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A possible role for systemic hypoxia in the reactive component of pulmonary hypertension in heart failure

Bryan J. Taylor, PhD¹, Cesar R. Mojica, MD², Thomas P. Olson, PhD¹, Paul R. Woods, PhD¹, Robert P. Frantz, MD¹, and Bruce D. Johnson, PhD¹

¹Division of Cardiovascular Diseases, College of Medicine, Mayo Clinic and Foundation, Rochester, MN 55905

²School of Medicine, University of Puerto Rico, San Juan, PR 00926

Abstract

Background—The mechanisms underlying the reactive component of pulmonary hypertension (PH) in heart failure (HF) are unclear. We examined whether resting systemic oxygen levels are related to pulmonary hemodynamics in HF.

Methods & Results—Thirty-nine HF patients underwent right heart catheterization. Subsequently, patients were classified as having 1) no PH ($n=12$), 2) passive PH ($n=10$), or 3) PH ($n=17$). Blood was drawn from the radial and pulmonary arteries for the determination of PaO₂, SaO₂, PvO₂, SvO₂, and vasoactive neurohormones. PaO₂ and PvO₂ were lower in reactive PH vs. no PH and passive PH patients (65.3 ± 8.6 vs. 78.3 ± 11.4 and 74.5 ± 14.0 mmHg; 29.2 ± 4.1 vs. 36.2 ± 2.8 and 33.4 ± 2.3 mmHg, $P<0.05$). SaO₂ and SvO₂ were lower in reactive PH vs. no PH patients (93 ± 3 vs. $96\pm 3\%$; 51 ± 11 vs. $68\pm 4\%$, $P<0.05$), but not different vs. passive PH patients. The transpulmonary pressure gradient (TPG) was inversely related to PaO₂, PvO₂, SaO₂ and SvO₂ in the reactive PH patients only ($r = -0.557$, $P<0.05$). Similarly, plasma endothelin-1 correlated with PaO₂, PvO₂, SvO₂ ($r = -0.495$) and TPG ($r = -0.662$) ($P<0.05$) in reactive PH patients only.

Conclusion—Systemic hypoxia may play a role in the reactive component of PH in HF, potentially via a hypoxia-induced increase in endothelial release of the vasoconstrictor endothelin-1.

Keywords

Transpulmonary pressure gradient; Neurohormones; Endothelin-1; Arterial and venous oxygen pressure and saturation

INTRODUCTION

Pulmonary hypertension (PH) is a hallmark of chronic heart failure (HF) and is associated with poor prognosis and increased mortality in these patients(1–3). Secondary PH in HF

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For correspondence and reprints: Bryan J. Taylor, PhD., Post-doctoral Research Fellow, Division of Cardiovascular Diseases, Mayo Clinic and Foundation, 200 1st Street SW, Rochester, MN 55905, Office: 507-293-1338, Fax: 507-255-4861, taylor.bryan@mayo.edu.

DISCLOSURES

None

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initially manifests as a “passive” increase in pulmonary venous pressure, with a concomitant increase in pulmonary artery pressure (P_{AP}), caused by the rise in left ventricle (LV) filling pressure consistent with a failing LV(4). However, with prolonged elevation of pulmonary capillary wedge pressure (P_{WP}), many HF patients develop a superimposed active component of PH that is associated with active vasoconstriction and/or fixed structural remodeling of pulmonary artery resistance vessels. This “reactive” component of PH is characterized by an excessive increase in P_{AP} relative to the increase in P_{WP} with a consequent rise in pulmonary vascular resistance (P_{VR})(5, 6). Importantly, the development of reactive PH is associated with a further increase in mortality rates in the HF population(7). Despite its apparent importance and prognostic value, the mechanisms that underpin reactive PH in HF remain unclear. One possible mechanism is hypoxia-mediated dysregulation of pulmonary vascular smooth muscle tone, through either a direct effect on the pulmonary vasculature(8, 9) or an increase in the synthesis and release of vasoactive neurohormones (e.g., endothelin-1)(6, 10, 11). The role of hypoxia as a mediator of reactive PH in HF, however, is unknown.

