ORIGINAL RESEARCH

Effects of Cardiopulmonary Exercise Rehabilitation on Left Ventricular Mechanical Efficiency and Ventricular-Arterial Coupling in Patients With Systolic Heart Failure

Emre Aslanger, MD; Benjamin Assous, MD; Nicolas Bihry, MD; Florence Beauvais, MD; Damien Logeart, MD, PhD; Alain Cohen-Solal, MD, PhD, FESC

***Background*—**Success of cardiac rehabilitation (CR) is generally assessed by the objective improvement in peak volume of inhaled oxygen (VO_2) measured by cardiopulmonary exercise test (CPX). However, cardiac mechanical efficiency and ventricular-arterial coupling (VAC) are the other important dimensions of the heart failure pathophysiology, which are not included in CPX-derived data. The effect of cardiac rehabilitation on left ventricular (LV) efficiency or VAC in unselected heart failure patients has not been studied thus far.

***Methods and Results*—**Thirty patients with an ejection fraction of ≤45% were recruited for 20 sessions of exercise-based CR. Noninvasive LV pressure-volume loops were constructed and VAC was calculated with the help of applanation tonometry and echocardiography before and after CR. VAC showed an improved mechanical efficiency profile and increased significantly from 0.56±0.18 to 0.67±0.21 (P=0.02). LV mechanical efficiency improved from 43.9±9.1% to 48.8±9.1% (P=0.01). The change in peak VO_2 was not in a significant correlation with the change in VAC (r=−0.18; P=0.31), mechanical efficiency (r=−0.16, P=0.39), or the change in ejection fraction (r=−0.07; P=0.68).

***Conclusions*—**CR is associated with an improvement in VAC and LV mechanical efficiency in heart failure patients. Further studies are needed to determine the incremental value of VAC and mechanical efficiency over CPX-derived data in predicting clinical outcomes. **(*J Am Heart Assoc*. 2015;4:e002084 doi: 10.1161/JAHA.115.002084)**

Key Words: cardiopulmonary exercise test • exercise training • ventricular function • ventricular-arterial coupling

Patients with heart failure experience a significant reduction in their exercise capacity, which has a negative effect on their quality of life and life expectancy. Exercise-based cardiac rehabilitation is a recommended component of heart failure treatment[1] and has a striking impact on symptoms, functional capacity, quality of life, and mortality.[2–4]

Success of cardiac rehabilitation is generally assessed by the objective improvement in peak volume of inhaled oxygen (VO_2) measured by cardiopulmonary exercise test (CPX).[5] Besides being a good surrogate for maximum cardiac performance, peak VO_2 also strongly predicts mortality, because perturbations in one of its major determinants (ie, cardiac output) is the main driving force for the neurohormonal activation and the progression of heart failure. With cardiac output-related parameters alone, however, prognostic information is incomplete, because these parameters do not take cardiac mechanical efficiency into account.

Cardiac mechanical efficiency is defined as the ratio of energy transferred to the arterial system (external work; EW) to the energy consumed for this action, which is estimated either by the amount of oxygen taken by the heart[6] or by total pressure-volume (PV) loop area that represents the total mechanical energy produced by the left ventricle.[7] Cardiac mechanical efficiency constitutes another important dimension of the heart failure pathophysiology, given that unfavorable mechanical efficiency correlates with a higher wall stress and an increased tendency to ischemia.[8,9] These factors are the leading triggers for ventricular remodeling and obviously have negative prognostic implications.[10,11] But this information is lacking in routine echocardiography or CPX-derived data.

From the Department of Cardiology, Yeditepe University Hospital, Ataşehir, Lariboisière Hospital, Department of Cardiology, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France (E.A., B.A., N.B.); Lariboisière Hospital, Department of Cardiology, Assistance Publique-Hôpitaux de Paris (AP-HP), UMR-S 942, Université Paris Diderot, DHU FIRE, Paris, France (F.B., D.L., A.C.-S.).

