Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease

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Background The assessment of aerobic exercise capacity is an important component in the clinical management of patients with heart failure (HF). Although a significant percentage of patients diagnosed with HF also present with chronic obstructive pulmonary disease (COPD) comorbidity, the combined impact of these chronic conditions on the aerobic exercise response is unknown and is therefore the purpose of the present investigation.

Methods Sixty-nine subjects with HF and COPD were matched to 69 subjects solely diagnosed with HF according to age, sex, and HF etiology. All subjects underwent resting pulmonary function and diffusion capacity testing, echocardiography with tissue Doppler imaging, and cardiopulmonary exercise testing (CPX).

Results Subjects with COPD comorbidity had significantly lower pulmonary function testing and diffusion capacity values versus HF alone ($P < .05$). In addition, subjects with both HF and COPD had significantly higher pulmonary artery systolic pressures (51.9 ± 9.0 vs 37.0 ± 7.8 mm Hg, $P < .001$) as assessed by pulsed Doppler echocardiography. Cardiopulmonary exercise testing revealed a significantly poorer response in subjects with HF and COPD by all variables that were analyzed, including peak oxygen consumption (12.1 ± 4.3 vs 16.3 ± 4.3 mL kg^{-1} min^{-1}, $P < .001$), minute ventilation/carbon dioxide production slope (42.7 ± 7.4 vs 33.3 ± 6.6, $P < .001$) and heart rate recovery at 1 minute (12.1 ± 2.5 vs 14.2 ± 2.9 beats, $P < .001$).

Conclusions Patients with HF and the comorbidity of COPD have significantly impaired CPX responses. This novel finding may impact the clinical interpretation of CPX data in patients with HF who also present with this chronic pulmonary condition. (Am Heart J 2010;160:900-5.)

Impaired aerobic capacity, ranging from mild to severe, is a hallmark clinical attribute in patients diagnosed with heart failure (HF). Many patients in this chronic disease population present with abnormal ventilatory efficiency (such as a heightened VE/VCO$_2$ (carbon dioxide production) slope) during physical exertion, which has been shown to reflect the extent of disease severity across a broad range.[1] Deficiencies in aerobic exercise performance can be quantified by cardiopulmonary exercise testing (CPX), an examination technique that provides comprehensive insight into disease severity and provides robust prognostic information in patients with HF.[2] As such, CPX is currently a well accepted clinical tool in the HF population, particularly to assess the risk for future adverse events.[3] Although CPX is not routinely used in patients with a primary diagnosis of chronic obstructive pulmonary disease (COPD), evidence indicates that individuals in this chronic disease population also present with varying degrees of diminished aerobic capacity and impaired ventilatory efficiency reflective of the level of disease severity.[4]

Previous reports indicate the prevalence of coexisting COPD in patients diagnosed with HF may approach 40%.[5] Given that HF and COPD both independently lead to impaired aerobic exercise performance, it is plausible to consider that the combination of these chronic diseases in a given patient may compound the abnormalities observed during CPX. However, the impact of comorbidities such as COPD on the CPX response in patients with HF is afforded little if any consideration in present-day clinical practice. Rather, it is assumed that CPX abnormalities are exclusively the consequence of HF-induced

pathophysiology. We are unaware of any previous investigations that have examined the impact of COPD comorbidity on the CPX response in patients primarily being assessed or treated for HF. The purpose of the present study was to therefore perform comparisons between patients referred for CPX who were diagnosed with HF but not COPD to those presenting with both chronic conditions. Given the potential independent impact COPD has on the response to aerobic exercise, we hypothesize that the CPX response would be significantly worse in subjects with this comorbidity compared to individuals exclusively diagnosed with HF.

