European Journal of Preventive Cardiology

http://cpr.sagepub.com/

Published by:
$SAGE
http://www.sagepublications.com

On behalf of:
European Society of Cardiology

European Association for Cardiovascular Prevention and Rehabilitation

EACPR

Additional services and information for *European Journal of Preventive Cardiology* can be found at:

Email Alerts: http://cpr.sagepub.com/cgi/alerts

Subscriptions: http://cpr.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - Feb 4, 2013

What is This?

Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction

Marco Guazzi[1], Valentina Labate[1], Lawrence P Cahalin[2] and Ross Arena[3]

Abstract

Background: We are unaware of any previous investigation that has compared the relationship of key cardiopulmonary exercise testing (CPX) variables to various measures of pathophysiology between heart failure-reduced ejection fraction (HFrEF) and HF-preserved ejection fraction (HFpEF) cohorts that are well matched with respect to baseline characteristics and their exercise response, which is the purpose of the present study.

Methods: Thirty-four patients with HFpEF were randomly matched to 34 subjects with HFrEF according to age and sex as well as peak oxygen consumption (VO_2), ventilatory efficiency (VE/VCO_2 slope), and exercise oscillatory ventilation (EOV). In addition to CPX, patients also underwent echocardiography with tissue Doppler imaging (TDI) and assessment of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Results: When matched for age, sex, and CPX variables, the HFrEF and HFpEF cohorts had similar echocardiography with TDI and NT-proBNP values, indicating comparable disease severity. In addition, the correlations between key CPX measures (peak VO_2 and VE/VCO_2 slope) and echocardiography with TDI and NT-proBNP measures were similar between HFrEF and HFpEF groups. Of note, the correlation between the VE/VCO_2 slope and pulmonary artery systolic pressure and NT-proBNP was highly significant in both groups ($r \geq 0.65$, $p < 0.01$). Moreover, subjects with EOV in both groups had a significantly higher PASP ($\sim$47 vs. $\sim$35 mmHg, $p < 0.05$).

Conclusions: The results of the current study indicate CPX equally represents disease severity in HFrEF and HFpEF patients. This is a novel finding supporting the key role of CPX in the clinical follow-up of HF patients irrespective of LVEF and cardiac phenotype.

Introduction

Cardiopulmonary exercise testing (CPX) has convincingly demonstrated the ability to predict adverse events and reflect disease severity in patients with heart failure-reduced ejection fraction (HFrEF).[1–3] Peak oxygen consumption (VO_2), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and exercise oscillatory ventilation (EOV) have emerged as core CPX variables in HFrEF. All three of these variables have consistently demonstrated strong prognostic value. Moreover, as peak VO_2 declines, VE/VCO_2 slope increases, and EOV becomes apparent, disease severity clearly worsens.

[1]University of Milan, San Donato Milanese, Italy
[2]University of Miami, Miami, USA
[3]University of New Mexico, Albuquerque, New Mexico

Corresponding author:
Marco Guazzi, Cardiology, Cardiopulmonary Laboratory I.R.C.C.S. Policlinico San Donato, University of Milan, Piazza E. Malan, 2, 20097 San Donato Milanese, Milan, Italy.
Email: marco.guazzi@unimi.it

While the body of evidence demonstrating the ability of CPX in HFrEF to reflect disease severity and prognosis is robust, similar analyses in patients with HF-preserved ejection fraction (HFpEF) are limited. In recent years, however, investigations demonstrating the clinical utility of CPX in HFpEF have begun to emerge. Guazzi et al.[4,5] demonstrated that VE/VCO_2 slope and EOV both are significant prognostic markers in HFpEF. Moreover, there is initial evidence to indicate CPX variables reflect disease severity in HFpEF.[6]

Moore et al.[7] compared HFrEF and HFpEF cohorts undergoing CPX and demonstrated a significantly higher peak VO_2 and lower VE/VCO_2 slope in the latter group. Other investigations have also demonstrated patients with HFpEF appear to have a more favourable CPX response when compared to patients with HFrEF.[5] Given these differences between the CPX responses of patients with HFrEF and HFpEF, questions remain with respect to the ability of CPX to reflect pathophysiology in these two unique populations.