Hypoxic pulmonary vasoconstriction (HPV) is a vasomotor property intrinsic to the lungs whereby hypoxia elicits constriction of the pulmonary vasculature to better distribute blood flow to optimally ventilated lung segments. Despite the prevailing view that HF patients exhibit little evidence of systemic hypoxia(12–15), it has been shown that transient but significant periods of arterial desaturation ($SpO_2 < 90\%$, > 5 s) can occur in HF patients that are greater in frequency, magnitude and duration relative to healthy subjects(16). Also, oxygen (O_2) enrichment of inspired gas has been shown to increase SpO_2 , decrease dyspnea and improve exercise tolerance in HF patients(17), although these are not consistent findings (18–21). Moreover, the respiratory alkalosis associated with HF may cause a leftward shift in the oxyhemoglobin dissociation curve with a resulting reduction in the partial pressure of arterial and mixed-venous O_2 (PaO_2 and PvO_2) for a given arterial SpO_2 (22). Thus, there appears to be several mechanisms by which HF patients may experience systemic hypoxia.

Based on the aforementioned considerations, it is possible that systemic hypoxia plays a role in the reactive component of PH in HF. Therefore, the primary aim of the present study was to determine the relationships between resting systemic oxygen levels and pulmonary hemodynamics in HF patients without PH, with passive PH and with reactive PH. A secondary aim was to determine the relationship, if any, between systemic oxygen levels and circulating neurohormonal markers implicated in the reactive component of PH in HF.

METHODS

Participant Characteristics

Thirty-nine adult patients (35 male, 4 female) from the Mayo Clinic Heart Failure Service undergoing right heart catheterization participated in this study (Table 1). 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. Post-hemodynamic evaluation, the patients were classified as either HF with PH, HF with passive PH or HF with reactive PH according to current guidelines(23, 24): 1) HF without PH [mean P_{AP} (mP_{AP}) < 25 mmHg, mean P_{WP} (mP_{WP}) < 15 mmHg and transpulmonary pressure gradient (TPG) < 12 mmHg], 2) HF with passive PH (mP_{AP} ≥ 25 mmHg, mP_{WP} ≥ 15 mmHg, TPG ≥ 12 mmHg), or 3) HF with reactive PH (mP_{AP} ≥ 25 mmHg, mP_{WP} ≥ 15 mmHg, TPG ≥ 12 mmHg) (Table 1). It is important to note that the reversibility of the reactive form of PH under acute vasodilator administration was not assessed. Accordingly, we considered reactive PH to be the result of both reversible active constriction and fixed structural remodeling of pulmonary artery resistance vessels(24).

Hemodynamic Evaluation and Blood Gases

Right-heart catheterization was conducted as described previously(25). 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 to the 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. Systemic systolic, diastolic and mean arterial pressure (SBP, DBP and MAP, respectively) were measured beat-by-beat using the radial catheter. In addition, systolic, diastolic and mean pulmonary artery pressure (sP_{AP} , dP_{AP} , mP_{AP}) and mP_{WP} were measured beat-by-beat via the pulmonary catheter. 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 and CO_2 partial pressure (PaO_2 , PvO_2 , $PaCO_2$, $PvCO_2$) as well as arterial and mixed venous oxygen saturation (SaO_2 and SvO_2). Arterial and mixed venous oxygen content (CaO_2 and CvO_2) were 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 (Q) was determined by the direct Fick method using measured oxygen consumption (VO_2) and the CaO_2 - CvO_2 ; VO_2 was measured breath-by-breath using a portable on-line gas analysis system integrated with a pneumotachograph (MedGraphics CPX/D, Medical Graphics, St. Paul, MN). TPG (i.e. the pressure difference across the pulmonary circulation independent of Q) was calculated as mP_{AP} minus mP_{WP} . Pulmonary vascular resistance (P_{VR}) was calculated as TPG divided by Q.

Circulating Vasoactive Neurohormones

After the blood draws for the assessment of blood gases were obtained, further arterial blood samples were taken from the radial artery via Vacutainer tubes that were immediately chilled ($4^\circ C$) before being centrifuged at 2500 rpm for 10 minutes. 1 ml serum and plasma aliquots were then transferred to 12×75 mm polystyrene tubes before being frozen until assayed. Endothelin-1 (ET-1) was measured via quantitative sandwich enzyme immunoassay (R & D Systems, Minneapolis, MN), whereas epinephrine, norepinephrine and angiotensin-II (Ang-II) were assessed according to standardized methods developed in the Mayo Clinic Immunochemical Core Laboratory. Serum angiotensin converting enzyme (ACE) activity was determined by a spectrophotometric method as described previously(26). Plasma brain natriuretic peptide (BNP) was measured by specific immunoradiometric assay using two monoclonal antibodies against human BNP.