Correspondence to: Emre Aslanger, MD, Department of Cardiology, Yeditepe University Hospital, İçerenköy Mahallesi, Hastane Yolu Sokak, No: 102-104, 34752 Ataşehir, İstanbul, Turkey. E-mail: mr_aslanger@hotmail.com

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Optimal cardiac mechanical performance also requires the heart to pump blood into the vascular tree at a rate and volume that matches the capability of the arterial system to receive it. Given that accurate and independent assessment of contractile performance is critical to evaluate this interaction, the widely used measure of systolic performance, that is,left ventricular (LV) ejection fraction (LVEF), cannot be used for this purpose, because it is a complex summary integrating several underlying physiological components, including ventricular size, contractile function, and afterload. A more powerful and largely load-independent measure of contractile function is LV end-systolic elastance (E_{es}), which can be defined as the stiffness of the left ventricle at the end of the systole. The arterial system can also be assessed in elastance terms; hence, ventricular-arterial coupling (VAC) can be expressed by the comparison of ventricular and arterial elastances (E_a).[12–15] Experimental models showed that LV EW is maximal when the VAC (E_{es}/E_a) ratio is 1,[12] whereas the mechanical efficiency is maximal when the ratio is 2.[13,14] In heart failure patients, arterial load increases to maintain systolic pressure and E_{es} decreases as cardiac function declines, thus both lead to a decrease in VAC and inefficient contraction. Therefore, VAC can be used as a useful framework for optimizing the interplay between already diseased left ventricle and the arterial load in patients with heart failure. In the past, to obtain these parameters, invasive pressure and volume measurements were required to be measured under a wide range of loading conditions. Recently, with the introduction of noninvasive, single-beat solutions for estimating E_{es},[15] it became possible to construct PV loop and assess VAC noninvasively. More important, it has been shown that VAC estimated by noninvasive methods is a strong predictor of prognosis in systolic heart failure.[16] But, the effect of cardiac rehabilitation on VAC in unselected heart failure patients has not been studied thus far.

In this study, we sought to explore the effects of exercise-based cardiac rehabilitation on LV efficiency and VAC in patients with systolic heart failure.

Material and Methods

Patients

Study was executed at Hopital Lariboisiere (Paris, France), a tertiary center for cardiac rehabilitation. Patients were recruited between September 2013 and February 2014. Heart failure patients with reduced LVEF (<45%) referred to our laboratory for cardiac rehabilitation were included. Patients with nonsinus rhythms or severe valvular disease were excluded. Patients were receiving optimal medical therapy, which was not altered during the study. All patients gave their informed consent. The study was approved by the institutional review board. Blood chemistry analysis, transthoracic echocardiography, arterial tonometry, and cardiopulmonary exercise tests were performed before and after the exercise training program, as detailed below.

Cardiac Rehabilitation

Patients underwent 2 to 3 training sessions per week for 7 to 10 weeks until a total of 20 sessions were completed. Each session was composed of an endurance training part with bicycle exercise and a resistance training part with gymnastics and low weightlifting. The bicycle exercise was executed at an intensity level corresponding to the ventilatory threshold determined at the initial CPX evaluation (assessed by heart rate). Patients who accomplished their assigned intensity level were allowed to gradually increase their work rate and duration. The cycling duration was started from 20 minutes and progressively increased to 45 minutes. Segmental training sessions with low weightlifting were systematically added to improve muscle strength. Sessions included a set of 8 to 10 different exercises that train the major muscle groups using small free weights (0.5 to 2 kg), elastic bands, weight machines, and group exercises with a repetition range of 10 to 15 at a low relative resistance. Weights were adjusted in accord with the patient's difficulty perception (13 to 16 on the Borg scale) and always kept less than 50% of the maximum weight that could be used to complete one repetition. Blood pressure and heart rate were monitored by measurements at rest, during cycling, and recovery.

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. The SphygmoCor device provides a quality index, which represents reproducibility of the waveform.

