Pulmonary vascular wall stiffness: An important contributor to the increased right ventricular afterload with pulmonary hypertension

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ABSTRACT

Pulmonary hypertension (PH) is associated with structural and mechanical changes in the pulmonary vascular bed that increase right ventricular (RV) afterload. These changes, characterized by narrowing and stiffening, occur in both proximal and distal pulmonary arteries (PAs). An important consequence of arterial narrowing is increased pulmonary vascular resistance (PVR). Arterial stiffening, which can occur in both the proximal and distal pulmonary arteries, is an important index of disease progression and is a significant contributor to increased RV afterload in PH. In particular, arterial narrowing and stiffening increase the RV afterload by increasing steady and oscillatory RV work, respectively. Here we review the current state of knowledge of the causes and consequences of pulmonary arterial stiffening in PH and its impact on RV function. We review direct and indirect techniques for measuring proximal and distal pulmonary arterial stiffness, measures of arterial stiffness including elastic modulus, incremental elastic modulus, stiffness coefficient b and others, the changes in cellular function and the extracellular matrix proteins that contribute to pulmonary arterial stiffening, the consequences of PA stiffening for RV function and the clinical implications of pulmonary vascular stiffening for PH progression. Future investigation of the relationship between PA stiffening and RV dysfunction may facilitate new therapies aimed at improving RV function and thus ultimately reducing mortality in PH.

Key Words: biomechanics, impedance, vascular-ventricular coupling, right ventricular dysfunction, hypertrophy

INTRODUCTION

Pulmonary hypertension (PH) is a complex disorder that manifests as abnormally high blood pressure in the vasculature of the lungs. Based on the causes of PH, the World Health Organization (WHO) has classified the disease into five categories including Group I, pulmonary arterial hypertension (PAH) resulting from increased pulmonary vascular resistance (PVR). Arterial stiffening, which can occur in both the proximal and distal pulmonary arteries, is an important index of disease progression and is a significant contributor to increased RV afterload in PH. In particular, arterial narrowing and stiffening increase the RV afterload by increasing steady and oscillatory RV work, respectively. Here we review the current state of knowledge of the causes and consequences of pulmonary arterial stiffening in PH and its impact on RV function. We review direct and indirect techniques for measuring proximal and distal pulmonary arterial stiffness, measures of arterial stiffness including elastic modulus, incremental elastic modulus, stiffness coefficient b and others, the changes in cellular function and the extracellular matrix proteins that contribute to pulmonary arterial stiffening, the consequences of PA stiffening for RV function and the clinical implications of pulmonary vascular stiffening for PH progression. Future investigation of the relationship between PA stiffening and RV dysfunction may facilitate new therapies aimed at improving RV function and thus ultimately reducing mortality in PH.
and arterioles. However, the decrease in compliance (i.e. increase in stiffness) is also important and affects the entire vasculature. Both narrowing and stiffening contribute to increased right ventricular (RV) afterload.

RV afterload is a critical metric of PH progression because typically the cause of death in PH is right heart failure due to RV overload. Left untreated, the estimated median survival of PAH is 2.8 years. Conventionally, mean pulmonary arterial pressure (mPAP) is used to diagnose and predict survival in PH. Because of the dominating influence of small artery narrowing on increases in mPAP, a traditional strategy for PH treatment has been to reduce or attempt to reverse this aspect of pulmonary vascular remodeling. However, it is becoming apparent that mPAP does not correlate with either the severity of symptoms or survival. More recently, parameters reflecting RV functional status, such as RV mass and size, mean right atrial pressure, ejection fraction and cardiac index, have been shown to be strong predictors of survival. As a consequence, there is growing interest in therapies that act directly on the RV to restore function. Importantly, RV function depends not only on the state of the heart muscle itself (oxygen supply and demand, metabolic status, etc.) but also the vascular bed to which it is coupled, which represents its afterload.

RV afterload results from a dynamic interplay between resistance, compliance and wave reflections. It can be measured by hydraulic load or hydraulic power, which is work per unit time generated by the heart to sustain forward blood flow. The power provided by RV consists of two components: the steady power required to produce net forward flow and the oscillatory power required to produce zero-mean oscillations in flow. Historically, the increase in RV afterload in PAH has been attributed to increased PVR, which only reflects the steady component of total RV power. However, over a third of the RV workload increase in PH is caused by large artery stiffening, which mostly influences the oscillatory RV power. In clinical studies, an increase in PA stiffness was found to be an excellent predictor of mortality in patients with PAH, which suggests an important role of PA stiffening in right heart failure. Thus, to obtain a comprehensive view of the contributions of the pulmonary vascular bed to RV function, one must consider the complete arterial tree and investigate both steady and oscillatory components of the RV power, which are determined by steady and oscillatory components of pulmonary hemodynamics. Pulmonary artery stiffness is an important determinant of the oscillatory component of pulmonary hemodynamics.