Statistical Analyses

One way ANOVA was used to compare subject characteristics, resting pulmonary hemodynamics, blood gases and circulating neurohormone levels between patient groups (no PH, passive PH and reactive PH). Following significant main effects, pairwise comparisons were made with the Bonferroni method. Pearson's product-moment correlation coefficient (r) was computed to assess the relationships between blood gases, pulmonary hemodynamics and circulating neurohormone levels in the three patient groups. Following the identification of significant zero-order relationships (reactive PH only), multiple linear regression models (stepwise method) were used to examine 1) the influence of systemic oxygen levels (PaO_2 , PvO_2 , SaO_2 , SvO_2) on the transpulmonary pressure gradient, and 2) the influence of systemic oxygen levels (PaO_2 , PvO_2 , SaO_2 , SvO_2) on plasma endothelin-1 concentration. The acceptable type I error was set at $P < 0.05$ and data are expressed as group means $\pm$ SD. Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS, Chicago, IL).

RESULTS

Participant Characteristics

The clinical characteristics and medications used by the participants are shown in Table 1. At the time of study, all patients were classified as stable and receiving standard pharmacologically optimized therapy. Of the 39 patients, 8 were considered NYHA class II, 22 NYHA class III and 9 NYHA class IV. Additionally, 12 patients were categorized as HF without PH, 10 as HF with passive PH and 17 as HF with reactive PH.

Hemodynamics, Pulmonary Vascular Pressures and Blood Gases

Resting hemodynamics, pulmonary vascular pressures, blood gases and circulating neurohormone levels for our patient population are shown in Table 2. Neither Q nor CI were different between patients with no, passive or reactive PH. HR was greater in reactive PH vs. no PH patients, but not different in reactive PH and passive PH patients. By contrast, SV was decreased in reactive vs. no PH patients; SV was not different between reactive PH and passive PH patients. SBP, SDP and MAP were within normal limits for all subjects. Arterial pH was greater in reactive PH patients vs. patients with no PH and passive PH, but not different in no PH and passive PH patients.

By definition, sP_{AP} , mP_{AP} , TPG and P_{VR} were greater in reactive PH patients compared to both no PH and passive PH patients. In addition, sP_{AP} and mP_{AP} were elevated in passive PH patients relative to no PH patients. Neither TPG nor P_{VR} were different between no PH and passive PH patients. mP_{WP} was greater in reactive PH vs. no PH patients, but not different in reactive PH and passive PH patients. Together, these data allow clear hemodynamic differentiation between HF patients with no PH, with passive PH and with reactive PH in our study cohort.

In patients with no PH, PaO_2 , PvO_2 , SaO_2 and SvO_2 were maintained at normal to low-normal levels (Table 2). Neither PaO_2 nor SaO_2 were different in passive PH vs. no PH patients; however both PvO_2 and SvO_2 were slightly and significantly lower in passive PH patients relative to no PH patients (Table 2). In patients with reactive PH, both PaO_2 and PvO_2 were markedly less compared to patients with no PH and with passive PH; the group mean PaO_2 in patients with reactive PH (65.3 ± 8.6 mmHg) was substantially lower than previously reported healthy normative values(27). Similarly, SaO_2 and SvO_2 were lower in reactive PH patients vs. patients with no PH and passive PH; however, only the differences between patients with reactive PH and patients with no PH were statistically significant (Table 2). In combination, these data show that systemic O_2 levels are significantly lower in HF patients with reactive PH compared to patients with no PH or passive PH. Moreover, PaO_2 in patients with reactive PH was low relative to previously reported healthy normative values(27), suggesting that HF patients with reactive PH experience significant systemic hypoxia.

Effect of Systemic Oxygen Levels on the Transpulmonary Pressure Gradient

In the patients with no PH, there was no relationship between TPG and PaO_2 , PvO_2 , SaO_2 or SvO_2 (P 0.11) (Fig. 1). Similarly, there was no relationship between TPG and PaO_2 , PvO_2 , SaO_2 or SvO_2 in the patients with passive PH (P 0.10) (Fig. 2). By contrast, there was a significant inverse relationship between TPG and PaO_2 ($r=-0.709$), PvO_2 ($r=-0.577$), SaO_2 ($r=-0.601$) and SvO_2 ($r=-0.681$) (all P 0.02) in patients with reactive PH (Fig. 3). Multiple linear regression analysis suggested that PaO_2 and PvO_2 were the strongest predictors of TPG and accounted for approximately 57% of the variance in TPG in HF patients with reactive PH. It should be noted that Q was not related to TPG (r -0.14), PVR (r -0.12) or any index of systemic oxygen levels (r -0.16) ($P>0.05$) in any of the patients studied.

