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ORIGINAL RESEARCH

Use of Noninvasive Gas Exchange to Track Pulmonary Vascular Responses to Exercise in Heart Failure

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Abstract: We determined whether a non-invasive gas exchange based estimate of pulmonary vascular (PV) capacitance [PV_{CAP} = stroke volume (SV) × pulmonary arterial pressure (Ppa)] (GX_{CAP}) tracked the PV response to exercise in heart-failure (HF) patients. Pulmonary wedge pressure (Ppw), Ppa, PV resistance (PVR), and gas exchange were measured simultaneously during cycle exercise in 42 HF patients undergoing right-heart catheterization. During exercise, $P_{ET}CO_2$ and V_E/VCO_2 were related to each other ($r = -0.93$, $P < 0.01$) and similarly related to mean Ppa (mPpa) ($r = -0.39$ and 0.36; $P < 0.05$); $P_{ET}CO_2$ was subsequently used as a metric of mPpa. Oxygen pulse (O_2 pulse) tracked the SV response to exercise ($r = 0.91$, $P < 0.01$). Thus, GX_{CAP} was calculated as O_2 pulse × $P_{ET}CO_2$. During exercise, invasively determined PV_{CAP} and non-invasive GX_{CAP} were related ($r = 0.86$, $P < 0.01$), and GX_{CAP} correlated with mPpa and PVR ($r = -0.46$ and -0.54; $P < 0.01$). In conclusion, noninvasive gas exchange measures may represent a simple way to track the PV response to exercise in HF.

Keywords: pulmonary vasculature, capacitance, vasculature, exercise, gas exchange

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Introduction

Simple, non-invasive metrics to accurately quantify pulmonary hypertension (PH), particularly to assess the pulmonary vascular (PV) response to exercise in these patients, are lacking.[1] Recent studies have suggested that non-invasive measures of pulmonary gas exchange during exercise, including end-tidal CO_2 ($P_{ET}CO_2$) and ventilatory efficiency (V_E/VCO_2), may be useful indicators of the altered PV pressures associated with PH.[2,3]

PH, however, is also a hallmark of chronic heart failure (HF). In patients with left ventricular (LV) dysfunction, PH initially manifests as a "passive" increase in pulmonary venous pressure caused by the elevation in LV filling pressure.[4] Subsequently, patients with chronically elevated pulmonary capillary wedge pressure (Ppw) develop a form of PV disease that is associated with vasoconstriction and/or remodeling of the pulmonary arterial resistance vessels. This "reactive" component of PH is characterized by an excessive rise in pulmonary arterial pressure (Ppa) relative to the increase in Ppw, with a rise in PV resistance (PVR).[5,6] Importantly, development of reactive PH is associated with a further increase in mortality in the HF population.[7] Like idiopathic pulmonary arterial hypertension (IPAH) patients, HF patients also demonstrate gas exchange abnormalities during exercise, including significant alterations in $P_{ET}CO_2$ and V_E/VCO_2.[8–10] Given that both disease processes (i.e. IPAH and chronic HF) have a significant impact on both $P_{ET}CO_2$ and V_E/VCO_2, the ability to detect or estimate the presence of PH in diagnosed HF patients using these gas exchange parameters is likely limited. Accordingly, identification of other simplified metrics to determine the presence and severity of PH secondary to HF may be important.

One such measure that has received attention is an assessment of PV capacitance (PV_{CAP}), which can be defined as the ability of the pulmonary vessels to accept a volume of blood under a given pressure (eg, PV_{CAP} = stroke volume/Ppa). This measure has been related to prognosis and survival in PH populations.[11,12] Typically, PV_{CAP} is calculated from highly invasive right heart catheterization or technically difficult echocardiographic measures.[11,12] It may be possible, however, to estimate PV_{CAP} using easily assessable non-invasive pulmonary gas exchange surrogates [ie, oxygen pulse (O_2 pulse) and $P_{ET}CO_2$, representing blood volume and PV pressure, respectively].[13] Indeed, it has been shown that there is a significant relationship between the O_2 pulse and SV responses to exercise.[14] Moreover, we have demonstrated previously that $P_{ET}CO_2$ measured during submaximal exercise allows discrimination between patients with differing severities of pulmonary arterial hypertension.[15]

Thus, the aim of the present study was to assess the validity of a gas exchange based estimate of PV_{CAP} (GX_{CAP}) relative to invasively obtained measures. We hypothesized that a combination of O_2 pulse and $P_{ET}CO_2$ would track invasive measures of PV_{CAP} better than the more common measures of either $P_{ET}CO_2$ or V_E/VCO_2 alone.

