Review

Pulmonary Hypertension and Cardiopulmonary Exercise in Heart Failure

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Key Words

Pulmonary hypertension · Heart failure · Gas exchanges · Submaximal exercise

Abstract

In heart failure (HF), pulmonary hypertension (PH) is initially associated with a rise in the left ventricular filling pressure. PH is defined by pulmonary hemodynamic measurements including pulmonary capillary wedge pressure, mean pulmonary arterial pressure and pulmonary vascular resistance. Eventually, PH in HF may become more of a reactive process. Although the mechanism of the reactive PH development is not clearly understood, vascular dysfunction induced by remodeling, vasoactive substances and genetic variation appear to contribute significantly to this form of PH. Noninvasive cardiopulmonary exercise testing has been extensively utilized to assess disease severity in HF patients. It provides integrated information that is dependent on cardiopulmonary hemodynamics, lung mechanics, breathing pattern and strategy. In this review, we will discuss the mechanisms of PH development in HF and how noninvasive gas exchange measures obtained with submaximal exercise are influenced by PH in this population.

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Introduction

Heart failure (HF) is a leading cause of hospitalization in people over the age of 65 years, and nearly 6 million people in the United States suffer from this condition [1]. Pulmonary hypertension (PH) is common in HF and is a major risk factor for morbidity and mortality [2]. According to previous reports, after a 28-month follow-up, the mortality rate is higher in HF

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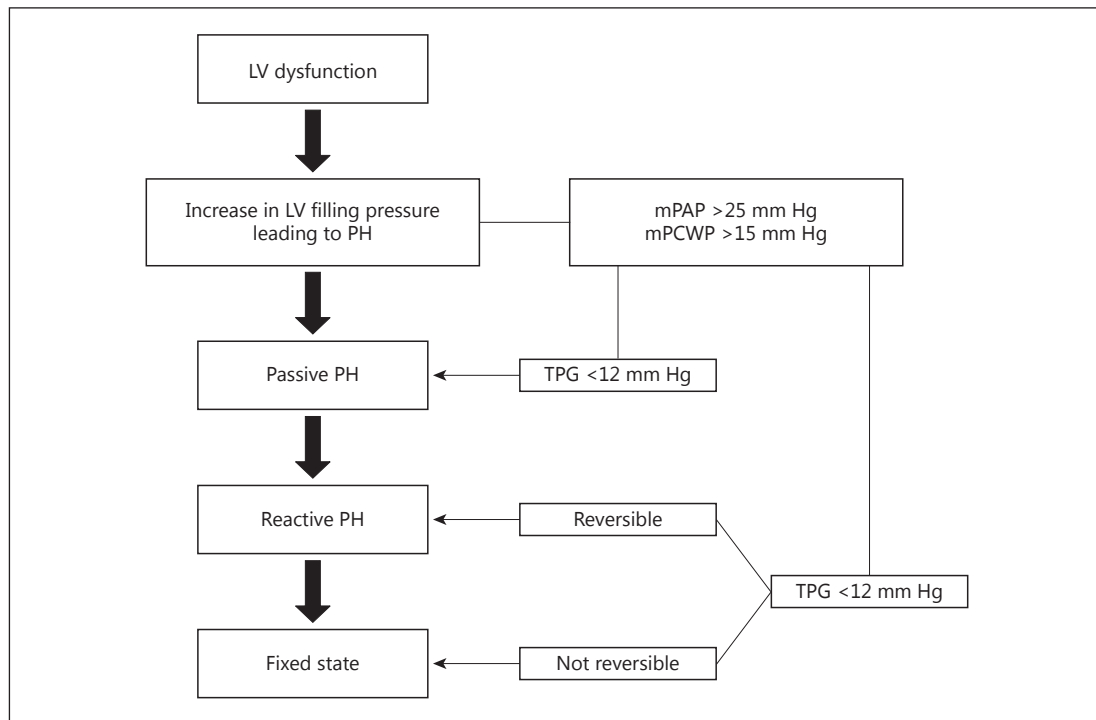Rochester, MN 55901 (USA)
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Fig. 1. Schematic progression and characteristics of PH in HF.

patients with moderate PH than in patients without PH [3]. Patients with HF are affected by the common symptoms dyspnea and fatigue, resulting in exercise intolerance [4–6]. The pulmonary circulation likely contributes significantly to the HF syndrome, and accordingly the interest in PH has recently increased in this population.

