Basic Science and Experimental Studies

Submaximal Exercise Pulmonary Gas Exchange in Left Heart Disease Patients With Different Forms of Pulmonary Hypertension

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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) versus HF patients with isolated post-capillary PH (IPC-PH) or no PH.

Methods and Results: Pulmonary hemodynamics and pulmonary gas exchange were assessed during rest and submaximal exercise in 39 HF patients undergoing right heart catheterization. After 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 versus PPC-PH patients (36.1 ± 3.2 vs 31.7 ± 4.5 vs 26.2 ± 4.7 mm Hg 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 $\left(\dot{V}_E/\dot{V}CO_2 \text{ ratio}\right)$ were lower in no-PH and IPC-PH versus 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.

Conclusions: Noninvasive pulmonary gas exchange indices during submaximal exercise are different in HF patients with combined post- and pre-capillary PH compared with patients with isolated post-capillary PH or no PH. (*J Cardiac Fail 2015;21:647–655*)

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

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- 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

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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 [eg, 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 mean pulmonary artery pressure (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 (ie, 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 mm Hg), 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 gas exchange during submaximal exercise differ in HF patients with combined post- and pre-capillary PH compared with 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 combined post- and pre-capillary PH from patients with isolated post-capillary PH.

Methods

Participants and Ethical Approval

Thirty-nine adult patients (32 male, 7 female) with a history of HF and 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) ejection fraction of ≤40%, and 3) body mass index <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 mm Hg], 2) HF with isolated post-capillary PH [mPAP ≥25 mm Hg, mean PWP (mPWP) >15 mm Hg, and DPD <7 mm Hg), or 3) HF with combined post-capillary and pre-capillary PH (mPAP ≥25 mm Hg, mPWP >15 mm Hg, and DPD ≥7 mm Hg; 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

Before catheterization, each patient completed a range of standard clinical tests, including pulmonary function, echocardiography, 6-minute walk test, and blood analysis. The standard clinical tests were performed during a single day ≥24 hours but not >7 days before the right heart catheterization procedure. This was consistent with the normal protocol followed for patients undergoing clinically indicated right heart catheterization.

Hemodynamic Evaluation and CPET

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-Fr 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 − mPWP and transpulmonary pressure gradient (TPG) was computed as mPAP − mPWP. Arterial and mixed venous blood was drawn simultaneously from the radial and the pulmonary arteries, 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 $TPG \div \dot{Q}$.

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, Kansas City, Missouri). 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, Minnesota) 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 seconds of each exercise stage, and at the end of 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 Corp, Irvine, California) and fingertip sensor.

Data Analysis

Minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f_R), oxygen consumption ($\dot{V}O_2$), carbon dioxide

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