Only measures with a quality index ≥80 were included in this study. The modified single-beat method was used to estimate E_{es}. Briefly, single-beat LV elastance ($E_{es(sb)}$) was calculated by:

$$E_{es(sb)} = [P_d - (E_{nd(est)} \times LVESP)]/[SV \times E_{nd(est)}]$$

where $E_{nd(est)}$ is the time and amplitude normalized estimated time varying elastance, P_d is central aortic diastolic pressure, LVESP is the LV end-systolic pressure, and SV is stroke volume. The $E_{nd(est)}$ was estimated form a regression model based on invasive PV data using a 7-term polynomial function,

LVEF, central aortic end-systolic and diastolic pressures, and the ratio of pre-ejection period to total systolic period, as described elsewhere.[15] E_a was estimated by dividing end-systolic pressure to stroke volume. VAC was estimated by the E_{es}/E_a ratio. Additional indices of end-systolic pressure-volume relationship (ESPVR) and the zero intercept of ESPVR on volume axis (V_0) were also estimated from E_{es}, end-sysolic volume, and end-systolic aortic pressure. PV loop area (EW) was calculated as (stroke volume×(end-systolic aortic pressure−mean left ventricular diastolic pressure)−(stroke volume×(end-systolic aortic pressure−end-diastolic aortic pressure)/2)). The area between end-systolic PV relationship, end-diastolic PV relationship and PV loop (internal work; IW) was calculated as ((end-systolic volume−V_0)×(end-systolic aortic pressure))/2. Cardiac mechanical efficiency is expressed as the hydraulic energy transferred to the arterial system, which is defined by the area inside the PV loop (EW), divided by the energy consumed for this action, which is estimated by total PV loop area (EW+IW) that represents the total mechanical energy produced by left ventricle.[11] Therefore, ventricular efficiency is calculated as EW/(EW+IW) (Figure 1).

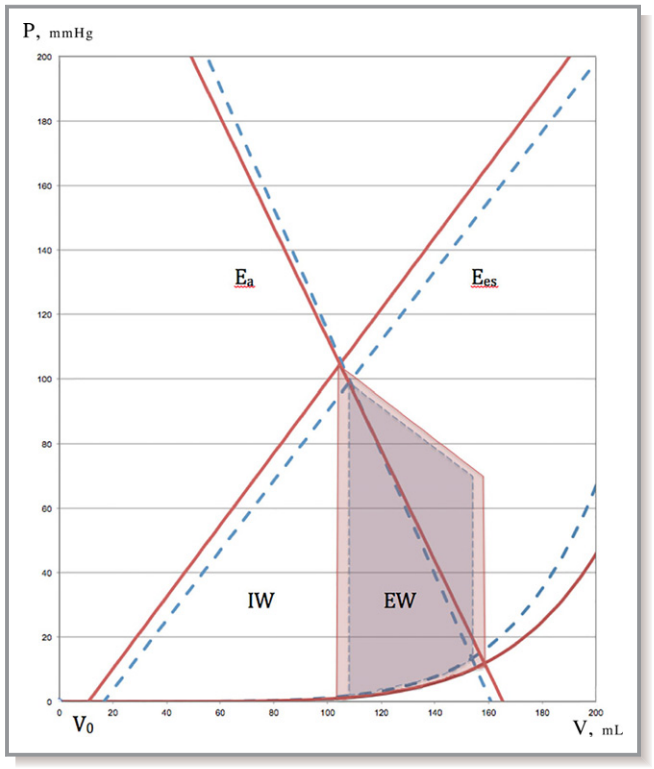

Figure 1. Blue dashed lines indicate pressure-volume relationships before cardiac rehabilitation and red solid lines indicate pressure-volume relationships after cardiac rehabilitation program. E_a indicates arterial elastance; E_{es}, end-systolic elastance; EW, external work; IW, internal work; V_0, zero intercept of end-systolic pressure-volume relationship.