We are unaware of any previous investigation that has compared the relationship of key CPX variables to various measures of pathophysiology (i.e. LV and RV cardiac performance indicators and brain natriuretic peptide levels) between HFrEF and HFpEF cohorts that are well matched with respect to baseline characteristics and their exercise response, which is a primary purpose of the present study. In patients with HFpEF who present with a poor CPX response, further exploration of pathophysiological mechanisms is needed. In addition, this study addresses whether pathophysiological mechanisms for CPX abnormalities are comparable in patients with HFrEF and HFpEF. We hypothesize that the pathophysiological mechanisms for CPX abnormalities will be comparable in the HFrEF and HFpEF cohorts, thus further supporting the clinical utility of CPX in the latter HF population.

Methods

Subjects

Thirty-four patients with HFpEF (left ventricular ejection fraction, LVEF, $\geq$50%) were randomly matched to 34 subjects with HFrEF (LVEF $\leq$40%). The HFrEF database consisted of more than 150 subjects. Subjects were matched according to the following factors: (1) age within 5 years; (2) sex; (3) peak VO_2 according to Weber class;[8] (4) VE/VCO_2 slope according to ventilatory class;[9] and (5) the presence or absence of exercise oscillatory ventilation (EOV). Random matching according to these five factors was performed while blinded to the results of echocardiography with tissue Doppler imaging (TDI) and the neurohormonal analysis. None of the subjects in the HFpEF group were receiving cardiac resynchronization therapy (CRT) although 10% were in atrial fibrillation. In the HFrEF group, 25% were receiving CRT and 20% were in atrial fibrillation.

Echocardiography and TDI

An experienced echocardiographer performed the echocardiographic analysis by transthoracic echocardiography accomplished with an IE33 Philips ultrasound unit (Andover, MD, USA), equipped with software for TDI, using a 2.5–5.0 MHz probe (S5). Standard M-mode, 2D, and Doppler blood flow measurements were performed according to the current American Society of Echocardiography Guidelines.[10]

The TDI images of the mitral annulus movement were obtained from the apical 4-chamber view. A 1.5 mm sample volume was placed sequentially at the lateral and septal annular sites. Analysis was performed for the early (E′) diastolic peak velocities. Pulsed wave Doppler echocardiography was used to assess mitral peak early (E) wave flow velocity. The ratio of early transmitral flow velocity to annular velocity (E/E′) was considered as an index of end-diastolic pressure.[11]

Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient using the modified Bernoulli equation. Right atrial pressure (clinically assessed jugular venous pressure) was added to the calculated gradient to yield PASP. No subjects had significant right ventricular outflow tract obstruction.

To obtain tricuspid annular plane systolic excursion (TAPSE), the apical four-chamber view was used and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Offline, the brightness was adjusted to maximize the contrast between the M-mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the total displacement of the tricuspid annulus (millimeters) from end-diastole to end-systole, with values representing the average TAPSE of three to five beats.

CPX procedures

Patients underwent an upright graded bicycle exercise using a personalized ramp protocol. Heart rate was continuously monitored by electrocardiography at rest and during exercise. Blood pressure was measured every 2 minutes and at peak exercise with a mercury sphygmomanometer. Respiratory gas analysis was carried out with a metabolic cart (Sensormedics Vmax29, Yorba Linda, CA, USA) which was calibrated with a standard gas of known concentration before each test.

Minute ventilation (VE, body temperature, atmospheric pressure saturated with water vapour), oxygen uptake (VO_2, standard temperature and pressure dry), and carbon dioxide output (VCO_2, standard temperature and pressure dry) were acquired breath-by-breath, averaged over 30 seconds, and printed in rolling averages every 10 seconds. Peak VO_2 and peak respiratory exchange ratio (RER) were defined as the highest 30-second averaged value obtained during exercise. Ten-second averaged VE and VCO_2 data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, WA, USA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, where m is slope). Evidence from different groups has convincingly shown this method of calculating the VE/VCO_2 slope to be optimal for estimating prognosis.[12,13] The occurrence of EOV was defined as an oscillatory pattern at rest that persisted for $\geq 60\%$ of the exercise test at an amplitude $\geq 15\%$ of the average resting value.[14] This analysis was carried out by a quite rapid manual calculation.

