The Critical Role of Pulmonary Arterial Compliance in Pulmonary Hypertension

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Abstract

The normal pulmonary circulation is a low-pressure, high-compliance system. Pulmonary arterial compliance decreases in the presence of pulmonary hypertension because of increased extracellular matrix/collagen deposition in the pulmonary arteries. Loss of pulmonary arterial compliance has been consistently shown to be a predictor of increased mortality in patients with pulmonary hypertension, even more so than pulmonary vascular resistance in some studies. Decreased pulmonary arterial compliance causes premature reflection of waves from the distal pulmonary vasculature, leading to increased pulsatile right ventricular afterload and eventually right ventricular failure. Evidence suggests that decreased pulmonary arterial compliance is a cause rather than a consequence of distal small vessel proliferative vasculopathy. Pulmonary arterial compliance decreases early in the disease process even when pulmonary artery pressure and pulmonary vascular resistance are normal, potentially enabling early diagnosis of pulmonary vascular disease, especially in high-risk populations. With the recognition of the prognostic importance of pulmonary arterial compliance, its impact on right ventricular function, and its contributory role in the development and progression of distal small-vessel proliferative vasculopathy, pulmonary arterial compliance is an attractive target for the treatment of pulmonary hypertension.

Keywords: stiffness; impedance; resistance; right ventricle; heart failure

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Arterial compliance permits passive arterial expansion during ventricular systole to accommodate much of the stroke volume and enable arterial recoil, thus continuing blood flow during diastole. Compliance is calculated as the change in cross-sectional area or volume over change in pressure at a fixed vessel length (1). Passive arterial expansion buffers ventricular contraction through arterial–ventricular coupling, the interaction between the ventricle and the arterial system, which maintains low pulse pressure and low pulsatile cardiac afterload. Loss of arterial compliance (increased arterial stiffness) increases pulse pressure, pulsatile afterload, and pulse wave velocity, causing premature wave reflections from the distal vessels to the proximal conduit arteries during late systole (1).

Systemic arterial stiffness increases with age and is strongly associated with systemic hypertension (2). Evidence indicates aortic stiffness precedes systemic hypertension (3–5). Importantly, increased systemic arterial stiffness predicts a heightened risk of myocardial infarction, stroke, and renal dysfunction (6–10). Pulmonary hypertension (PH) is also characterized by increased pulmonary arterial stiffness. There is a growing appreciation of the prognostic value of pulmonary arterial compliance in PH (11–16), and some evidence indicates pulmonary arterial compliance is a better predictor of outcomes than pulmonary vascular resistance (PVR) (17, 18). Here, we review the critical role of pulmonary arterial compliance in PH.

Right Ventricular Afterload

Right ventricular (RV) afterload is composed of steady and pulsatile components. The steady component represents opposition to forward flow, and the pulsatile component represents the energy required to overcome increased systolic pressure during ejection. In the systemic circulation, the pulsatile aortic component contributes only 10% of the total

afterload, but in the pulmonary circulation the pulsatile afterload contributes approximately 23% of the workload (19), and this percentage changes minimally with pulmonary vascular disease (19). Total RV afterload is described by pulmonary input impedance, which is physiologically difficult to measure and interpret (20). A more practical model for estimating RV afterload is the three-element Windkessel model (21), which defines RV afterload in three parameters: resistance, compliance, and characteristic impedance (21).

PVR represents resistance in the Windkessel model: the mean resistive or "static" afterload. PVR is determined by the small distal pulmonary arteries based on Poiseuille's law, which states that resistance is inversely proportional to the fourth power of the radius of the blood vessel and directly proportional to the length of the blood vessel and viscosity of the blood. PVR is defined as the ratio of the transpulmonary gradient (difference between mean pulmonary artery [PA] pressure and pulmonary capillary wedge pressure) over cardiac output. Although PVR accounts for only about 75% of the RV afterload and does not account for the pulsatile component, it is commonly used clinically to describe total RV afterload (22).

