Submaximal exercise pulmonary gas exchange in left heart disease patients with different forms of pulmonary hypertension

Short Title:
Pulmonary gas exchange in HF patients with PH

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Funding Sources:
This work was supported by grants from NIH (HL71478, HL98663).
BJT was supported by the American Heart Association (AHA12POST12070084).

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ABSTRACT

Background. We determined whether pulmonary gas exchange indices during submaximal exercise are different in heart-failure (HF) patients with combined post- and pre-capillary pulmonary hypertension (PPC-PH) vs. HF patients with isolated post-capillary PH (IPC-PH) or no-PH. **Methods & Results.** Pulmonary hemodynamics and pulmonary gas exchange were assessed during rest and submaximal exercise in 39 HF patients undergoing right-heart catheterization. Post-hemodynamic evaluation, patients were classified as having no-PH (*n*=11), IPC-PH (*n*=12) or PPC-PH (*n*=16). At an equivalent oxygen consumption, end-tidal CO_2 ($PETCO_2$) and arterial oxygen saturation (SaO_2) were greater in no-PH and IPC-PH vs. PPC-PH patients (36.1±3.2 vs. 31.7±4.5 vs. 26.2±4.7 mmHg and 97±2 vs. 96 ±3 vs. 91±1%, respectively). Conversely, dead-space ventilation (V_D/V_T) and the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$ ratio) were lower in no-PH and IPC-PH vs. PPC-PH patients (0.37±0.05 vs. 0.38±0.04 vs. 0.47±0.03 and 38±5 vs. 42±8 vs. 51±8, respectively). The exercise-induced change in V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ ratio and $PETCO_2$ correlated significantly with the change in mean pulmonary arterial pressure, diastolic pressure difference and transpulmonary pressure gradient in PPC-PH patients only. **Conclusion.** Noninvasive pulmonary gas exchange indices during submaximal exercise are different in HF patients with combined post-and pre-capillary PH compared to patients with isolated post-capillary PH or no-PH.

Key Words. Diastolic pressure difference; pre- and post-capillary pulmonary hypertension; right-heart catheterization; submaximal exercise.

INTRODUCTION

Pulmonary hypertension (PH) is a hallmark of chronic heart failure (HF) and is associated with pulmonary edema, dyspnea, exercise intolerance, poor prognosis and increased mortality in HF patients (1-4). In patients with left heart disease (LHD), PH first manifests as a "passive" increase in post-capillary pulmonary venous pressure with a concomitant elevation in pulmonary arterial pressure (PAP) secondary to the increase in left ventricular filling pressure consistent with a failing left ventricle (5). However, many LHD patients also develop a form of pulmonary vascular disease that is associated with vasoconstriction and/or fixed structural remodeling of the pulmonary arterial resistance vessels. Previously termed "reactive" or "out-of-proportion" PH, this combined post-capillary and pre-capillary form of PH is characterized by an excessive increase in PAP relative to the increase in pulmonary wedge pressure (PWP), an increase in the diastolic pressure difference (DPD) (defined as diastolic PAP – mean PWP), and an increase in pulmonary vascular resistance (PVR) (6-8). Although the temporality and precise etiology of the development of PPC-PH are relatively unknown, the development of post-capillary PH with a pre-capillary component is, importantly, associated with a further increase in mortality rate in the HF population (9).

Chronic HF is also associated with derangements in ventilatory and pulmonary gas exchange indices at rest and during submaximal and maximal exercise [e.g., low end-tidal CO_2 ($PETCO_2$), reduced ventilatory efficiency (increased $\dot{V}_E/\dot{V}CO_2$)] that are likely related to the development and severity of PH (10-14). Indeed, we have shown that $\dot{V}_E/\dot{V}CO_2$ and $PETCO_2$ are both significantly related to invasively determined mPAP and PVR during submaximal exercise in HF patients (13). Moreover, administration of the vasodilator sildenafil causes a significant reduction in PAP and PVR with a concomitant decrease in $\dot{V}_E/\dot{V}CO_2$ slope during exercise (i.e. improved breathing efficiency) in HF (10). More recently, Guazzi et al. (15) reported that a $\dot{V}_E/\dot{V}CO_2$ slope ≥ 36 in response to exercise was an excellent predictor of the presence of left sided PH in HF patients. In addition, it has been

shown that the $\dot{V}_E/\dot{V}CO_2$ slope (> 41), the change in $PETCO_2$ (<1.2 mmHg) and the severity of oscillatory ventilation during exercise are associated with "reactive" PH in HF patients (14). Taken together, the aforementioned data suggest that the deleterious alterations in ventilatory parameters and pulmonary gas exchange during exercise in patients with HF are related to the development and severity of PH. The aim of the present study was to further determine whether measures of pulmonary exchange during submaximal exercise differed in HF patients with combined post- and pre-capillary PH compared to HF patients with isolated post-capillary PH or no PH. As such, it was anticipated that the findings of the present study would 1) reinforce the concept that measures of pulmonary gas exchange during cardiopulmonary exercise testing (CPET) provide a suitable tool for noninvasive detection of PH, and 2) add to the most recent literature suggesting that measures of pulmonary gas exchange during CPET allow differentiation of HF patients with post- and pre-capillary pulmonary hypertension from patients with isolated post-capillary pulmonary hypertension.