Exercise Test

Exercise test was performed on a bicycle ergometer with 10 W/min workload increments up to exhaustion (peak respiratory exchange ratio, >1.1).[17] Respiratory gas analysis involved use of an Oxycon Pro Jaeger (CareFusion, San Diego, CA). 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 maximal predicted peak VO_2 according to the values reported by Wasserman et al.[18] The peak circulatory power was defined as peak VO_2×peak systolic blood pressure and is expressed in mL·mm Hg·min^{-1}·kg^{-1}. Exercise tests were performed before and after completion of the rehabilitation program on the same machine.

Echocardiography

Two-dimensional images, flow, and tissue Doppler recordings were obtained for all patients with use of a Doppler transthoracic echocardiograph with a 3.5-MHz transducer (GE Vivid I or 7; GE Healthcare Horten, Norway). LV volumes were calculated by modified Simpson's biplane method from apical 4 chamber and 2 chamber views. Doppler recordings were obtained in the apical 4-chamber view by positioning sample volume at the tips of the mitral leaflets. The sample volume was positioned at the medial mitral annulus on an apical 4-chamber view to measure early diastolic tissue Doppler velocity (e′). Mitral Doppler E wave to e′ ratio was used as a surrogate of mean LV diastolic pressure.[19,20] LV diastolic pressure-volume relationship was calculated as described elsewhere.[21] All recordings were taken by the same operator (E.A.).

Statistical Analysis

Baseline characteristics were summarized using median (25th, 75th percentiles) or mean±SD, as appropriate. Pre- and postexercise training comparisons were made using paired samples *t* test. Pearson's correlation test was used to analyze correlations between the change in VAC, peak VO_2, EW, and ventricular mechanical efficiency. All analyses were computed using Statistical Package for Social Sciences software (SPSS Version 22; IBM Corp, Armonk, New York).

Results

Patients

Thirty-five patients were enrolled. Five of them did not complete the rehabilitation program; therefore, final analysis group was composed of 30 patients. There were no procedure-related adverse events during study. Baseline characteristics were summarized in Table 1.

Change in Echocardiographic Parameters and Tonometric Measurements

At the end of the rehabilitation program, none of the blood pressure measurements, including systolic brachial artery pressure (from 111±14 to 112±18 mm Hg; P=0.59), diastolic brachial artery pressure (from 68.2±9 to 68.2±9 mm Hg; P=1.00), aortic systolic pressure (from 101.2±13 to 102±16 mm Hg, P=0.61), and aortic diastolic pressure (from 69.23±9 to 69±9 mm Hg; P=0.91), changed significantly compared to baseline measurements. LV diastolic volumes (from 168±63 to 165±59 mL, P=0.56) and diastolic volume index (from 88±33 to 86±33 mL/m^2, P=0.63) did not show a meaningful change, but LV systolic volumes and systolic volume index decreased 37.5% (from 116±58 to 105±48 mL; P=0.02) and 9.8% (from 61±30 to 55±27 mL/m^2; P=0.02), respectively. LV ejection fraction improved significantly (from 33±9% to 38±9%; P<0.001).

Table 1. Baseline Characteristics (N=30)*

Demographic characteristics	
Age, y	55 (46, 65)
Male	27 (90)
White	27 (90)
Medical history	
Hypertension	12 (40)
Dyslipidemia	30 (100)
Diabetes	7 (23)
Tobacco use	18 (60)
Coronary artery disease	21 (70)
Previous MI	19 (63)
Ischemic etiology	20 (66)
NYHA functional class	
I	10 (33)
II	8 (26)
III	12 (40)
Clinical measurements	
Weight, kg	82 (65, 90)
Height, m	1.71 (1.67, 1.78)
BMI, kg/m^2	26 (22, 28)
BSA, m^2	1.97 (1.76, 2.07)
Systolic blood pressure, mm Hg	110 (100, 120)
Diastolic blood pressure, mm Hg	68 (61, 70)
Heart rate, bpm	67 (58, 77)
BNP, pg/mL	318 (105, 875)
Ccr, mL/min	71 (56, 97)
Treatment	
ACE-I/ARB	29 (96)
Beta-blockers	27 (90)
Diuretics	15 (50)
Aldosterone blocker	13 (43)
Statins	30 (100)
Digoxin	0 (0)
ICD/CRT	4 (13)

ACE-I indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BSA, body surface area (DuBois); Ccr, creatinine clearance (Cockcroft-Gault formula); CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NYHA, New York Heart Association.
*Values are median (25th and 75th percentiles) or n (%).