Pulmonary arterial compliance is the compliance portion of the three-element Windkessel model. It describes the pulsatile afterload that accounts for approximately one-fourth of the total RV afterload (21). Unlike the systemic circulation, where 80% of the compliance is attributable to proximal aortic elasticity, in the pulmonary circulation, owing to a large number of branching vessels, compliance is distributed throughout the pulmonary circuit (19). The main, proximal left and right pulmonary arteries together contribute only 15–20% of the total pulmonary arterial compliance (23); the distal pulmonary arterial bed contributes the major portion of both resistance and compliance in the pulmonary circulation. However, the proximal pulmonary arteries do play an important role in buffering pulsatile RV ejection and in RV–PA coupling. Table 1 compares and contrasts the elements of the Windkessel model (resistance and compliance) in the systemic and pulmonary circulation. Pulmonary arterial compliance is being increasingly used to evaluate RV afterload, along with PVR, as PVR alone inconsistently predicts outcomes in pulmonary artery hypertension (PAH).

The third element of the Windkessel model is the characteristic input impedance of the proximal pulmonary arteries, which describes the effects of blood mass on RV afterload (21). It is a relatively small component of RV afterload (21) and is not routinely used.

Methods to Measure Pulmonary Arterial Compliance

Several methods have been proposed to measure total arterial compliance in the systemic and pulmonary circulations, based on the Windkessel model (24). Of these, the ratio of stroke volume to PA pulse pressure measured by right heart catheterization is the simplest and most practical method for estimating pulmonary artery compliance (15). This method overestimates compliance, as it does not account for blood flow from the pulmonary circulation into the capillary bed during systole. Nevertheless, it highly correlates with pulmonary artery compliance measured on the basis of the lumped two-element and three-element Windkessel models (25). Stroke volume and PA pressure can also be estimated noninvasively by two-dimensional and Doppler echocardiography. Mahapatra and colleagues estimated PA systolic and diastolic pressures, using the peak systolic tricuspid regurgitation velocity and the end-diastolic pulmonary regurgitation velocity, and stroke volume, by volumetric flow through the left ventricular outflow tract (14). Although indicative of compliance, this noninvasive method lacks accuracy because of the numerous estimates involved.

More recently, cardiac magnetic resonance imaging (MRI) has been used to estimate pulmonary artery compliance by combining invasive pressure measurements and cardiac MRI–derived flow data (26). Pulmonary artery compliance derived by this method strongly correlates with compliance estimated by stroke volume over PA pulse pressure (27).

Insights into pulmonary artery compliance can be gained through noninvasive measurements (28, 29). These measurements of PA stiffness (pulsatility, compliance, capacitance, distensibility, elastic modulus, and stiffness index) obtained using cardiac MRI–derived PA dimensions, in combination with right heart catheterization–derived pressure data performed on the same day, correlate with PH severity (30).

Pulmonary Arterial Compliance Is Decreased in Pulmonary Hypertension

The normal pulmonary circulation is a low-pressure, high-compliance system that can handle large increases in cardiac output that

Table 1. Comparison of elements of Windkessel model in systemic and pulmonary circulation

Characteristic (Ref. No.)	Pulmonary Circulation		Systemic Circulation	
	Normal	Pulmonary Hypertension	Normal	Systemic Hypertension
Location of vascular compliance (21)	20% compliance in main, left and right pulmonary arteries; 80% located beyond first branches	20% compliance in main, left and right pulmonary arteries; 80% located beyond first branches	80% of compliance in proximal conduit vessels	80% of compliance in proximal conduit vessels
Pulsatile load, % (19, 21)	25	25	5–10	5–10
Compliance, ml/mm Hg (15, 17, 21)	3.8–12	0.4–3.8	2.5	0.8
Resistance, mm Hg·s/ml (21, 60)	0.11	>0.18	1.0	1.2