METHODS

Participants and ethical approval

Thirty-nine adult patients (32 male, 7 female) with a history of HF undergoing right heart catheterization volunteered to participate in the present study. The patients recruited for the study were required to meet the following criteria: 1) ≥1 y history of known HF, 2) an ejection fraction of ≤40%, and 3) a BMI <36. At the time of study, all patients were receiving standard, optimized pharmacotherapies for the management of HF. Post-hemodynamic evaluation, the patients were classified as either 1) HF without PH [mean PAP (mPAP) < 25 mmHg], 2) HF with isolated post-capillary PH [mPAP ≥ 25 mmHg, mean PWP (mPWP) > 15 mmHg, DPD < 7 mmHg), or 3) HF with combined post-capillary and pre-capillary PH (mPAP ≥ 25 mmHg, mPWP > 15 mmHg, DPD ≥ 7 mmHg) (all pressures measured at rest) according to current guidelines (8). Each participant gave written informed consent after being provided a detailed description of the study requirements. The experimental procedures were approved by the Mayo Clinic Institutional Review Board and were performed in accordance with the ethical standards of the Declaration of Helsinki.

Standard clinical tests

Prior to catheterization, each patient completed a range of standard clinical tests, including pulmonary function, echocardiography, six-minute walk test and blood analysis. The standard clinical tests were performed during a single day at least 24 h but not more than 7 days prior to the right-heart catheterization procedure. This was consistent with the normal protocol followed for patients undergoing clinically indicated right-heart catheterization.

Hemodynamic evaluation and cardiopulmonary exercise test

Right-heart catheterization was conducted as described previously (16). Briefly, with subjects well rested and in the supine position, a 22-gauge indwelling catheter was placed in the radial artery and a

7-French Swan-Ganz balloon-tipped catheter was advanced through the right side of the heart to the pulmonary artery via the right internal jugular vein. Minimal sedation was given only to the participants who required it. Diastolic PAP (dPAP) as well as mPAP and mPWP were measured via the pulmonary catheter. DPD was calculated as dPAP minus mPWP and TPG was computed as mPAP minus mPWP. Arterial and mixed venous blood was drawn simultaneously from the radial and the pulmonary artery, respectively, for measurement of arterial and mixed venous O_2 partial pressure (PaO_2 and PvO_2) and saturation (SaO_2 and SvO_2). Arterial and mixed venous oxygen content (CaO_2 and CvO_2) were then computed as $CaO_2 = (1.34 \times Hgb \times SaO_2) + (PaO_2 \times 0.0031)$ and $CvO_2 = (1.34 \times Hgb \times SvO_2) + (PvO_2 \times 0.0031)$. Cardiac output ($\dot{Q}$) was subsequently determined via direct Fick as oxygen consumption divided by (CaO_2-CvO_2). Pulmonary vascular resistance (PVR) was calculated as TPG divided by $\dot{Q}$.

Once the radial and pulmonary arterial catheters were placed, each patient rested quietly for 5 minutes before performing submaximal exercise on a stationary recumbent cycle ergometer (Stress EchoBed, Medical Positioning Inc., Kansas City, MO). The exercise protocol commenced at a workload of 10 W, after which the workload was increased by 10 W every 3 minutes. A pedal cadence of 60 rpm was maintained by each patient until they had completed 2-3 exercise stages and/or reached a perceived exertion of 12-13 (“somewhat hard”) on the Borg 6-20 scale. The aforementioned measures of pulmonary vascular pressures and central hemodynamics were assessed simultaneously with ventilatory and pulmonary gas exchange indices (Ultima CPX, MGC Diagnostics, St. Paul, MN) at rest and throughout exercise in each patient. Cardiac rhythm and heart rate (HR) were also monitored continually during exercise. Arterial and mixed venous blood was sampled at rest, during the final 30 s of each exercise stage, and at end exercise for the determination of PaO_2, PvO_2, SaO_2 and SvO_2. Additionally, SaO_2 was estimated at rest and throughout exercise

with the use of a pulse oximeter (Masimo Rad-9, Masimo Corporation, Irvine, CA) and finger-tip sensor.

Data analysis

Minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f_R), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), respiratory exchange ratio (RER) and end-tidal CO_2 ($PETCO_2$) were obtained breath-by-breath and averaged over a 30 s period at rest and the last 30 s of each stage during exercise. Similarly, HR and SaO_2 (via pulse oximetry) were assessed beat-by-beat and averaged over a 30 s period at rest and the last 30 s of each stage during exercise. From these data, derived variables including $\dot{V}_E/\dot{V}CO_2$ ratio, dead-space ventilation (V_D/V_T, where $V_D = [PaCO_2 - P_ECO_2]/PaCO_2$), and oxygen pulse ($\dot{V}O_2$/HR) were calculated at rest and during exercise and averaged as described above.

Statistical analyses

One way analysis of variance (ANOVA), with Bonferroni post-hoc correction, was performed to compare 1) subject demographics, 2) clinical data, and 3) measures of pulmonary hemodynamics and pulmonary gas exchange at rest and during exercise between the 3 patient groups (HF with no PH vs. HF with isolated post-capillary PH vs. HF with combined post- and pre-capillary PH). Pearson product-moment correlation coefficient (r) was computed to assess the relationships between the change in key gas exchange and the change in hemodynamic measures associated with submaximal exercise. The acceptable type I error was set at $P < 0.05$ and data are expressed as group means ± SD. Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS, Chicago, IL).

RESULTS

Patient demographics and clinical data

Patient demographics, medications and clinical data including right-heart catheterization, pulmonary function, echocardiography, six-minute walk distance and hematologic measurements are shown in Tables 1 and 2. Of the 39 patients studied, 10 were NYHA class II, 28 NYHA class III, and one NYHA class IV. Post-catheterization, 11 patients were categorized as HF without PH (no-PH), 12 as HF with isolated post-capillary PH (IPC-PH), and 16 as HF with combined post- and pre-capillary PH (PPC-PH). While the IPC-PH patients were a little older than the no-PH and PPC-PH patients, the three patient groups were well matched for sex distribution, height, weight and left ventricular ejection fraction (Table 1). On average, $\dot{V}O_{2peak}$ and six-minute walk distance were greater in the no-PH patients compared to IPC-PH and PPC-PH patients (Tables 1 and 2). Similarly, pulmonary function was more impaired in the IPC-PH and PPC-PH patients relative to the no-PH patients, but only significantly so for forced vital capacity (Table 2).