Materials and Methods

Participants

Forty-two adult patients from the Mayo Clinic Heart Failure Service undergoing right heart catheterization participated in this study (Table 1). Of the 42 patients, 29 were classed as HF with PH and 13 were classed as HF only. Each participant gave written informed consent after being provided a detailed description

Table 1. Subject characteristics and resting pulmonary hemodynamics.

Demographics	
Gender, % male	93
Age, yr	54 ± 9
Height, cm	175 ± 7
Weight, kg	87 ± 16
BSA, m^2	2.04 ± 0.21
HF etiology, % ischemic/idiopathic	50/48
NYHA class	3.1 ± 0.7
II	8 (19)
III	22 (52)
IV	12 (29)
LV ejection fraction, %	20 ± 6
Resting hemodynamics	
mPpa, mmHg	33 ± 12
mPpw, mmHg	20 ± 9
PVR, WU	3.8 ± 2.6
Q, L/min	3.9 ± 1.4
MAP, mmHg	83 ± 11

Note: Data are presented as group means ± SD or as number of participants (percent of participant population) where appropriate for 42 subjects.
Abbreviations: BSA, body surface area; NYHA, New York Hear Association; LV, left ventricular; mPpa, mean pulmonary artery pressure; mPpw, mean pulmonary wedge pressure; PVR, pulmonary vascular resistance; Q, cardiac output; MAP, mean arterial pressure.

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. Functional class ranged from New York Heart Association (NYHA) classification II-IV and patients were prescribed a range of typical cardiac medications, including beta blockers, ACE inhibitors, angiotensin II antagonists, aspirin, and diuretics.

Experimental procedures

With patients 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 to the pulmonary artery through the right side of the heart via the right internal jugular vein. This allowed for the measurement of systolic, diastolic, and mean arterial pressure (SBP, DBP, and MAP), mean pulmonary artery and pulmonary wedge pressure (mPpa and mPpw), and arterial and mixed-venous blood gases. Cardiac output (Q) was calculated via the direct Fick method ($Q = VO_2/CaO_2\text{-}CvO_2$). PVR (PVR = mPpa -mPpw/Q) and pulmonary artery capacitance (PV_{CAP} = SV/mPpa) were also calculated.

Following instrumentation, the patients performed incremental cycle exercise on a semi-recumbent ergometer (starting at 20 W and increasing by 10 W every 3 min) until they achieved a perceived exertion (RPE) of ~16 on the Borg Scale 6–20. Patients maintained a constant cadence (~60 rpm) throughout exercise. Pulmonary hemodynamics as well as simultaneous breath-by-breath measures of minute ventilation (V_E), breathing frequency (f_b), tidal volume (V_T), oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), and the partial pressure of end tidal CO_2 ($P_{ET}CO_2$) (via a metabolic gas analysis system) were taken at rest and throughout exercise. Ventilatory efficiency (V_E/VCO_2), oxygen pulse (VO_2/HR), and a gas exchange equivalent of PV_{CAP} ($GX_{CAP} = O_{2pulse} \times P_{ET}CO_2$) were also calculated. All data were averaged over 60 s intervals.

Data analyses

Linear regression analysis was performed using all HF patient data to assess the relationships between hemodynamic and pulmonary gas exchange data during exercise. To assess the ability of gas exchange metrics to differentiate between patients with and without PH, the HF group was split according to resting mPpa. Following current guidelines, patients with an mPpa >25 mmHg were deemed to have PH (HF-PH, n = 29). Independent sample *t*-test was used to compare hemodynamic and gas exchange measures during the final minutes of exercise in HF vs. HF-PH patients. Results are expressed as means ± SD and the acceptable type I error was set at $P < 0.05$. Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS, Chicago, IL).

Results

Subject characteristics

Participant characteristics are shown in Table 1. The majority of patients were male with a relatively even number of ischemic and idiopathic HF etiologies. Patients were predominantly NYHA functional class III, with a modest number of class II and class IV patients. LV ejection fraction was on average severely reduced with moderate elevations in mPpa, mPpw, and PVR relative to reported normal values.