Table 2. Summary of key points

Key Points
1. Pulmonary arterial compliance represents pulsatile afterload of the right ventricle, which contributes to approximately one-fourth of the total right ventricular afterload. Unlike in the systemic circulation, it is distributed uniformly across the entire pulmonary circuit
2. Pulmonary arterial compliance is a strong and independent predictor of mortality in patients with pulmonary hypertension, better than pulmonary vascular resistance
3. Growing evidence suggests that decreased pulmonary arterial compliance is a cause rather than a consequence of distal small-vessel proliferative vasculopathy
4. Pulmonary arterial compliance decreases early in the disease process even when pulmonary artery pressure and pulmonary vascular resistance are normal, potentially enabling early diagnosis and treatment of pulmonary vascular disease, especially in high-risk populations

occur during exercise. As in systemic hypertension, pulmonary arterial compliance decreases in PH (15, 30), and it consistently correlates with PH severity (30). Loss of vascular compliance in PH is clearly associated with accumulation of collagen and loss of elastin in the proximal pulmonary arteries in adult-onset and neonatal PH (31–34).

Decreased Pulmonary Arterial Compliance Induces Distal Proliferative Vasculopathy

The understanding of the temporal relationship between PH and decreased pulmonary artery compliance has evolved. Initially, decreased pulmonary artery compliance in PH was thought to be a consequence of distal small-vessel proliferative vasculopathy leading to increased PVR and mean PA pressure. Certainly, increased mean PA pressure decreases compliance as a result of the nonlinear elasticity of the arteries (35). However, evidence suggests loss of pulmonary artery compliance may actually initiate PH (Figure 1) (36). Patients with exercise-induced PH and those with mild pulmonary vascular disease have reduced pulmonary artery compliance, despite a normal resting PA pressure (30, 37, 38). This indicates pulmonary artery compliance changes early, even when the resting pulmonary artery pressures are within normal limits, and thus, loss of pulmonary artery compliance could contribute to the development and progression of PH (30). It is also possible that the mild increase in PVR with exercise could potentially decrease compliance because of nonlinear elasticity of the arteries.

In support of the hypothesis that loss of pulmonary arterial compliance causes distal proliferative vasculopathy, disruption of the internal elastic lamina occurs before the onset of pulmonary artery smooth muscle cell hypertrophy and endothelial cell proliferation (39). In the monocrotaline-induced rat PH model, fragmentation of the internal elastic lamina in the hilar pulmonary arteries occurs 2 days after monocrotaline injection and 14 days before pulmonary artery smooth muscle hypertrophy. Disruption of the internal elastic lamina is associated with increased elastolytic activity of serine elastases and matrix metalloproteinases in this animal model.

Similar findings are reported in animal models of chronic hypoxic PH (40). Inhibition of serine elastases prevents development of PH in both these animal models, suggesting that disruption of the elastic lamina is the inciting event for the pulmonary artery vasculopathy rather than a consequence (40–43). Although pulmonary artery compliance was not assessed during the early stages of PH in these animal models, loss of elastic tissue has been consistently associated with decreased vascular compliance (31, 44). Pulmonary vasoconstriction is clearly an early contributor to the development of PH in hypoxia and other models. It is likely that vasoconstriction coexists with morphological changes such as disruption of internal elastic lamina.

A mechanism by which reduced pulmonary artery compliance can induce proliferative vasculopathy in the distal small pulmonary arteries has been identified (36). In a process known as mechanotransduction, endothelial cells of the distal small pulmonary arteries sense highly pulsatile flow from decreased vascular compliance and transduce it into a signaling cascade leading to a proinflammatory response and activation of vasoactive cytokines and growth factors, characterized by increased Toll-like receptor-2 expression and NF-κB activation (45). Similar findings are observed in endothelial cells from small pulmonary arteries of animals with experimental PH and of human patients with PAH (45, 46).

Furthermore, highly pulsatile flow decreases expression of endothelial nitric oxide synthase (a potent vasodilator) and increases expression of endothelin and angiotensin-converting enzyme (potent vasoconstrictors and smooth muscle mitogens) and transforming growth factor-β_1 in pulmonary artery endothelial cells (47). Collectively, the inflammatory response, vasoactive cytokines, and growth factors cause pulmonary artery smooth muscle hypertrophy with increased expression of contractile proteins, smooth muscle α-actin, and smooth muscle myosin heavy chain (47). Finally, highly pulsatile flow increases expression of mechanosensitive transient receptor potential (TRP) channels in pulmonary artery smooth muscle cells, leading to more intracellular calcium signaling and smooth muscle proliferation (48).