Effect of Neurohormonal Status on the Transpulmonary Pressure Gradient

As stated above, TPG was related to measures of systemic O₂ in HF patients with reactive PH but not in patients with no PH or passive PH; accordingly, we examined the relationships between TPG and vasoactive neurohormonal markers in patients with reactive PH only. In these patients, there was a significant positive relationship between TPG and plasma ET-1 concentration ($r=0.662$, $P<0.01$) (Fig. 4). Conversely, TPG was not related to circulating Ang-II, ANP, BNP, epinephrine or norepinephrine levels (Fig. 4).

Effect of Systemic Oxygen Levels on Neurohormonal Status

As ET-1 was the only neurohormonal marker that related to TPG in patients with reactive PH, we examined the relationship between ET-1 and PaO₂, PvO₂, SaO₂ and SvO₂ in these patients. While plasma ET-1 was not related to SaO₂, there was a weak but significant negative correlation between ET-1 and PaO₂ ($r=-0.495$, $P=0.03$) (Fig. 5). Additionally, there was a strong negative correlation between ET-1 and PvO₂ ($r=-0.851$) and SvO₂ ($r=-0.747$) (both $P<0.01$) (Fig. 5). Multiple linear regression analysis revealed that PvO₂ was the strongest predictor of plasma ET-1 and that approximately 64% of the variance in plasma ET-1 was explained by variations in PvO₂.

Discussion

Main Findings

The aim of the present study was to determine the relationships between resting systemic oxygen levels and pulmonary hemodynamics in HF patients without pulmonary hypertension (PH), HF patients with passive PH, and HF patients with reactive PH. The main findings were 1) systemic O₂ levels were significantly lower in HF patients with reactive PH compared to patients with no PH or passive PH, suggesting that HF patients with reactive PH experience systemic hypoxia, 2) the transpulmonary pressure gradient (TPG) was inversely related to PaO₂, PvO₂, SaO₂ and SvO₂ in HF patients with reactive PH; no such relationships were observed in the patients with no PH or with passive PH, and 3) plasma endothelin-1 (ET-1) concentration was positively related to TPG but negatively related to PaO₂, PvO₂ and SvO₂ in patients with reactive PH. Multiple linear regression analysis suggested that PaO₂ and PvO₂ were the strongest predictors of TPG, and that PvO₂ was the strongest predictor of plasma ET-1 in HF patients with reactive PH. In combination, these data identify a possible role for systemic hypoxia in the reactive component of PH in HF. We postulate that a potential mediator in this pathway may be a hypoxia-induced increase in endothelial release of the potent vasoconstrictor ET-1.

A Potential Role for Heart Failure Disease Severity?

One important consideration is that the occurrence of the reactive form of PH and systemic hypoxia may simply be coincident with more severe chronic illness rather than low systemic oxygen levels mediating the development of reactive PH in these patients. Indeed, in the present study the propensity of NYHA class IV patients was greater in the reactive PH group compared to the no PH and passive PH groups. However, given its largely subjective nature, the lack of a consistent method of assessment, and the relatively high level of inter-operator variability (28), whether NYHA classification provides an accurate representation of disease severity is questionable. Moreover, we observed little to no difference in objective markers of disease severity between patients with no, passive or reactive PH. For example, neither HF duration nor lung diffusing capacity was different between any of the patient groups (Table 1). In addition, while left ventricular ejection fraction was lower in patients with reactive PH vs. no PH, no such difference was observed in reactive PH compared to passive PH patients (Table 1). Similarly, although cardiac output and VO_{2peak} were lower in patients

with passive and reactive PH relative to patients with no PH, neither of these variables were different in the passive vs. the reactive PH patients (Tables 1 and 2). These data suggest that by in large disease severity was not different between our patient groups, especially between patients with passive PH and patients with reactive PH. Despite the uniformity in disease severity between these patients, only the reactive PH group presented with evidence of systemic hypoxia (i.e. markedly reduced arterial and mixed-venous O₂ levels) and elevated plasma ET-1 concentration (Table 2). Furthermore, the significant relationships between the severity of PH, systemic oxygen levels and plasma ET-1 were present in the reactive PH patients only. Thus, while we cannot definitively rule out that the presence of the reactive component of PH and systemic hypoxia are coincidentally the result of more severe disease status, we believe that the aforementioned observations identify an interesting and previously underappreciated role for systemic hypoxia in the manifestation of the reactive component of PH, and thus the pathophysiology of HF, that is largely independent of disease severity.

