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

Emre Aslanger, Benjamin Assous¹, Nicolas Bihry¹, Florence Beauvais², Damien Logeart², Alain Cohen-Solal²

Department of Cardiology, Yeditepe University Hospital; İstanbul-Turkey
1Department of Cardiology, Lariboisière Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP); Paris-France
2UMR-S 942, Université Paris Diderot, DHU FIRE, Department of Cardiology, Lariboisière Hospital, Assistance Publique-Hôpitaux de Paris; (AP-HP) Paris-France

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 (VO₂) (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 (Alx), p=0.63; heart rate-corrected Alx, p=0.68] emerged as significant factors correlated with peak VO₂ 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-
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.s⁻¹. Total arterial compliance (Cₐ) 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 (V₁₅), and ventricular compliance (Cᵥₑᵥₑ) 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 ≥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 (Alx) was defined as augmentation pressure divided by pulse pressure. Alx 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 Alx@75. The modified single-beat method was used to estimate end-systolic elastance (Eₑₛₛ) (4). Arterial elastance (Eₐ) was estimated by dividing end-systolic pressure by the stroke volume (15). Ventriculo-arterial coupling was calculated by the Eₑₛₛ/Eₐ ratio. Zero intercept of the end-systolic PV relationship (V₀) was projected from Eₑₛₛ, 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, Eₑₛₛ, and V₀), (b) diastolic parameters (V₁₅, ß, and Cᵥₑᵥₑ), (c) vascular parameters [Eₐ, SVR, Cₐ, and wave reflection parameters (AP, Alx, and Alx@75)], and (d) ventriculo-arterial coupling (Eₑₛₛ/Eₐ).

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). VO₂, CO₂ production (VCO₂), and ventilation (Vₑ) were measured on a breath-by-breath basis. The percent predicted peak VO₂ was calculated as peak VO₂ divided by the maximal predicted peak VO₂ according to the values reported by Wasserman et al. (17). The anaerobic threshold was measured by classical methods (18). The Vₑ/VCO₂ 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 VO₂ and
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/m²             | 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. †Fisher’s exact test; ‡P indicates the difference between 2 groups

ACE-I - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blocker; 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

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 (Ees), which is the slope of the end-systolic PV relationship; V0, which is the zero intercept of Ees; LVEF, left ventricular ejection fraction, which can be deduced from the PV width divided by the PV width plus V0. Diastolic parameters are V15 (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. EDPβ), and ventricular compliance (Cvent; ventricular volume divided by diastolic pressure). Arterial parameters were obtained from tonometric measurements. These parameters are follows: arterial compliance (Ca from the diastolic decay curve), arterial elastance (Ea), augmentation pressure (AP; systolic blood pressure minus the pressure at the first peak shoulder of the aortic pulse wave), augmentation index (Alx; AP divided by pulse pressure), and augmentation index at a heart rate of 75 beats per minute (Alx@75). Lastly, ventriculo-arterial coupling is defined as Ees divided by Ea.
Table 2. Comparison of CPET variables

| Parameter                  | All     | Group I | Group II | P  |
|----------------------------|---------|---------|----------|----|
| Peak VO2, mL·kg⁻¹·min⁻¹    | 17.9±4.5| 16.9±4.6| 18.8±4.3 | 0.14|
| Percent predicted VO2      | 67±15   | 62±17   | 72±11    | 0.02|
| VO2, mL·O₂·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|
| V̇E/V̇CO₂                   | 35±9    | 39±8    | 31±8     | <0.01|

Table 3. Comparison of resting cardiovascular mechanics

| Parameter                  | Group I | Group II | P  |
|----------------------------|---------|----------|----|
| Systolic parameters        |         |          |    |
| LVEF, %                    | 39±7    | 64±6     | <0.01|
| Ees, mm Hg·mL⁻¹            | 1.2±0.4 | 1.6±0.6  | <0.01|
| V̇O₂, mL                   | 6.5±33  | -34±20   | <0.01|
| Diastolic parameters       |         |          |    |
| V15, mL                    | 156±57  | 109±23   | <0.01|
| β                          | 6.4±2.4 | 5.8±0.1  | 0.26|
| Cvent                      | 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        |         |          |    |
| Eₐₐ, mm Hg·mL⁻¹            | 1.9±0.7 | 1.8±0.5  | 0.60|
| Cₐₐ, mL·mm Hg⁻¹            | 1.9±0.8 | 1.7±0.8  | 0.50|
| SVR, dyne.s.cm⁻³           | 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|
| Venticulo-arterial coupling|         |          |    |
| ĖE/Eₐₐ                    | 1.6±0.5 | 1.1±0.3  | <0.01|

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 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 VO₂ in either group.