In this review, we will focus on the current state of knowledge of the impact of pulmonary arterial remodeling (narrowing and stiffening) on RV afterload during PH progression, with a particular focus on stiffening. To do so, we review direct and indirect techniques for measuring proximal and distal pulmonary arterial stiffness, metrics of arterial stiffness including elastic modulus, incremental elastic modulus, stiffness coefficient β and others, the changes in cellular function and the extracellular matrix proteins that contribute to the pulmonary arterial stiffening, and the consequences of PA stiffening for RV function. We also discuss the coupling between RV and pulmonary circulation and interactions between the proximal and distal vascular beds. Finally, we recommend directions for future studies to better understand pulmonary vascular stiffening and its relationship to RV function, dysfunction and failure in PH.

**MEASUREMENTS OF PULMONARY ARTERIAL STIFFENING**

**Direct measurements**

Direct measurement of pulmonary vascular stiffness can be performed in vivo and in vitro by quantifying arterial diameter as a function of pressure to generate pressure-diameter relationships or PD curves. In large animals, large and small arteries can be tested; in small animals, typically only large arteries are tested. In vivo, usually either inner or outer diameter is measured as a function of pressure and wall thickness is either assumed or ignored. In vitro, both inner and outer diameter can be measured as a function of pressure, as well as factors that influence the mechanical behavior of the tissue. The most direct technique to measure stiffness is an isolated vessel mechanical test in which the vessel inner and outer diameter are measured over a range of physiological and pathological pressures. This type of test allows fine control of the test conditions such that the effect of single parameter (e.g., SMC tone, collagen and/or elastin content, drug treatment, etc.) on stiffness can be determined. Biaxial (in two directions) tests of arterial sections and uniaxial (in one direction) tests of tissue either in strips or rings can also be performed. Most biaxial and strip test methods do not allow the effects of smooth muscle cell (SMC) tone to be investigated but isolated vessel and ring tests do. Indirect measures of proximal and distal arterial stiffness also exist, which we will review in the next section.

The most commonly used approach for assessing structural mechanical properties of arteries is PD curves. If wall thickness is measured optically or histologically, material properties can also be calculated. Because transmural pressure results in circumferential stretch of the arterial wall, most mechanical properties are characterized in the direction of circumference and sometimes derived from calculation of circumferential wall stress and strain. However, recent studies on systemic arteries have...
considered changes in longitudinal stretch with disease as well.\textsuperscript{[30,32]} Calculated parameters either represent the whole vessel stiffness but dependent on geometry, such as pressure-strain modulus (\(E_p\))\textsuperscript{[17,33-35]} stiffness constant \(\beta\)\textsuperscript{[36,37]} distensibility (D)\textsuperscript{[23,38-41]} and compliance (C)\textsuperscript{[23,38,42-44]} or describe the material properties of the wall independent of geometry, such as elastic modulus (E)\textsuperscript{[34,45]} and incremental elastic modulus (\(E_{\text{inc}}\))\textsuperscript{[21,45,46]} Sometimes the geometric-dependent mechanical properties are termed “extrinsic” since they depend on the amount of wall material whereas the geometry-independent material properties are termed “intrinsic” since they depend only on the constitutive materials themselves. For example, two arteries made of the exact same material but different wall thicknesses would have the same intrinsic properties but different extrinsic properties. A summary of commonly used arterial intrinsic and extrinsic mechanical and material properties are presented in Table 1. Consistently, pulmonary artery wall stiffness is found to increase during PH progression.\textsuperscript{[16-18,26,47,48]}

It is important to note that all of these parameters are linear approximations of non-linear relationships. That is, for sufficiently large changes in stress and strain (for E) or volume and pressure (for D), a single calculation (of E or D) will be a poor approximation of the true material or mechanical behavior. In a physiological pressure range, most of the above metrics are good approximations but when testing is performed over a larger range, curve fits may be applied to individual sections. The best example is elastic modulus, E, which for most arteries is low in a low strain range due to loading of elastin and high in a high strain range due to collagen engagement. Thus, low and high strain moduli (\(E_{\text{low}}\) and \(E_{\text{high}}\) respectively) are often calculated separately.\textsuperscript{[17,26,47]}