Systemic Hypoxia in Heart Failure

While it is well known that sleep disordered breathing causes intermittent nocturnal hypoxia in a large portion of HF patients(29), whether HF patients exhibit similar periods of hypoxia during wakeful rest remains controversial. Despite the prevailing view that SaO₂ and PaO₂ are maintained at or even above normal values at rest and during exercise in HF patients(12–15), there is evidence that transient but significant periods of arterial desaturation (SaO₂ <90% for > 5s) that are greater in frequency, magnitude and total duration (over 24 hours) relative to healthy subjects can occur in HF patients(16). In addition, O₂ supplementation of inspired gas has been shown to increase SaO₂, reduce perceived exertion and increase exercise time in HF patients(17), although this is not a consistent finding(21). Moreover, it is probable that there is a reduction in both PaO₂ and PvO₂ in HF patients that is masked by a somewhat normal/low-normal SaO₂(22). Such a reduction in PaO₂ for a given SaO₂ may be the result of a leftward shift in the oxyhemoglobin dissociation curve secondary to the alkalosis associated with the chronic mild hyperventilation in HF patients (a finding observed in this study, *see* Table 2) and/or a widening of alveolar-arterial O₂ difference due to an exaggeration in ventilation/perfusion inhomogeneities.

In the present study, systemic O₂ levels were maintained at normal to low-normal levels in HF patients with no PH and with passive PH (Table 2). Conversely, PaO₂, PvO₂, SaO₂ and SvO₂ were substantially reduced in patients with reactive PH (Table 2). Additionally, there was a significant inverse relationship between TPG and PaO₂, PvO₂, SaO₂ and SvO₂ (all *P* 0.02) in patients with reactive PH (Fig. 3). These data suggest that 1) HF patients with reactive PH exhibit substantial systemic hypoxia, and 2) systemic hypoxia may play a role in the reactive component of PH in this population.

Is Hypoxic Pulmonary Vasoconstriction a Mediator of Reactive Pulmonary Hypertension in HF?

Hypoxic pulmonary vasoconstriction (HPV) is a self-regulatory vasomotor property intrinsic to the lungs whereby hypoxia elicits constriction of the pulmonary vasculature to better distribute pulmonary capillary blood flow to optimally ventilated lung segments. As noted above, we found that HF patients with reactive PH presented with systemic hypoxia/hypoxia and that this hypoxia was related to the severity of PH in these patients (Table 2 and Fig 3). Based on previous literature, we propose two primary mechanisms by which hypoxia may mediate the vascular smooth muscle dysregulation associated with the reactive component of PH commonly observed in HF.

First, it is becoming increasingly clear that a hypoxia-induced increase in endothelial synthesis and release of the potent vasoconstrictor ET-1 is a major factor in the development of HPV in healthy animals and humans(9). It has been shown previously that endothelial denudation of seventh generation porcine pulmonary arteries abolished the hypoxic constrictor response observed in preparations with an intact endothelium(30). Moreover, “priming” with low concentrations of ET-1 restored the normal HPV response in the endothelial denuded preparations(30). In healthy humans, exposure to high-altitude causes a marked increase in plasma ET-1 that is related to the reduction in PaO_2 and the increase in P_{AP} (31). Additionally, it has been shown that administration of an ET-1 receptor antagonist blunts the HPV response to high-altitude and/or normobaric hypoxia (i.e. reduces pulmonary vascular pressures and P_{VR}) (32–36), improves lung diffusing capacity(32) and increases exercise tolerance in such subjects(33, 36). These data implicate hypoxia-induced endothelial ET-1 release as a major mediator of HPV in healthy animal and humans. In HF patients, there is a marked elevation in basal plasma ET-1 concentration that is significantly related to P_{AP} and P_{VR} (10, 37), but not cardiac index, P_{WP} or systemic vascular resistance(10). Additionally, there is some evidence that ET-1 receptor blockade may improve pulmonary hemodynamics and reduce the severity of symptoms in HF patients(38), although clinical trials of such agents have been disappointing due in part to issues of fluid retention and risk of pulmonary congestion. In the present study, plasma ET-1 concentration was significantly related to TPG in HF patients with reactive PH (Fig. 4). Moreover, plasma ET-1 was negatively related to PaO_2 , PvO_2 , SaO_2 and SvO_2 in these patients (Fig. 5). Multiple linear regression analysis suggested that PvO_2 was the strongest predictor of plasma ET-1 and that approximately 64% of the variance in ET-1 was explained by variations in PvO_2 . Thus, we conclude that systemic hypoxia, specifically a reduction in mixed-venous oxygen levels likely secondary to high extraction in the presence of an impaired cardiac output, exaggerates pulmonary artery and arteriole endothelial synthesis and release of ET-1 with a resultant constriction of the pulmonary vasculature in HF patients with reactive PH.