Suppression of cyclooxygenase (COX-2) expression is also implicated in the pathogenesis of pulmonary vascular remodeling induced by decreased pulmonary artery compliance. *In vitro* experiments show that the absence of COX-2 enhances stiffness-induced proliferation of human pulmonary artery smooth muscle cells and increases production of the extracellular matrix proteins collagen and fibronectin. Overexpression of COX-2 reduces stiffness-induced increases in extracellular matrix deposition. In addition, COX-2 deficiency (e.g., COX-2–deficient mice or wild-type mice in which COX-2 is pharmacologically inhibited) exacerbates hypoxia-induced PH and pulmonary artery smooth muscle cell hypertrophy (49).

Increased stiffness not only promotes vascular smooth muscle proliferation, but also activates fibroblasts in a feedback loop mechanism, leading to further extracellular matrix deposition and fibrosis. There is increased fibroblast proliferation, contraction, and matrix synthesis when fibroblasts are grown in stiff matrices but not in physiologically compliant matrices.

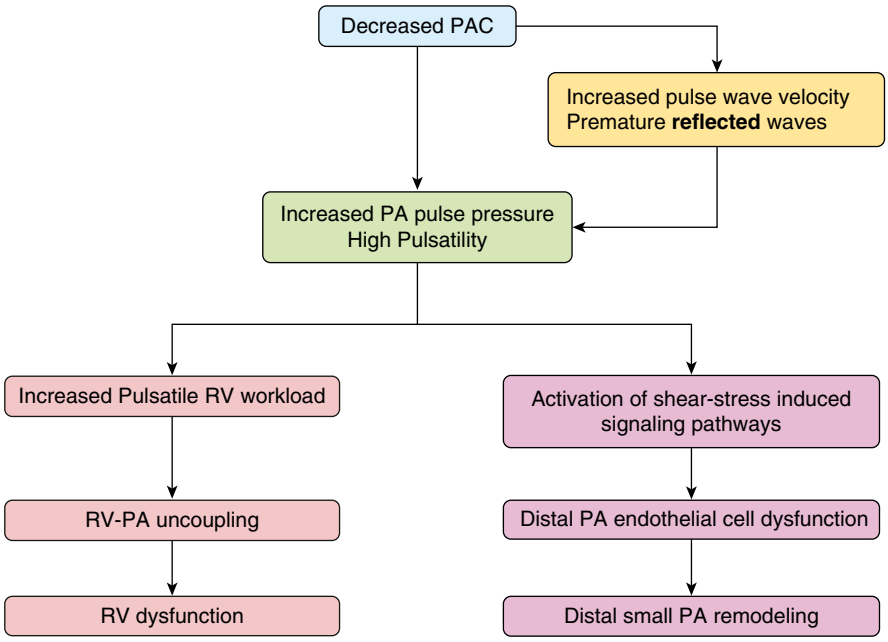

Figure 1. Effect of decreased pulmonary arterial compliance in pulmonary hypertension. PA = pulmonary artery; PAC = pulmonary arterial compliance; RV = right ventricle.

Stiffness-induced fibroblast activation is mediated through activation of transcription factors, "Yes-associated proteins" (YAP), and transcriptional coactivator with PDZ-binding motif (TAZ) (50, 51).

There is an interesting parallel between the proliferative effect of the stiffer matrix on fibroblasts and pulmonary artery smooth muscle cells and a similar effect described in airway smooth muscle cells (52) and cancer cells (53). Work by Barman and colleagues suggests a central role for adventitial fibroblasts in the pathophysiology of pulmonary vascular remodeling in three animal models of PAH (54). These observations raise the possibility that therapy that increases pulmonary artery compliance might prevent or reverse pulmonary vascular remodeling in PH. However, this concept needs to be tested.