Besides these structural and material properties that can be measured from PD and sometimes pressure-length curves, other parameters that require less information and thus are more feasible for clinical measurements have been introduced to investigate PA stiffening during PH progression. One example is the relative area change (RAC).\textsuperscript{[14]} RAC is calculated as the relative cross-section area change (\(\Delta A/A\)) of the proximal PA from systole to diastole and it is reduced significantly in PH patients.\textsuperscript{[14]} RAC shows a moderate inverse curvilinear relationship with mPAP and predicts mortality better than area distensibility. Interestingly, RAC does not require knowledge of the distending pressure, so it is neither a material nor structural property; instead it is a geometrical property.

It is well known that blood vessels are not purely elastic but in fact viscoelastic materials, which means the elastic deformation under dynamic loads exhibits time-dependent behavior. A consequence of arterial viscoelasticity is pressure energy loss. When a purely viscous material is deformed, all the energy is dissipated.

### Table 1: Summary of parameters commonly used to measure arterial elasticity

| Definition (unit) | Formula | Notes |
|------------------|---------|-------|
| Pressure-strain modulus \(E_p\) (Pa) | \(E_p = \frac{\Delta P}{\Delta R}\) | R can also be replaced with diameter (D). Extrinsic mechanical property |
| Elastic modulus E (Pa) | \(E = \frac{\sigma}{\varepsilon}\) | The slope of stress-strain (\(\sigma-\varepsilon\)) curve, assuming linear homogeneous, incompressible wall material. Thin-wall or thick-wall assumptions lead to different calculations of \(\sigma\) and \(\varepsilon\). Intrinsic material property |
| Incremental elastic modulus\(^1\) \(E_{\text{inc}}\) (Pa) | \(E_{\text{inc}} = \frac{\Delta P}{\Delta R_o} \cdot \frac{2(1-v^2)R^2_o}{(R_o^2 - R_i^2)}\) | R\(_o\) and R\(_i\) are external and internal radii and can be replaced with corresponding diameters (D). Assuming locally linear, homogenous, incompressible (if \(v=0.5\)) wall material. Thick wall assumption. Intrinsic material property |
| Incremental elastic modulus\(^2\) \(E_{\text{inc}}\) (Pa) | \(E_{\text{inc}} = \frac{\Delta P}{\Delta D_s} \cdot \frac{2D_s^2 D_o}{(D_o^2 - D_s^2)} + 2PD_o^2\) | Modified \(E_{\text{inc}}\) assuming orthotropic cylindrical tube. Intrinsic material property |
| Stiffness constant \(\beta\) (dimension-less) | \(\beta = \frac{\ln(P_s/P_d)}{R_s/R_i - 1}\) | P\(_s\) and P\(_d\) are systolic and diastolic pressures. Radius R can be replaced with diameter (D). Assume homogeneous, incompressible, isotropic material. Extrinsic mechanical property |
| Distensibility D (1/Pa) | \(D = \frac{\Delta V}{V \cdot \Delta P}\) | V (volume) can be replaced with A (area). Extrinsic mechanical property |
| Compliance C (m\(^3\)/Pa) | \(C = \frac{\Delta V}{\Delta P}\) | V (volume) can be replaced with A (area). Extrinsic mechanical property |

\(P\): pressure; \(R\): radius; \(D\): diameter; \(V\): volume; \(A\): area
Advantages of the isolated, perfused and
v
level of sympathetic nervous system
and these are still difficult to compare to in vivo measurements
obtained with physiological flow waveforms.

In systemic arteries, viscosity has been shown to change with aging, with atherosclerosis and systemic hypertension. [50-52] The effect of acute PH on arterial viscosity has been investigated by the group of Armentano. [53,54] Our group, to our knowledge, is the only one that has investigated changes in proximal PA viscoelasticity in chronic PH. [16,47,55] Traditionally, SMCs are considered to be the primary source of arterial viscosity [29,56] but our results suggest that SMCs may not be the only determinant. The damping capacity of large PAs increases after chronic hypoxia [16,47,53] and this increase correlates with the accumulation of collagen. [55] The clinical implications of increased PA viscosity during PH are unclear, but arterial viscosity likely increases circulatory energy loss [56] and affects wave reflections, [57] thus impairing dynamic interactions between heart and lung and increasing RV afterload.

