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Pulmonary vascular mechanics: Important contributors to the increased right ventricular afterload of pulmonary hypertension

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Abstract

Chronic hypoxia causes pulmonary vasoconstriction and vascular remodeling, which lead to hypoxic pulmonary hypertension (HPH). HPH is associated with living at high altitudes and is a complication of many lung diseases, including chronic obstructive pulmonary disease, cystic fibrosis, and obstructive sleep apnea. Pulmonary vascular changes that occur with HPH include stiffening and narrowing of the pulmonary arteries that appear to involve all vascular cell types and sub-layers of the arterial wall. Right ventricular (RV) changes that occur with HPH include RV hypertrophy and RV fibrosis, often with preserved systolic and diastolic function and ventricular-vascular coupling efficiency. Both vascular stiffening and narrowing are important contributors to RV afterload via increases in oscillatory and steady ventricular work, respectively. The increased blood viscosity that occurs in HPH can be quite dramatic and is another important contributor to RV afterload. However, the viscosity, vascular mechanics and ventricular changes that occur with HPH are all reversible. Furthermore, even with continued hypoxia vascular remodeling does not progress to the obliterative, plexiform lesions that are seen clinically in severe pulmonary hypertension. In animal models, the RV changes appear adaptive, not maladaptive. In summary, HPH-induced vascular mechanical changes affect ventricular function but both are adaptive and reversible, which differentiates HPH from severe pulmonary hypertension. The mechanisms of adaptation and reversibility may provide useful insight into therapeutic targets for the clinical disease state.

Keywords

Hypoxia; pulmonary artery; ventricle

Introduction

Pulmonary hypertension (PH) is manifested as the elevation of pulmonary arterial pressure (Ppa) and is often hemodynamically defined as a mean resting Ppa greater than 25 mmHg. PH is a complex pulmonary disorder associated with a variety of causes; hypoxia-induced PH (HPH) is categorized in the third group of PH according to revised WHO classifications (McLaughlin *et al.*, 2009). Clinically, HPH can be caused by living at high altitudes and is a complication of many lung diseases, including chronic obstructive pulmonary disease, cystic fibrosis, and obstructive sleep apnea. The preclinical animal model of HPH was introduced in 1970s (Zaiman *et al.*, 2005) and is now widely used in rodents and calves to study the biological and functional changes in the pulmonary vasculature during PH progression.

While the pulmonary vascular changes in the most severe form of clinical PH – pulmonary arterial hypertension (PAH) – can be dramatic, the cause of death is typically right ventricular (RV) failure. Therefore, biological and functional changes in the RV with PH progression, and the interactions between pulmonary vascular and RV dysfunction have gained more attention recently. In this context, it is necessary to revisit the current

understanding of HPH as well as its use as a model to study vascular and ventricular changes in PH progression.

Biological changes in pulmonary arteries during HPH

Hypoxia, the pathological condition in which one is deprived of adequate oxygen supply, can be achieved by exposing subjects to high altitude (which causes hypobaric hypoxia) or a low oxygen environment at normal barometric pressure (which causes normobaric hypoxia). Acutely, hypoxia leads to pulmonary vasoconstriction, mostly in the pre-capillary small pulmonary arteries (PAs) as evidenced by recent synchrotron radiation experiments (Schwenke *et al.*, 2007). The cellular and molecular mechanisms of acute hypoxic pulmonary vasoconstriction have been extensively reviewed recently (Sylvester *et al.*, 2012). Chronically, both continuous and intermittent hypoxia causes remodeling in large, proximal arteries and small, distal arterioles as well as RV hypertrophy (Stenmark *et al.*, 2006). These arterial changes involve all vascular cell types (i.e., endothelial cells, smooth muscle cells and adventitial fibroblasts) and include altered cell proliferation and apoptosis, expression of growth factors, cytokines and receptors, as well as inflammatory responses (Humbert *et al.*, 2004; Stenmark *et al.*, 2006; Zhang *et al.*, 2012).

While the HPH model continues to serve as a model of human PH, and is especially suitable for studying forms of PH associated with respiratory disorders, it is also well recognized that the HPH-induced remodeling in PAs lacks the marked distal luminal reduction by intimal growth and complex vascular lesions found in severe PAH (Zaiman *et al.*, 2005; Nicolls *et al.*, 2012). The absence of this biological signature of PAH in HPH may explain the mild to moderate and reversible functional changes in PAs and RV that we will discuss later.

