Pulmonary Capillary Wedge Pressure Augments Right Ventricular Pulsatile Loading

Running title: Tedford et al.; PCWP augments RV afterload

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and disease
Abstract:

Background - Right ventricular (RV) failure from increased pulmonary vascular loading is a major cause of morbidity and mortality, yet its modulation by disease remains poorly understood. We tested the hypotheses that, unlike the systemic circulation, pulmonary vascular resistance (R_{PA}) and compliance (C_{PA}) are consistently and inversely related regardless of age, pulmonary hypertension (PH), or interstitial fibrosis, and that this relation may be changed by elevated pulmonary capillary wedge pressure (PCWP), augmenting RV pulsatile load.

Methods and Results - Several large clinical databases with right heart/pulmonary catheterization data were analyzed to determine the R_{PA}-C_{PA} relationship with PH, pulmonary fibrosis, patient age, and varying PCWP. Patients with suspected or documented PH (n=1009) and normal PCWP displayed a consistent R_{PA}-C_{PA} hyperbolic (inverse) dependence; C_{PA}=0.564/(0.047+R_{PA}), with a near constant resistance-compliance product (RC) (0.48±0.17 seconds). In the same patients, the systemic RC was highly variable. Severe pulmonary fibrosis (n=89) did not change the R_{PA}-C_{PA} relation. Increasing patient age led to a very small though statistically significant change in the relation. However, elevation of the PCWP (n=8142) had a larger impact, significantly lowering C_{PA} for any R_{PA}, and negatively correlating RC (p<0.0001).

Conclusions - PH and pulmonary fibrosis do not significantly change the hyperbolic dependence between R_{PA} and C_{PA}, while patient age has only minimal affects. This fixed relationship helps explain the difficulty of reducing total RV afterload by therapies that have modest impact on mean R_{PA}. Higher PCWP appears to enhance net RV afterload by elevating pulsatile, relative to resistive load, and may contribute to RV dysfunction.

Key words: ventricular/vascular coupling hemodynamics, heart failure, pulmonary hypertension, pulmonary vascular changes, right ventricle
Introduction

When the left heart ejects blood into the systemic arteries, it must overcome both a mean resistive load, regulated by small peripheral vessels, and a pulsatile load related mostly to proximal aortic compliance. This geographic distribution of different vessels dominating resistive versus capacitive properties is important to understanding how left heart load varies with aging and disease. With aging, aortic stiffening and faster flow transmission to the periphery (enhancing wave reflection) results in systolic hypertension with less change in resistance.1-3 Increases in resistance with resulting elevation of mean pressure also reduces overall arterial compliance (e.g. essential hypertension in a young patient), although not as much as with primary stiffening of the thoracic aorta.

The pulmonary circulation is very different, though this disparity has only recently been highlighted, as pulmonary hypertension (PH) and right heart disease are attracting more attention. In a series of relatively small studies involving patients with and without PH, the Vonk-Noordegraaf laboratory showed that mean pulmonary vascular resistance (RPA) and pulmonary arterial compliance (CPA) are consistently inversely related.4-6 More recently, Bonderman et al reported similar findings in patients after pulmonary endartectomy.7 As a consequence, the product of resistance and compliance (RC time) is nearly constant and CPA can be predicted by knowing RPA. This means that the vessels responsible for pulmonary resistance and compliance are more or less the same (e.g. distal), and that this geographic distribution is unaltered by PH. The generalizability of these findings to other patient types, including patients with abnormal left ventricular (LV) function, different ages, or under conditions of acute hemodynamic stress is unknown. We performed a retrospective analysis of pulmonary (and
systemic) arterial hemodynamics from several large patient populations to robustly test the $R_{PA}-C_{PA}$ dependence, and to determine its sensitivity to pulmonary fibrosis, patient age, and pulmonary venous capillary wedge pressure (PCWP). Unlike the situation in systemic arteries, we found a hyperbolic $R_{PA}-C_{PA}$ dependence for lung that varies minimally with the cause of PH (excluding World Health Organization (WHO) group II PH), with severe interstitial fibrosis, or with patient age. We also found that PCWP has a significant effect on this dependence resulting in a higher right ventricular (RV) pulsatile load.