Exercise hemodynamics and gas exchange

Hemodynamic and non-invasive gas exchange responses to the final minute of exercise are shown in Table 2. With exercise, there was an increase in cardiac output (48% ± 32%, range 0.11 to 3.95 L/min), mPpa (58% ± 53%, range 1 to 35 mmHg) and mPpw (61% ± 86%, range −4 to 31 mmHg). Group mean PVR increased minimally during exercise (+6% ± 55%, range −8 to +3 WU). The average V_E/VCO_2 ratio was elevated and consistent with poor breathing efficiency while $P_{ET}CO_2$ was reduced.

During exercise, $P_{ET}CO_2$ and V_E/VCO_2 were similarly and modestly related to mPpa (Table 3 and Figure 1). Since V_E/VCO_2 and $P_{ET}CO_2$ were highly correlated with each other ($r = 0.93$, $P < 0.01$), we chose to use $P_{ET}CO_2$ as a general metric of mPpa with exercise. In addition, O_2 pulse tracked the stroke volume response to exercise in HF ($r = 0.91$, $P < 0.01$) (Fig. 1). Accordingly, we used O_2 pulse as a non-invasive estimate of SV for calculating the GX_{CAP}.

There was a highly significant positive relationship between the invasively derived measure of PV_{CAP} and GX_{CAP} with exercise ($r = 0.86$, $P < 0.01$) (Fig. 1). Moreover, GX_{CAP} correlated modestly with mPpa,

Table 2. Hemodynamic and gas exchange responses to the final minute of exercise.

Hemodynamics	
HR, beats/min	109 ± 22
SV, mL	57 ± 26
Q, L/min	6.1 ± 3.0
QI, L/min/m^2	3.0 ± 1.4
SBP, mmHg	138 ± 26
DBP, mmHg	70 ± 12
MAP, mmHg	92 ± 15
mPpa, mmHg	49 ± 11
mPpw, mmHg	32 ± 9
PVR, WU	3.5 ± 2.4
PV_{CAP}, mL/mmHg	1.3 ± 0.8
Gas exchange	
VO_2, L/min	0.75 ± 0.25
VO_2, mL/kg/min	8.7 ± 2.6
VCO_2, L/min	0.79 ± 0.24
RER	1.07 ± 0.10
V_E, L/min	33.8 ± 9.6
f_b, breaths/min	30 ± 7
V_T, L	1.16 ± 0.34
$P_{ET}CO_2$, mmHg	29 ± 6
O_2 pulse	7.2 ± 3.0
V_E/VCO_2 ratio	44 ± 10
GX_{CAP}	215 ± 109

Note: Data are presented as group means ± SD for 42 subjects.
Abbreviations: HR, heart rate; SV, stroke volume; Q, cardiac output; QI, cardiac output index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; mPpa, mean pulmonary artery pressure; mPpw, mean pulmonary wedge pressure; PVR, pulmonary vascular resistance; VO_2, oxygen consumption; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; V_E, minute ventilation; f_b, breathing frequency; V_T, tidal volume; $P_{ET}CO_2$, end-tidal CO_2; GX_{CAP}, gas exchange estimate of pulmonary vascular capacitance.

Q, and PVR, with incremental improvements over the correlation between these variables and the V_E/VCO_2 ratio or $P_{ET}CO_2$ alone (Table 3).

Comparison of HF with and without PH

Exercise VO_2, VCO_2, O_2 pulse, SV, and Q were markedly reduced in HF-PH patients compared to HF patients without PH (Table 4). By contrast, V_E/VCO_2 was greater in HF-PH vs. HF patients, indicating poorer ventilatory efficiency in HF patients with PH (Fig. 2). Similarly, mPpa and PVR were elevated in HF-PH patients relative to patients with HF only (Fig. 2). Finally, both PV_{CAP} and GX_{CAP} were significantly reduced in the HF-PH group vs. the HF only group, suggesting that this metric may be used as an index to differentiate HF patients with and without PH.