Methods

Subject characteristics

One hundred thirty-eight subjects with compensated HF, undergoing a clinical evaluation for their condition at San Paolo Hospital in Milano, Italy, that included b-type natriuretic peptide (BNP) assessment, echocardiography with tissue Doppler imaging (TDI), CPX, pulmonary function testing (PFT), and pulmonary diffusing capacity assessment were enrolled in this study. All were receiving stable pharmacologic management before initiation of the study. Inclusion criteria consisted of a diagnosis of HF[6] and evidence of left ventricular dysfunction by echocardiography. Sixty-nine subjects with a coexisting diagnosis of COPD before assessment were randomly matched to 69 subjects not diagnosed with COPD according to age, sex, and HF etiology. A diagnosis of COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease.[7] Randomization was conducted a priori according to the aforementioned baseline characteristics while blinded to all results obtained from clinical assessment. Any subject unable to perform a maximal exercise test was excluded from the study. Informed consent and institutional review board approval was obtained before study initiation. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Echocardiography

Standard M-mode and 2-dimensional echocardiography and Doppler blood flow measurements were performed in agreement with the American Society of Echocardiography Guidelines.[8] Septal and posterior left ventricular (LV) wall thickness was obtained from the parasternal long-axis view. The LV end-systolic volumes (LVESV) were obtained from 2-dimensional apical images. The LV ejection fraction was calculated according to Simpson's method from 2-dimensional apical images. The LV mass was calculated according to the formula proposed by Devereux et al.[9]

Conventional Doppler and TDI measurements

Mitral inflow measurements included peak early (E) and peak late (A) flow velocities and the E/A ratio. The TDI of the mitral annulus was obtained from the apical 4-chamber view. A 1.5 sample was placed sequentially at the lateral and septal annular sites. Analysis was performed for the early (E') diastolic peak velocity. The ratio of early transmitral flow velocity to annular mitral velocity of the lateral LV wall (E/E') was taken as an estimate of LV filling pressure.[10] Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic transtricuspid pressure gradient using the modified Bernulli equation (4× the peak tricuspid regurgitant velocity squared), adding right atrial pressure to the calculated gradient.[11] None of the subjects had significant right ventricular outflow tract obstruction.

Cardiopulmonary exercise testing

Each patient performed a CPX to maximum tolerance on an electromagnetically braked cycle ergometer (individualized ramp protocol). The aim was to achieve peak exercise in approximately 10 minutes. Ventilatory expired gas analysis was obtained using a metabolic cart (Medgraphics CPX-D, Minneapolis, MN), which was calibrated before each test. Monitoring consisted of continuous 12-lead electrocardiography, manual blood pressure measurements every 2 minutes, heart rate recordings each minute via the electrocardiogram, oxygen saturation via pulse oximetry (SpO_2), and rating of perceived dyspnea (Borg, 0-10 scale) each minute. A decrease in SpO_2 to a level ≥88% was considered to be a clinically significant desaturation.[12] Heart rate recovery (HRR) was defined as the difference in HR between HR at maximal exercise and 1-minute posttest termination. Test termination criteria consisted of patient request, ventricular tachycardia, ≥2 mm of horizontal or downsloping ST-segment depression or a drop in systolic blood pressure ≥20 mm Hg during exercise. A qualified exercise physiologist with physician supervision conducted each test.

Oxygen consumption (mL·kg^{-1}·min^{-1}), VCO_2 (L/min), and VE (L/min) were collected continuously throughout the exercise test. Peak oxygen consumption per unit time (VO_2) and VE were expressed as the highest 30-second average value obtained during the last stage of the exercise test. Peak respiratory exchange ratio (RER) was the highest 30-second averaged value during the last stage of the test. 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) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). Exercise oscillatory ventilation (EOV) was defined as an oscillatory pattern at rest that persisted for ≥60% of the exercise test at an amplitude ≥15% of the average resting value.[13]

Six-minute walk test

The 6-minute walk test (6MWT) was performed on a level surface by a physician unaware of CPX and clinical results. Each subject underwent 2 tests performed on separate days. The first was performed for familiarization purposes, and the second was taken as representative of true submaximal exercise capacity. Patients were instructed to cover the greatest distance possible during the allotted time, at a self-determined walking speed, pausing to rest when needed. The distance covered was measured by a body-borne pedometer (Pedometer 1-100000; Eschenbach, Germany) according to the following formula: $d = y \times 10 \ m/x$, where d is distance walked in meters, x is the number of steps needed to cover a 10-m distance, and y is the total step number over the entire 6-minute test, as previously reported by Roul et al.[14]