Test termination criteria consisted of patient request, ventricular tachycardia, ≥ 2.0 mm of horizontal or downsloping ST segment depression, or a drop in systolic blood pressure ≥ 20 mmHg during progressive exercise. A qualified exercise physiologist with physician supervision conducted each exercise test.

Blood sampling procedures and hormonal assays

All patients had a measurement of plasma N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) on the same day before exercise. Venous blood samples were obtained after at least 30 minutes of rest from an indwelling catheter and collected in tubes containing EDTA buffer. They were immediately placed on ice and centrifuged at $4°C$. Plasma samples were stored at $-20°C$ until assay. Blood samplings were obtained 10 minutes before CPET procedure, at peak exercise, and 1 minute recovery phase.

Statistical analysis

A statistical software package (SPSS 19.0, Chicago, IL, USA) was used to perform all analyses. With the exception of NT-proBNP, continuous and categorical data are reported as mean $\pm$ standard deviation and percentages, respectively. NT-proBNP is reported as median and range due to skewed distribution. With the exception of NT-proBNP, paired t-testing compared key continuous variables between HFrEF and HFpEF groups. The Wilcoxon signed rank sum test compared NT-proBNP values between HFrEF and HFpEF groups. Chi-squared testing was used to compare dichotomous data. Within HFrEF and HFpEF groups, unpaired t-testing was used to compare CPX and echocardiography with TDI variables while the Mann–Whitney U test compared NT-proBNP according to the presence or absence of EOV. Unpaired t-testing also compared differences in peak VO_2 and VE/VCO_2 slope in the HFrEF and HFpEF groups according to EOV. Lastly, unpaired t-tests were used to compare PASP according to the ventilatory classification system (classes I/II vs. III/IV).[9] Pearson's correlation was used to assess the relationship between key CPX variables and echocardiography with TDI measurements as well as NT-proBNP in HFrEF and HFpEF groups. Pearson's correlation also assessed the relationship between peak VO_2 and VE/VCO_2 slope in the HFrEF and HFpEF groups. Linear and logistic regression was performed to examine predictors of peak VO_2, VE/VCO_2 slope, and EOV. Multicollinearity diagnostics were performed to identify which independent variables to include in the regression models due to the limited number of subjects in each group. The results of multicollinearity diagnostics reduced the number of independent variables to five and included LVEF, PASP, TAPSE, E/E′, and peak exercise NT-proBNP. These five independent variables were used in all linear and logistic regression models. Two separate logistic regression models examining predictors of EOV in patients with HFrEF and HFpEF were developed. Two separate linear regression models were developed to examine predictors of peak VO_2 in patients with HFrEF and HFpEF and two separate linear regression models were developed to examine predictors of the VE/VCO_2 slope in patients with HFrEF and HFpEF. A *p*-value <0.05 was considered statistically significant for all tests.

Results

Table 1 shows baseline subject characteristics as well as the CPX response. With the exception of angiotensin-converting enzyme inhibitor use, which was significantly higher in the HFrEF group, the two groups were well matched.

Table 2 shows the differences in clinical, echocardiography with TDI, and NT-proBNP variables between HFrEF and HFpEF groups. As expected, LVEF was significantly greater in the HFpEF group. All other variables in Table 2 were comparable between groups.

Table 3 shows the correlation results between primary continuous CPX variables (i.e. peak VO_2 and VE/VCO_2 slope) and echocardiography with TDI and NT-proBNP variables. With the exception of LVEF, which only correlated with peak VO_2 in the HFpEF group, all other correlations were significant in both groups. Moreover, the correlation between peak VO_2

and VE/VCO_2 slope was significant and strikingly similar in the HFrEF ($r = -0.61$, $p < 0.001$) and HFpEF ($r = -0.59$, $p < 0.001$) groups.