Effect of Decreased Pulmonary Artery Compliance on Right Ventricular Function

Decreased pulmonary artery compliance in PH increases RV pulsatile workload (22, 55), and therefore the RV must generate increased pressure to eject blood. Under normal conditions, reflected waves from the pulmonary vasculature return to the pulmonic valve during diastole, at or just before the dicrotic notch of the pulmonary artery waveform, and thus do not impact right ventricular ejection. However, with decreased pulmonary artery compliance and increased pulse wave velocity, reflected waves appear during mid or late systole, resulting in increased PA systolic pressure, pulse pressure, and RV pulsatile afterload (56). The elevated pulmonary artery systolic pressure increases RV wall stress and oxygen consumption. This over time leads to RV hypertrophy, RV dilation, and reduced cardiac output (RV–PA uncoupling) regardless of any improvement achieved in PVR, ultimately leading to right heart failure and death (Figure 1) (22, 57, 58).

It has been proposed that the RV initially adapts by compensatory hypertrophy to maintain cardiac output, but over time this compensatory method fails, leading to right heart failure and decreased cardiac output (57). However, whether there are such distinct adaptive or maladaptive RV hypertrophy programs that differentially determine the timing and degree of RV–PA uncoupling is unclear (59).

Decreased pulmonary artery compliance is independently associated with RV dysfunction, dilatation, and hypertrophy (60). The relative contribution of pulmonary artery compliance to RV stroke work index (a measure of RV contractility and workload) is 1.2- to 18-fold higher than PVR (60), further emphasizing the important contribution of pulmonary artery compliance to RV function and energetics.

The Resistance–Compliance Relationship in the Pulmonary Circulation

Resistance and compliance in the pulmonary circulation exhibit an inverse hyperbolic relationship. The product of resistance and compliance (RC time) is mostly constant (61, 62) in both healthy and diseased states, except for a few exceptions discussed below (61, 62).

RC Time Is Constant

Lankhaar and colleagues quantified RV afterload, using the three-element Windkessel model in patients with idiopathic PAH, patients with chronic thromboembolic PH, and healthy control subjects (62). They showed that PVR and pulmonary artery compliance exhibited an inverse-hyperbolic relationship and that the RC time was constant (0.48 $\pm$ 0.17 s), regardless of the underlying disease state (63) (Figure 2A). Similarly, Tedford and colleagues demonstrated an inverse-hyperbolic relationship between PVR and pulmonary artery compliance with a constant RC time (0.48 $\pm$ 0.17 s) in 1,009 patients with suspected or confirmed PH and normal pulmonary capillary wedge pressure (Figure 2B). This relationship was unaffected by interstitial lung disease and was minimally affected by age (61). Similarly, in the study by Lankhaar and colleagues of 52 patients with PAH and 10 patients with distal chronic thromboembolic disease, mentioned previously, RC time did not change with PAH-specific therapy (62).

Determinants of Resistance–Compliance Relationship

Two reasons have been proposed for the constant relationship between PVR and pulmonary artery compliance. First, increased resistance raises intravascular pressure, which decreases compliance because of the nonlinear elasticity of the arteries (35). The second reason is based on the uniform distribution of compliance