Table I. Baseline, echocardiography with TDI, and pharmacotherapy characteristics

	HF − COPD (n = 69)	HF + COPD (n = 69)
Baseline characteristics		
Age, y	64.7 ± 8.7	65.0 ± 9.7
Sex, male/female	57/12	57/12
Body mass index, kg/m^2	25.7 ± 3.6	26.3 ± 4.0
Etiology, ischemia/nonischemia	43/26	43/26
NYHA class	2.1 ± 0.72	2.6 ± 0.77*
BNP, pg/mL	965.7 ± 617.0	1794.4 ± 700.2†
Echocardiography with TDI		
LV ejection fraction, %	34.8 ± 9.7	33.8 ± 11.9
LVESV, mL	113.6 ± 23.4	115.6 ± 37.3
LV mass, g	224.8 ± 22.9	233.7 ± 28.0*
E/A ratio	1.3 ± 0.39	1.3 ± 0.48
E/E′ ratio	8.6 ± 3.2	10.2 ± 3.4*
PASP, mm Hg	37.0 ± 7.8	51.9 ± 9.0†
Therapy distribution, %		
ACE inhibitor	91	70†
Antialdosterone	39	49
Diuretic	60	90†
β-Blocker	62	61

* P < .05.
† P < .001.

Pulmonary function testing

Spirometry was performed with equipment that met the American Thoracic Society performance criteria.[15] To adjust for height, age, and gender, we used published prediction equations for forced expiratory volume in 1 s (FEV$_1$) and forced vital capacity (FVC).[16] Maximal voluntary ventilation (MVV in L/min) was estimated by the following equation: FEV$_1$ × 40.[17] The VE/MVV ratio was then calculated using peak VE during exercise (described in the CPX section) and estimated MVV.

Gas diffusion measurement

Lung diffusing capacity for carbon monoxide (DLco) was determined with washout intervals of at least 4 minutes with a standard single breath technique. The maneuver was performed using a test gas with 0.28% carbon monoxide, 0.3% acetylene, 0.3% methane, 21% oxygen (O$_2$), and the balance made up of nitrogen, and was then repeated using test gases with 40% and with 60% O$_2$ concentrations. The conductance of the alveolar-capillary membrane (Dm) and pulmonary capillary blood volume available for gas exchange (Vc) were determined using the classic method of Roughton and Forster.[18] This method partitions pulmonary diffusing capacity into its component resistances, the diffusive resistance of the alveolar-capillary membrane (1/Dm), and the reactive resistance due to pulmonary capillary blood (1/θ Vc, where θ = the rate of reaction of carbon monoxide with hemoglobin), according to the following equation: 1/DLco = 1/Dm + 1/ θVc.

The 1/θ value was determined using the following equation, which assumes that the red cell membrane has a negligible resistance to gas exchange: 1/θ = 14.6/Hb × [0.001 × PAo$_2$ + 0.0134], where Hb is the subject's hemoglobin concentration (g/dL) and PAo$_2$ is the alveolar O$_2$ partial pressure. Measuring DLco at different fraction of inspired oxygen (20%,

Table II. Pulmonary function test and diffusion capacity data

	HF − COPD (n = 69)	HF + COPD (n = 69)
Measured FEV$_1$, L	2.7 ± 0.70	2.4 ± 0.68*
Percent-predicted FEV$_1$, %	82.2 ± 14.6	72.9 ± 14.3†
Measured FVC, L	3.1 ± 0.71	2.8 ± 0.70*
Percent-predicted FVC, %	81.8 ± 12.4	76.0 ± 12.6*
Estimated MVV, L/min	106.8 ± 28.0	94.0 ± 27.3*
DLco, mL CO/min/mm Hg	23.2 ± 5.6	17.0 ± 3.7†
Percent-predicted DLco, %	92.3 ± 22.2	69.0 ± 16.5†
Dm, mL/mm Hg/min	28.8 ± 8.4	20.7 ± 7.3†
Vc, mL	107.6 ± 28.0	122.9 ± 22.4*

* P < .05.
† P < .001.