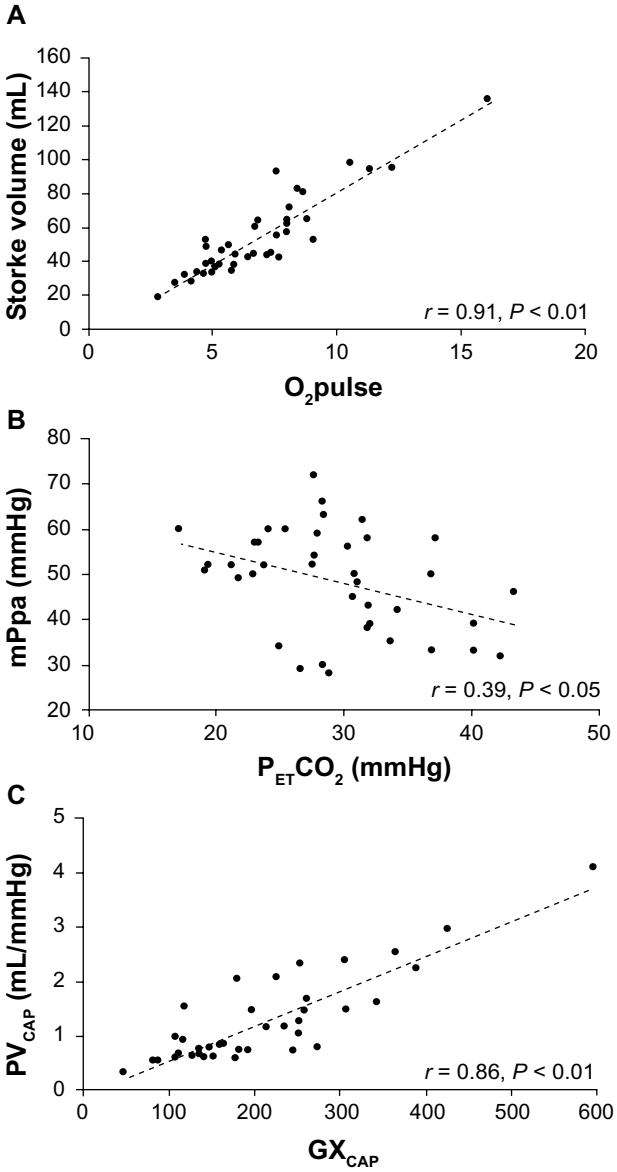

Figure 1. Linear regression analysis of all HF (42 subjects) data examining the relationship of invasive hemodynamic and non-invasive gas analysis measures during exercise. The relationship of SV and O_2 pulse (**A**) and mPAP and $P_{ET}CO_2$ (**B**) were assessed before a non-invasive gas exchange equivalent (GX_{CAP}) of PV_{CAP} (PV_{CAP} = SV/mPAP) was developed, where O_2 pulse and $P_{ET}CO_2$ were used as surrogate markers of pulmonary blood flow and pressure, respectively (O_2 pulse x $P_{ET}CO_2$ = GX_{CAP}). This new gas exchange metric (GX_{CAP}) was compared with PV_{CAP} (**C**).

Discussion

Main findings

The primary findings of the present study were that (1) non-invasive measures of $P_{ET}CO_2$ and O_2 pulse correlated closely with measures of mPpa and SV, respectively, (2) a non-invasive estimate of PV_{CAP} (GX_{CAP}) developed using the aforementioned surrogates of PV pressure and blood volume ($GX_{CAP} = O_{2pulse} \times P_{ET}CO_2$) correlated well with invasively derived PV_{CAP},

Table 3. Correlations between key exercise hemodynamic and pulmonary gas exchange measures.

	V_E/VCO_2 ratio	$P_{ET}CO_2$ (mmHg)	GX_{CAP}
mPpa (mmHg)	0.36*	–0.39*	–0.46**
mPpw (mmHg)	0.31*	–0.37*	–0.30
Q (L/min)	–0.38*	0.49*	0.64**
PVR (WU)	0.47**	–0.42*	–0.54**
PV_{CAP} (mL/mmHg)	–0.49**	0.48**	0.86**

Note: Data are Pearson's product-moment correlation coefficients (*r*) for 42 subjects. *$P < 0.05$, **$P < 0.01$; significant relationship between two variables.
Abbreviations: mPpa, mean pulmonary artery pressure; mPpw, mean pulmonary wedge pressure; Q, cardiac output; PVR, pulmonary vascular resistance; PV_{CAP}, pulmonary vascular capacitance; P_ETCO_2, end-tidal carbon dioxide; GX_{CAP}, gas exchange estimate of pulmonary vascular capacitance.