Effects of Exercise Training on Cardiopulmonary Exercise Test Results

Effects of exercise training on cardiopulmonary exercise test results were summarized in Table 2. Exercise capacity increased significantly as evidenced by increases in peak VO_2 (from 17.2±4.7 to 19.8±6.3 mL·kg^{-1}·min^{-1}; P<0.001) and maximum workload (from 93.8±34.9 to 107.77±38.7 W; P<0.001). Neither the change in E_{es} (r=−0.18; P=0.66) nor the change in E_a (r=0.25; P=0. 17) was correlated with the change in peak VO_2.

Effects of Exercise Training on Ventricular-Arterial Coupling and Mechanical Efficiency

Prerehabilitation E_{es} was 1.08±0.52 mm Hg·mL^{-1} and it did not change significantly after rehabilitation (1.11±0.48; P=0.71). E_a showed an insignificant change from 1.89±0.60 to 1.72±0.60 mm Hg·mL^{-1} (P=0.15). VAC showed an improved mechanical efficiency profile and increased

Table 2. Cardiopulmonary Exercise Test Parameters Before and After Cardiac Rehabilitation*

Parameter	Before	After	P Value
Peak VO_2, mL·kg^{-1}·min^{-1}	17.2±4.7	19.8±6.3	<0.001
Maximum workload, W	93.8±34.9	107.77±38.7	<0.001
Peak oxygen pulse, mL·O_2·kg^{-1}·beat^{-1}	14.4±3.0	16.3±4.2	0.002
V_E/VCO_2	39±8	36±11	0.16
Circulatory power, mL·mm Hg·min^{-1}·kg^{-1}	1567±995	3090±1262	0.001
Baseline heart rate, bpm	67±13	67.4±10	0.87
Peak heart rate, bpm	118±19	121±23	0.26

bpm indicates beats per minute; VCO_2, volume of exhaled carbon dioxide; V_E, expiratory minute volume; VO_2, volume of inhaled oxygen.
*Values are mean±SD.

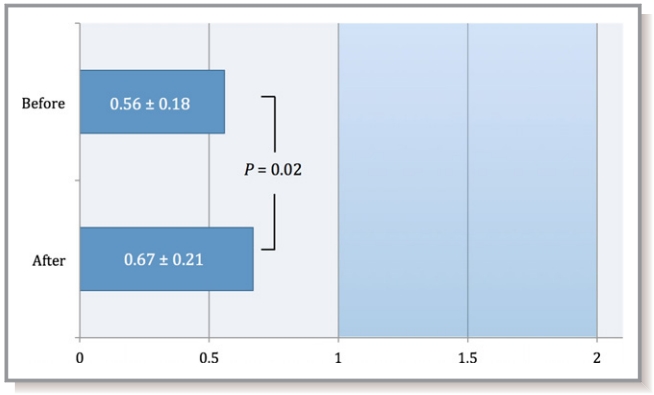

Figure 2. Ventricular-arterial coupling before and after exercise-based cardiac rehabilitation. Shaded area shows the optimal value in terms of maximum mechanical efficiency and maximum left ventricular power output. Values are mean±SD.

significantly from 0.56±0.18 to 0.67±0.21 (P=0.02; Figure 2). The change in V_0 did not reach statistical significance (from 11±47 to 7±40 mL; P=0.66). IW did not show a significant change (from 4747±1874 to 4627±2489 mm Hg·mL; P=0.79), but EW increased significantly (from 3533±944 to 4160±1444 mm Hg·mL; P=0.02). LV mechanical efficiency improved from 43.9±9.1% to 48.8±9.1% (P=0.01; Figure 3). A full pressure-volume relationship with superimposed E_{es} and E_a from averaged values is represented in Figure 1, which compares pressure volume loops before and after exercise rehabilitation.