Methods

Clinical Data Sets and Patient Populations

For the Johns Hopkins cohort, the Institutional Review Board approved retrospective access to de-identified patient data under a HIPAA waiver. The Mayo Clinic and Columbia University Institutional Review Boards approved the prospective data collection for all individuals included in this analysis and signed consents were obtained. The hemodynamic data required for each patient analysis were mean cardiac output (thermodilution or Fick based), right atrial, mean, systolic, and diastolic pulmonary arterial and/or systemic arterial pressures, and heart rate. In addition, we obtained demographic information and primary cardiac or pulmonary disease diagnosis. Data were examined from four different databases:

1) **Cohort A: Suspected or Known PH:** The Johns Hopkins Hospital Cardiac Catheterization Database was queried to identify all patients receiving an isolated right heart catheterization (RHC) for suspected or known PH between 2000-2010. Patients receiving a RHC at the time of left heart catheterization or coronary angiogram were excluded. All RHC procedures and subsequent waveform analysis in this database were performed by a clinical
cardiologist who specializes in heart failure. Pressures are reported at end-expiration. All patients found to have a PCWP > 15 mmHg (i.e. World Health Organization group II PH) were also excluded from this analysis. 1009 patients with a PCWP ≤ 15 mmHg were identified with adequate hemodynamic data. This cohort included patients with WHO group I, III, IV, and V PH.

2) **Cohort B: Interstitial Lung Disease:** We queried the New York Presbyterian (NYP) Interstitial Lung Disease (ILD) Program database at Columbia University, identifying 86 patients with idiopathic pulmonary fibrosis and 3 patients with fibrosis due to chronic eosinophilic pneumonia who had complete hemodynamic data and PCWP ≤ 15 mmHg. PCWP tracings were independently interpreted by two pulmonologists and differences were decided by consensus. Pressures are reported at end-expiration. Patients were enrolled between February 2007 and April 2011. RHC was performed for suspected PH or as a routine component of lung transplant evaluation. Carbon monoxide diffusion capacity (DLCO) analysis was obtained in 95% of the patients, all of whom had DLCO <41% of predicted.

3) **Cohort C: General RHC Analysis:** The Johns Hopkins Hospital Cardiac Catheterization Database was queried for all patients receiving an isolated RHC between 2000-2010 for any indication, yielding 8463 patients. Data collection and analysis were performed as in Cohort A, and all patients in cohort A were included in cohort C. Of these, 8142 had adequate hemodynamic data sets. A subgroup of cohort C (n=207) was identified with a diagnosis of heart failure and at least two clinical cardiac catheterizations at distinct time points, one with a measured PCWP ≤ 10 mmHg and another when PCWP ≥ 20 mmHg. Multiple catheterizations were done for either ongoing management of heart failure or as part of a cardiac transplant/left ventricular assist device evaluation or post-transplant/left ventricular assist device follow-up.
4) **Cohort D: Early-Stage Heart Failure with Preserved Ejection Fraction (HFpEF):**

Rest and supine exercise hemodynamic data from 24 patients with early stage HFpEF were obtained at the Mayo Clinic. All RHC procedures and subsequent waveform analysis in this database were performed by a clinical cardiologist specializing in heart failure. Patients were classified as early-stage HFpEF if resting PCWP was ≤15 mmHg and peak exercise PCWP was ≥25 mm Hg. Resting and exercise pressures were reported at end-expiration. A detailed description of this protocol has been previously published.\(^8\)

To further test the reliability of the PCWP recordings from the clinical database, we randomly selected 50 patients from cohort C and 10 from cohort B, had the tracings reviewed blinded to patient by two cardiologists (RJT, OHC), their values averaged, and then compared to the recorded clinical entry, using Bland-Altman analysis (**Supplemental Figure 1**). The results show excellent agreement, (95% limits of agreement were -5.9 to 2.6 mmHg, with slight underestimation (-1.7 mmHg) in the clinical recorded database.