Another major characteristic of PA remodeling during HPH is the accumulation of extracellular matrix (ECM) including elastin and collagen, especially in the proximal PAs (Poiani *et al.*, 1990; Tozzi *et al.*, 1994; Kobs *et al.*, 2005; Drexler, 2008; Lammers *et al.*, 2008; Estrada & Chesler, 2009; Ooi *et al.*, 2010; Wang & Chesler, 2011b; Wang *et al.*, 2013b). A recent study suggests elastin remodeling contributes to proximal PA stiffening in response to HPH in neonatal calves (Lammers *et al.*, 2008), but discrepant observations are also reported in other species in adults. For example, there is no change in elastin content in rodent large PAs after chronic hypoxia (Merklinger *et al.*, 2005; Drexler, 2008; Ooi *et al.*, 2010). Our group has found that in mouse HPH, the ECM changes are dominated by collagen and in particular the type I isoform is elevated significantly (Ooi *et al.*, 2010; Wang & Chesler, 2011b; Wang *et al.*, 2013b). Changes in collagen cross-linking also occur with HPH progression and may affect blood flow dynamics (Wang & Chesler, 2011b; Wang *et al.*, 2013b). Moreover, limiting collagen synthesis has been shown to limit HPH severity and RV dysfunction although the mechanism is unclear (Kerr *et al.*, 1984; Kerr *et al.*, 1987; Schreier *et al.*, 2013). These studies suggest an important role of collagen in HPH severity and progression. The ECM remodeling that occurs with HPH has been postulated to be preceded by endothelial dysfunction, which in turn increases SMC-mediated proteolysis (Budhiraja *et al.*, 2004; Rabinovitch, 2012). The proteolytic enzymes include matrix metalloproteinases (MMP) and their counteracting inhibitors (TIMP), which are elevated in experimental HPH as well as in clinical PAH (Hassoun, 2005). Therefore, the exact regulatory mechanisms of ECM remodeling in PAs may be essential keys to potential therapeutic targets in PH.

Mechanical changes in pulmonary arteries during HPH

Functionally, acute and chronic HPH cause distal pulmonary arteriolar narrowing that increases pulmonary vascular resistance (PVR), which is defined as $(mP_{pa} - P_{la})/Q$, where mP_{pa} is the mean P_{pa} , P_{la} is the left atrial pressure, and Q is the mean pulmonary flow (or

cardiac output). PVR is thus a useful parameter describing the degree of narrowing in the distal, small PAs and is markedly increased in HPH. From the mean pressure-flow relationship, one can also derive distal PA stiffness assuming a fully recruited and dilated pulmonary vasculature (Linehan *et al.*, 1992); in particular, the distal PA distensibility, which is the inverse of the distal PA stiffness, is:

$$mP_{pa} = \frac{[(1 + \alpha P_v)^5 + 5\alpha R_0(Hct)CO]^{1/5} - 1}{\alpha}$$

where P_v is pulmonary venous pressure, CO is cardiac output, R_0 is the vascular resistance of the unstressed lung (when vascular pressure approaches zero), Hct is the hematocrit, and α is the distal PA distensibility (mmHg^{-1}), which is assumed to be constant throughout the pulmonary vascular bed. Since the equation above cannot be explicitly solved for α , typically the distensibility (α) is obtained by curve-fitting the experimental data to this equation. In vivo (Reeves *et al.*, 2005; Blyth *et al.*, 2007) and ex vivo (Chesler *et al.*, 2009) studies have demonstrated that chronic PH decreases α . However, no change in α has been observed in acute HPH (Reeves *et al.*, 2005).

In proximal arteries, there is no evidence that acute HPH has an effect but chronic HPH leads to remodeling and stiffening via increased ECM production and wall thickening. The stiffness of proximal, extralobar PAs is often measured by ex vivo or in vivo pressure-diameter relationships (Wang & Chesler, 2011a). In clinical settings, parameters that can be obtained non-invasively have been introduced, such as relative area change (RAC). RAC is not a stiffness but an area strain and is calculated as the relative cross-section area change ($\Delta A/A$) of the proximal PA from systole to diastole; it is reduced significantly in PH patients (Gan *et al.*, 2007). Another parameter frequently used in clinics to assess PA stiffening is the compliance (C), which is calculated as the ratio of stroke volume (SV) to pulse pressure (PP). Whereas in the systemic circulation, this metric reflects aortic stiffness because of the substantial length of the aorta before it branches into smaller arteries, in the pulmonary circulation it may depend on intermediate and distal PA stiffness as well as proximal PA stiffness (Saouti *et al.*, 2010). Our recent data show that in mouse models of HPH, C does not always correlate with large, extralobar PA stiffness measured ex vivo (Fig. 1) (Wang *et al.*, 2013a).

