VO_2 as an objective and quantitative measure of functional capacity

In Group I, none of the systolic (LVEF, p=0.65; E_{es}, p=0.26; V_0, p=0.09), diastolic (V_{15}, p=0.82; ß, p=0.24; C_{vent}, p=0.64), or arterial parameters (E_a, p=0.79; SVR, p=0.69; C_a, p=0.69; AP, p=0.55; AIx, p=0.86; AIx@75, p=0.76) were correlated with peak oxygen consumption (VO_2). However, ventriculo-arterial coupling showed a moderate correlation with peak VO_2 (r=0.410, p=0.04) in these patients (Fig. 2a). In Group II, neither systolic parameters (LVEF, p=0.52; E_{es}, p=0.15; V_0, p=0.38) nor ventriculo-arterial coupling showed a significant correlation with peak VO_2 (p=0.86). Only V_{15} (r=0.514, p<0.01) in diastolic parameters (ß, p=0.75; C_{vent}, p=0.17) and C_a (r=0.467, p=0.01) in arterial parameters (Ea, p=0.27; SVR, p=0.45; AP, p=0.85; AIx, p=0.63; AIx@75, p=0.68) emerged as significant factors correlated with peak oxygen consumption (Fig. 2b, c). Routine echocardiographic measurements of diastolic function, including the E/A ratio and E/e', were not correlated with peak VO_2 in either group.

Table 3. Comparison of resting cardiovascular mechanics

	Group I (n=25)	Group II (n=25)	*P*
Systolic parameters			
LVEF, %	39±7	64±6	<0.01
E_{es}, $mm\ Hg.mL^{-1}$	1.2±0.4	1.6±0.6	<0.01
V_0, mL	6.5±33	-34±20	<0.01
Diastolic parameters			
V_{15}, mL	156±57	109±23	<0.01
ß	6.4±2.4	5.8±0.1	0.26
C_{vent}	0.08±0.04	0.09±0.03	0.45
E/A ratio	1.6±1.4	1.1±0.5	0.11
E/e'	11.8±4.8	9.3±2.6	0.03
Arterial parameters			
E_a, $mm\ Hg.mL^{-1}$	1.9±0.7	1.8±0.5	0.60
C_a, $mL.mm\ Hg^{-1}$	1.9±0.8	1.7±0.8	0.50
SVR, $dyne.s.cm^{-5}$	1665±664	1705±666	0.83
AP, mm Hg	7.6±4.9	10.2±6.9	0.13
AIx, %	22±11	26±10	0.18
AIx@75, %	18±12	21±9	0.29
Ventriculo-arterial coupling			
E_{es}/E_a	1.6±0.5	1.1±0.3	<0.01

Values are mean±standard deviation
P value was calculated using independent samples t-test
AIx - augmentation index; AIx@75 - augmentation index at 75 beats per minute; AP - augmentation pressure; ß - left ventricular stiffness constant; C_a - total arterial compliance; C_{vent} - left ventricular compliance; E/A - mitral Doppler early to late diastolic velocity ratio; E/e' - early diastolic mitral Doppler to mitral annular tissue Doppler ratio; E_a - end-systolic arterial elastance; E_{es} - end-systolic left ventricular elastance; LVEF - left ventricular ejection fraction; SVR - systemic vascular resistance; V_0 - zero intercept of the end-systolic pressure–volume relationship; V_{15} - volume on the diastolic pressure–volume relationship curve corresponding to 15 mm Hg

When the abovementioned correlations were corrected for baseline differences (systolic and diastolic blood pressure, BNP levels, estimated glomerular filtration rate, and aldosterone blocker use) with partial correlation analysis, ventriculo-arterial coupling in Group I (r=0.441, p=0.05) and V_{15} in Group II (r=0.462, p=0.04) remained significantly correlated with peak VO_2; C_a lost its significance but retained its trend (r=0.416, p=0.06).

Discussion

The results of the current study indicate that a comprehensive cardiovascular mechanics evaluation can give clues about exercise-recruited reserves of the cardiovascular system, contrary to routine parameters such as the number of diseased coronary vessels or LVEF. To the best of our knowledge, the current study shows