40%, 60%), a plot of 1/DLco against 1/θ will yield a straight line with a y intercept of 1/Dm and a gradient of 1/Vc. Alveolar volume was derived by methane dilution. Percent-predicted DLco was determined by equations put forth by the European Respiratory Society.[19]

Statistical analysis

A statistical software package was used for all analyses (SPSS 13.0; SPSS Inc, Chicago, IL). All continuous data are reported as mean values ± SD, whereas all categorical variables are reported as percentages. Paired t testing was used to compare continuous variables between subjects with and without COPD comorbidity. The Wilcoxon signed rank test compared differences in New York Heart Association (NYHA) class and maximal dyspnea during exercise, whereas χ^2 analysis assessed differences in categorical variables between groups. Pearson product moment correlation was used to assess the relationships between key CPX variables and echocardiography with TDI, PFT, and diffusion capacity in both groups (no COPD and COPD). Statistical differences with a P value <.05 were considered significant.

Results

Baseline characteristics, echocardiography with TDI data, and pharmacotherapy distribution are listed in Table I. Groups were of comparable age, sex, and HF etiology, whereas NYHA class was significantly higher in subjects with COPD comorbidity, as was BNP, LV mass, E/E′, and PASP. Prescription of angiotensin-converting enzyme (ACE) inhibitors was higher in subjects without a diagnosis of COPD, whereas the converse was true for diuretics. Antialdosterone and β-blocker prescriptions were comparable between groups.

Pulmonary function testing and diffusion capacity results listed in Table II reveal a significant difference in all variables between groups. Subjects with COPD comorbidity presented with significantly lower actual and percent-predicted PFT and DLco values as well as actual Dm values. Estimated MVV was likewise lower in subjects with both chronic conditions. Conversely, Vc was significantly higher in subjects with COPD comorbidity.

Table III. CPX and 6MWT data

	HF – COPD (n = 69)	HF + COPD (n = 69)
Peak VO_2, mL·kg^{-1}·min^{-1}	16.3 ± 4.3	12.1 ± 4.3[†]
VE/VCO_2 slope	33.3 ± 6.6	42.7 ± 7.4[†]
Peak RER	1.06 ± 0.13	1.07 ± 0.10
Maximal HR, beat/min	132.7 ± 15.5	120.6 ± 15.6[†]
HRR, beat/min	14.2 ± 2.9	12.1 ± 2.5[†]
Subjects with EOV, %	41%	70%[†]
Peak VE, L/min	62.0 ± 18.4	60.8 ± 15.9
VE/MVV, %	59.4 ± 15.0	66.4 ± 14.5[†]
Peak dyspnea	6.0 ± 1.1	6.6 ± 1.1[*]
6MWT, m	366.8 ± 79.4	295.0 ± 95.2[†]

[*] $P < .05$.
[†] $P < .001$.

Table IV. Correlation analysis between CPX and key resting variables

	HF – COPD (n = 69)		HF + COPD (n = 69)	
	Peak VO_2	VE/VCO_2 slope	Peak VO_2	VE/VCO_2 slope
Echocardiography with TDI				
LV ejection fraction	0.19	–0.21	0.10	–0.01
E/E'	–0.10	0.33[*]	–0.03	–0.03
LV mass	–0.04	0.10	0.03	0.02
LVESV	–0.26[*]	0.13	–0.04	–0.06
PASP	–0.20	0.69[†]	0.04	0.06
PFT				
FEV$_1$	0.13	–0.13	0.47[†]	–0.25[*]
FVC	0.11	–0.16	0.43[†]	–0.29[*]
Diffusion capacity				
DL$_{CO}$	0.17	–0.56[†]	0.05	–0.05
Percent-predicted DL$_{CO}$	–0.3	–0.44[†]	–0.09	–0.03
DM	0.21	–0.48[†]	0.06	–0.06
Vc	–0.09	–0.08	0.25[*]	–0.23

[*] $P < .05$.
[†] $P < .01$.

Only one subject with COPD comorbidity reached an SpO_2 ≤88% at peak exercise (actual value = 87%). Exercise testing data are presented in Table III. Exercise effort was comparable between groups as indicated by peak RER. With the exception of peak VE, all other variables were, however, significantly different. Peak VO_2, maximal HR, HRR, and 6MWT distance were significantly lower, whereas the VE/VCO_2 slope, frequency of EOV, VE/MVV, and peak dyspnea were significantly higher in subjects with COPD comorbidity.