(3) noninvasive measures of pulmonary gas exchange, specifically V_E/VCO_2, $P_{ET}CO_2$ and GX_{CAP}, correlated significantly with invasive hemodynamic indices, including mPpa and PVR, and (4) V_E/VCO_2 and GX_{CAP} during exercise were significantly different between HF patients with and without PH. In combination, these data potentially identify a unique non-invasive gas exchange parameter (ie, GX_{CAP}) that may be used to track PV changes during exercise in HF patients. In addition, although somewhat speculative, it is possible that the GX_{CAP} parameter may allow differentiation between HF patients with and without PH at rest.

Table 4. Hemodynamic and gas exchange responses to the final minute of exercise in heart failure patients with and without PH.

	HF	HF-PH
VO_2, L/min	0.91 ± 0.30	0.67 ± 0.18*
VO_2, mL/kg/min	10.4 ± 2.5	8.0 ± 2.3*
VCO_2, L/min	0.94 ± 0.29	0.73 ± 0.18*
RER	1.04 ± 0.10	1.09 ± 0.10
V_E, L/min	35.2 ± 9.0	33.2 ± 9.9
f_b, breaths/min	31 ± 7	30 ± 8
V_T, L	1.20 ± 0.37	1.14 ± 0.34
O_2 pulse	9.5 ± 3.7	6.1 ± 1.9*
HR, beats/min	100 ± 21	113 ± 22
SV, mL	79 ± 25	47 ± 21*
Q, L/min	7.8 ± 2.7	5.3 ± 2.8*

Notes: Data are presented as group means ± SD (HF, $n = 13$; HF-PH, $n = 29$). *$P < 0.05$; value significantly different between heart failure patients without PH (HF) and heart failure patients with PH (HF-PH).
Abbreviations: VO_2, oxygen consumption; VCO_2, carbon dioxide production; RER, respiratory exchange ratio; V_E, minute ventilation; f_b, breathing frequency; V_T, tidal volume; HR, heart rate; SV, stroke volume; Q, cardiac output.

Further studies, however, are needed to support this conclusion.

The link between the heart and the lungs

The lungs lie in series with the heart. Indeed, both organs share a common surface area and are exposed to similar intrathoracic pressures, receive nearly all of the cardiac output, and have receptors that are sensitive to pressure and extravascular fluid changes. Thus, it is unsurprising that diseases which influence one organ system (ie, the lungs or the heart) would affect the other.

It has been shown previously that the simple non-invasive gas exchange metrics V_E/VCO_2 and $P_{ET}CO_2$ are markedly increased and decreased, respectively, during exercise in HF patients.[16] Moreover, both metrics are highly prognostic in the HF population and appear to track disease severity and response to therapy.[17–19] The initial alterations in the V_E/VCO_2 and $P_{ET}CO_2$ response to exercise in the HF population are most likely the result of a reduced blood flow to the pulmonary blood vessels with a consequent increase in the inhomogeneity of ventilation and perfusion matching, in particular high VA/Qc ratios in the lungs resulting in high dead space ventilation.[17,20] Also, the reduction in blood supply to the skeletal muscles, arterial hypoxemia, and right-to-left shunting, all of which alter blood carbon dioxide, oxygen, and H^+ ion concentration, are likely contributors to the enhanced drive to breathe, the greater hyperventilatory response, and altered V_E/VCO_2 and $P_{ET}CO_2$ response to exercise in this population secondary to stimulation of the peripheral chemoreceptors. With the development of substantial PH (ie, a marked increase in PV pressures) there is a widening of the arterial to $P_{ET}CO_2$ difference and presumably a significant limitation in forward flow of blood through the pulmonary vasculature, particularly with exercise, secondary to the increase left atrial and pulmonary venous pressures. This not only would further impair pulmonary gas exchange but would blunt the rise in stroke volume and thus the PV_{CAP}. Accordingly, we theorized that taking into account the stroke volume relative to the pressure should be a good index of the severity of PH in the HF population.