The second mechanism by which hypoxia may mediate PH in HF is through a direct effect of low systemic oxygen on the pulmonary vasculature itself. It has been shown previously that acute hypoxia can induce significant constriction of isolated porcine and feline pulmonary myocytes(8, 39). Although the precise mechanisms underlying the hypoxia-mediated smooth muscle contraction remain debated, it is likely that hypoxic inhibition of outward K^+ , either through intracellular Ca^{2+} release or a change in redox status, causes depolarization of the smooth muscle cells with a subsequent influx of Ca^{2+} entry via voltage gated Ca^{2+} channels and contraction of smooth muscle cells (8, 40, 41). Thus, there is evidence that hypoxia can elicit pulmonary vasoconstriction via a direct effect on the smooth muscle cells of the pulmonary vasculature. As stated above, we observed that systemic oxygen levels were significantly inversely related with TPG. Therefore, we postulate that the reactive component of PH in HF may, at least in part, be mediated by an increase in pulmonary vascular pressures secondary to a direct effect of low mixed-venous oxygen levels on pulmonary arterial smooth muscle cells.

Impaired Cardiac Output and Reactive Pulmonary Hypertension

Based on previous literature, it is possible that the impairment in cardiac output associated with the heart failure may cause HF patients to experience a hypoxic like response secondary to a reduction in carotid body (CB) blood flow and oxygen delivery rather than direct arterial hypoxia *per se*. HF is associated with a chronic elevation in sympathetic vasoconstrictor outflow that is likely, at least in part, mediated by enhanced CB activity (42). In rabbits, the changes in voltage-gated K^+ channel function in the glomus cells of the CB are remarkably similar in animals with HF (43) compared to those exposed to chronic hypoxia (44). Moreover, it has been shown that progressive occlusion of carotid artery blood

flow not only enhanced the CB response to hypoxia but also increased basal CB discharge to a level similar to that observed in HF(45). These findings suggest that a reduction in CB blood flow and oxygen delivery secondary to impaired cardiac function is sufficient to mimic hypoxic effects on the CB. That is, attenuation of CB perfusion rather than frank arterial hypoxia *per se* may be a source of hypoxic stimulus in HF. In the present study, however, neither Q nor CI was different in patients with no PH, with passive PH and with reactive PH (Table 2). In addition, Q was not related to TPG, PVR or any index of systemic oxygen levels in any of the patients studied. Thus, it is unlikely that a hypoxic like response to impaired cardiac output and CB blood flow contributed to the reactive component of PH observed in this study.

Future Directions: O₂ Therapy as a Potential Therapeutic Aid?

An obvious extension to the present study would be to determine the effect of O₂ supplementation on pulmonary hemodynamics in HF patients with reactive PH, perhaps identifying oxygen therapy as an efficacious adjunct to therapy in these patients. In theory, partial reversal of the reactive component of PH in HF via O₂ therapy would reduce breathlessness, increase exercise tolerance and quality of life, and ultimately improve prognosis. While O₂ therapy has been shown by some to reduce the frequency of apneic episodes during sleep(46) and elicit small improvements in LV function and exercise capacity(17, 46, 47) in HF patients, others have suggested that similar therapy has no effect on breathlessness or exercise tolerance in these patients(18–21). Thus, it is currently unclear whether O₂ supplementation would be of therapeutic benefit, especially in the treatment of PH, in HF patients. Accordingly, the efficacy of long term O₂ therapy in HF requires further examination.