Resting and exercise pulmonary vascular pressures and hemodynamics

Pulmonary vascular pressures measured at rest are shown in Table 2. To accurately compare data from HF patients with PPC-PH, IPC-PH and no-PH during submaximal exercise, we compared pulmonary vascular pressures at a matched $\dot{Q}$ of ~4.5 L/min; this was the level of cardiac output reached by every patient during exercise. At this given $\dot{Q}$, mPAP was greater in the PPC-PH versus the no-PH (54.7 ± 6.6 vs. 31.9 ± 6.3 mmHg, $P = 0.014$) and, to a lesser extent, the IPC-PH patients (54.7 ± 6.6 vs. 45.1 ±7.4 mmHg, $P = 0.033$). In addition, mPWP was greater in the PPC-PH patients compared to the no-PH patients (31.6 ± 6.7 vs. 21.9 ± 7.5 mmHg, $P = 0.011$); mPWP was not different in the PPC-PH versus IPC-PH patients at this level of exercise (31.6 ± 6.7 vs. 33.7 ± 5.3 mmHg, $P = 0.527$). Exercise was associated with a modest increase in group mean DPD in the PPC-PH and IPC-PH patients only, but was greater at the matched $\dot{Q}$ in the PPC-PH compared to both the

IPC-PH and no-PH patients (11.1 ± 7.0 vs. 4.2 ± 3.7 vs. 2.7 ± 2.6 mmHg, $P \leq 0.029$). Moreover, PVR was largely unchanged from rest to submaximal exercise in all patient groups but was greater at a matched $\dot{Q}$ in the PPC-PH patients compared to the no-PH patients (6.0 ± 2.7 vs. 1.9 ± 1.3 WU, P = 0.014). It should be noted that although group mean PVR did not change with exercise in any patient group, we did observe substantial inter-individual differences in PVR response with 6 of the 11(55%), 5 of the 12 (42%) and 6 of the 16 (35%) no PH, IPC-PH and PPC-PH patients, respectively, showing a reduction in PVR with exercise. Together, these data show that pulmonary vascular pressures and resistance were greater in the PPC-PH versus the IPC-PH and no-PH patients at rest *and* in response to submaximal exercise.

Resting and exercise pulmonary gas exchange

At rest, $\dot{V}_E$ was slightly but significantly greater in patients with PPC-PH versus patients with no-PH; all other key ventilatory and gas exchange indices were similar and not statistically different between the patient groups at rest (Table 3 and Figure 1). To accurately compare data between patient groups during submaximal exercise, we compared pulmonary vascular pressures at a matched $\dot{V}O_2$ of ~0.60 L/min. During exercise at this matched $\dot{V}O_2$, $PETCO_2$ was lower in patients with IPC-PH compared to patients with no-PH (31.7 ± 4.5 vs. 36.1 ± 3.2 mmHg, P = 0.021) (Figure 1); this was the only gas exchange variable that was different during exercise in these two patient groups. At the same level of exercise, $\dot{V}_E$ and $\dot{V}_E/\dot{V}O_2$ were greater in patients with PPC-PH versus patients with no-PH (Table 4). Additionally, V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ and the $PaCO_2$-$PETCO_2$ difference were higher whereas $PETCO_2$ and SaO_2 were lower in patients with PPC-PH compared to patients with no-PH and patients with IPC-PH (Table 4 and Figure 1). In combination, these data indicated pulmonary gas exchange, particularly measures of V_D/V_T, $\dot{V}_E/\dot{V}CO_2$, $PaCO_2$-$PETCO_2$ difference, $PETCO_2$ and SaO_2, are substantially impaired in PPC-PH compared to IPC-PH and no-PH patients during submaximal exercise.

Relationship between exercise gas exchange and pulmonary vascular pressures during submaximal exercise

To determine the effect of pulmonary vascular pressure and resistance on pulmonary gas exchange during exercise, we assessed the relationships between the exercise-associated changes in key pulmonary gas exchange (V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ ratio, $P_{ET}CO_2$, SaO_2) and pulmonary hemodynamic variables (mPAP, mPWP, DPD, TPG,) (i.e. from rest to exercise at a matched $\dot{V}O_2$). There was no relationship between the change in any pulmonary gas exchange measure and the change in any measure of pulmonary vascular pressure associated with submaximal exercise in the IPC-PH patients (Table 5). Conversely, there was a positive correlation between mPAP and $\dot{V}_E/\dot{V}CO_2$ ratio (P = 0.012), and a negative relationship between mPAP and $P_{ET}CO_2$ (P = 0.009) in patients with PPC-PH (Table 5). In addition, there was a positive relationship between DPD and V_D/V_T (P = 0.025) and $\dot{V}_E/\dot{V}CO_2$ ratio (P = 0.046), and a negative relationship between DPD and $P_{ET}CO_2$ (P = 0.0182) (Figure 2). Moreover, TPG was positively related to V_D/V_T (P = 0.008) and $\dot{V}_E/\dot{V}CO_2$ ratio (P = 0.001), and negatively related to $P_{ET}CO_2$ (P = 0.002) in the PPC-PH patients (Table 5).. These findings suggest that the exacerbation in exercise pulmonary gas exchange abnormalities in patients with PPC-PH are related to the excessive rise in pulmonary vascular pressures experienced by these patients.