In healthy individuals, the pulmonary circulation is compliant and under low pressure, and is thus well suited to large increases in blood flow during exercise. However, by definition, patients with classical systolic HF demonstrate high cardiac filling pressures, which in turn increase pulmonary vascular pressures and eventually can evolve over time to right ventricular (RV) failure [7, 8]. These abnormalities in cardiopulmonary relationships along with the sequelae of the HF syndrome can influence pulmonary vascular tone and in turn result in pulmonary arteriole dysfunction and elevated pulmonary vascular resistance (PVR).

Pathophysiology of PH in HF

Progression of PH

The classical mechanism of PH in HF is generally elicited by a 'passive' component. Figure 1 demonstrates the schematic progression of PH in HF. Due to left ventricular (LV) dysfunction, forward blood flow decreases and diastolic pressure increases. This causes an increase in pulmonary venous pressure and in turn results in elevations in a surrogate measure of the left atrial pressure, namely the pulmonary capillary wedge pressure (PCWP). This passive transmission of pressure elevation further increases pulmonary arterial pressure (PAP). The chronic elevation in pulmonary vascular pressures (originating from pulmonary venous hypertension) can eventually influence the vasomotor tone of the pulmonary arterioles

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(vasoconstriction) and may induce a vascular obstructive remodeling of the pulmonary arteries and arterioles [8–10]. The development of a precapillary vasoconstriction has been termed 'reactive' PH and includes a further rise in PAP out of proportion to the rise caused by LV failure. Chronically elevated PVR and PAP can eventually lead to RV dysfunction, which is associated with a reduced exercise tolerance and increased mortality in the HF population. Finally, pulmonary vascular smooth muscles may develop an irreversible or 'fixed' state, which is not altered with acute vasoactive pharmacological treatment.

Characteristics of PH

The development of PH can be defined by hemodynamic and pressure measurements, i.e. mean PCWP (mPCWP), mean PAP (mPAP) and transpulmonary gradient (TPG; the difference between mPAP and mPCWP). Based on these pressures, the type of PH (pre- vs. postcapillary) and disease severity can be determined (fig. 1). In healthy individuals, mPAP is <25 mm Hg and mPCWP is <15 mm Hg. In HF, PH is defined by mPAP ≥25 mm Hg and mPCWP >15 mm Hg. In addition, TPG <12 mm Hg is considered passive PH and TPG ≥12 mm Hg is considered reactive (fig. 1). The types and progression of PH can be explained further using the equation below for PVR:

$$PVR = (mPAP – mPCWP)/cardiac\ output.$$

In passive PH, both mPAP and mPCWP increase and TPG is normal; thus, if PVR is elevated, it is primarily due to a decreased cardiac output. However, in reactive PH, TPG is greater than normal due to the increased mPAP. Therefore, a decreased cardiac output due to LV dysfunction and an increased mPAP contribute to an exaggerated increase in PVR.

Vascular Dysfunction due to Remodeling, Vasoactive Substances and Genetic Variation

Classical systolic HF is defined by elevated LV filling pressures and a passive rise in the left atrial pressure causing pulmonary venous hypertension. If the RV function is relatively stable, the increased pressure in the pulmonary vasculature results in a mismatch output and may increase the capillary hydrostatic pressure, leading to congestion. This causes fluid to cross the microvascular barrier and eventually results in interstitial pulmonary edema and, in more severe cases, alveolar fluid accumulation [11]. Under chronic conditions with high pulmonary vascular pressures and interstitial fluid, this may contribute to the pathophysiological remodeling of the pulmonary vasculature.