Conclusion

In conclusion, systemic hypoxia may play a role in the reactive component of pulmonary hypertension in heart failure. Evidence from the present study suggests that a hypoxaemia-mediated increase in endothelial synthesis and release of the potent vasoconstrictor endothelin-1 may be a primary mechanism.

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Fig. 1.

Scatter-plots showing the relationships between individual subject values of transpulmonary pressure gradient (TPG) (mean pulmonary artery pressure – mean pulmonary capillary wedge pressure) and partial pressure of arterial oxygen (PaO₂), partial pressure of mixed venous oxygen (PvO₂), arterial oxygen saturation (SaO₂) and mixed venous oxygen saturation (SvO₂) in HF patients without pulmonary hypertension (PH) ($n = 12$).

Fig. 2.

Definitions are the same as in Fig. 1. Scatter-plots showing the relationships between individual subject values of TPG and PaO₂, PvO₂, SaO₂ and SvO₂ in HF patients with passive PH ($n = 10$).

Fig. 3.

Definitions are the same as in Fig. 1. Scatter-plots showing the relationships between individual subject values of TPG and PaO₂, PvO₂, SaO₂ and SvO₂ in HF patients with reactive PH ($n = 17$).

* $P < 0.05$, ** $P < 0.01$, significant relationship between two parameters

Fig. 4. Scatter-plots showing the relationships between individual subject ($n = 17$) values of TPG and plasma levels of endothelin-1, angiotensin-II, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), epinephrine and norepinephrine in HF patients with reactive PH only.

$^{**}P < 0.01$, significant relationship between two parameters.

Fig. 5. Scatter-plots showing the relationships between individual subject ($n = 17$) values of plasma endothelin-1 (ET-1) and PaO₂, PvO₂, SaO₂ and SvO₂ in HF patients with reactive pulmonary hypertension only.

* $P < 0.05$, ** $P < 0.01$, significant relationship between two parameters.

Table 1

Participant characteristics and medications

	No PH	Passive PH	Reactive PH
Demographics			
<i>n</i>	12	10	17
Age, y	51 ± 12	57 ± 8	55 ± 8
Gender, M/F	10/2	9/1	14/3
Stature, cm	173 ± 9	174 ± 7	176 ± 8
Body mass, kg	85 ± 17	80 ± 10	90 ± 16
BMI, kg/m ²	28.2 ± 3.7	26.7 ± 3.8	29.1 ± 4.6
BSA, m ²	2.0 ± 0.2	2.0 ± 0.1	2.1 ± 0.2
HF etiology, IS/DCM	5/7	5/5	11/6
HF duration, mo	50 ± 37	70 ± 76	67 ± 77
LVEF, %	23.7 ± 8.1	21.0 ± 5.7	18.3 ± 4.6 [†]
NYHA class			
II	4 (33)	1 (10)	3 (18)
III	6 (50)	8 (80)	8 (47)
IV	2 (17)	1 (10)	6 (35)
VO _{2peak} , ml/min	906 ± 313	641 ± 145*	660 ± 192*
DLCO, ml/min/mmHg	21 ± 4	19 ± 6	18 ± 5
Medications			
ACE inhibitors	8 (67)	6 (60)	14 (82)
Ang-II receptor blockers	9 (75)	5 (50)	15 (88)
Aspirin	1 (8)	3 (30)	2 (12)
β-blockers	11 (92)	8 (80)	14 (82)
Digitalis	8 (67)	9 (90)	17 (100)
Diuretics	8 (67)	6 (60)	13 (76)

Data are presented as group means ± SD or as number of participants (percent of participant population) where appropriate for 39 subjects. No PH (pulmonary hypertension), passive PH and reactive PH groups are as defined in *Methods, Participant Characteristics* section. BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; HF, heart failure; IS, ischemic; DCM, dilated cardiomyopathy; NYHA, New York Heart Association; VO_{2peak}, peak oxygen consumption during exercise; DLCO, lung diffusing capacity for carbon monoxide; ACE, angiotensin converting enzyme; Ang-II, angiotensin-II.

[†]*P* < 0.05, value significantly different vs. no-PH group.