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 V15 in Group II (r=0.462, p=0.04) remained significantly correlated with peak VO₂; Cₐₐ 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
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 VO₂. 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 V₁₅, 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, V₁₅ 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 V₁₅ and peak VO₂ should not be regarded as a reflection of the relationship between diastolic function and exercise capacity. Because V₁₅ 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 VO₂. Given the previous study results, an association between diastolic functions and peak VO₂ 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 VO₂ and factors other than the parameters showed statistically significant relationship with peak VO₂.
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.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – E.A., B.A., N.B., F.B., D.L., A.C.S.; Design – E.A., B.A., N.B., F.B., D.L., A.C.S.; Supervision – E.A., B.A., N.B., F.B., D.L., A.C.S.; Funding – E.A., B.A., N.B., F.B., D.L., A.C.S.; Materials – E.A., B.A., N.B., F.B., D.L., A.C.S.; Data collection &/or processing – E.A., B.A., N.B., F.B., D.L., A.C.S.; Analysis and/or interpretation – E.A., B.A., N.B., F.B., D.L., A.C.S.; Literature search – E.A., B.A., N.B., F.B., D.L., A.C.S.; Writing – E.A., B.A., N.B., F.B., D.L., A.C.S.; Critical review – E.A., B.A., N.B., F.B., D.L., A.C.S.

**References**

1. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al; American Heart Association; Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention); Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); American association of Cardiovascular and Pulmonary Rehabilitation. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2005; 111: 369-76.

2. Cohen-Solal A, Logeat D, Gutti C, Dahan M, Gourgon R. Cardiac and peripheral responses to exercise in patients with chronic heart failure. Eur Heart J 1999; 20: 931-45.

3. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981; 47: 33-9.

4. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiu KR, Ding PA, et al. Non-invasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001; 38: 2028-34.

5. Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, et al. Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. Am J Physiol Heart Circ Physiol 2006; 291: H403-12.

6. de Backer TL, Carlier SG, Segers P, Armstrong G, Haluska B, Greenberg N, et al. Total arterial compliance is a major determinant of peak oxygen uptake. Comput Cardiol 2001; 28: 181-4.

7. Morrison DA, Stovall JR, Barbire C. Left and right ventricular systolic function and exercise capacity with coronary artery disease. Am J Cardiol 1991; 67:1079-83.

8. Ehsani AA, Biello D, Seals DR, Austin MB, Schultz J. The effect of left ventricular systolic function on maximal aerobic exercise capacity in asymptomatic patients with coronary artery disease. Circulation 1984; 70: 552-60.

9. Lele SS, Macfarlane D, Morrison S, Thomson H, Khaefagi F, Frenean M. Determinants of exercise capacity in patients with coronary artery disease and mild to moderate systolic dysfunction. Role of heart rate and diastolic filling abnormalities. Eur Heart J 1996; 17: 204-12.

10. Van de Veire NR, De Winter O, Philippe J, De Buyzere M, Bernard D, Langlois M, et al. Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved left ventricular function: the role of inflammation on top of tissue Doppler-derived systolic and diastolic function. Am J Heart 2006; 152: 297.e1-7.

11. Podolec P, Rubis P, Tomkiewicz-Pajak L, Kopeć G, Tracz W. Usefulness of the evaluation of left ventricular diastolic function changes during stress echocardiography in predicting exercise capacity in patients with ischemic heart failure. J Am Soc Echocardiogr 2008; 21: 834-40.

12. Fontes-Carvalho R, Sampaio F, Teixeira M, Roche-Gonçalves F, Gama V, Azevedo A, et al. Left ventricular diastolic dysfunction and e/e’ ratio as the strongest echocardiographic predictors of reduced exercise capacity after acute myocardial infarction. Clin Cardiol 2015; 38: 222-9.

13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-6.

14. Stergiopulos N, Meister JJ, Wexterhoff N. Evaluation of methods for estimating total arterial compliance. Am J Physiol 1995; 268: H1540-85.

15. Suga H. Total mechanical energy of a ventricular model and cardiac oxygen consumption. Am J Physiol 1979; 236: H498-505.

16. Balady GJ, Arena R, Siesjöva K, Myers J, Coke L, Fletcher GF, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician’s Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association’s guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-6.

17. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60: 72-85.

18. Wasserman K, Hansen J, Sue D, Whipp B. Principles of exercise testing and interpretation. Philadelphia: Lea and Fibiger 1987. p. 72-85.

19. Balady GJ, Arena R, Siesjöva K, Myers J, Coke L, Fletcher GF, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician’s Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010; 122: 191-225.