In the HF syndrome, neurohormonal and biochemical substances [e.g., angiotensin II (ANG II), catecholamines, endothelin-1 (ET-1) and inflammatory mediators] are activated and may contribute to pulmonary vascular remodeling or vasoreactivity. For example, in HF, a decreased renal perfusion due to cardiac dysfunction increases the release of renin, which results in increased ANG II that is a potent vasoconstrictor. This alteration in the renin-angiotensin system is associated with systemic vascular resistance [12] and accelerates cell proliferation, thus resulting in vascular and structural remodeling [13, 14]. In addition, ANG II may trigger the release of other biochemical substances such as ET-1 and the breakdown of bradykinin [14, 15].

ET-1 is a powerful vasoconstrictor peptide which is predominantly involved in the regulation of vascular tone in the cardiopulmonary system. There are multiple factors that may increase the synthesis of ET-1 (i.e., hypoxia and shear stress), and a complex process is required to form this peptide. A number of previous studies have demonstrated that an elevation in ET-1 is significantly associated with PAP and PVR [16] as well as disease severity in HF patients with PH [17–19]. The actions of ET-1 begin with binding 2 receptors: the type A (ET_A) receptor that is mainly found on vascular smooth muscle cells and the type B (ET_B) receptor that is mainly found on endothelial cells and to a lesser extent on smooth muscle

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cells. While ET-1 coupled with ET_A, short- and long-term effects, induces vasoconstriction and cell proliferation, ET-1 coupled with ET_B promotes both vasodilation and vasoconstriction effects and participates in the clearance of circulating ET-1 [20]. Both ET_A and ET_B receptors increase in HF and PH; however, the upregulation of ET_A receptors may be dominant. In the pathological state, ET_A and ET_B receptors may be differently controlled, and therefore vaso-constriction and cell proliferation effects occur more likely [21]. Increases in ET-1 and pulmonary vascular remodeling by proliferation and hypertrophy of smooth muscle cells due to the upregulation of ET_A receptors may contribute significantly to the progression of PH [7, 22].

Nitric oxide (NO) is an endothelium-dependent vasodilator which is involved in vaso-motor control and regulates pulmonary perfusion to ensure optimized ventilation/perfusion (V/Q) in the lungs [23, 24]. This vasoactive substance appears to decrease in patients with HF and/or PH [7, 23, 25]. Previous studies have demonstrated that a limited availability of NO is partially attributable to a diminished synthetic activity of the L-arginine and NO pathway following decreased expression of endothelial NO synthase [26, 27]. The degradation of NO is increased by phosphodiesterase so that potassium (K^+) channel activation decreases and calcium (Ca^{++}) channel-induced vasoconstriction occurs [23, 25]. Furthermore, an increased breakdown of bradykinin decreases NO availability [14, 28].

There are also genetic variations that may influence the pulmonary vasculature. In patients with HF, the prevalence and/or severity of PH vary at a given level of LV dysfunction and disease severity, and thus genetic variation may account for a part of this variability. Bradykinin is a potent endothelium-dependent vasodilator in the cardiovascular system. A recent study tested the association between bradykinin β_2-receptor (G protein-coupled kinin receptor subtype) and systolic PAP and demonstrated that HF patients homozygous for the +9 polymorphism of bradykinin $\beta2$-receptor had an increased risk of higher PAP [29]. In addition, the long allele variant of the serotonin transporter gene was found to be highly asso-ciated with elevated PAP [30], and the angiotensin-converting enzyme DD genotype was shown to be significantly associated with altered pulmonary function [31].