Usefulness of non-invasive gas exchange

Invasive measures of pulmonary hemodynamics are costly and subject to a number of errors, particularly

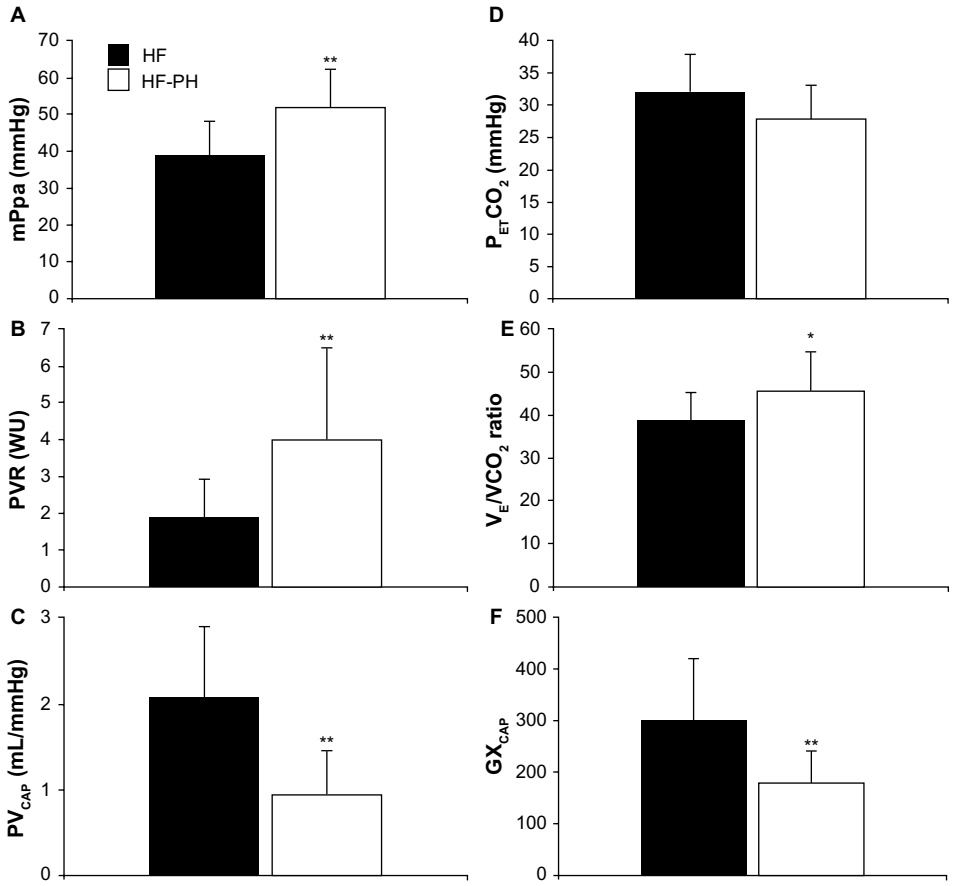

Figure 2. Key exercise hemodynamic and gas exchange differences between HF patients with (HF-PH, n = 29) and without (HF, n = 13) PH. Mean and standard deviation are presented for mPpa (**A**), PVR (**B**), PV_{CAP} (**C**), $P_{ET}CO_2$ (**D**), V_E/VCO_2 ratio (**E**) and GX_{CAP} (**F**). * $P < 0.05$,** $P < 0.01$ represent significant differences between HF and HF-PH patients.

during exercise. Patient anxiety, large fluctuations in intrathoracic pressures, assumptions related to valvular regurgitation, timing of measures, variation in blood/plasma volume, and, in some cases, use of estimates of cardiac output and/or VO_2 can have profound influences on the calculations of PVR.[21,22] Moreover, the classic measure of mPpw may also ignore much of the pulmonary circulation (smaller arterioles, capillaries and veins) that may be subject to adverse manifestation with HF progression.[23,24] Additionally, resting measures of PV pressures may not be reflective of the hemodynamic pressure response to exercise.