**Calculations of Resistance, Compliance, and RC time**

\[ R_{PA} \text{ is calculated as } \frac{\text{mean pulmonary artery (PA) pressure} - \text{PCWP}}{\text{cardiac output}}, \]

expressed as mmHg\cdot\text{seconds}\cdot\text{mL}^{-1}. \[ C_{PA} \text{ is estimated by } \frac{\text{stroke volume}}{\text{PA pulse pressure}}, \]

(mL\cdot\text{mmHg}^{-1}), as validated by several studies.\(^1,4,9\) \[ R_{SA} \text{ is } \frac{\text{mean systemic arterial pressure} - \text{mean right atrial pressure}}{\text{cardiac output}}, \] and \[ C_{SA} = \frac{\text{stroke volume}}{\text{systemic arterial pulse pressure}}. \] The RC time (product of resistance and compliance) is therefore expressed as units of seconds.

**Statistics**

Data are presented as the mean±SD. Curve fits (linear or non-linear) were generated and statistical analysis was performed using SigmaPlot version 11.0/Systat version 10.2. SigmaPlot
uses Marquardt-Levenberg algorithm for curve fits. Comparison of various patient cohorts was performed with either unpaired Student t-test or Mann-Whitney Rank-Sum test as appropriate, or for multiple groups, by one-way ANOVA or ANOVA on ranks. Holm-Sidak or Dunn’s method was used for post-hoc multiple comparisons. Pearson chi-square test was performed for two-way cross-tabulation. An F-test was used to compare variances of pulmonary and systemic RC times. Other analysis, such as multiple linear regressions are indicated where appropriate. A p value <0.05 was considered statistically significant.

Results

R_{PA} – C_{PA} Dependence in Patients with Suspected or Known PH (SPH/PH)

Demographic and hemodynamic data for all cohorts are summarized in Table 1. Figure 1A displays the scatter plot of R_{PA} versus C_{PA} from the 1009 patients in Cohort A. There was a consistent inverse dependence fit by the 2nd order hyperbolic decay: \( R_{PA} = 0.564 / (0.047 + C_{PA}) \); \( r^2 = 0.74 \). By contrast, a similar plot of systemic arterial R_{SA} versus C_{SA} (Figure 1B, shown with curve fit to PA data) showed greater dispersion (\( r^2 = 0.46 \)). The inverse dependence between R_{PA} and C_{PA} was not dictated by their sharing of stroke volume (SV) in the numerator of one and denominator of the other. Removing SV from C_{PA} (i.e. 1/pulmonary artery pulse pressure) and CO from R_{PA} (PA_{mean}-PCWP) yielded a similar relation (Supplemental Figure 2A). Reintroducing heart rate into the latter also did not alter the relation (not shown). To better quantify the disparity between circulations, RC time was plotted versus mean pressure for each respective vascular bed (Figure 1C). The RC time was narrowly constrained in the pulmonary system (mean 0.48±0.17 sec), but highly variable in the systemic arteries for any mean pressure (variance = 0.027 vs. 0.163; p<10^{-5}). Lastly, we tested whether the R_{PA}-C_{PA} dependence was
changed by lung interstitial stiffness in cohort (B) comprised of patients with severe pulmonary fibrosis. A near identical dependence was observed (Figure 1D) with the mean RC time (0.48±0.16 sec, Supplemental Figure 2B).