DISCUSSION

Main findings

The main findings of the present study were: 1) at a similar level of submaximal exercise (matched $\dot{Q}$), mean pulmonary artery pressure (mPAP), the diastolic pressure difference (DPD) and the transpulmonary pressure gradient (TPG) were greater in HF patients with combined post- and pre-capillary PH (PPC-PH) compared to HF patients with isolated post-capillary PH (IPC-PH) and HF

patients with normal pulmonary vascular pressures (no-PH), 2) at a matched level of $\dot{V}O_2$, V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ and the $PaCO_2$-$PETCO_2$ difference were higher whereas $PETCO_2$ and SaO_2 were lower in patients with PPC-PH compared to patients with either IPC-PH or no-PH, and 3) the exercise associated change in V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ ratio and $P_{ET}CO_2$ correlated significantly with the change in mPAP, DPD and TPG in the PPC-PH patients only. Importantly, we believe that this is the first study to 1) report that the pulmonary gas exchange responses to submaximal exercise are different in HF patients with different forms of PH with HF patients stratified according to PH type based on the most recent World Symposium on PAH recommendations (8), and 2) demonstrate significant relationships between several indices of pulmonary gas exchange and pulmonary haemodynamics *made simultaneously during exercise* in HF patients with PPC-PH. These findings add to the recent and growing body of evidence which suggests that noninvasive measures of pulmonary gas exchange during submaximal exercise are different in HF patients with PPC-PH compared to patients with IPC-PH or no-PH, and that the exacerbation in pulmonary gas exchange abnormalities in patients with PPC-PH are related to the excessive rise in pulmonary vascular pressures and resistance experienced by these patients.

Can exercise pulmonary gas exchange variables differentiate PH type and severity in HF?

Patients with chronic HF commonly exhibit an excessive ventilatory response to exercise (12, 17) and experience significant derangements in pulmonary gas exchange at rest and during exercise (10-13, 18). Previously, we have shown that the frequently observed increase in V_D/V_T and $\dot{V}_E/\dot{V}CO_2$ during exercise in HF is due, at least in part, to a relative hyperventilation and a rapid and shallow breathing pattern (12), both of which are likely related to a reduction in lung compliance secondary to pulmonary congestion (19) and/or cardiomegaly (20). However, it is becoming increasingly clear that the progressive deterioration in pulmonary vascular function and the occurrence of PH in HF is not only associated with exercise intolerance (3, 21) but also further exacerbates pulmonary gas

exchange abnormalities in these patients. For example, we have shown that $\dot{V}_E/\dot{V}CO_2$ and $PETCO_2$ are both significantly related to invasively determined mPAP during submaximal exercise in HF patients, and that $\dot{V}_E/\dot{V}CO_2$ was greater and $PETCO_2$ lower during exercise in HF patients with PH compared to HF patients without PH, although the difference in $PETCO_2$ did not reach statistical significance (13). In addition, Guazzi et al. (15) reported that a $\dot{V}_E/\dot{V}CO_2$ slope $\geq$ 36 and, to a lesser extent, a peak $PETCO_2 \leq 34$ mmHg and the presence of oscillatory ventilation in response to exercise were excellent predictors of the presence of left sided PH in HF patients. Most recently, and perhaps most importantly, it has been shown that the $\dot{V}_E/\dot{V}CO_2$ slope (> 41) the change in $PETCO_2$ (<1.2 mmHg) and the severity of oscillatory ventilation during exercise are associated with "reactive" (or PPC-PH) PH in HF patients (14). In the present study, the main gas exchange abnormalities found in PPC-PH patients during submaximal exercise were an elevated V_D/V_T and $\dot{V}_E/\dot{V}CO_2$ and a lower $PETCO_2$ and SaO_2 compared to patients with IPC-PH or no-PH. Importantly, we also found that the exercise associated change in V_D/V_T, $\dot{V}_E/\dot{V}CO_2$ ratio and $P_{ET}CO_2$ correlated significantly with the change in mPAP, DPD and TPG in the PPC-PH patients only; a finding novel to this study. In combination, the aforementioned findings suggest that the development of PH plays a role in the impaired pulmonary gas exchange commonly associated with HF, with the development of PPC-PH particularly associated with abnormal gas exchange during exercise in these patients. The mechanisms by which the elevated pulmonary vascular pressures associated with PPC-PH worsen exercise pulmonary gas exchange in these patients are multifactorial, but likely include the following.

First, it is probable that the impaired pulmonary gas exchange observed in HF patients with PPC-PH is related to an inability to adequately increase pulmonary vascular perfusion during exercise secondary to the elevation in pulmonary vascular resistance and/or any fixed structural remodeling of the pulmonary arterial resistance vessels (6, 7). Indeed, the elevated PAP and PVR associated with PPC-PH likely restricts forward flow of blood from the right ventricle to the pulmonary vasculature,

while remodeling of the pulmonary resistance vessels would limit recruitment and distention of the pulmonary vasculature during exercise thus impairing expansion of the pulmonary vascular bed. Both of the aforementioned occurrences would cause an under-perfusion of ventilated alveoli and substantial ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching with an increase in the number of high $\dot{V}/\dot{Q}$ lung units. This $\dot{V}/\dot{Q}$ mismatching is likely a significant source of the elevated V_D/V_T and $\dot{V}_E/\dot{V}CO_2$, the reduced $PETCO_2$ and the widening of the $PaCO_2$-$PETCO_2$ difference during submaximal exercise in HF patients with PPC-PH compared to patients with IPC-PH or no-PH observed in the present study (11, 18, 22-24).