Potential Role of Hypoxia

Although controversial, we have suggested that systemic hypoxia may also play a role in the pathophysiology of reactive PH in HF patients. This could be due to a tendency for low normal PaO_2 values, high extraction rates and low mixed venous O_2 values returning to the lungs, low perfusion to systemic tissue-stimulating hypoxic pathways or low perfusion to the carotid body, essentially triggering or stimulating the sympathetic nervous system with a potential reflex influence on the pulmonary vasculature (fig. 2) [32].

Influence of PH on Lung Mechanics, Breathing Patterns and Respiratory Gas Exchange in HF

Classical Gas Exchange Responses to Exercise in HF

The lungs and heart can be viewed as an integrated organ system because they are hemo-dynamically and neuromechanically linked. They not only share a common surface area, but nearly all of the cardiac output goes through the lungs, and changes in intrathoracic pressure not only influence respiration but also cardiac pre- and afterload. Therefore, alterations in cardiac function will influence the lungs and vice versa. Thus, though the HF syndrome alone influences lung mechanics and gas exchange, progressive changes in the pulmonary vascu-lature appear to exaggerate the abnormalities observed, which are further accentuated with exercise.
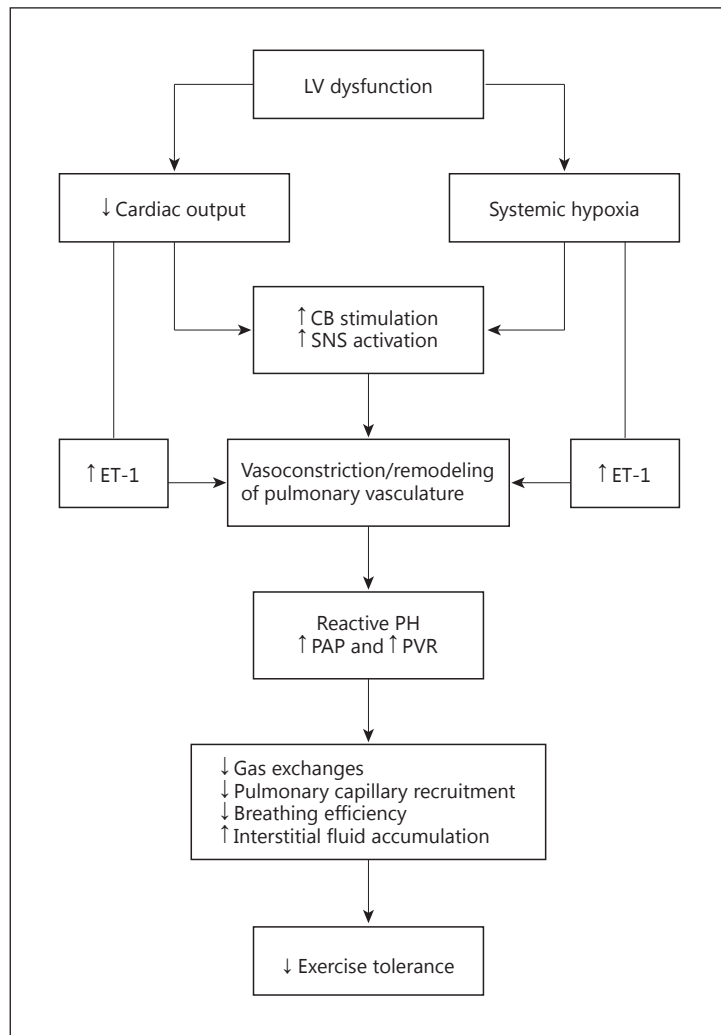
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Fig. 2. Conceptual mechanism showing that PH influences breathing efficiency and exercise tolerance. CB = Carotid body; SNS = sympathetic nervous stimulation.