A volume of more recent empirical data, however, has shown that HF is associated derangement of pulmonary gas exchange during submaximal exercise [low $P_{ET}CO_2$ and reduced ventilatory efficiency (ie, increased V_E/VCO_2)] that is likely related to the development and severity of PH.[24–27] Furthermore, administration of the pulmonary vasodilator sildenafil causes a significant reduction in Ppa and PVR with a concomitant decrease in V_E/VCO_2 slope during exercise (ie, improved breathing efficiency) in HF.[25] Together, these data suggest that the deleterious alterations in pulmonary gas exchange with HF are related to the development of PH in these patients. In addition, our laboratory has demonstrated that the same key pulmonary gas exchange variables (ie, V_E/VCO_2, $P_{ET}CO_2$) are similarly altered in patients with pulmonary arterial hypertension.[15] Given that both HF and pulmonary arterial hypertension have a significant and similar impact on both $P_{ET}CO_2$ and V_E/VCO_2, the ability to detect or estimate the presence of PH in diagnosed HF patients using these gas exchange parameters is likely limited. Thus, we proposed that identification of other simplified metrics to determine the presence and severity of PH secondary to HF may be important.

In the present study, we found that measures of $P_{ET}CO_2$ and O_2 pulse closely reflect the changes in mPpa (ie, PV pressure) and SV (ie, blood volume), respectively, that occur during exercise in HF patients.

Moreover, a unique index of PV_{CAP} using a combination of $P_{ET}CO_2$ and O_2 pulse (GX_{CAP}) was found to closely relate to an invasively derived measure of pulmonary arterial capacitance during exercise. Importantly, GX_{CAP} along with V_E/VCO_2 was different between HF patients with and without PH at rest. Accordingly, the novel gas exchange based measure of PV function assessed in the present study may provide a simple metric to estimate the degree of PV derangement in the HF population. Moreover, although further studies are needed, these data suggest that GX_{CAP} may allow differentiation between HF patients with and without PH at rest.

Clinical implications

Development of the "reactive" form of PH (see Introduction) is associated with a further increase in mortality in the HF population,[7] making it an attractive target for detection and therapeutic intervention. To date, cardiopulmonary gas exchange measures have been used extensively to track disease severity in the HF population. However, the focus clinically has primarily been on maximal measures of oxygen consumption (VO_{2max}). Recently, it has become clear that other gas exchange measures, particularly during submaximal exercise, are more reproducible and may have equal or be of greater prognostic value in the HF population. With simplified commercial gas exchange systems available, shortened, submaximal protocols (eg, 3 min) may be a convenient way to quickly grade severity of disease and track response to therapy.[28] Our current findings identify a novel noninvasive gas exchange based estimate of PV_{CAP} that appears to track the PV response to exercise in the HF population and may also allow differentiation between HF patients with and without PH at rest. To further determine whether GX_{CAP} can be used clinically to assess the progression of PH and the efficacy of therapeutic intervention in this population, further studies must be performed. Of particular interest may be the concurrent effect of pulmonary vasodilator therapy on pulmonary hemodynamics and pulmonary gas exchange indices. If our present observation that key gas exchange variables can track PV responses to exercise, then any reduction in PV pressures and PVR with vasodilator therapy should be matched by changes in key gas exchange variables, including GX_{CAP}. Such a finding would only strengthen the argument that GX_{CAP} could be used as a clinically based assessment of PH severity, progression, and the response to therapeutic aid.

Limitations

We tested a HF population with relatively severe disease without significant additional co-morbidities (eg, severe chronic obstructive pulmonary disease) and gathered data during moderate supine cycle ergometry exercise. There tends to be large ranges in gas exchange and ventilatory responses to exercise, with the potential for volitional influences. However, we found a strong relationship between an invasive measure of PV_{CAP} and the non-invasive estimate, and both measures appeared to clearly separate HF patients with and without resting PH.

Conclusion

In conclusion, non-invasive exercise gas exchange may represent a relatively simple way of tracking PV changes in HF. GX_{CAP}, an estimate of pulmonary capacitance, appears to be a combination of variables that separate HF patients with and without resting PH.

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Author Contributions

Conceived and designed the experiments: BJT, TPO, CK, DM, BDJ. Analyzed the data: BJT, CK. Wrote first draft of the manuscript: BJT, BDJ. Contributed to writing the manuscript: BJT, CK, BDJ. Agree with manuscript results and conclusions: BJT, TPO, CK, DM, BDJ. Jointly developed structure and arguments for paper: BJT, CK, DM, BDJ. Made critical revisions and approved final version: BJT, TPO, CK, DM, BDJ. All authors reviewed and approved the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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