Correlation results are listed in Table IV. In subjects without COPD comorbidity, the VE/VCO_2 slope was significantly correlated with *E/E'*, PASP, measured and percent-predicted DL$_{CO}$, and Dm. Conversely, the VE/VCO_2 slope was significantly correlated with FEV$_1$ and FVC in subjects with COPD comorbidity. The correlations with peak VO_2 were likewise different between groups with LVESV, being the only variable reaching significance in the group without COPD comorbidity, whereas FEV$_1$, FVC, and Vc all demonstrated significant relationships with aerobic capacity in those with COPD comorbidity.

Discussion

Previous research has demonstrated that exercise testing characteristics are abnormal in patients exclusively diagnosed with COPD compared to healthy controls.[20] To our knowledge, however, the present investigation is the first to report on the compounding impact of COPD comorbidity on the exercise response in patients diagnosed with HF. This type of assessment may be of particular interest given the clinical importance of CPX in patients with HF and the substantial prevalence of COPD in this population.[5] When matched for age, sex, and HF etiology, we observed that patients with COPD comorbidity presented with (1) a significantly higher NYHA class and BNP, (2) a significantly higher LV mass, *E/E'*, and PASP assessed by echocardiography with TDI, and (3) significantly lower PFT and diffusion capacity values. A higher BNP level in patients diagnosed with both HF

and COPD has been previously reported, which is consistent with the findings of the current investigation.[21] With respect to echocardiography with TDI, previous research indicates COPD can independently lead to LV diastolic dysfunction.[22] Although mean *E/E'* values were elevated in both groups, it was significantly higher in patients with coexisting COPD compared to subjects only diagnosed with HF. This finding indicates COPD may further worsen diastolic function in patients with HF and contribute to the apparent increase in disease severity and functional limitation when both chronic conditions are present. Pharmacologic therapy also differed between groups with a significantly lower percentage of subjects with both HF and COPD being prescribed an ACE inhibitor, whereas this same group was prescribed a diuretic more frequently. The reason for this being subjects included in the present study that were diagnosed with both chronic conditions had a higher incidence of intolerance to ACE inhibitors due to collateral effects, mainly cough and hypotension. Most pertinent to the present investigation is the differences in exercise testing responses between groups. Subjects with HF and COPD comorbidity presented with a more impaired exercise testing response by all measures including aerobic capacity, ventilatory efficiency (VE/VCO_2 slope, EOV prevalence, and VE/MVV), peak HR, HRR, perception of dyspnea at maximal exercise, and 6MWT distance. Moreover, effort during CPX appeared comparable between groups by peak RER indicating these differences were a reflection of worsening physiologic function of the cardiac, pulmonary, and/or skeletal muscle systems in the presence of COPD comorbidity. These findings indicate that HF and COPD work

synergistically to worsen the physiologic response to physical exertion and further limit functional capacity compared to the already apparent exertional limitations in patients solely having HF.

Previous research indicates the abnormal exercise response in patients with HF is multifactorial, involving the cardiac, skeletal muscle, and pulmonary systems to varying degrees.[2] The present investigation indicates the pathophysiologic mechanisms most closely associated with aerobic exercise abnormalities in patients with HF may be influenced by COPD comorbidity. With respect to peak Vo_2, correlations were poor and only reached a relatively weak level of statistical significance with LVESV in subjects without COPD. For those subjects with COPD, the correlation between peak Vo_2 and PFT measures were more robust, indicating pulmonary function accounts for a greater degree of variability in aerobic capacity. However, the relationship between peak Vo_2 and PFT measures remained only modest. Previous research has found the correlation between peak Vo_2 and the same PFT measures collected in the present study to be stronger in subjects exclusively diagnosed with COPD.[23] The weaker relationship between peak Vo_2 and pulmonary function we found may indicate the pathophysiologic mechanisms associated with HF in subjects with concomitant COPD likely have some role in modulating the exercise response.