In HF, abnormal breathing patterns and gas exchange during exercise are mainly a result of stiff lungs, an enlarged heart and V/Q inhomogeneities leading to increased dead space (V_D/V_T). End-tidal carbon dioxide ($P_{ET}CO_2$) and ventilatory efficiency for carbon dioxide (V_E/VCO_2) are the most commonly documented parameters used to track disease severity [33–36]. The reported increase in V_E/VCO_2 is associated with the noted elevated V_D/V_T due primarily to a rapid shallow breathing pattern but also due to a tendency for relative hyperventilation [8, 34, 37]. A recent study by Woods et al. [35] demonstrated that HF patients had a lower $PaCO_2$ (due to hyperventilation) and a lower V_T (thus higher V_D/V_T) than healthy controls. In addition, these authors noted that both lower $PaCO_2$ and higher V_D/V_T provided similar contributions to the elevation in V_E/VCO_2. Also of interest was the widening of the $PaCO_2$ and $P_{ET}CO_2$ difference during exercise consistent with the V/Q abnormalities. Moreover, a marked drop in $P_{ET}CO_2$ with exercise has been associated with a higher ventilation and a limited rise in cardiac output [33, 34, 36, 37]. A decrease in $P_{ET}CO_2$ may also reflect reduced PAO_2 due to V/Q inhomogeneity [36]. In most cases, the change in $P_{ET}CO_2$ is inversely related to the change in V_E/VCO_2.

Impact of PH on Cardiopulmonary Responses to Exercise in HF

The impact of PH on pulmonary gas exchange and exercise tolerance in HF is not clearly understood. However, based on the results from previous studies, it is speculated that PH generally exacerbates cardiopulmonary abnormalities (i.e., lower $P_{ET}CO_2$ and higher V_E/VCO_2) during exercise in HF patients. Figure 2 demonstrates a conceptual pathway of the potential influence of LV dysfunction and PH on exercise capacity. A number of studies have demonstrated that in HF patients with PH, pulmonary gas exchange measures were more significantly impaired [33, 34, 38], as was pulmonary diffusing capacity [39, 40]. A previous study using sildenafil (a phosphodiesterase-5 inhibitor with vasodilatory effects on the pulmonary vasculature) found that PVR and exercise capacity improved in systolic HF patients with PH [41]. In addition, in a review Guazzi et al. [42] illustrated that PAP, PVR, ventilatory efficiency (V_E/VCO_2) slope and peak oxygen consumption (peak VO_2) were improved after treatment with sildenafil. According to these previous data, it is clear that pulmonary vascular hypertension plays a critical role in impaired gas exchange and exercise capacity in HF patients. A study by Butler et al. [5] confirmed that patients with elevated PVR demonstrate impaired exercise capacity and that the severity of PVR is related to the degree of exercise abnormalities. These authors also noted that several patients with severe disease had reduced PCWP during exercise and a higher right atrial pressure, and this may result from impaired blood delivery to the left ventricle due to RV failure [5].

Recently, a number of studies have identified those noninvasive gas exchange measures that are associated specifically with PH. As mentioned earlier, $P_{ET}CO_2$ and V_E/VCO_2 are the most common variables used to evaluate disease prognosis in HF. In addition, the oxygen uptake efficiency slope, which is the slope of oxygen uptake relative to the log of minute ventilation during submaximal exercise [43], oxygen saturation (SaO_2) [44] and pulmonary capacitance (Pcap), which is a calculated gas exchange variable and obtained from the oxygen pulse (O_2 pulse) multiplied by $P_{ET}CO_2$, have been shown to be associated with disease severity in PH [45]. Recently, we have attempted to identify the noninvasive measures associated with pulmonary vascular hemodynamic indices in HF. Our work confirmed that the noninvasive gas exchange measures were significantly associated with the invasive measures. $P_{ET}CO_2$ was significantly correlated with mPAP, and O_2 pulse was significantly correlated with stroke volume. Thus, an estimated pulmonary vascular capacitance was estimated, which was highly associated with the invasive measures of Pcap using catheter-based measures. In addition, we recently determined that Pcap might differentiate HF with and without PH better than other gas exchange measures [8].