Second, an increase in pulmonary vascular pressures also impairs the cardiac output response to exercise with a resultant impairment in blood flow and subsequently O_2 delivery to the working muscles (23). Any such reduction in O_2 delivery to the working tissues likely induces early lactic acidosis during exercise with subsequent stimulation of ergoreceptors and/or chemoreceptors secondary to an elevation in CO_2 and H^+ concentration and a consequent relative hyper-ventilatory response to exercise (23, 25). It is possible that such hyperventilation played a role in the increased V_D/V_T, the inefficient breathing (i.e. elevated $\dot{V}_E/\dot{V}CO_2$), and the reduced $PETCO_2$ observed in patients with PPC-PH during submaximal exercise in present study. Indeed, in addition to the larger degree of impairment in key pulmonary gas exchange indices during submaximal exercise, we also found that PPC-PH patients exhibit an elevated $\dot{V}_E$ response to exercise at an equivalent $\dot{V}O_2$ and work rate compared to patients with IPC-PH and no-PH. Thus, it is possible that a relative hyper-ventilatory response to exercise caused by stimulation of ergoreceptors and/or chemoreceptors is a source of worsened pulmonary gas exchange in patients with PPC-PH.

Finally, it is possible that an exercise-induced arterial hypoxemia increased ventilatory drive secondary to carotid body stimulation with a resultant exacerbation in the changes in V_D/V_T,

$\dot{V}_E/\dot{V}CO_2$ and $PETCO_2$ in our PPC-PH patients. Despite the prevailing view that arterial oxygen levels are maintained at or above normal values in HF patients (26, 27), we have recently shown that HF patients with PPC-PH experience significant systemic hypoxemia relative to HF patients with IPC-PH or no-PH (16). In the present study, SaO_2 was significantly reduced during submaximal exercise in the PPC-PH patients relative to the patients with IPC-PH or no-PH, with this reduction likely due to one or a combination of $V/\dot{Q}$ mismatching, a reduction in the alveolar-capillary membrane for effective gas transfer, a reduction in cardiac output, and the possible occurrence of a right to left intra-atrial shunt(18, 22). While this hypoxemia may have contributed to the elevated $\dot{V}_E$ and the abnormal exercise pulmonary gas exchange presently found in PPC-PH patients, it is likely that this effect was minimal owing to the fact that PPC-PH patients exhibited only a mild arterial hypoxemia (SaO_2 during exercise ~91%) compared to the patients with IPC-PH or no-PH.

Clinical relevance

In current clinical practice, the presence and severity of PH in HF is determined via right-heart catheterization and disease status is tracked over time using a number of clinical and laboratory based measurements, including the six-minute walk test and echocardiography. While catheterization represents the gold standard for assessing pulmonary vascular pressures and function, it is highly invasive and the pressure signals are subject to interference from factors such as changes in lung volume and intrathoracic pressure swings. In addition, the 6-minute walk test is subject to a "plateau effect" that limits its sensitivity for detecting improvements in patients with greater walk distances, typically underestimates disease severity in younger patients, and ultimately provides limited physiological insight into the determinants of exercise intolerance (28, 29). Measurement of ventilatory and pulmonary gas exchange responses to exercise has a well-established role in the assessment of HF. Adding to the vast body of literature that has identified characteristic derangements in pulmonary gas exchange related to abnormal pulmonary hemodynamics, as well a

recent report which has shown that $\dot{V}_E/\dot{V}CO_2$ slope, the change in $PETCO_2$ and the severity of oscillatory ventilation during exercise are associated with "reactive" PH in HF patients, the findings of the present study suggest that pulmonary gas exchange measures during clinical assessment may provide an efficacious adjunct to traditional clinical metrics for differentiation of PH type and severity in HF patients, and may help track disease status over time and assess the effectiveness of therapeutic aid.

Conclusion

Noninvasive measures of pulmonary gas exchange during submaximal exercise, specifically V_D/V_T, $\dot{V}_E/\dot{V}CO_2$, $PETCO_2$ and SaO_2, may help differentiate HF patients with combined post- and pre-capillary PH from HF patients with isolated post-capillary PH or no PH, and may be a useful adjunct to invasive catheterization in assessing PH type and severity in patients with HF while providing a useful tool in tracking disease status, progression and response to therapy.

ACKNOWLEDGEMENTS

The authors thank Andrew D. Miller and Kathy A. O'Malley for assistance with patient recruitment and data acquisition and management.

FUNDING SOURCES

This work was supported by National Institute of Health Grant Numbers HL71478 and HL98663, Gilead Sciences. BJT was supported by an American Heart Association Postdoctoral Fellowship (AHA12POST12070084).

DISCLOSURES

None

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FIGURE LEGENDS

Figure 1. Group mean ± SD mean dead-space ventilation (V_D/V_T) (A), ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$) (B), end-tidal carbon dioxide ($PETCO_2$) (C), and arterial oxygen saturation (SaO_2) (D) at rest and during submaximal exercise at a matched level of oxygen consumption ($\dot{V}O_2$) in heart failure patients (HF) with combined post-capillary and pre-capillary pulmonary hypertension (PPC-PH) (open diamonds), HF patients with isolated post-capillary pulmonary hypertension (IPC-PH) (open circles), and HF patients with normal pulmonary vascular pressures (No-PH) (open squares). $^{*}P < 0.05$, group mean value significantly different vs. No-PH group during exercise; $^{\dagger}P < 0.05$, group mean value significantly different vs. IPC-PH group during exercise.

Figure 2. Scatter plots showing the relationships between the individual subject change in dead-space ventilation (V_D/V_T; *panel A*), ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$ ratio; *panel B*), partial pressure of end-tidal CO_2 ($PETCO_2$, *panel C*), and arterial oxygen saturation (SaO_2) and the change in the diastolic pressure difference (DPD) associated with submaximal exercise in heart failure patients with combined post-capillary and pre-capillary pulmonary hypertension only.