Indirect measurements
Both proximal and distal pulmonary arterial stiffness can be measured indirectly from pulmonary pressure-flow relationships in vivo [58-63] or ex vivo in isolated whole lungs. [63-69] Advantages of the isolated, perfused and ventilated lung preparation are that pressure-flow relationships are not affected by anesthesia, [60] volume status [59] and level of sympathetic nervous system activation. [58] In addition, the effect of drugs on the pulmonary vasculature can be investigated independent of the effects of those drugs on the systemic vasculature. [70] However, in most isolated, ventilated, perfused lung preparations, only steady pressure-flow relationships are obtained, from which only distal arterial stiffness can be derived. Our group has used pulsatile flow waveforms to obtain pulsatile pressure-flow relationships, which allow estimates of proximal artery stiffness to be made, although these are still difficult to compare to in vivo measurements obtained with physiological flow waveforms. [60,70-72] The metrics of proximal and distal pulmonary arterial stiffness that can be obtained by in vivo and ex vivo methods are reviewed below.

Steady pressure-flow relationships
Increases in mPAP that occur with increases in flow whether in vivo (due to exercise or drugs) or ex vivo (due to imposed flow waveforms) can provide insight into distal arterial stiffness. If one imagines the distal pulmonary arterial bed to be a parallel network of rigid tubes, then any increase in flow will lead to a proportional increase in pressure. If more rigid tubes open as a result of increased flow (i.e., are recruited), then the increase in pressure will be less at high flows. If these rigid tubes increase in diameter with increased flow (i.e., by the mechanism of flow-induced vasodilation), then the increase in pressure at high flows will be less still. Finally, if the tubes are not in fact rigid but can distend, then the pressure-flow curve may plateau at high flow. A theoretical approach to measuring this distal arterial distensibility, assuming a fully recruited and dilated pulmonary vasculature, was first described by Linehan et al. [73]:

\[
\frac{mPAP}{\alpha} = \frac{(1 + \alpha P_f)^5 + 5\alpha R_o (Hct) CO}{1/5} - 1
\]

where \( P_f \) is pulmonary venous pressure, \( CO \) is cardiac output, \( R_o \) is the total pulmonary vascular resistance (mPAP/CO) at rest, \( Hct \) is the hematocrit, and \( \alpha \) is the pulmonary arterial distensibility, which is assumed to be constant throughout the pulmonary vascular bed.

In vivo [74] and ex vivo [75] studies have demonstrated that PH decreases \( \alpha \). However, whether distal arterial stiffening impairs exercise capacity in PH by exacerbating flow-induced increases in mPAP remains unknown.

Pulsatile pressure-flow relationships
From pulsatile pressure-flow relationships obtained either in vivo or ex vivo, indirect measurements of proximal arterial stiffness can be obtained. In addition, other characteristics of the pulmonary circulation can be determined such as PVR and wave reflections. Two approaches to analyze these pulsatile pressure-flow relationships are commonly used: a frequency domain method; and a time domain method.

Impedance (Frequency domain analysis)
The relationship between pulsatile blood pressure and flow can be quantified by the impedance. [76] Its calculation requires synchronized pulmonary arterial pressure and flow measurements, which are typically obtained with a right heart catheterization and either ultrasound [77,78] or a catheter-based flow sensor [79,80] in vivo or by direct recording of pressure and flow ex vivo. From these data, a comprehensive measurement of RV afterload is
given by pulmonary arterial input impedance (PVZ). The calculation of PVZ requires a spectral analysis of the pulmonary arterial pressure waveform P and flow waveform Q and a mathematical elaboration (Fourier analysis) to derive a PVZ spectrum, which is expressed as the ratio of P to Q moduli and a phase angle (θ), both as a function of frequency:

\[
PVZ(\omega) = \left| \frac{P(\omega)}{Q(\omega)} \right|
\]

where \( \omega \) is the frequency, \( \Phi \) is the pressure phase and \( \varphi \) is the flow phase. This approach has been adopted in PH animal models using in vivo and ex vivo techniques and in patients. Details of how to calculate impedance for the pulmonary circulation have been reviewed previously.