Cardiopulmonary Exercise Testing in Clinical Practice

In clinical practice, maximal cardiopulmonary exercise testing with noninvasive measures of gas exchange has been widely used to identify the disease severity of HF patients and to help determine the prognosis or response to therapy. However, there are several impediments to applying this technique to HF patients. In some cases, it is not safe to push HF patients to maximal exercise, and given the variability in protocol across clinical laboratories, outcomes can vary considerably. In addition, there are possible difficulties and anxieties for frail patients to undergo this type of testing, and these tests traditionally require relatively sophisticated centers with expertise [46]. Moreover, it is hard to compare data if centers or laboratories use different protocols and stopping criteria. More recently, it has become evident that submaximal exercise is more easily obtainable, with less patient anxiety and with less variability, than maximal exercise measures, but yet provides similar prognostic value [47, 48]. In addition, since many of the key gas exchange measures are simply slopes of change from the resting condition, they are relatively insensitive to exercise intensity [49, 50].

Simplifying Gas Exchange for Clinical Practice

Noninvasive commercial gas exchange systems have been developed and provide a large amount of information about breathing patterns and gas exchange. However, given this large number of variables and a general lack of training in clinical centers regarding integrative exercise physiology, their interpretation has always been challenging. Thus, we recently developed a scoring system to quantify gas exchange measures into a single representative gas exchange severity or abnormality score [50]. Based on our previous work and the literature published so far, we used multiple key gas exchange variables (e.g., resting $P_{ET}CO_2$, $\Delta P_{ET}CO_2$, V_E/VCO_2 slope, SaO_2, Pcap, oxygen uptake efficiency slope) and developed a scoring system to primarily identify the disease severity of PH and HF. We observed that the multivariable scoring system was well correlated with the cardiac index and NYHA class in HF populations, and also highly associated with RV systolic pressure and WHO classification in PH populations. Although more studies are needed, this multivariable scoring system provides a better assessment than any single variable because it obtains comprehensive information on cardiopulmonary functions. Moreover, it allows avoiding complications in the interpretation of multiple variables and misinterpretations due to noise of outcomes and/or outliers and only requires submaximal data.

Summary and Conclusions

PH is an increasingly recognized problem in HF patients. It is classically defined by pulmonary hemodynamic measurements including PCWP, mPAP and PVR. Vascular dysfunction associated with vascular remodeling, vasoactive substances and genetic variation contribute to the reactive form of PH. Pulmonary vascular abnormalities impair lung mechanics and gas exchange at rest and exercise, and this adverse effect of PH accentuates the abnormalities observed in HF. Noninvasive gas exchange measures with light submaximal exercise allow assessing integrated information on cardiopulmonary functions in HF patients, yielding less variable data than and similar information as maximal testing. In addition, multivariable scoring systems for quantifying gas exchange measures are emerging, simplifying the interpretation of multiple variables and providing important tracking and disease prognosis information to clinicians.

Acknowledgement

References

1 Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al: Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation 2012;125:e2–e220.

2 Abramson SV, Burke JF, Kelly JJ, Kitchen JG, Dougherty MJ, Yih DF, et al: Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888–895.

3 Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al: Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009;30:2493–2537.

4 Agostoni P, Cattadori G, Bianchi M, Wasserman K: Exercise-induced pulmonary edema in heart failure. Circulation 2003;108:2666–2671.

5 Butler J, Chomsky DB, Wilson JR: Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 1999;34:1802–1806.

6 Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, et al: Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146–1150.

KARGER

7   Moraes DL, Colucci WS, Givertz MM: Secondary pulmonary hypertension in chronic heart failure – the role of the endothelium in pathophysiology and management. Circulation 2000;102:1718–1723.