Table 1. *Patient demographics and medications*

	No-PH	IPC-PH	PPC-PH
n, % female	11 (18)	12 (18)	16 (17)
Age, y	52 ± 12	62 ± 6*	57 ± 9
Height, cm	172 ± 8	172 ± 8	175 ± 8
Weight, kg	83 ± 15	82 ± 14	90 ± 17
$VO2_{peak}$, ml/min	1012 ± 180	856 ± 168*	835 ± 163*
HF etiology			
Ischemic	5 (45)	4 (36)	12 (71)
Idiopathic dilated	6 (55)	7 (66)	5 (29)
HF duration, mo	48 ± 38	83 ± 97	63 ± 47
LVEF, %	24 ± 8	25 ± 13	21 ± 9
NYHA functional class			
II	6 (55)	4 (33)	0 (0)
III	5 (45)	8 (67)	15 (94)
IV	0 (0)	0 (0)	1 (6)
Medications			
ACE inhibitor	11 (100)	6 (55)	9 (53)
β-blocker	10 (91)	8 (73)	14 (82)
Aspirin	8 (73)	6 (55)	12 (71)
Digitalis	7 (64)	5 (45)	12 (71)
Diuretic	8 (73)	10 (91)	16 (94)
Endothelinantagonist	0 (0)	0 (0)	0 (0)
PDE-5 inhibitor	0 (0)	1 (9)	0 (0)

Data are presented as group mean ± SD or *n* (%). No-PH, normal pulmonary vascular pressures; IPC-PH, isolated post-capillary pulmonary hypertension; PPC-PH, combined post-capillary and pre-capillary pulmonary hypertension; $VO2_{peak}$, peak oxygen consumption; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; PDE, phosphodiesterase.

*Value significantly different vs. No-PH group ($P < 0.05$).

Table 2. *Resting pulmonary vascular pressures, pulmonary function and standard clinical measurements*

	No-PH	IPC-PH	PPC-PH
RHC			
mPAP, mmHg	17.3 ± 4.7	33.5 ± 5.6*	43.5 ± 6.8*†
	(12 - 22)	(26 - 40)	(37 - 55)
mPWP, mmHg	9.1 ± 3.5	25.2 ± 5.2*	24.9 ± 7.3*
	(3 - 14)	(16 - 31)	(13 - 37)
DPD, mmHg	2.95 ± 2.36	2.77 ± 2.00	8.46 ± 4.90*†
	(−1 - 6)	(−1 - 6)	(7 - 24)
TPG, mmHg	8.2 ± 2.4	8.4 ± 2.5	18.6 ± 4.8*†
	(4 - 11)	(4 - 11)	(13 - 29)
PVR, Wood units	2.0 ± 0.8	2.4 ± 1.0	5.8 ± 2.8*†
	(1.2 - 2.8)	(1.1 - 3.2)	(2.8 - 11.4)
Pulmonary function			
FVC, % predicted	90 ± 10	68 ± 21*	74 ± 18*
FEV_1, % predicted	83 ± 19	66 ± 21	68 ± 17
FEV_1/FVC, %	73 ± 12	74 ± 7	72 ± 7
Echocardiography			
RAP, mmHg	3.8 ± 2.3	13.0 ± 4.7*	13.3 ± 6.7*
RVSP, mmHg	28.8 ± 7.2	47.1 ± 8.3*	64.5 ± 10.6*†
Six-minute walk test			
Distance, m	437 ± 139	360 ± 75	365 ± 70
Distance. % predicted	74 ± 26	70 ± 23	64 ± 14
Blood work			
Hemoglobin, g/dL	13.3 ± 1.4	12.4 ± 1.2	12.8 ± 1.9
BNP, pg/mL	195 ± 148	573 ± 462*	419 ± 389*
Endothlin-1, pg/mL	1.22 ± 0.50	2.26 ± 1.00	2.88 ± 1.78*
Angiotensin-II, pg/mL	13.02 ± 11.49	14.4 ± 10.8	16.8 ± 18.6
Epinephrine, pg/mL	79 ± 44	166 ± 132	86 ± 69
Norepinephrine, pg/mL	340 ± 187	549 ± 311	582 ± 256*

Data are presented as group mean ± SD or group range (in parentheses). No-PH, normal pulmonary vascular pressures; IPC-PH, isolated post-capillary pulmonary hypertension; PPC-PH, combined post-capillary and pre-capillary pulmonary hypertension; RHC, right-heart catheterization; mPAP, mean pulmonary arterial pressure; mPWP, mean pulmonary wedge pressure; DPD, diastolic PAP – mean PWP; TPG, transpulmonary pressure gradient; PVR, pulmonary vascular resistance; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; BNP, brain natriuretic peptide.

*Value significantly different vs. No-PH group ($P < 0.05$); †Value significantly different vs. IPC-PH group ($P < 0.05$).

Table 3. *Resting gas exchange, breathing pattern and hemodynamic variables*

	No-PH	IPC-PH	PPC-PH
VO2, L/min	0.23 ± 0.06	0.23 ± 0.06	0.27 ± 0.08
VCO2, L/min	0.19 ± 0.05	0.19 ± 0.06	0.24 ± 0.07
RER	0.84 ± 0.07	0.84 ± 0.11	0.91 ± 0.11
V_E, L/min	8.1 ± 1.7	9.0 ± 3.4	11.1 ± 2.1*
V_T, L	0.52 ± 0.24	0.50 ± 0.24	0.68 ± 0.28
f_R, breaths/min	17 ± 4	19 ± 7	18 ± 6
V_E/VO2 ratio	46 ± 8	50 ± 16	49 ± 9
Q, L/min	4.6 ± 2.3	3.8 ± 1.5	3.8 ± 1.5
SV, mL	72 ± 35	53 ± 22*	52 ± 21*
HR, beats/min	64 ± 8	74 ± 11	75 ± 12
PaCO2-PETCO2, mmHg	3.53 ± 2.42	4.11 ± 4.66	5.81 ± 2.87*†
O2pulse, mL/beat	3.6 ± 1.0	3.1 ± 0.8	3.6 ± 1.1