With respect to ventilatory efficiency, several echocardiography with TDI and diffusion capacity variables significantly correlated with the VE/Vco_2 slope in HF subjects without COPD. In this subgroup, it appears that cardiac function, pulmonary hemodynamics, and ventilation-perfusion matching explain a greater degree of this important CPX variable. Previous research has posited similar pathophysiologic mechanisms for an abnormally elevated VE/Vco_2 slope in patients with HF and no COPD comorbidity.[24] In the presence of COPD comorbidity, however, significant correlations with the VE/Vco_2 slope were only achieved with PFT measures. In this instance, it appears that alterations in interstitial lung function brought about by COPD further worsened ventilatory efficiency and potentially masks the normally expected relationship between the VE/Vco_2 slope and both pulmonary hemodynamics and ventilation-perfusion matching in patients with HF. It should be noted that for the most part, correlations between resting measures of cardiovascular and pulmonary function in the present study and key CPX variables that reached statistical significance were relatively weak and thus did not provide a strong explanatory relationship between pathophysiology and the degree of exercise limitation. Currently, the degree of CPX abnormalities in patients with HF is most often thought to reflect global disease severity, involving multiple pathophysiologic processes. The results from the present study indicate the link between CPX data and pathophysiologic mechanisms

may differ according to the absence or presence of concomitant COPD in patients with HF.

The coexistence of COPD also significantly increased the prevalence of EOV, a phenomenon that to this point has been reported on patients with HF without considering the potential influence of pulmonary disease. Several hypotheses may be put forth for explaining a higher incidence in EOV in patients with both HF and COPD. Pathophysiologic factors that may be overexpressed in patients with both diseases are a marked sympathetic activation with further deregulation of chemo and ergoreflex activity[25] and/or an increased impairment in LV filling pressures and pulmonary wedge pressure. [26]

Patients with both HF and COPD possess skeletal muscle abnormalities that have been linked to poor aerobic exercise performance.[27,28] That these skeletal muscle metabolic abnormalities were not included in the present analysis is a clear limitation. Future research should determine the impact that concomitant COPD has on the already apparent and detrimental skeletal muscle alterations in patients exclusively diagnosed with HF and determine if peripheral adaptations differently modulate the aerobic exercise response in patients with both chronic diseases. Moreover, a group of patients exclusively diagnosed with COPD for comparative purposes would have strengthened this analysis. There is some indication that, although diminished according to normative values, aerobic capacity may be higher in patients exclusively diagnosed with COPD compared to those exclusively diagnosed with HF.[29] Given the findings of previous investigations in addition to the results presented in this study, we hypothesize that the coexistence of HF and COPD further compounds exercise deficiencies as detected by CPX.

In present-day clinical practice, CPX is most often used to assess prognosis in patients with HF.[3] The use of CPX for this purpose is supported by a wealth of original research consistently demonstrating the ability of peak Vo_2 and the VE/Vco_2 slope to identify those individuals at significantly higher risk for adverse events.[2] This body of literature has, however, established the clinical value of CPX without considering the potential impact COPD comorbidity may have. Moreover, the presence of COPD itself portends a worse prognosis in the HF population.[30] Future research must therefore confirm the prognostic ability of CPX in patients with HF and COPD. If found to be similarly prognostic, determining optimal threshold values for both peak Vo_2 and the VE/Vco_2 slope to define increased risk for adverse events would be an important next step. Present dichotomous and multilevel thresholds for these CPX variables have been established without considering the impact of COPD comorbidity.[2] The results of the present study suggest that CPX results may be profoundly influenced by COPD comorbidity, and it is therefore reasonable to suspect peak Vo_2 and VE/Vco_2 slope threshold values that identify increased risk

may also differ. Lastly, other CPX measures, such as HRR and EOV, also provide important prognostic insight in patients with HF. However, the influence of COPD on the predictive value of these emerging CPX variables has not been assessed. Future research should therefore address this issue.

In conclusion, the results of the present study indicate marked differences in resting cardiac and pulmonary measures as well as exercise performance in patients with HF according to the presence or absence of concomitant COPD. To our knowledge, this is the first investigation to report on these differences. These findings have applications for the clinical interpretation of CPX data in patients with HF when COPD comorbidity is present.

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