Age and the pulmonary resistance-compliance relation

We next evenly divided the 1009 SPH/PH subjects into age tertiles to test the impact of patient age. Figure 2A highlights the very different effects of patient age on the pulmonary versus systemic vasculature. In the pulmonary plot, the distribution of patients in each age tertile was scattered throughout the hyperbola, whereas the data were clustered for the systemic circulation, with the oldest tertile dominating the lower right region, and youngest the upper left. Figure 2B depicts this in graphic form, showing the percentage of patients within each age tertile that lay within each compliance or resistance tertile for the two circulations. In the systemic circulation, there was a marked age-dependent shift from higher to lower compliance, and lower to higher resistance (both p<0.00001; p-values are for $\chi^2$ 2-way cross-tabulation). The distribution was more even among age groups for the pulmonary data, and older patients were more prevalent in the high compliance tertile. As a result, the impact of patient age on the pulmonary $R_{PA}$-$C_{PA}$ relation was small, though statistically significant. This was formally tested by log-transformation of each curve, and subsequent analysis of covariance, using age as a categorical (and continuous) variable (p<0.001; Supplemental Figure 3). For a median $R_{PA}$ of 3 Wood units, $C_{PA}$ fell from 2.64→2.15 mL/mmHg as age rose from 20→90, or a 19% decline over 70 years.

Increasing PCWP and the pulmonary resistance-compliance relation

Figure 3A displays the $R_{PA}$-$C_{PA}$ relationship from the 8,142 patients in Cohort C. The curve fit based on the PH/SPH population is reproduced for comparison. Unlike Cohorts A and
B, in whom PCWP was in the normal range, the broader patient group had many subjects with reduced $C_{PA}$ for a given $R_{PA}$. This change depended on PCWP, as those patients with a PCWP $\leq 10$ mmHg (black) lay on the previously derived curve, whereas those with PCWP $\geq 20$ mmHg had a disproportionate decline in $C_{PA}$ (red). We again confirmed that this change was not driven by SV (Supplemental Figure 4A). Converting the data to a log ($R_{PA}$)-log ($C_{PA}$) plot (Figure 3B) showed the impact of PCWP was continuous, with a downward-leftward shift in the relation with higher PCWP. The magnitude of the shift was much greater than that observed by age. For example, at a given $R_{PA}$ of 3 Wood unit, $C_{PA}$ is be lowered from 3.34 to 1.65 to 0.82 as PCWP increases from 0 to 25 to 50 mmHg respectively ($C_{PA}$ range of 2.52 ml/mmHg). Increased PCWP therefore also resulted in a lower RC time, due principally to lower compliance (Figure 3C, $RC = -0.0063 \cdot PCWP + 0.46$, $r^2=0.98$, $p<0.002$). This is also displayed in RC versus mean pressure plots (Supplemental Figure 4B). The magnitude of RC decline was much greater than that observed with patient age.

To further test the impact of PCWP on the $R_{PA}$-$C_{PA}$ dependence, we examined a subgroup of Cohort C ($n=207$) who had a diagnosis of heart failure and two RHC’s at different time points; one when PCWP was $\leq 10$ mmHg and another when PCWP $\geq 20$ mmHg. We also examined 24 patients (Cohort D) with early-stage HFpEF, meaning a PCWP $\leq 15$ mmHg at rest, but in whom PCWP rose $\geq 25$mmHg during supine exercise. As shown in Figure 4A and B, an elevated PCWP in the same individual at different time points or with exercise shifted the $R_{PA}$-$C_{PA}$ relation downward to the left, reducing the RC time constant ($0.43\pm0.15$ to $0.28\pm0.12$ seconds; $0.43\pm0.17$ to $0.26\pm0.10$ seconds); both $p<0.001$). The shift in both curves was statistically significant (Supplemental Figure 5A, B). Thus, unlike mechanisms involved with
PH, both acute and chronic elevation of PCWP may enhance the pulsatile relative to resistive load on the right heart.