Data are presented as group mean ± SD. No-PH, normal pulmonary vascular pressures; IPC-PH, isolated post-capillary pulmonary hypertension; PPC-PH, combined post-capillary and pre-capillary pulmonary hypertension; VO2, oxygen consumption; VCO2, carbon dioxide production; RER, respiratory exchange ratio; V_E, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; Q, cardiac output; SV, stroke volume; HR, heart rate; PaCO2, partial pressure of arterial carbon dioxide; PETCO2, partial pressure of end-tidal carbon dioxide; O2pulse, oxygen pulse; OUES, oxygen uptake efficiency slope;
*Value significantly different vs. No-PH group ($P < 0.05$); †Value significantly different vs. IPC-PH group ($P < 0.05$).

Table 4. *Exercise responses at a matched oxygen consumption*

	No-PH	IPC-PH	PPC-PH
Work rate, W	20 ± 0	28 ± 12*	22 ± 6
VO2, L/min	0.59 ± 0.08	0.60 ± 0.07	0.60 ± 0.10
VCO2, L/min	0.45 ± 0.08	0.54 ± 0.12	0.55 ± 0.13
RER	0.92 ± 0.13	0.90 ± 0.11	0.93 ± 0.12
V_E, L/min	18.1 ± 3.9	23.5 ± 7.8	26.1 ± 7.5*
V_T, L	0.78 ± 0.26	0.82 ± 0.31	0.94 ± 0.30
f_R, breaths/min	25 ± 8	27 ± 8	29 ± 6
V_E/VO2 ratio	35 ± 9	45 ± 12	50 ± 16*
Q, L/min	5.1 ± 1.1	4.6 ± 1.7	4.3 ± 1.4*
SV, mL	55 ± 15	44 ± 17	46 ± 20
HR, beats/min	95 ± 9	102 ± 16	106 ± 18
PaCO2-PETCO2, mmHg	2.24 ± 1.78	4.07 ± 2.74	6.06 ± 2.06*†
O2pulse, mL/beat	5.7 ± 1.0	5.3 ± 1.5	5.2 ± 1.4

Data are presented as group mean ± SD. No-PH, normal pulmonary vascular pressures; IPC-PH, isolated post-capillary pulmonary hypertension; PPC-PH, combined post-capillary and pre-capillary pulmonary hypertension; VO2, oxygen consumption; VCO2, carbon dioxide production; RER, respiratory exchange ratio; V_E, minute ventilation; V_T, tidal volume; f_R, respiratory frequency; Q, cardiac output; SV, stroke volume; HR, heart rate; PaCO2, partial pressure of arterial carbon dioxide; PETCO2, partial pressure of end-tidal carbon dioxide; O2pulse, oxygen pulse; OUES, oxygen uptake efficiency slope;
*Value significantly different vs. No-PH group ($P < 0.05$); †Value significantly different vs. IPC-PH group ($P < 0.05$).

Table 5. *Relationships between the change in key pulmonary gas exchange measures and the change in hemodynamic measures associated with submaximal exercise [(i.e. from rest to exercise at a matched oxygen consumption (VO_2 ~0.60 L/min)]*

	Isolated Post-capillary Pulmonary Hypertension			
	V_D/V_T	V_E/VCO2	PETCO2 (mmHg)	SaO2 (%)
mPAP, mmHg	0.058	0.345	0.208	0.504
mPWP, mmHg	0.179	0.602‡	0.089	0.128
DPD, mmHg	0.087	−0.113	0.152	0.288
TPG, mmHg	−0.191	−0.486	0.093	0.348

	Combined Post- and Pre-capillary Pulmonary Hypertension			
	V_D/V_T	V_E/VCO2	PETCO2 (mmHg)	SaO2 (%)
mPAP, mmHg	0.377	0.528*	−0.649†	0.090
mPWP, mmHg	-0.217	-0.119	−0.051	0.104
DPD, mmHg	0.616*	0.599*	−0.485*	0.034
TPG, mmHg	0.618†	0.710†	−0.706†	0.017

Data are presented as Pearson-product moment correlation coefficients (*r*-values). mPAP, mean pulmonary arterial pressure; mPWP, mean pulmonary wedge pressure; DPD, diastolic pressure difference; TPG, transpulmonary pressure gradient.
*Significant relationship between two variables ($P < 0.05$); †Significant relationship between two variables ($P < 0.01$); ‡Trend suggesting a significant relationship between two variables ($P < 0.09$).