The impedance spectra in systemic and pulmonary circulations share a similar, classic pattern of a high 0-Hz value (\( Z_0 \)) followed by a local minimum and oscillations at high frequencies (Fig. 1). \( Z_0 \) increases during PH progression and this parameter is equal to total PVR. Like PVR, \( Z_0 \) is essentially as a measure of distal pulmonary resistance; it is the input impedance in the absence of flow oscillations. The average of the impedance modulus at higher harmonics is used as an estimation of characteristic impedance (\( Z_c \)), which is the input impedance in the absence of wave reflection. \( Z_c \) is determined principally by the ratio of stiffness of the proximal arteries to fluid inertia. It is dependent on both the size and material properties of the proximal PAs. For example, an increase in proximal PA radius decreases \( Z_c \), whereas an increase in stiffness has the opposite effect. These relationships are described theoretically by:

\[
Z_c = \frac{\rho E h}{2\pi^2 r^2}
\]

where \( E \), \( h \), and \( r \) are proximal PA elastic modulus, wall thickness and luminal radius, respectively, and \( \rho \) is the density of blood. \( Z_0 \) is usually found to remain constant in subjects with PH which may be a combined result of increased proximal PA stiffness and diameter. This observation suggests that during PH, the RV and pulmonary vasculature adapt to maintain the mechanical load on the RV and conserve energy. \( Z_c \) has also been found to change (increase or decrease) with PH depending on the animal model used or different pathological mechanisms of PH.

A third parameter that can be derived from the impedance spectrum is pulse wave reflection (\( \Gamma \)), which is calculated by:

\[
\Gamma = \left( \frac{Z_0 - Z_c}{Z_0 + Z_c} \right)
\]

The wave reflection increases significantly with PH, which suggests a bigger impedance mismatch between the proximal and distal pulmonary vasculature and may have detrimental effects on the RV function as reported to occur in the systemic circulation.

Overall, PVZ has the potential to be a better prognostic indicator than PVR alone because it captures both static and dynamic characteristics of the opposition to flow in the pulmonary circulation. PVR is typically a single-value measurement assuming a linear relationship between the pressure difference \( \Delta P \) (\( \Delta P = \) Pulmonary arterial pressure - left atrial pressure) and the flow (Q). When left atrial pressure is normal, total PVR can be measured by the ratio of mean pulmonary pressure and mean pulmonary flow (mPAP/Q). Both PVR and total PVR characterize the steady, time-averaged hemodynamics and represent only the static component of RV afterload. It is well known that progressive pulmonary artery remodeling during PH increases PVR. However, PVR is likely limited as a prognostic parameter because PVR alone is not sufficient to measure total RV afterload. In fact, more and more evidence suggests that a global stiffness measurement that includes both static and dynamic components is a better representative and potentially prognostic parameter for PH progression.

**Time domain analysis**

Although the rapid development of new technologies...
and instrumentation may allow more widespread use of impedance analysis in the frequency domain, current clinical applications are limited because of the complexity of performing and interpreting the frequency domain analysis and results, respectively. Instead, the time domain analysis of the pulse pressure waveform is a useful surrogate for assessing Zv, Zc, and other clinical indices of pulsatile pulmonary hemodynamics.\[^{[6]}\]

In the time domain analysis, Zc is calculated as mean pressure divided by mean flow, which is the same as in the frequency domain, and Zv is calculated as

\[
Z_v = \frac{dP}{dQ}
\]

where dP and dQ are pressure and flow increases taken prior to when flow reaches 95% of its maximal value during one cardiac cycle.\[^{[97]}\] Because of the rapid upstroke of the waveforms at this early ejection phase, the reflected waves do not have time to return to the proximal bed and thus the system is reasonably assumed to be free from wave reflections.\[^{[97]}\] From Zv, the instantaneous pressure waveform is decomposed into forward (Pf) and backward (Pb) traveling waves using the linear wave separation method.\[^{[99]}\] The global wave reflection index (\(R_g\)) is then calculated as the ratio of the amplitude of \(P_b\) to \(P_f\). In contrast to the wave reflection (\(\Gamma\)) that is most applicable for simple systems of one or two tubes\[^{[100]}\] and thus characterizes mismatch between proximal and distal beds, \(R_g\) captures the wave reflections of the whole vascular bed.\[^{[101]}\]

Correlation between impedance measurements performed using frequency and time domain analyses requires further investigation. Our preliminary results have shown good agreement between the two methods.\[^{[102]}\]