Hemodynamic consequences of pulmonary arterial mechanical changes during HPH

The hemodynamic consequences of changes in both distal and proximal PAs as well as their interactions (e.g., pulse wave reflection) can be measured via the pulmonary vascular impedance (PVZ), which is derived from pulsatile pressure-flow relationships. Two approaches are commonly used to obtain PVZ – a frequency domain method and a time domain method (Wang & Chesler, 2011a). Both methods yield two important impedance metrics: the input impedance (Z_0), which is either calculated as the impedance magnitude at 0 Hz (in the frequency domain) or total PVR (in the time domain), and the characteristic impedance (Z_c), which is either calculated as the impedance magnitude at high frequencies (in the frequency domain) or the slope of the pressure-flow relationship in early systole (in the time domain).

Z_0 is essentially as a measure of distal pulmonary constriction and increases with HPH progression; it is the PVZ in the absence of flow oscillations. Z_c depends principally on the ratio of stiffness of the proximal arteries to fluid inertia in the proximal arteries; it is PVZ in the absence of wave reflections. In animal studies, Z_c increases with PH in some species

(Maggiorini *et al.*, 1998; Wauthy *et al.*, 2004) but not others (Ewalenko *et al.*, 1997; Pagnamenta *et al.*, 2003; Wauthy *et al.*, 2004; Vanderpool *et al.*, 2010b; Tabima *et al.*, 2012), which likely reflects species-dependent differences in proximal PA stiffening vs. dilation in response to PH.

It is important to note also that PA stiffness itself is pressure-dependent. That is, as pressure increases, the PAs distend and more collagen fibers engage such that stiffness increases. Thus, it can be difficult to separate the effects of remodeling-induced stiffening from strain- or dilation-induced stiffening. Ideally, stiffness measurements should be made at multiple strain levels such that these two mechanisms of stiffening can be differentiated (Vanderpool *et al.*, 2010a).

Changes in right ventricle during HPH

Proximal and distal arterial stiffening and narrowing are important contributors to RV afterload via increases in steady and oscillatory ventricular work. The steady work of the RV is typically calculated as the product of mP_{pa} and stroke volume. Thus, it is the work required to overcome total PVR and to produce forward blood flow into pulmonary circulation; it largely depends on distal PA narrowing. The oscillatory work of the RV is calculated as the difference between the total work (stroke work) and the steady work. The oscillatory work is the work required to produce zero-mean oscillations in blood flow; it largely depends on pulmonary arterial compliance. Typically, oscillatory work is considered 'wasted' so an increase in the ratio of oscillatory to total work is considered a sign of decreased RV efficiency. See (Bellofiore & Chesler, 2013) for a recent review of this topic. It is currently not known whether the RV remodels differently in response to increased steady and oscillatory work demands.

Known consequences of increased RV afterload include RV hypertrophy and fibrosis. RV hypertrophy is typically quantified by the Fulton index, which is the weight ratio of right ventricle to the sum of left ventricle and septum ($RV/(LV+S)$). Increased Fulton index is universally observed in HPH. RV fibrosis, which is a hallmark of dysfunctional or failing RV, is seldom reported (or examined) in HPH. Our group has recently found a significant increase in collagen content in mouse RVs after 10 days of hypoxia (Schreier *et al.*, 2013). But the structural and functional changes in the RV with chronic HPH have been less well studied than those in the pulmonary circulation until recently (Tabima *et al.*, 2010; Walker *et al.*, 2011; Schreier *et al.*, 2013).