Table 4 compares echocardiography with TDI and NT-proBNP variables according to EOV in both HFrEF and HFpEF groups. The differences according to EOV were more frequently significant in the HFrEF group, although trends were similar in the HFpEF group. Additionally, in the HFrEF group, subjects with EOV had a significantly lower peak VO_2 (11.0 ± 3.6 vs. 16.4 ± 4.7 ml·kg^{-1}·min^{-1}, $p < 0.01$) and significantly higher VE/VCO_2 slope (40.2 ± 11.1 vs. 31.0 ± 5.1, $p < 0.01$) compared to subjects without EOV. Likewise, in the HFpEF group, subjects with

EOV had a significantly lower peak VO_2 (10.5 ± 3.2 vs. 16.6 ± 5.6 ml·kg^{-1}·min^{-1}, $p < 0.01$) and significantly higher VE/VCO_2 slope (38.7 ± 8.2 vs. 30.3 ± 7.8, $p < 0.01$) compared to subjects without EOV. Differences in peak VO_2 and VE/VCO_2 slope according to EOV were similar in HFrEF and HFpEF groups.

The results of logistic regression analyses found only LVEF to be a significant predictor of EOV in patients with HFpEF (OR 1.24, 95% CI 1.005–1.541; $p = 0.04$) and peak exercise NT-proBNP was a nearly significant predictor of EOV in patients with HFrEF (OR 1.002, 95% CI 1.000–1.005; $p = 0.05$).

The results of linear regression analyses of peak VO_2 and VE/VCO_2 slope in patients with HFrEF found only PASP to be a significant predictor of peak VO_2 (model $r^2 = 0.45$; standardized beta coefficient -0.620; $p = 0.01$) while PASP, E/E′, and peak exercise NT-proBNP were significant predictors of the VE/VCO_2 slope (model $r^2 = 0.80$; standardized beta coefficients 0.439, 0.332, and 0.352; $p = 0.004$, 0.01, and 0.001, respectively). The results of linear regression analyses of peak VO_2 and VE/VCO_2 slope in patients with HFpEF found only LVEF to be a significant predictor of peak VO_2 (model $r^2 = 0.43$; standardized beta coefficient -0.305; $p = 0.04$) while PASP and peak exercise NT-proBNP were significant predictors of the VE/VCO_2 slope (model $r^2 = 0.88$; standardized beta coefficients 0.599 and 0.515; $p = 0.000$ and 0.000, respectively).

Figure 1 illustrates the difference in PASP according to the ventilatory classification system (i.e. VE/VCO_2 slope $\leq$ or >36) for the HFrEF and HFpEF groups. In both groups, PASP was significantly higher in subjects with a VE/VCO_2 slope >36 (HFrEF 33.7 ± 7.2 vs. 48.8 ± 11.4; HFpEF 32.2 ± 7.5 vs. 55.6 ± 9.5; $p < 0.01$).

Table 1. Matching results according to key baseline and CPX variables

	HFrEF (n = 34)	HFpEF (n = 34)	p-value
Age (years)	63.0 ± 9.0	62.7 ± 9.3	0.77
Sex (male)	76	76	1.00
HF aetiology (ischaemic)	65	62	0.72
Prescribed ACE inhibitor	88	74	<0.01
Prescribed beta-blocker	68	59	0.27
Peak VO_2 (ml·kg^{-1}·min^{-1})	14.3 ± 5.0	14.3 ± 5.6	0.98
Peak RER	1.06 ± 0.10	1.08 ± 0.11	0.28
VE/VCO_2 slope	34.5 ± 9.0	33.5 ± 8.8	0.20
EOV	38	38	1.00

Values are mean $\pm$ SD or %.; ACE, angiotensin-converting enzyme; EOV, exercise oscillatory ventilation; HF, heart failure; pEF, preserved ejection fraction; rEF, reduced ejection fraction; RER, respiratory exchange ratio; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

Table 2. Differences in variables reflecting cardiac function and disease severity according to heart failure type

	HFrEF (n = 34)	HFpEF (n = 34)	p-value
NYHA class	2.3 ± 0.75	2.1 ± 0.81	0.15
LVEF (%)	28.6 ± 6.7	55.8 ± 4.5	<0.001
PASP (mmHg)	39.0 ± 11.4	40.4 ± 13.9	0.40
TAPSE (mm)	17.5 ± 2.9	17.6 ± 3.3	0.93
E/E′	13.2 ± 6.4	11.9 ± 6.2	0.32
Resting NT-proBNP (pg/ml)	982.5 (5890.0)	735.5 (3490.0)	0.16
NT-proBNP at peak exercise (pg/ml)	1109.5 (6080.0)	782.5 (3601.0)	0.22
NT-proBNP post exercise (pg/ml)	1067.5 (6306.0)	735.0 (3672.0)	0.26