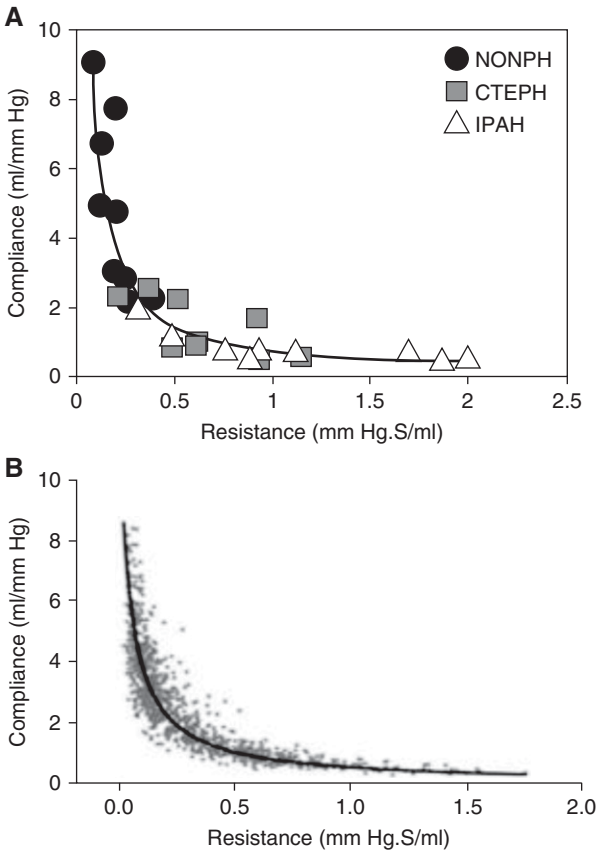

Figure 2. Inverse hyperbolic relationship between resistance and compliance in the pulmonary circulation as depicted by (*A*) Lankhaar and colleagues (adapted by permission from Reference 62) and (*B*) Tedford and colleagues (adapted by permission from Reference 61). CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary artery hypertension; NONPH = healthy control subjects.

throughout the pulmonary circulation. The small distal vessels account for most of the resistance and compliance in the pulmonary circulation. This is due to the 10 times greater number of distal small arterioles in the pulmonary compared with the systemic circulation (21, 23). In patients with PAH and an acute vasodilator response, after inhalation of nitric oxide, pulmonary arterial compliance decreases immediately with a proportional decrease in PVR (64). Because inhaled nitric oxide is believed to act locally adjacent to the alveolar space, this would suggest that the distal pulmonary arteries are the major determinant of both pulmonary arterial compliance and PVR.

Clinical Implications of a Constant Resistance–Compliance Relationship

The constant relationship between PVR and pulmonary artery compliance has important clinical applications. The hyperbolic shape of the pulmonary artery compliance–PVR curve suggests that substantial declines in pulmonary artery compliance occur before increases in PVR (61, 62), as suggested earlier. Thus, assessment of pulmonary artery compliance may allow for diagnosis of pulmonary vascular disease before PVR elevations.

Factors Influencing the Resistance–Compliance Relationship in the Pulmonary Circulation

Elevated Left-Heart Filling Pressures

Elevated left-sided filling pressures affect the PVR and pulmonary artery compliance relationship by shifting the curve leftward and downward (Figure 3A). Thus, for any given PVR, the pulmonary artery compliance is lower, with a lower RC time, when pulmonary capillary wedge pressure is elevated (61). Reduced RC time in the setting of elevated left-sided filling pressures increases the pulsatile afterload of the RV (61). Hence, patients with PH due to left heart disease are more prone to develop right heart failure due to lower pulmonary artery compliance for any given PVR compared with those who have normal pulmonary capillary wedge pressures. This may explain why RV function is a leading outcome determinant in patients with impaired systolic and/or diastolic left ventricular function (65, 66).

Influence of Proximal Chronic Thromboembolic Pulmonary Hypertension and Pulmonary Endarterectomy

Patients with proximal chronic thromboembolic pulmonary vascular disease also have reduced RC time. Ross and colleagues demonstrated lower RC time in patients with proximal chronic thromboembolic PH compared with idiopathic PAH or distal chronic thromboembolic pulmonary hypertension (CTEPH) (Figure 3B) (67). This is caused by increased wave reflection from proximal obstructions. Similar findings were observed when Pagnamenta and colleagues compared RC time in experimental animal models of proximal and distal CTEPH. Compared with dogs with distal CTEPH induced by microembolization, dogs with proximal CTEPH induced by pulmonary artery ensnarement had a lower RC time and increased RV pulsatile afterload (68).

Finally, age affects the relationship between resistance and compliance in the pulmonary circulation. Increased age is associated with a slightly lower RC time, with a 20% reduction in pulmonary artery compliance in those at least 70 years old (61). There is also a sex-based difference in proximal aortic stiffness and ventriculo–vascular interaction. Proximal aortic stiffness is greater in women than men, predisposing them to increased pulsatile afterload of the left ventricle (69, 70). Whether sex affects RC time in the pulmonary circulation is not known.