Our group has successfully established methods to measure RV function in mice in vivo (Tabima *et al.*, 2010). With HPH progression, we have consistently observed increased right ventricular systolic pressure, significant RV hypertrophy, and increased effective arterial elastance (E_a), which is an index of RV afterload (Tabima *et al.*, 2010; Schreier *et al.*, 2013). Because of the pressure overload, RV contractility increases as measured by preload recruitable stroke work and ventricular end-systolic elastance (E_{es}). The ratio of E_{es} to E_a , which is an index of ventricular-vascular coupling efficiency, is typically maintained (Tabima *et al.*, 2010; Schreier *et al.*, 2013). To date we have seen no significant changes in cardiac output or ejection fraction in mice with chronic HPH. In large animals exposed to acute hypoxia, both E_{es} and E_a increase but E_{es}/E_a remains at control levels, which indicates preserved ventricular-vascular coupling (Wauthy *et al.*, 2004). Therefore, RV functional changes during HPH seem to be adaptive and moderate, with preserved systolic and diastolic function.

Hematocrit and blood viscosity increases

A unique change associated with HPH but not other types of PH is the increased expression of erythropoietin, resulting in increased red blood cells, hematocrit (Hct) and hemoglobin levels. Hct can increase from ~45% at normal levels to up to 80% after chronic hypoxia exposure. This increases blood viscosity, which consequently increases pulmonary resistance. Whittaker and Winston found an power-law relationship between PVR and hematocrit (Whittaker & Winton, 1933):

$$R_0(45\%)=R_0(Hct)\frac{1-\phi^{1/3}}{0.234}$$

where R_0 is PVR at a Hct of 45% (normal) and ϕ is the measured Hct.

We recently measured PVZ in control mice and those exposed to 21 days of hypoxia at different hematocrits by partially replacing high viscosity blood with hydroxyethylstarch (unpublished data). By reducing the hemoglobin to normal levels (i.e. Hct~42%), Z_0 (or PVR) decreased about 31% and Z_c decreased about 47% (Fig. 2). These data suggest that the increase in hematocrit is a significant contributor to the increased RV afterload in chronic HPH.

HPH: A moderate and reversible type of PH

It is well known that even with prolonged hypoxia exposure, distal vascular remodeling does not progress to the obliterative, plexiform lesions that are seen clinically in severe PH (Gomez-Arroyo *et al.*, 2012; Nicolls *et al.*, 2012), suggesting the vascular changes are only moderate in HPH. Another important characteristic of HPH that is different from severe PH is its reversibility. It has been shown in many studies that if allowed to recover in normoxic conditions, subjects will undergo a reverse remodeling in PAs and a decrease of Ppa, with a reduction in Hct as well (Rabinovitch *et al.*, 1981; Liu, 1997; Tozzi *et al.*, 1998; Riley *et al.*, 2000; Li *et al.*, 2004; Ooi *et al.*, 2010; Tabima *et al.*, 2012). In terms of vascular mechanics, the recovery process is accompanied by reduced proximal PA stiffening and reduced distal PA narrowing (Ooi *et al.*, 2010; Tabima *et al.*, 2012), which then significantly reduces the RV afterload. As a consequence, a regression in RV hypertrophy is often observed.

Because HPH is a moderate and reversible type of PH, it does not capture the key features of severe, clinical PH. Recently, the appropriate usage of this model has been reconsidered (Gomez-Arroyo *et al.*, 2012; Nicolls *et al.*, 2012). Instead of a limitation, however, the reversibility of HPH may in fact be an advantage; that is, the contrasts between HPH and severe PH may shed light on key factors that determine the reversibility of RV and PA remodeling and the critically important transition from RV adaptation to RV failure.

Summary and conclusions

In summary, HPH-induced vascular mechanical changes affect ventricular function but both are adaptive and reversible, which differentiates HPH from severe pulmonary hypertension. The mechanisms of adaptation and reversibility may provide useful insight into therapeutic targets for the clinical disease state.

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New Findings

This article reviews pulmonary vascular and right ventricular (RV) changes due to hypoxic pulmonary hypertension (HPH), which is a type of pulmonary hypertension (PH) found clinically and has been widely used to induce PH in animal models. As research into clinical PH progression broadens to include RV as well as pulmonary vascular remodeling, an improved understanding of the effects of HPH on the RV is required. This article highlights the moderate, adaptive and reversible nature of RV and pulmonary vascular remodeling in HPH. Moreover, we show that increased hematocrit in HPH contributes significantly to RV overload, which warrants additional attention.