8   Taylor BJ, Olson TP, Kim CH, Maccarter D, Johnson BD: Use of noninvasive gas exchange to track pulmonary vascular responses to exercise in heart failure. Clin Med Insights Circ Respir Pulm Med 2013;7:53–60.

9   Delgado JF, Conde E, Sanchez V, Lopez-Rios F, Gomez-Sanchez MA, Escribano P, et al: Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005;7:1011–1016.

10 McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–1619.

11 Gehlbach BK, Geppert E: The pulmonary manifestations of left heart failure. Chest 2004;125:669–682.

12 Curtiss C, Cohn JN, Vrobel T, Franciosa JA: Role of the renin-angiotensin system in the systemic vasoconstriction of chronic congestive heart failure. Circulation 1978;58:763–770.

13 Unger T, Li J: The role of the renin-angiotensin-aldosterone system in heart failure. J Renin Angiotensin Aldosterone Syst 2004;5(suppl 1):S7–S10.

14 Willenheimer R, Dahlof B, Rydberg E, Erhardt L: AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. Eur Heart J 1999;20:997–1008.

15 Moreau P, d'Uscio LV, Shaw S, Takase H, Barton M, Luscher TF: Angiotensin II increases tissue endothelin and induces vascular hypertrophy: reversal by ET(A)-receptor antagonist. Circulation 1997;96:1593–1597.

16 Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R: Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 1992;85:504–509.

17 Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, et al: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732–1739.

18 Kiowski W, Sutsch G, Hunziker P, Muller P, Kim J, Oechslin E, et al: Evidence for endothelin-1-mediated vasoconstriction in severe chronic heart failure. Lancet 1995;346:732–736.

19 Sakai S, Miyauchi T, Sakurai T, Yamaguchi I, Kobayashi M, Goto K, et al: Pulmonary hypertension caused by congestive heart failure is ameliorated by long-term application of an endothelin receptor antagonist. Increased expression of endothelin-1 messenger ribonucleic acid and endothelin-1-like immunoreactivity in the lung in congestive heart failure in rats. J Am Coll Cardiol 1996;28:1580–1588.

20 Bauer M, Wilkens HC, Langer F, Schneider SO, Lausberg H, Schafers HJ: Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. Circulation 2002;105:1034–1036.

21 Attina T, Camidge R, Newby DE, Webb DJ: Endothelin antagonism in pulmonary hypertension, heart failure, and beyond. Heart 2005;91:825–831.

22 Zamora MA, Dempsey EC, Walchak SJ, Stelzner TJ: Bq123, an ETA receptor antagonist, inhibits endothelin-1-mediated proliferation of human pulmonary artery smooth muscle cells. Am J Respir Cell Mol Biol 1993;9:429–433.

23 Ghofrani HA, Pepke-Zaba J, Barbera JA, Channick R, Keogh AM, Gomez-Sanchez MA, et al: Nitric oxide pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:68s–72s.

24 Ide H, Nakano H, Ogasa T, Osanai S, Kikuchi K, Iwamoto J: Regulation of pulmonary circulation by alveolar oxygen tension via airway nitric oxide. J Appl Physiol 1999;87:1629–1636.

25 Katz SD, Khan T, Zeballos GA, Mathew L, Potharlanka P, Knecht M, et al: Decreased activity of the L-arginine-nitric oxide metabolic pathway in patients with congestive heart failure. Circulation 1999;99:2113–2117.

26 Giaid A, Saleh D: Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995;333:214–221.

27 Katz SD, Hryniewicz K, Hriljac I, Balidemaj K, Dimayuga C, Hudaihed A, et al: Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005;111:310–314.

28 Cody RJ: The integrated effects of angiotensin II. Am J Cardiol 1997;79:9–11.

29 Olson TP, Frantz RP, Turner ST, Bailey KR, Wood CM, Johnson BD: Gene variant of the bradykinin B2 receptor influences pulmonary arterial pressures in heart failure patients. Clin Med Circ Respirat Pulm Med 2009;2009:9–17.