Prognostic Significance of Pulmonary Artery Compliance

Decreased pulmonary artery compliance increases the risk of mortality in patients with PAH (13–16). In a landmark study

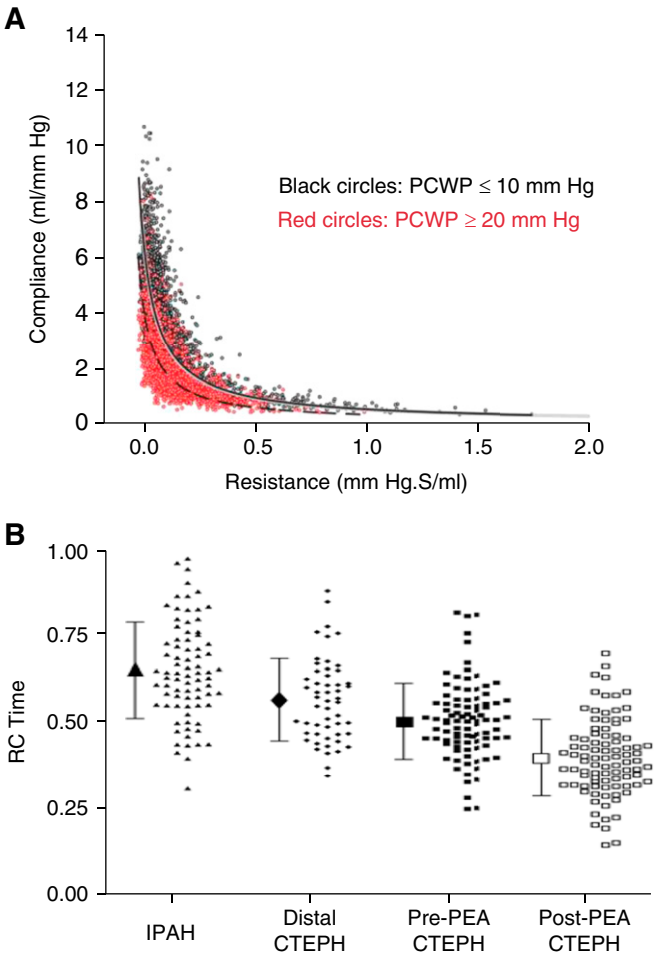

Figure 3. Alteration in resistance–compliance relationship in pulmonary hypertension. (*A*) Elevated pulmonary capillary wedge pressure shifts the PVR–PAC curve to the left as depicted by Tedford and colleagues (adapted by permission from Reference 61). (*B*) RC time is reduced in CTEPH patients both pre- and postendarterectomy as depicted by MacKenzie and colleagues (adapted by permission from Reference 67). CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary artery hypertension; PCWP = pulmonary capillary wedge pressure; PEA = pulmonary endarterectomy; RC = resistance and compliance.

of 109 patients with PAH, pulmonary artery compliance was the strongest predictor of mortality. Every 1-unit (ml/mm Hg) decrease in pulmonary artery compliance resulted in a 17-fold increased risk of death. Patients with the lowest quartile pulmonary artery compliance (<0.81 ml/mm Hg) had less than 40% survival at 4 years, but patients with the highest quartile pulmonary artery compliance (>2.00 ml/mm Hg) had 100% survival at 4 years (15). In this study, PVR was not associated with increased mortality, suggesting pulmonary artery compliance is a better predictor of outcomes. Decreased pulmonary artery compliance has also been associated with increased mortality in children with PAH (11).

Furthermore, increased pulmonary artery stiffness measured by cardiac MRI is associated with increased mortality in patients with PAH (16). When compared with control subjects, patients with PAH have a smaller relative area change of the right pulmonary artery. As in pulmonary artery compliance, relative area change has a hyperbolic relationship with mean pulmonary artery pressure. Relative area change less than 16% is associated with poor survival (16).

Decreased pulmonary artery compliance is also associated with increased mortality in patients with PH due to left heart failure (World Health Organization group II) (12, 17, 18, 71). In 463 ambulatory patients with heart failure and reduced ejection fraction, pulmonary artery compliance not exceeding 2.0 ml/mm Hg had a 3.5-fold increased risk of death compared with those with pulmonary artery compliance greater than 5.0 ml/mm Hg (71). Moreover, Pellegrini and colleagues examined 306 patients with similar characteristics and found decreased pulmonary artery compliance (<2.15 ml/mm Hg) increased risk of mortality (17). Importantly, reduced pulmonary artery compliance (<2.15 ml/mm Hg) predicted increased risk of death, even in patients with normal PVR (17). More recently, pulmonary artery compliance was found to be a better predictor of mortality than PVR in patients with PH due to heart failure with preserved ejection fraction (18), reinforcing the importance of pulmonary artery compliance in clinical practice.