Pulse pressure (PP) is often measured in the time domain analysis of pulmonary hemodynamics and has been found to be a useful indicator of heart health.\[^{[103,104]}\] PP is defined as the difference between systolic and diastolic pressure (Fig. 2) and is determined by the characteristics of ventricular ejection and proximal arterial stiffness. In both systemic and pulmonary circulations, PP is elevated when large arteries stiffen, even without changes in the distal vasculature.\[^{[105-108]}\]

Another parameter derived from the pressure waveform is the augmentation index (AI, Fig. 2), defined as the ratio of the height from the inflection point (Pi) to peak systolic pressure (\(\Delta P\)), which is an estimate of the magnitude of the reflected pressure wave to the PP\[^{[96]}\] which may correlate with proximal PA stiffness. In normal subjects there is very little wave reflection, and PP increases wave reflection.\[^{[79,93,96,109]}\]

Figure 2: An illustrative example of pressure waveform and the derivation of pulse pressure (PP) and augmentation index (AI). Pi is the inflection point, which may present either in the systolic or diastolic phase.

AI can differentiate different types of PH, i.e., chronic pulmonary thromboembolism (CPTE) and primary pulmonary hypertension (PPH)\[^{[95,96]}\] but it may be more sensitive to the proximal arteries than the whole vascular bed and can be confounded by other factors such as heart rate.\[^{[100,101]}\] Finally, the relationship between AI and the severity of PH remains unknown.

A potentially more useful parameter is compliance, which conceptually is the inverse of stiffness. Compliance (C) is calculated as the ratio of stroke volume (SV) to PP\[^{[110,111]}\] Similar parameters measured in the systemic circulation have been shown to be related to conduit artery stiffening and correlated with mortality in patients with left ventricular dysfunction.\[^{[112]}\] In PAH patients, compliance, which is sometimes called capacitance, has been shown to have prognostic value as well.\[^{[13,13]}\] It is important to point out that unlike in the systemic circulation where arterial compliance is mainly localized to the aorta, arterial compliance in pulmonary circulation is distributed over the entire vascular bed.\[^{[111]}\] An interesting relationship between compliance and resistance (PVR) has recently been observed in the pulmonary circulation: the product of PVR and C is constant.\[^{[23,39,111,114]}\] In particular, Lankhaar et al. have shown that the product of PVR and C is a constant for patients with and without PH\[^{[91]}\] and that treatment does not change this time constant.\[^{[114]}\] Importantly, these results explain why changes in PVR alone do not reflect the clinical outcomes of PH patients. PH leads to increased PVR and decreased C; but for a similar decrease of PVR due to therapy, the patients with higher starting PVR (more severe PH) will have a smaller increase in C than the patients with lower starting PVR (milder PH). Thus the former group of patients has improvement
mainly in steady RV power requirements (due to a decrease in PVR) whereas the latter group of patients has improvement in both steady and oscillatory RV power requirements (due to comparable decrease in PVR and increase in C).

CELLULAR AND MOLECULAR CONTRIBUTORS TO PULMONARY ARTERIAL TIFffenING

The arterial remodeling that occurs in the progression of PH involves all three layers of the arterial wall. Histological evidence of remodeling consists of intimal fibrosis, increased medial thickness, accumulation of extracellular matrix proteins such as collagen, increased adventitial thickness, pulmonary arteriolar occlusion and plexiform lesions. The process is characterized by proliferative and obstructive changes that involve cell types such as endothelial, smooth muscle and fibroblast. Detailed reviews on the cellular and molecular mechanisms of PA remodeling including genetic factors have been reported previously.

Stiffening of large PAs is linked with accumulation of collagen and, in some studies, elastin. However, if collagen and elastin concomitantly increase during PH, one cannot discern which is more responsible for arterial stiffening. A recent study suggests elastin remodeling contributes to PA stiffening in response to hypoxia-induced pulmonary hypertension (HPH) in neonatal calves, but discrepant observations are also reported in other species in adults. For example, there was no change in elastin content in rodent large PAs after chronic hypoxia. Our latest studies using a novel transgenic mouse model (Col1a1<sup>−/−</sup>) suggests changes in collagen rather than elastin track large PA stiffness during HPH progression and recovery. Furthermore, we specifically examined the effects of collagen content vs. cross-linking in the passive, dynamic mechanical behavior of large PAs in chronic PH and found that collagen content is critical to large PA stiffening.