Relation of VAC With Other Parameters

The change in peak VO_2 was not in a significant correlation with the change in VAC (r=−0.18; P=0.31), EW (r=−0.15; P=0.42), mechanical efficiency (r=−0.16; P=0.39), or the change in ejection fraction (r=−0.07; P=0.68). Scatterplots also did not reveal any nonlinear associations. Moreover, the change in VAC was not correlated with the change in ejection fraction (r=0.22; P=0.23). On the other hand, the change in mechanical efficiency showed a very strong correlation with VAC (r=0.91; P<0.001).

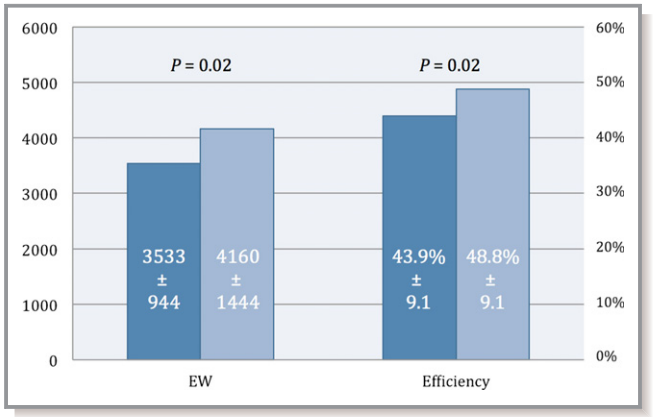

Figure 3. Mechanical efficiency and left ventricular external work output before (dark blue) and after (light blue) exercise-based cardiac rehabilitation. Values are mean±SD. EW indicates external work.

Discussion

VAC offers a valuable framework for assessing cardiac efficiency and the interaction between ventricle and arterial load. For maximal cardiac work, power, and efficiency, the coupling ratio of E_{es}/E_a typically resides between 1 and 2.[12–14] As cardiac function declines, arterial load increases to maintain systolic pressure and E_{es} decreases, thus both lead to a decrease in this ratio representing inefficient contraction.[22–26] Recently, this derangement has been shown to be strongly associated with adverse clinical outcomes in patients with heart failure irrespective of ejection fraction.[16] To our knowledge, this is the first time that VAC is shown to be improved by cardiopulmonary rehabilitation in an unselected heart failure patient population. Although exercise capacity, as assessed by peak VO_2 measurement, also improved in accord with previous studies, VAC provides a different insight into heart failure pathophysiology by adding mechanical performance information. Thus, these results may lay a foundation for exploration of the future role for VAC in serial evaluation of heart failure patients undergoing exercise rehabilitation.

Despite a significant change in VAC, neither the change in E_{es} nor E_a reached statistical significance in our study cohort. Minor changes in both variables may have summed up to produce a significant change in VAC, but the prevailing change was observed in E_a. Theoretically, the most profound effect of exercise training is expected to be on E_a, given that several lines of evidence support that exercise training shows its favorable effects on peak VO_2 improvement principally by peripheral adaptations.[27] Indeed, it has been shown that exercise training induces significant improvements in arterial compliance,[28] peripheral resistance,[29] wave reflections,[30] skeletal muscle oxidative function,[31,32] and arterial-venous O_2 difference.[33] The modest change in E_a in our cohort may be caused by the limited time duration of cardiopulmonary exercise intervention. But, our data suggest that even a minor improvement in E_a can translate VAC into a better state and increase mechanical efficiency. Also, E_{es} showed virtually no change with exercise training. This is remarkable because LV systolic volumes decreased and ejection fraction increased significantly. This fact may be pointing to one of the limitations of the VAC concept, which does not have V_0 data in it. Any change in E_{es} should always be interpreted with the change in V_0, which has been claimed to be superior and less load dependent than E_{es} for assessment of ventricular contractility.[34] Owing to the fact that E_{es}/E_a ratio loses