Values are mean $\pm$ SD or median (range).; E/E′, ratio of early transmitral flow velocity to annular velocity; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; pEF, preserved ejection fraction; rEF, reduced ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

Discussion

Several CPX variables have consistently demonstrated a strong ability to predict adverse events in patients with HFrEF. The variables that have garnered the greatest amount of attention as prognostic markers to this point are peak VO_2, VE/VCO_2 slope, and EOV.[14–17] More recently, evidence has begun to emerge demonstrating these CPX variables may well define dyspnoea sensation[18] and are also prognostic in patients with HFpEF,[4,5] although more work is needed to verify these initial findings. In patients with HFrEF, the strong prognostic value of these CPX variables is attributable to their ability to reflect the degree of pathophysiology associated with this chronic cardiac condition.[1,19–21] Because of these demonstrated relationships, CPX also has clinical utility as a gauge of

disease severity in the HFrEF population. The ability of these CPX variables to reflect pathophysiology and thus gauge disease severity in patients with HFpEF is unclear. Previous research intimates that patients with HFpEF who undergo CPX may have a more favourable CPX response compared to patients with HFrEF, although both patient populations demonstrate an abnormal response compared to apparently healthy controls.[5,7] These differences in the CPX response may lead one to hypothesize that the relationship between key exercise variables (i.e. peak VO_2, VE/VCO_2 slope, and EOV) and other established markers of pathophysiology associated with HF differs between patients with HFrEF and HFpEF. To our knowledge, this is the first investigation to match HFrEF and HFpEF patients according to baseline characteristics and the CPX response to determine if the relationships

Table 3. Correlation analysis between key variables according to heart failure type

	HFrEF (*n* = 34)		HFpEF (*n* = 34)	
	Peak VO_2	VE/VCO_2 slope	Peak VO_2	VE/VCO_2 slope
LVEF	0.14	−0.29	−0.34*	0.12
PASP	−0.64**	0.77**	−0.54**	0.88**
TAPSE	0.34*	−0.41*	0.38*	−0.56**
E/E′	−0.45**	0.76**	−0.44**	0.59**
Resting NT-proBNP	−0.44**	0.66**	−0.54**	0.86**
NT-proBNP at peak exercise	−0.45**	0.67**	−0.56**	0.88**
NT-proBNP post exercise	−0.42*	0.66**	−0.56**	0.88**

Values are correlation coefficients. *$p < 0.05$. **$p < 0.01$; E/E′, ratio of early transmitral flow velocity to annular velocity; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; pEF, preserved ejection fraction; rEF, reduced ejection fraction; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.

Table 4. Comparison between key variables according to presence of exercise oscillatory ventilation in both heart failure groups

	HFrEF (*n* = 34)		HFpEF (*n* = 34)	
	No EOV (*n* = 21)	EOV (*n* = 13)	No EOV (*n* = 21)	EOV (*n* = 13)
LVEF (%)	30.0 ± 6.6	26.4 ± 6.4	54.5 ± 4.4	57.8 ± 4.1*
PASP (mmHg)	34.4 ± 7.7	46.5 ± 12.6**	35.9 ± 12.4	47.9 ± 13.3*
TAPSE (mm)	18.6 ± 2.6	15.8 ± 2.6**	18.4 ± 3.0	16.3 ± 3.5
E/E′	10.8 ± 3.4	17.1 ± 8.2*	10.3 ± 5.6	14.5 ± 6.5
Resting NT-proBNP (pg/ml)	786.0 (1844.0)	1450.0 (5420.0)**	645.0 (3490.0)	1800.0 (2725.0)
NT-proBNP at peak exercise (pg/ml)	865.0 (2020.0)	1593.0 (5300.0)**	666.0 (3601.0)	1950.0 (2906.0)*
NT-proBNP post exercise (pg/ml)	840.0 (2051.0)	1570.0 (5510.0)**	657.0 (3672.0)	2000.0 (3000.0)*