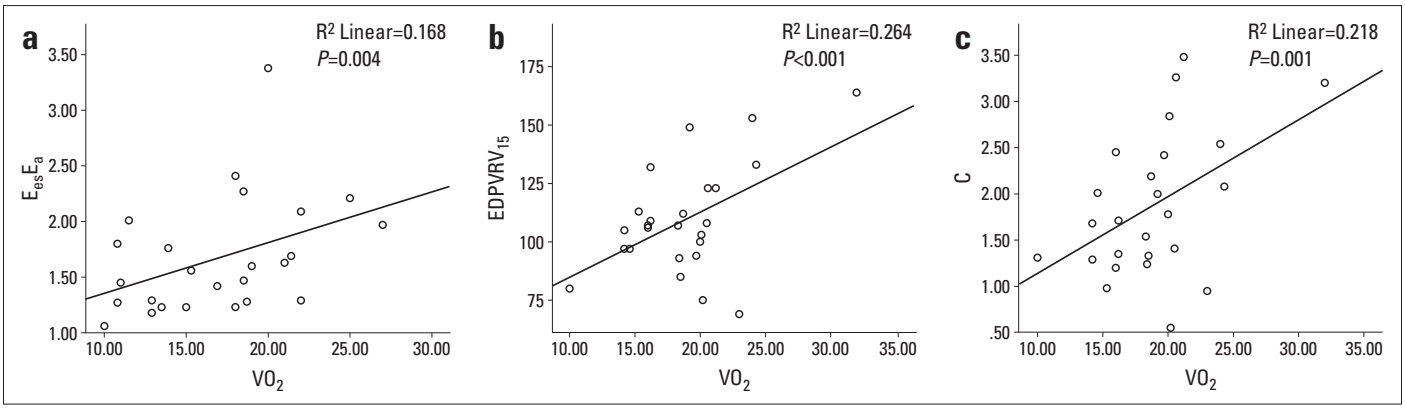

Figure 2. Correlations between the peak VO_2 and ventriculo-arterial coupling in patients with abnormal LVEF (<55%) (a) and volume corresponding to 15 mm Hg in the end-diastolic pressure–volume relationship (EDPVRV15) (b) and arterial compliance (c) in patients with normal LVEF (≥55%)

P values were calculated with Pearson's correlation test

for the first time that different cardiovascular mechanics parameters influence exercise capacity in patients with CAD and different levels of left ventricular involvement. In addition, the results presented here shed some light on the underlying pathophysiology of the functional limitation in patients with CAD.

In patients with abnormal LVEF, ventriculo-arterial coupling emerged as a good predictor of exercise capacity. This association was not valid for patients with normal LVEF. This is not surprising, given that experimental models have shown that left ventricular external work is maximal when the ventriculo-arterial coupling ratio is 1, whereas the mechanical efficiency is maximal when the ratio is 2. Therefore, a higher ventriculo-arterial coupling ratio in certain limits is compatible with the maximal power output (19, 20). With ventriculovascular coupling aiming at the maximal power output, a minor variability around the mean value would not be expected to translate into a meaningful improvement in peak VO_2. On the other hand, with limited contractile function in the abnormal LVEF group, ventriculo-arterial coupling is adjusted to preserve left ventricular efficiency, which is, in turn, critically influenced by the minor changes in ventriculo-arterial interaction. This finding is very important and relevant, because it indicates that keeping ventriculo-arterial coupling in optimal limits with medications or other interventions, such as exercise rehabilitation, is of crucial importance for patients with CAD and abnormal LVEF, but it may not be as vital in patients with CAD and normal LVEF.

In patients with normal LVEF, an arterial parameter, namely arterial compliance, and a diastolic function parameter, namely V_{15}, appeared to be correlated with exercise capacity.

Arterial compliance is a fundamental arterial factor, which acts as a hydraulic cushion and dampens pressure and flow oscillations to minimize left ventricular load and optimize diastolic flow in the coronary arteries (6). Therefore, decreased arterial compliance can limit the exercise-recruited power output by increasing the ventricular afterload and exerting detrimental effects on coronary perfusion, even in the presence of patent coronary arteries. In our cohort, none of these 2 components appeared to predominate. The other determinants of pulsatile afterload, such as arterial elastance and wave reflection parameters, did not turn out to be significant predictors of exercise capacity. Moreover, no evidence of ischemia was found in the exercise test. These findings suggest that both these effects might have been additively operative. Moreover, no relationship between compliance and exercise capacity was observed in patients with reduced LVEF. The reason for this finding is unclear but may be partly explained by the already deranged ventriculo-arterial coupling, which negates the potential favorable effects of compliant arteries in these patients.

Our findings with regard to diastolic function are not completely in line with those of previous studies on the relationship between diastolic function and exercise capacity. Several studies have shown that surrogates of high left ventricular diastolic pressure are associated with exercise capacity (9–12). In our study, however, V_{15} showed a moderate correlation with exercise capacity, whereas the E/A ratio, E/e', ventricular stiffness constant, and ventricular compliance did not. Without other diastolic parameters, the association between V_{15} and peak VO_2 should not be regarded as a reflection of the relationship between diastolic function and exercise capacity. Because V_{15} is the only diastolic function parameter that is based on ventricular volume data, it might have solely mirrored the association between the size of the left ventricle and the stroke volume, which is a direct determinant of peak VO_2. Given the previous study results, an association between diastolic functions and peak VO_2 cannot be excluded because of our limited sample size. However, considering the more comprehensive mechanics picture in hand, one can conclude that its effect on exercise performance appears to be less than the effect of arterial compliance. Because arterial stiffness causes diastolic dysfunction, the real link between diastolic function and exercise capacity observed in previous studies may be arterial compliance itself. Whether arterial compliance constitutes a possible therapeutic target in the treatment of exercise limitation needs to be evaluated further.

Study limitations

Our sample size was limited to exclude possible causal relationships between peak VO_2 and factors other than the parameters showed statistically significant relationship with peak VO_2.

Extensive use of formulas with mathematical assumptions may lead to incorrect estimations. The PV loop and arterial waveform are not based on data related to non-cardiovascular factors that can influence peak oxygen consumption, such as muscular oxygen extraction capability, oxygen-carrying capacity of blood, and oxygenation processes in lungs. The confounding effects of medications may not have been eliminated because they were not withdrawn in the study, even if these medications are usually used in patients with CAD.

Conclusion

Comprehensive evaluation of resting cardiovascular mechanics can give clues about exercise-recruited reserves of the cardiovascular system. Optimization of ventriculo-arterial coupling in patients with reduced LVEF and arterial compliance in patients with normal LVEF should be the main target in patients with CAD and limited functional capacity.

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Peer-review: Externally peer-reviewed.

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