Could Assessment of Pulmonary Artery Compliance Promote Early Diagnosis of Pulmonary Hypertension?

At present, there is an unmet need for earlier diagnosis of PAH. Although survival in PAH has improved in the last two decades, it remains a fatal disease with a 1-year mortality of approximately 15–20% (72, 73). In the contemporary PAH registries, mean PVR at diagnosis ranges between 8 and 10 Wood units, which is associated with reduced pulmonary artery compliance (74–76), suggesting the disease is well established at diagnosis. Unfortunately, none of the currently available pulmonary vasodilator therapies, both mono- and combination therapies, effectively or consistently decrease PVR to a level on the RC curve with higher compliance (61). Sequential combination therapy with phosphodiesterase-5 inhibitors and endothelin receptor antagonists in the ATHENA (Add-on Ambrisentan Therapy to Background Phosphodiesterase Type-5 Inhibitor Therapy in Pulmonary Arterial Hypertension) study increased pulmonary artery compliance in some but not in all patients (77).

Assessment of pulmonary artery compliance can be a tool for the early diagnosis of PAH. In the early stages of pulmonary vascular disease, pulmonary artery compliance drops considerably

while PVR increases minimally. Hence, serial assessment of pulmonary artery compliance can promote early diagnosis of pulmonary vascular disease even when PVR is within normal limits. This strategy might be useful especially in screening "high risk" patients (patients with connective tissue disease, portal hypertension, HIV, lung disease, left-sided heart disease, or a strong family history of PAH), as noninvasive measures of pulmonary artery compliance become more widely implemented. Serial echocardiography or cardiac MRI can potentially detect the onset of pulmonary vascular disease earlier when pulmonary arterial compliance decreases despite normal pulmonary artery pressures and PVR. Early diagnosis may potentially improve outcomes in PAH via early initiation of therapy; however, this has not yet been studied.

Pulmonary Artery Compliance as a Novel Therapeutic Target in Pulmonary Hypertension

With the recognition of the prognostic importance of pulmonary artery compliance, its role in the development and progression of distal small-vessel proliferative vasculopathy, and its impact on RV function, pulmonary artery compliance is an attractive target for the treatment of PH. However, whether a significant improvement in pulmonary arterial compliance will lead to an improvement in hard clinical outcomes, such as time to clinical worsening or more importantly survival, remains to be tested.

None of the currently available PAH-specific therapies, except parenteral prostacyclin, improve pulmonary arterial compliance (78). In a small single-center study, parenteral prostacyclin therapy improved pulmonary arterial compliance minimally, and this was associated with improvement in 6-minute-walk distance (78). A pooled analysis of four randomized controlled trials in PAH showed a small (0.2 ml/mm Hg), but significant, improvement in pulmonary artery compliance with pulmonary vasodilator therapy (79). However, change in compliance was not associated with a reduction in short-term (12 wk) clinical outcomes, likely due to the small magnitude of change (79). Thus, there is an unmet need for novel approaches to increase pulmonary artery compliance significantly and thereby hopefully improve RV function, the major determinant of long-term outcomes in PAH.

In conclusion, PH is associated with an early and progressive decrease in pulmonary artery compliance. Loss of vascular compliance increases the pulsatile afterload of the RV by causing premature reflection of waves from the distal pulmonary circulation (Figure 1). Furthermore, evidence suggests that highly pulsatile flow, resulting from decreased pulmonary artery compliance, plays an important role in the development and progression of distal small pulmonary artery vasculopathy (Figure 1). Loss of pulmonary artery compliance occurs early in the course of the disease process, even when PVR is normal, and is an independent and consistent predictor of mortality (Table 2 summarizes these key points). Going forward, pulmonary artery compliance may be an attractive target for treatment and an early screening tool for at-risk populations in PH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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