Differential impacts of elastin and collagen metabolism on PH progression may exist and can be attributed to the age and type of PH developed. There is evidence suggesting that elastin may play a more important role in PH in newborns whereas collagen may have a larger impact in PH developed in adults. Studying the biomechanics of newborn calf extralobar arteries, Lammers et al. showed a significant increase in low-strain elastic modulus with chronic hypoxia that was dependent on elastin. However, it is well known that newborn animals develop more severe pulmonary hypertension than adults with more dramatic vascular changes. Since the neonatal period is associated with significant elastin production in the pulmonary trunk even in normoxic conditions, elastin synthesis may be particularly sensitive to modulation by hypoxia during this time of rapid growth. Another study using a set of transgenic and knockout mice with graded elastin insufficiency found that reduced elastin content in large PAs predisposed the mice to elevated RV pressures and RV hypertrophy. With the genetic deficiency in elastin, peripheral PAs developed muscularization and proximal PAs exhibited increased overall stiffness, but the $E_{\text{inc}}$ remained constant over a wide range of pressure change (0-90 mmHg). However, the extent of pathological remodeling of heart and pulmonary vasculature was limited compared to those with similar pressure elevation induced by hypoxia, which suggests an adaptation occurred during the development from fetus to adult. Therefore, it is likely that different mechanisms (elastin vs. collagen) may dominate the development of PH, depending on the type of disease.

The SMC tone changes significantly during PH development. This is especially prominent in the distal vasculature. It is well accepted that the acute phase of PH is manifested by vasoconstriction. In the chronic phase of PAH, remodeling occurs with endothelial layer thickening (and formation of plexiform lesions in severe PAH) and smooth muscle hypertrophy, which leads to reduced smooth muscle contractility. The proximal PAs seem to have limited changes in SMC tone, but discrepant results are also reported. The impact of SMC tone on proximal PA mechanical behavior in large animals or humans is an important area of future research.

CONSEQUENCES/CLINICAL RELEVANCE OF PULMONARY ARTERIAL STIFFENING

Right ventricular overload and heart failure

Right heart function is closely tied to survival in PH. For instance, RV function assessed via right atrial pressure and cardiac output is associated with mortality in addition to mPAP in patients with PAH. Previously, much attention has been paid to the pulmonary circulation and basic mechanisms underlying pulmonary arterial dysfunction; however, little is known about the RV in health and diseased states. It is recognized now that effective treatment for PH should not only impact the pulmonary vasculature but also improve RV function.

Stiffening of the pulmonary vascular bed can increase RV workload, which may be caused by impaired conduit and buffering function of the proximal PAs and early wave reflections to the RV (Fig. 3). Under normal circumstances, the oscillatory RV power is about 25% of the total...
(oscillatory + steady) RV power, which is higher than the proportion in the systemic circulation (~10%).[76,127] A recent study on the RV pulsatile hydraulic load in PAH patients has shown that while both oscillatory RV work and total RV work increase with PAH severity, the proportion remains constant (~23%).[111] The oscillatory RV work correlates with pulse pressure, which increases with proximal PA stiffening.[127,128] Therefore, PA stiffness increases oscillatory RV work; however, the direct impact on RV function remains undefined. The effects of distal PA stiffening (loss of distensibility α) on RV afterload are also unknown.

Increased RV afterload leads to augmented myocardial oxygen demand and the RV adapts primarily by hypertrophy. Hypertrophy serves to decrease the ventricular wall stress and maintain cardiac output initially and thus could be a healthy response. However, during PH progression, severe hypertrophy reduces cardiac output and cardiac index, which are the hallmarks of right heart dysfunction and failure.[9] The indicators of the transition from healthy adaptive hypertrophy to pathological maladaptive remodeling remain unknown. To understand the molecular pathways that differentiate adaptive from maladaptive ventricular hypertrophy is an important area of current research.[129]