Values are mean ± SD or median (range). *$p < 0.05$. **$p < 0.01$.; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; pEF, preserved ejection fraction; rEF, reduced ejection fraction; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen consumption.
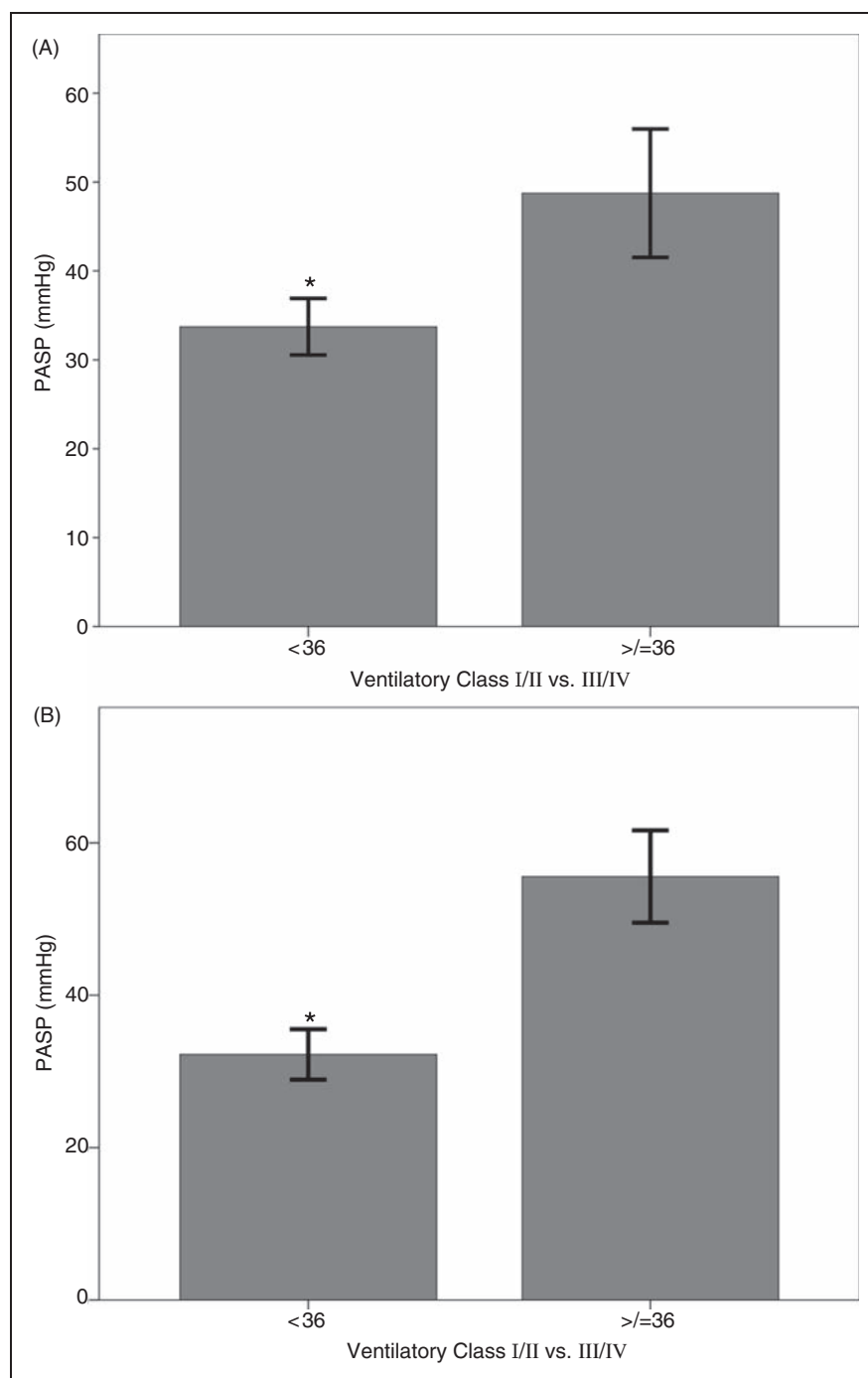
Figure 1. Difference in pulmonary artery systolic pressure according to the ventilatory classification system for HF-reduced ejection fraction (A) and HF-preserved ejection fraction (B).
Ventilatory classes: I, VE/VCO$_2$ slope <30.0; II, VE/VCO$_2$ slope 30–35.9; III, VE/VCO$_2$ slope 36–44.9; IV, VE/VCO$_2$ slope ≥45.0.
*$p < 0.01$
HF, heart failure; PASP, pulmonary artery systolic pressure; pEF, preserved ejection fraction; rEF, reduced ejection fraction.