**Discussion**

After nearly half a century, there has been broad acceptance that the systemic arterial circulation combines a resistive and capacitive load, and that these can vary at least partially independent of one another. The pulmonary vasculature is very different, coupling resistance and compliance in a very constrained manner so long as pulmonary venous pressure is low. Increasing PCWP appears to alter this behavior to augment right heart pulsatile load. The current study establishes key properties for right heart-pulmonary vascular coupling and illustrates a previously unappreciated deleterious impact of left heart pressures on pulsatile RV load. This is important, as right ventricular dysfunction is a major independent predictor of death from cardiac and/or pulmonary vascular disease.\(^{10-13}\)

It has previously been shown that the R\(_{PA}\)-C\(_{PA}\) relation does not change with treatment of PH.\(^5\) The consistency and shape of the R\(_{PA}\)-C\(_{PA}\) relation, which our study confirms in large patient groups with normal-range PCWP, have important clinical implications. The relationship’s overall predictability means that a simple set of RHC data defines a given patient’s position on a shared continuum curve, allowing one to possibly predict a therapeutic target. Based on this relation, clinicians may be able to estimate how much R\(_{PA}\) must be lowered to have any meaningful change in C\(_{PA}\), and thus, pulsatile (and net) afterload. It also indicates that unlike the proximal aorta in the systemic circulation, the main pulmonary artery adds relatively little to overall pulmonary vascular compliance, since if the PA stiffened independent of resistance with PH, the RC time would decline. This is further supported by work of Saouti et
al\textsuperscript{6}, who determined that proximal pulmonary arteries contribute only 19\% to overall compliance and that, unlike systemic arteries, pulmonary vascular compliance is distributed evenly throughout the peripheral lung in conjunction with resistance. Small age-dependent changes in C\textsubscript{PA} also support this notion and are consistent with little rise in pulse wave velocity from the main PA to peripheral lung with aging.\textsuperscript{14}

While some change in main PA distensibility can occur with disease or age, this is small and has less impact on RV load than what is determined by the peripheral vessels. The flatness of the curve at elevated R\textsubscript{PA} means that resistance must decline substantially to meaningfully impact net RV loading, since pulmonary compliance would still be quite low. This was first suggested by Lankhaar et al\textsuperscript{4}, and may underscore why hemodynamic measurements including R\textsubscript{PA} have been generally unreliable endpoints for clinical PH management.\textsuperscript{15} One can appreciate this problem by plotting the average pre- and post- treatment R\textsubscript{PA} from three large therapeutic PH trials involving sildenafil, treprostinil, or prostacyclin (Figure 5).\textsuperscript{16-18} A high baseline R\textsubscript{PA} (0.62,0.77, or 0.96 mmHg*S*mL\textsuperscript{-1} respectively) and modest decline with treatment (0.50, 0.71, 0.63 mmHg*S*mL\textsuperscript{-1}, respectively) would mean little to no change in estimated compliance, thus maintaining a high RV pulsatile load. While these therapies are clinically used, one would anticipate more effective treatment would need to reduce R\textsubscript{PA} further or differentially enhance C\textsubscript{PA} to also impact pulsatile load.

The R\textsubscript{PA}-C\textsubscript{PA} relation’s sensitivity to pulmonary venous pressure introduces a new way of considering the hemodynamic consequences of elevated left-sided filling pressures. We initially considered that a high PCWP might impact parenchymal stiffness, with the lung acting as more of a wet than dry sponge. Distensibility of small vessels in the lung tissue is enhanced when surrounded by compressible air, but this would be diminished if the parenchyma stiffened. One
counter to this theory is the data showing severe pulmonary fibrosis does not generate the same effect. An alternative is that PCWP is the downstream pressure that amplifies a peripheral pulse reflection, thereby augmenting systolic pulmonary arterial pressure (PAP) and leading to a decline in total compliance.

The impact of PCWP on pulmonary arterial and thus right heart loading is likely relevant to clinical symptoms in heart failure patients. Such individuals become dyspneic during exercise when PCWP frequently rises. Lewis et al\textsuperscript{19} recently showed that symptoms and clinical outcomes of patients with LV dysfunction correlate better with augmentation in PAP than the change in PCWP. At first glance, this may seem in contrast to the findings in this study. However, we would suggest this observation could be explained by the effect of PCWP on the $R_{PA} - C_{PA}$ relationship. Elevations in PCWP lowers $C_{PA}$ for a given $R_{PA}$, resulting in enhanced pulmonary arterial wave reflections and augmentation of the systolic PAP, and thus, mean PAP. Therefore, the higher proportional rise in mean PAP compared to PCWP could be explained by the indirect effect of rising PCWP lowering $C_{PA}$. Our findings also indicate that with the rise in PCWP, there will be enhanced pulsatile RV load, which would further limit RV ejection, and in turn LV filling. Indeed, in the patients in whom mean PAP augmentation plateaued during exercise (indicating RV dysfunction), prognosis was worse.