Table 2

Resting hemodynamics, blood gases and plasma neurohormones

	No PH	Passive PH	Reactive PH
Q, L/min	4.7 ± 2.2	3.7 ± 1.4	3.7 ± 1.4
HR, bpm	64 ± 8	72 ± 12	77 ± 17 *
SV, ml	74 ± 33	53 ± 20	49 ± 20 *
CI, L/min/m ²	2.4 ± 1.1	1.9 ± 0.7	1.8 ± 0.6
SBP, mmHg	117 ± 23	115 ± 11	118 ± 21
DBP, mmHg	62 ± 11	67 ± 6	66 ± 9
MAP, mmHg	81 ± 14	83 ± 6	83 ± 12
sPAP, mmHg	28.0 ± 6.3	46.7 ± 10.4 *	65.5 ± 11.4 * [†]
dPAP, mmHg	10.3 ± 4.3	24.9 ± 4.6 *	29.0 ± 7.5 *
mPAP, mmHg	17.8 ± 4.9	33.8 ± 5.9 *	43.6 ± 6.8 * [†]
mPWP, mmHg	9.5 ± 3.7	25.7 ± 4.7 *	24.8 ± 7.4 *
TPG, mmHg	8.3 ± 2.3	8.1 ± 2.7	18.5 ± 4.9 * [†]
PVR, woods units	1.9 ± 0.8	2.4 ± 1.1	5.9 ± 2.7 * [†]
PaO ₂ , mmHg	78.3 ± 11.4	74.5 ± 14.0	65.3 ± 8.6 * [†]
PaCO ₂ , mmHg	39.1 ± 4.6	37.8 ± 6.6	35.3 ± 3.8 *
PvO ₂ , mmHg	36.2 ± 2.8	32.4 ± 2.3 *	29.2 ± 4.1 * [†]
PvCO ₂ , mmHg	44.7 ± 2.8	45.5 ± 5.3	42.9 ± 4.6
CaO ₂ , mlO ₂ /100 ml blood	17.9 ± 1.9	17.3 ± 1.9	17.1 ± 2.7
CvO ₂ , ml O ₂ /100 ml blood	12.7 ± 1.6	10.4 ± 6.9 *	9.4 ± 2.8 *
Ca-vO ₂ difference	5.2 ± 1.0	6.9 ± 1.1 *	7.7 ± 1.6 *
SaO ₂ , %	96 ± 3	95 ± 4	93 ± 4 *
SvO ₂ , %	68 ± 4	56 ± 7 *	51 ± 11 *
pHa	7.40 ± 0.03	7.41 ± 0.03	7.44 ± 0.04 * [†]
SOT, ml/min/m ²	849 ± 403	648 ± 250	623 ± 229
HgB, g/dL	13.3 ± 1.3	12.9 ± 1.2	13.1 ± 1.9
ET-1, pg/mL	1.18 ± 0.50	2.09 ± 0.98 *	2.82 ± 1.05 * [†]
Ang-II, pg/mL	12.8 ± 11.0	14.4 ± 10.8	21.1 ± 25.0
ANP, pg/mL	1442 ± 977	3366 ± 1088 *	4252 ± 3472 *
BNP, pg/mL	180 ± 150	564 ± 428 *	496 ± 485 *
Epinephrine, pg/mL	76.8 ± 42.7	142.9 ± 126.5	86.0 ± 64.4
Norepinephrine, pg/mL	345 ± 179	472 ± 323	572 ± 242 *

Data are presented as group means ± SD. No PH (pulmonary hypertension), passive PH and reactive PH groups are as defined in *Methods, Participant Characteristics* section. Q, cardiac output; HR, heart rate; SV, stroke volume; CI, cardiac index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; mPWP, mean pulmonary capillary wedge pressure; TPG, transpulmonary pressure gradient; PVR, pulmonary vascular resistance; PaO₂, partial pressure of arterial oxygen; PaCO₂, partial pressure of arterial carbon dioxide; PvO₂, partial pressure of mixed venous oxygen; PvCO₂, partial pressure of mixed venous carbon dioxide; CaO₂, arterial oxygen content; CvO₂, mixed venous oxygen

content; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation; pHa, arterial PH; SOT, systemic oxygen transport; HgB, arterial hemoglobin concentration; ET-1, endothelin-1; Ang-II, angiotensin-II; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

*
 $P < 0.05$, value significantly different vs. no-PH group;

[†]
 $P < 0.05$, value significantly different vs. p-PH group