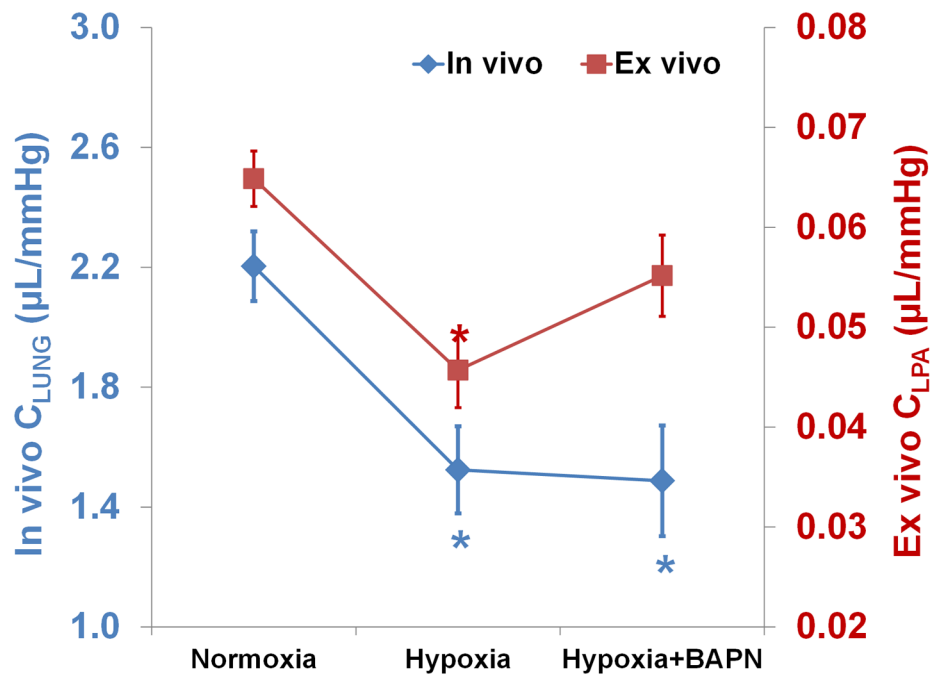


Figure 1.

Compliance measured in vivo for whole lung (C_{LUNG} , by SV/PP) and ex vivo for extralobar left PAs (C_{LPA} , by $\Delta V/\Delta P$) in mice with a collagen mutation (see (Wang *et al.*, 2013b) for a description of this strain and the experimental protocol for C_{LPA} measurements) exposed to normoxia, 10 days of hypoxia, and 10 days of hypoxia with beta-aminopropionitrile (BAPN). The hypoxia+BAPN group showed persistently low in vivo compliance compared to the hypoxia group, suggesting similar levels of overall pulmonary vascular stiffening. However, extralobar left PA compliance tended to increase in the hypoxia+BAPN group compared to the hypoxia group, suggesting more compliant proximal large PAs with BAPN treatment. Results are shown as mean \pm SE. * $p < 0.05$ vs. Normoxia.

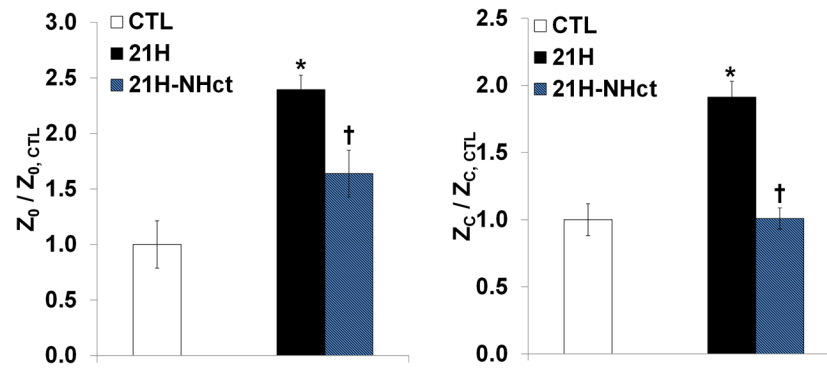


Figure 2. Pulmonary vascular Z_0 and Z_c in wild-type mice exposed to 21 days of hypoxia normalized to those measured in normoxic mice. Measurements were obtained in chronically hypoxic mice with elevated Hct (21H) as well as normal levels of Hct (21H-NHct) by blood dilution to show that decreased hematocrit led to significant reductions in Z_0 and Z_c . Results are shown as mean \pm SE. * $p < 0.05$ vs. Normoxia; † $p < 0.05$ vs. 21H.