reflecting pathophysiology are comparable between these unique cardiac populations. Our findings indicate that key CPX variables do reflect pathophysiology and thus disease severity associated with HFrEF and HFpEF in a comparable fashion. This is strengthened by the finding that even NT-proBNP levels at peak exercise are quite similar in the two groups. Moreover, the relationship amongst these key CPX

variables, well established in HFrEF, is likewise comparable in HFpEF. Collectively, the results of the present study support the clinical utility of CPX as a non-invasive, cost-efficient indicator of disease severity in HFpEF. This demonstrated relationship also lends credence to the potential of CPX to become an important prognostic assessment tool in the HFpEF population, which has recently been demonstrated in previous investigations.[4,5]

Perhaps one of the most compelling findings in the current study is the ability of an elevated VE/VCO_2 slope and EOV to reflect an elevated pulmonary pressure, the latter of which has been shown to be an important prognostic maker in the HF population.[22,23] Previous research has found PASP estimated by echocardiography with TDI closely approximates invasive measures,[24] validating our approach to pulmonary haemodynamic assessment and lending credence to the hypothesis that an elevated VE/VCO_2 slope and EOV portend a higher likelihood of secondary pulmonary hypertension. Given the demonstrated relationship between an elevated VE/VCO_2 slope and ventilation-perfusion mismatching,[25,26] as well as the relationship between EOV and fluctuations in pulmonary blood flow,[27] it is not surprising they both are indicative of elevated pulmonary pressures in HF. In this context, the ability of VE/VCO_2 slope and EOV to reflect this disconcerting secondary consequence of HFrEF and HFpEF has a high level of clinical value.

Previous research has suggested that the VE/VCO_2 slope may be a better reflector of HF disease severity compared to peak VO_2.[1] The correlation analysis presented in Table 3 is consistent with previous research making this comparison, both in patients with HFrEF and HFpEF. The VE/VCO_2 slope, while significantly correlated to peak VO_2, is relatively independent of subject effort and uniquely reflects physiological processes that differ from aerobic capacity (e.g. ventilation-perfusion mismatching). The relative effort independence and unique relationship to pathophysiology in HF may be primary reasons why VE/VCO_2 slope holds key advantages over peak VO_2 as a primary CPX variable, both as a prognostic marker and measure of disease severity. There is a rather compelling body of research to support this view point in patients with HFrEF, although the consensus is both VE/VCO_2 slope and peak VO_2 should be assessed in combination to improve prognostic resolution.[3] While the current investigation supports a similar pattern in HFpEF with respect to VE/VCO_2 slope and peak VO_2, future research should be performed to confirm these findings.

The relatively small sample size is an obvious limitation to the current investigation. Moreover, there were a limited number of female subjects included in the current analysis, which should be addressed in future investigations. Given the small sample size, our linear and logistic regression analysis results should be viewed as exploratory at this point, requiring verification in larger datasets before considering clinical application. In addition, even though echocardiography with TDI has been shown to accurately estimate cardiopulmonary haemodynamics, inclusion of invasive assessments of pulmonary pressure would have strengthened the current investigation. Lastly, both atrial fibrillation and CRT have been shown to impact exercise performance in patients with HF; the former diminishing performance[28] and the latter improving performance.[29] As described in the first paragraph of the methods section, differences in the number of subjects with atrial fibrillation and CRT use existed between HFrEF and HFpEF groups. These were not baseline characteristics we could control for and thus should be addressed in future investigations. Despite these limitations, the relationships demonstrated in the HFrEF cohort in this study are consistent with previous investigations, which lend credence to our findings in subjects with HFpEF.