30 Olson TP, Snyder EM, Frantz RP, Turner ST, Johnson BD: Repeat length polymorphism of the serotonin transporter gene influences pulmonary artery pressure in heart failure. Am Heart J 2007;153:426–432.

31 Abraham MR, Olson LJ, Joyner MJ, Turner ST, Beck KC, Johnson BD: Angiotensin-converting enzyme genotype modulates pulmonary function and exercise capacity in treated patients with congestive stable heart failure. Circulation 2002;106:1794–1799.

32 Taylor BJ, Mojica CR, Olson TP, Woods PR, Frantz RP, Johnson BD: A possible role for systemic hypoxia in the reactive component of pulmonary hypertension in heart failure. J Card Fail 2013;19:50–59.

33 Matsumoto A, Itoh H, Eto Y, Kobayashi T, Kato M, Omata M, et al: End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. J Am Coll Cardiol 2000;36:242–249.

34 Woods PR, Bailey KR, Wood CM, Johnson BD: Submaximal exercise gas exchange is an important prognostic tool to predict adverse outcomes in heart failure. Eur J Heart Fail 2011;13:303–310.

35 Woods PR, Olson TP, Frantz RP, Johnson BD: Causes of breathing inefficiency during exercise in heart failure. J Card Fail 2010;16:835–842.

36 Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K: End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest 2005;127:1637–1646.

37 Woods PR, Frantz RP, Taylor BJ, Olson TP, Johnson BD: The usefulness of submaximal exercise gas exchange to define pulmonary arterial hypertension. J Heart Lung Transplant 2011;30:1133–1142.

38 Milani RV, Mehra MR, Reddy TK, Lavie CJ, Ventura HO: Ventilation carbon dioxide production ratio in early exercise predicts poor functional capacity in congestive heart failure. Heart 1996;76:393–396.

39 Agostoni P, Bussotti M, Cattadori G, Margutti E, Contini M, Muratori M, et al: Gas diffusion and alveolar-capillary unit in chronic heart failure. Eur Heart J 2006;27:2538–2543.

40 Guazzi M: Alveolar gas diffusion abnormalities in heart failure. J Card Fail 2008;14:695–702.

41 Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al: Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555–1562.

42 Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R: Ventilatory efficiency and dyspnea on exertion improvements are related to reduced pulmonary pressure in heart failure patients receiving Sildenafil. Int J Cardiol 2010;144:410–412.

43 Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Kitzman D, et al: Prognostic significance of the oxygen uptake efficiency slope: percent-predicted versus actual value. Am J Cardiol 2010;105:757–758.

44 Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M: Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001;17:647–652.

45 Woods PR, Taylor BJ, Frantz RP, Johnson BD: A pulmonary hypertension gas exchange severity (PH-GXS) score to assist with the assessment and monitoring of pulmonary arterial hypertension. Am J Cardiol 2012;109:1066–1072.

46 American Thoracic Society; American College of Chest Physicians: ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211–277.

47 Meyer K, Westbrook S, Schwaibold M, Hajric R, Peters K, Roskamm H: Short-term reproducibility of cardio-pulmonary measurements during exercise testing in patients with severe chronic heart failure. Am Heart J 1997;134:20–26.

48 Miller AD, Woods PR, Olson TP, Hulsebus ML, O'Malley KA, MacCarter D, Johnson BD: Validation of a simplified, portable cardiopulmonary gas exchange system for submaximal exercise testing. Open Sports Med J 2010;4:34–40.

49 Hansen JE, Sun XG, Yasunobu Y, Garafano RP, Gates G, Barst RJ, et al: Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. Chest 2004;126:816–824.

50 Kim CH, Anderson S, Maccarter DJ, Johnson B: A multivariable index for grading exercise severity in patients with pulmonary hypertension and heart failure. Pulm Med 2012;2012:962598.