Our study has several limitations. We relied on the recorded clinical indication for RHC for identifying patients with suspected PH or known PH, and while the actual diagnosis was more mixed and indeed some did not have PH, the consistency of the $R_{PA} - C_{PA}$ relation despite this further supports the idea of its constancy so long as PCWP is in the normal range. Similarly for all cohorts, we relied on the original operator’s recordings and interpretation of hemodynamic data. It is possible that interpretations of tracings may have been different among individual
operators. However, the primary data were all interpreted by heart failure cardiologists or pulmonologists, and our blinded review found minimal inter-observer error on a random subset of studies. Lastly, we relied on an indirect estimate of total pulmonary vascular compliance. Alternative approaches using pulsatile pressure-flow analysis are difficult and impractical for large population studies, but the estimation method has favorably compared to such alternative approaches in smaller controlled studies.\textsuperscript{1-3,4}

In conclusion, the pulmonary circulation and the afterload it imposes on the RV are very different from the systemic circulation. PH, interstitial fibrosis, and patient age do not appear to have much effect on the inverse, hyperbolic $R_{PA}-C_{PA}$ relationship. Because of the consistency of this relationship, one can estimate pulmonary vascular compliance from resistance using a simple equation, identify where a given patient lies relative to normal, and possibly anticipate what therapy would need to achieve for a robust clinical benefit. The findings that a higher PCWP may impact pulmonary arterial and thus RV pulsatile loading offers new insight into the symptomatology of HFpEF and other left heart failure disorders.

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**Conflict of Interest Disclosures:** Dr. Lederer is a consultant for Gilead and on the clinical trial steering committee for Intermune.
References:


Table 1. Clinical Characteristics and Hemodynamics

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<th>A. SPH/PH (n=1009)</th>
<th>B. ILD (n=89)</th>
<th>C. All RHC (n=8142)</th>
<th>C. High PCWP (n=207)</th>
<th>C. Low PCWP (n=207)</th>
<th>D. HFpEF rest (n=24)</th>
<th>D. HFpEF exercise (n=24)</th>
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<td><strong>Pulmonary Vascular Compliance (mL mmHg⁻¹)</strong></td>
<td>2.5 ± 1.6</td>
<td>3.0 ± 1.2</td>
<td>3.5 ± 1.7</td>
<td>2.4 ± 1.2</td>
<td>4.0 ± 1.5</td>
<td>5.2 ± 2.8</td>
<td>3.5 ± 1.3</td>
</tr>
<tr>
<td><strong>Mean Systemic Arterial Pressure (mmHg)</strong></td>
<td>91 ± 14</td>
<td>96 ± 12</td>
<td>92 ± 15</td>
<td>88 ± 17</td>
<td>89 ± 15</td>
<td>99 ± 16 (n=17)</td>
<td>119±21 (n=17)</td>
</tr>
</tbody>
</table>

*Discrete variables with percentages in parenthesis; Continuous variables reported as mean +/- standard deviation (SD)*
Figure Legends:

**Figure 1.** Pulmonary Vascular Resistance-Compliance Relationship.  **A)** Pulmonary vascular resistance ($R_{PA}$) versus pulmonary arterial compliance ($C_{PA}$) in patients with known or suspected pulmonary hypertension (PH). The best fit curve is given by $y=0.564/(0.047+x)$.  **B)** Systemic arterial resistance ($R_{SA}$)-compliance ($C_{SA}$) relationship for the same patient cohort, with curve fit for pulmonary data also shown.  **C)** RC time for pulmonary or systemic vasculature plot versus mean artery pressure.  **D)** $R_{PA}$-$C_{PA}$ relationship in patients with severe pulmonary fibrosis. The best fit hyperbolic decay for these patients (dotted) is compared to Cohort A result (gray solid line), and were identical.