In conclusion, due to the robust body of literature demonstrating prognostic utility as well as the ability to accurately gauge disease severity and therapeutic efficacy, CPX is a well-established clinical assessment in the HFrEF population. Evidence is beginning to emerge indicating CPX may be equally valuable in patients with HFpEF. The results of the present study lend further support to this position by demonstrating key CPX variables are equally reflective of pathophysiology and thus disease severity in well-matched HFrEF and HFpEF cohorts. Research should continue to examine the value of CPX in the HFpEF population to determine if support for utilization of this exercise assessment as a clinical standard of care is warranted.

Funding

Conflict of interest

The authors declare that there are no conflicts of interest.

References

1. Arena R, Myers J and Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev* 2008; 13: 245–269.
2. Piepoli MF, Corra U, Agostoni PG, et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part III: Interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 485–494.

3. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults. A scientific statement from the American Heart Association. *Circulation* 2010; 122: 191–225.

4. Guazzi M, Myers J, Peberdy MA, et al. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J* 2008; 29: 2751–2759.

5. Guazzi M, Myers J and Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005; 46: 1883–1890.

6. Guazzi M, Myers J, Peberdy MA, et al. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure-normal ejection fraction. *J Cardiopulm Rehabil Prev* 2010; 30: 165–172.

7. Moore B, Brubaker PH, Stewart KP, et al. VE/VCO_2 slope in older heart failure patients with normal versus reduced ejection fraction compared with age-matched healthy controls. *J Card Fail* 2007; 13: 259–262.

8. Weber KT, Janicki JS and McElroy PA. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. *Circulation* 1987; 76: VI40–VI45.

9. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation* 2007; 115: 2410–2417.

10. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003; 108: 1146–1162.

11. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000; 102: 1788–1794.

12. Arena R, Myers J, Aslam S, et al. Technical considerations related to the minute ventialtion/carbon dioxide output slope in patients with heart failure. *Chest* 2003; 124: 720–727.

13. Ingle L, Goode K, Carroll S, et al. Prognostic value of the VE/VCO_2 slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol* 2007; 118: 350–355.

14. Corra U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest* 2002; 121: 1572–1580.

15. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). *Eur Heart J* 2000; 21: 154–161.

16. Guazzi M, Arena R, Ascione A, et al. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J* 2007; 153: 859–867.

17. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83: 778–786.

18. Witte KKA, Nikitin NP, Cleland JGF, et al. Excessive breathlessness in patients with diastolic heart failure. *Heart* 2006; 92: 1425–1429.

19. Francis DP, Davies LC, Piepoli M, et al. Origin of oscillatory kinetics of respiratory gas exchange in chronic heart failure. *Circulation* 1999; 100: 1065–1070.

20. Piepoli MF, Ponikowski PP, Volterrani M, et al. Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in chronic heart failure Do Cheyne and Stokes have an important message for modern-day patients with heart failure?. *Eur Heart J* 1999; 20: 946–953.

21. Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation* 1999; 100: 2418–2424.

22. Carrasco-Sanchez FJ, Ortiz-Lopez E, Galisteo-Almeda L, et al. [Prognostic importance of pulmonary hypertension in heart failure with preserved ejection fraction]. *Rev Clin Esp* 2010; 210: 489–496.

23. Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J* 2010; 31: 2280–2290.

24. Nagueh SF, Bhatt R, Vivo RP, et al. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. *Circ Cardiovasc Imaging* 2011; 4: 220–227.

25. Wada O, Asanoi H, Miyagi K, et al. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J* 1993; 125: 790–798.

26. Reindl I, Wernecke KD, Opitz C, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J* 1998; 136: 778–785.

27. Yajima T, Koike A, Sugimoto K, et al. Mechanism of periodic breathing in patients with cardiovascular disease. *Chest* 1994; 106: 142–146.

28. Agostoni P, Emdin M, Corra U, et al. Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J* 2008; 29: 2367–2372.

29. Laveneziana P, O'Donnell DE, Ofir D, et al. Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J Appl Physiol* 2009; 106: 1574–1583.