**Ventricular vascular coupling (VVC) efficiency**

To understand how pulmonary vascular remodeling affects ventricular output during PH progression, investigations into ventricular function alone or vascular function alone are not sufficient. Ideally, vascular function is efficiently matched to ventricular function, and vice versa. Ventricular pressure-volume (PV) loop analysis was first developed by Sagawa et al.[130] to describe the coupling efficiency between the left ventricle and systemic circulation, i.e., vascular-ventricular coupling (VVC). In this approach, the ventricular and arterial dynamic behaviors are quantified by ventricular end-systolic elastance (E_{es}, which represents contractility of the ventricle) and arterial effective elastance (E_{a}, which represents ventricular afterload), respectively, which are derived from the pressure-volume loops at different levels of preload (Fig. 4). The ratio of these two parameters (E_{es}/E_{a}) yields a direct assessment of VVC efficiency. When the ventricle and vasculature are efficiently coupled, minimal energy is wasted in the pulse pressure and maximal energy is transmitted in the mean pressure. The optimal coupling efficiency (E_{es}/E_{a}) has been identified and is comparable for both sides of the heart.[131,132] Recently, there is increasing interest in PV loop analysis for PH because RV contractility is a more reliable way to differentiate the effect of therapies than mPAP.[84] In addition, the linkage between RV function and vascular function, which is characterized by coupling efficiency (E_{es}/E_{a}), may reveal the mechanisms that differentiate physiological and pathological ventricular remodeling. During acute PH, the optimal ventricular-arterial coupling appears to be maintained regardless of species and the way in which PH is induced.[82] As effective afterload (E_{a}) increases, the ventricle increases contractility (E_{es}) such that optimal coupling (E_{es}/E_{a}) is maintained. However, such a balance may not exist in chronic PH due to both pulmonary vascular and right ventricular remodeling. Our recent study in mice demonstrated decreased pulmonary vascular-ventricular coupling efficiency after chronic hypoxia.[132]

A potentially important consequence of PA wall stiffening may be impaired VVC efficiency via increased E_{a}. Optimal coupling between the RV and the pulmonary circulation in a healthy cardiopulmonary system is likely important to the adaptive response to acute stresses such as hypoxia or exercise. In conditions of impaired VVC, however, the RV may not be able to maintain cardiac output sufficiently to meet these challenges, leading to dysfunction and failure.
Because very few studies have examined ventricular-vascular coupling and pulmonary arterial stiffening concurrently, the linkage between changes in vascular and ventricular function is not established. For example, the arterial effective elastance (E_e) is thought to represent the RV afterload presented by the pulmonary vasculature. However, the influences of proximal arterial stiffness, distal arterial stiffness and distal arterial narrowing on E_e are not clear. Understanding the relationship between right heart function and pulmonary vascular remodeling will aid in discerning critical factors that are relevant to clinical outcomes of PH.

**Interactions between proximal and distal pulmonary arteries**

Finally, while there are different initiating mechanisms of PH (e.g., proximal occlusion and distal embolism), abnormalities in the upstream (proximal) and downstream (distal) PAs can affect each other via hemodynamics and result in a vicious cycle of remodeling (Fig. 3). In particular, large, conduit PA stiffening increases distal arterial cyclic strain damage, which promotes SMC proliferation and narrowing. Increased flow pulsatility at distal arteries has been shown to induce inflammatory gene expression, leukocyte adhesion and cell proliferation in endothelial cells. A similar mechanism has been demonstrated in the systemic circulation in which aortic stiffening causes damage to renal arterioles. In turn, distal arterial narrowing increases mean pulmonary arterial pressure, which dilates the proximal arteries, increasing circumferential stress and promoting SMC-mediated wall thickening, which increase stiffness.

**SUMMARY AND FUTURE DIRECTIONS**

It is vital to examine the structure-function relationship of pulmonary vascular system in the context of RV function, which predicts clinical outcomes and ultimately determines mortality in PH. Recently, pulmonary arterial stiffness has gained increasing recognition due to its clinical relevance to PH outcomes; however, studies that examine local properties such as stiffness typically do not quantify global cardiopulmonary function so the relationship between the two remains poorly defined. Studies that quantify impedance, as a more comprehensive metric of RV afterload, and vascular-ventricular coupling, to assess the efficiency of the whole cardiopulmonary system, are required to address this gap in our knowledge. Impedance provides insight into steady (distal) and pulsatile (proximal) components of the pulmonary hemodynamics; VVC measurements demonstrate the impact of pulmonary hemodynamics on RV function and vice versa. In addition, the role of arterial viscoelasticity in VVC efficiency remains to be determined. Furthermore, at the cellular and molecular level, it would be useful to identify the cells and cellular signaling pathways that control PA stiffening and should be targets of treatment. Finally, a better understanding of the impact of pulmonary hemodynamics on RV function and vice versa may allow more accurate prognoses of RV failure. That is, the hemodynamic indicators of the transition from adaptive ventricular remodeling to maladaptive ventricular remodeling, the precursor of ventricular failure, may lead to better care and treatment for patients with PH.

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