pressure data and only contains volume data (stroke volume/end-systolic volume$-V_0$), it is a corollary that LVEF improves with a decrease in V_0 without any change in E_{es} when stroke volume is kept constant. Moreover, when V_0 is negligible, which is, of course, not the case for heart failure patients with dilated hearts, but may be important for assessment of patients with preserved ejection fraction, VAC approaches to: $(1/LVEF)-1$.[35] These considerations may explain why E_{es} seemed to be insensitive to the changes in ventricular systolic volumes, LVEF, and mechanical efficiency in our study and call for a modification in VAC with the inclusion of V_0.

Whereas VAC gives an optimal working range between maximal power output and maximal mechanical efficiency, a full PV loop analysis gives further information about the individual components, cardiac mechanical performance and energetics. The current study shows that exercise training is correlated with an improvement in both LV energy output and mechanical efficiency. This is especially interesting for 2 reasons. First, it has long been known that interventions that aim to increase ventricular systolic performance increase the risk of death in patients with heart failure, whereas energy-sparing treatments, such as angiotensin-converting enzyme inhibitors or beta-blockers, improve prognosis in heart failure. It has been thought that exercise-based cardiac rehabilitation might be an exception to this rule in patients with nonischemic heart failure, given that 2 previous studies showed significant improvements in LV mechanical efficiency in patients with dilated cardiomyopathy.[36,37] Our findings support and extend these findings to patients with systolic heart failure of ischemic origin, in whom efficient energy utilization is of greatest importance. Second, the change in neither VAC nor mechanical efficiency correlated with the change in peak VO_2 in our cohort. These findings may be explained by the predominant dependence of peak VO_2 improvement on peripheral adaptations,[27] whereas VAC and left ventricular mechanical efficiency represent the interaction between peripheral adaptations and LV function. Despite that peak VO_2 has been focused on as a target to gauge cardiac rehabilitation success in previous studies, VAC and mechanical efficiency are not necessarily to be represented by an improvement in peak VO_2 and may provide complementary data on prognosis in heart failure patients.[16]

Whether there is a supplementary effect of the improvement in VAC or mechanical efficiency, in addition to the improvement in exercise capacity, with regard to clinical outcomes is beyond the scope of our study, but further studies are needed to answer this critical question.

Limitations

The small sample size might have led to a low-powered analysis to exclude possible relationships. The lack of a control group makes interpretation of the impact of CR alone difficult. However, the change in the main outcome measure (ie, peak VO_2) observed in our cohort was twice the established within-subject variation of peak VO_2.[38] Because patients served as their own controls, such a wide variation without any other intervention in the limited time span of our study can be attributed to cardiac rehabilitation. We acknowledge that other methods used in estimating ventricular PV loop data may not have the same reproducibility and did not show a similar dramatic improvement. Even though a causal relationship between CR and the improvement in VAC and mechanical efficiency cannot be claimed, it can be stated that there was a correlation between these parameters. Even if they are fairly well validated, extensive use of formulas with mathematical assumptions may lead to incorrect estimations. Despite that echocardiographic E/e' has a strong relationship with LV diastolic pressure,[20,39] using E/e' as a surrogate for LV diastolic pressure has some limitations because of the large scatter around correlation relationship. However, this results a minor error in the estimation of external work, given that the area under LV diastolic pressure curve is much less than the area in PV loop. Confounding effects of medications may not be eliminated because they were not withdrawn in the study, even if these medications are usually used in heart failure patients. Our patients had only 20 exercise training sessions; longer training duration might have caused more-dramatic changes and might have caused some relationships to be more significant.

Conclusion

Cardiopulmonary rehabilitation, on top of optimal treatment, is associated with an improvement in VAC and LV mechanical efficiency in systolic heart failure patients. Further studies are needed to determine the additional value of VAC and mechanical efficiency over CPX-derived data in predicting clinical outcomes.

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Disclosures

None.

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