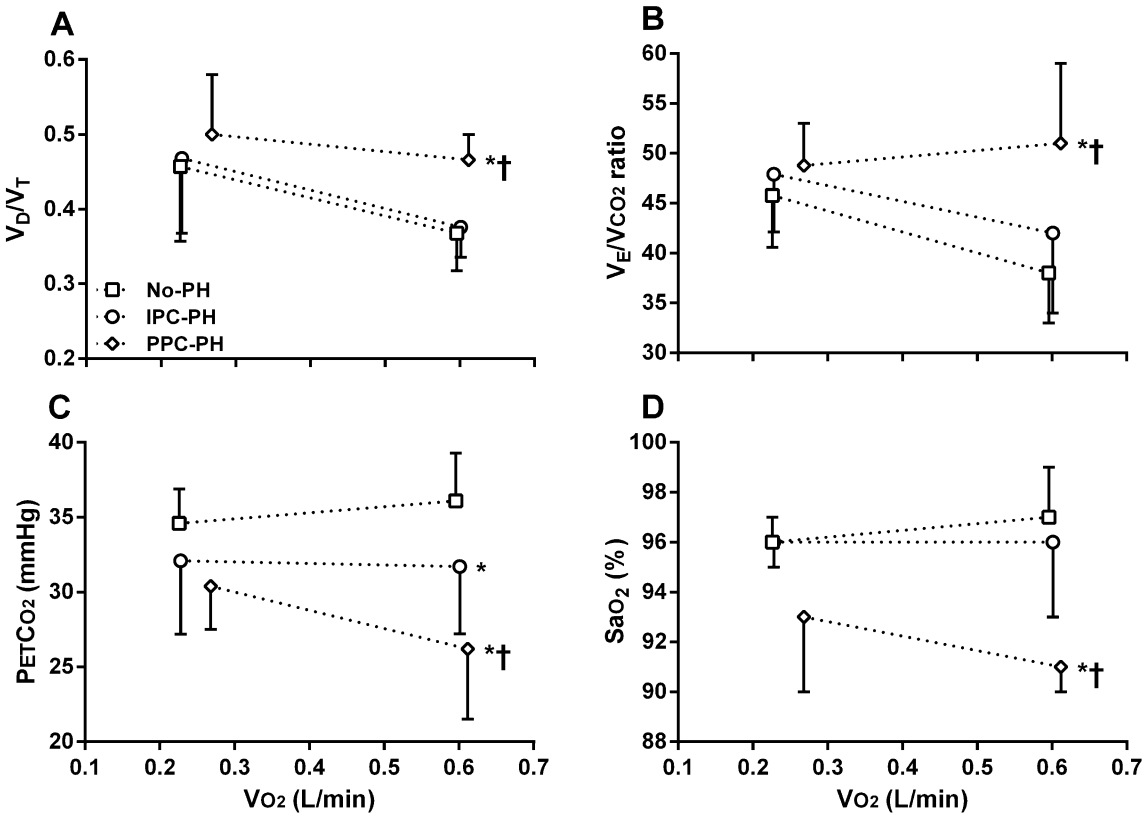
A
B
C
D
No-PH
IPC-PH
PPC-PH
V_D/V_T
V_E/V_{CO2} ratio
P_{ETCO2} (mmHg)
SaO_2 (%)
V_{O2} (L/min)
V_{O2} (L/min)
*
*†

Figure 1.

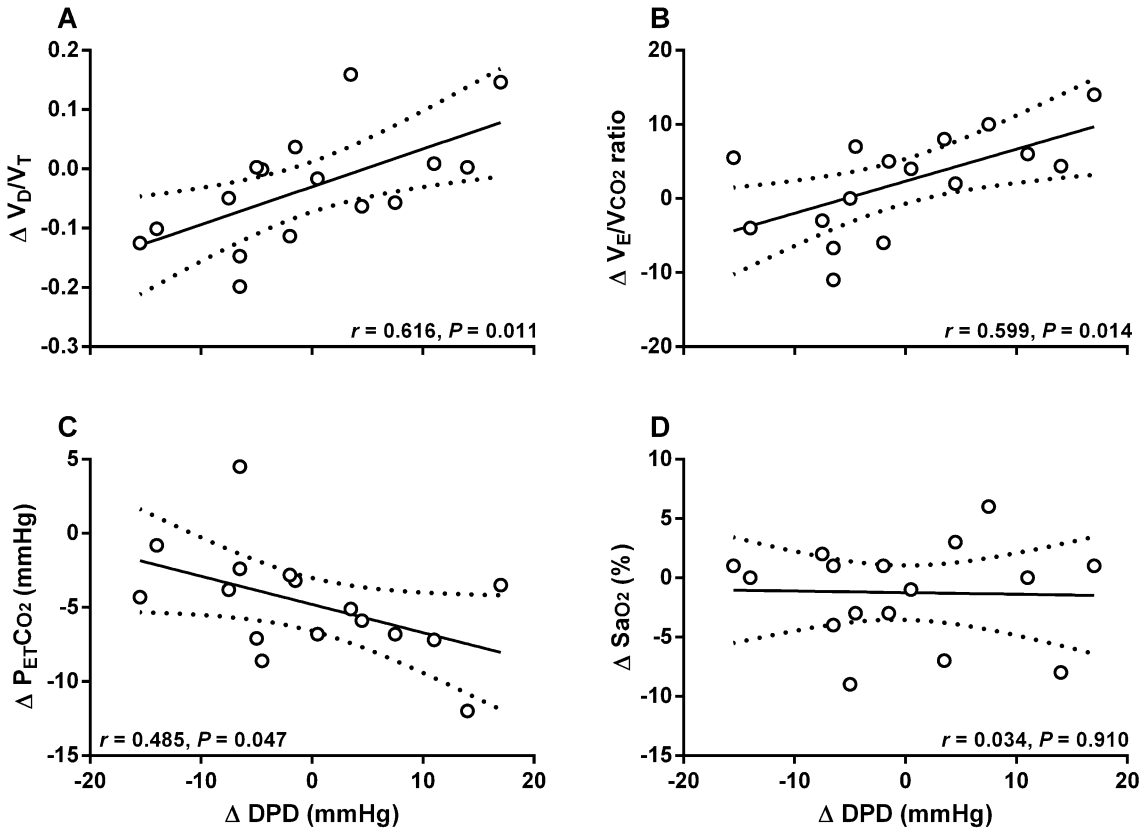
A
B
C
D
Δ VD/VT
Δ VE/VCO2 ratio
Δ PETCO2 (mmHg)
Δ SaO2 (%)
Δ DPD (mmHg)
Δ DPD (mmHg)
r = 0.616, P = 0.011
r = 0.599, P = 0.014
r = 0.485, P = 0.047
r = 0.034, P = 0.910

Figure 2.