**Figure 2.** Age Effect on Pulmonary Vascular Resistance-Compliance Relationship.  **A) Left Panel:** $R_{PA}$-$C_{PA}$ relationship, **Right Panel:** $R_{SA}$-$C_{SA}$ relationship. Data are sub-grouped (color coding) into three age tertiles. Dashed lines identify tertiles for compliance and resistance based on these data. **B)** Percentage of patients within each age tertile separated among tertiles for compliance or resistance in pulmonary or systemic arteries, respectively. P-values are for cross-tabulation analysis, $\chi^2$ test. See text for details.

**Figure 3.** Effect of Elevated PCWP on Pulmonary Vascular Resistance-Compliance Relationship.  **A)** $R_{PA}$-$C_{PA}$ relationship from two subgroups of Cohort C, those with normal range or elevated PCWP. Gray line is best fit curve from Figure 1A (Cohort A).  **B)** Log($R_{PA}$)-Log($C_{PA}$) plot (n=4735), color coded into five subgroups based on PCWP; $p<0.001$  **C)** Mean RC time for each PCWP sub-group versus PCWP.
Figure 4. Effect of $R_{PA}-C_{PA}$ relationship by change in PCWP within an individual patient.

A) $R_{PA}-C_{PA}$ for each patient is plot at two different study times, one when the patient had a low (PCWP $\leq$ 10 mmHg) and the other a high PCWP (PCWP $\geq$ 20mmHg).  

B) Effect of increasing PCWP during supine exercise on $R_{PA}-C_{PA}$ in 24 patients with early heart failure with preserved ejection fraction.

Figure 5. Effect of PH treatment on $R_{PA}-C_{PA}$ data. The curve fit from Cohort A (PH/SPH) is shown, and superimposed on it are mean pre- and post-treatment $R_{PA}$ and $C_{PA}$ derived from three PH therapeutic trials involving sildenafil, treprostinil, or prostacyclin$^{16-18}$. There was high resting $R_{PA}$ and low $C_{PA}$ and only modest decline in $R_{PA}$ with treatment; thus $C_{PA}$ remained low and so pulsatile load remained high after therapy.
**A**

Pulmonary Vascular Resistance (mmHg*S*mL$^{-1}$)

- 0.0 0.5 1.0 1.5 2.0

Pulmonary Vascular Compliance (mL mmHg$^{-1}$)

- 0 2 4 6 8 10

**B**

Systemic Vascular Resistance (mmHg*S*mL$^{-1}$)

- 0.0 0.5 1.0 1.5 2.0 2.5 3.0

Systemic Vascular Compliance (mL mmHg$^{-1}$)

- 0 2 4 6 8 10 12

Systemic Vasculature (n=1009)

\[ y = \frac{1.54}{0.19 + x}; \quad R^2 = 0.46 \]

**C**

Mean Pulmonary or Systemic Artery Pressure (mmHg)

- 0 2 4 6 8 10 12 14 16 18 20

RC Time (in seconds)

- 0.0 0.5 1.0 1.5 2.0

- Pulmonary Vasculature
- Systemic Vasculature

\[ P < 0.00001 \]

**D**

Pulmonary Vascular Compliance (mL mmHg$^{-1}$)

- 0 2 4 6 8 10 12

Pulmonary Vascular Resistance (mmHg*S*mL$^{-1}$)

- 0.0 0.5 1.0 1.5 2.0

- SPH/PH Cohort
- Severe pulmonary fibrosis (n=89)

\[ y = \frac{0.586}{0.049 + x}; \quad R^2 = 0.25 \]
Log [Pulmonary Vascular Resistance (mmHg•S•mL⁻¹)]

PCWP <= 10 mmHg; n=3315
PCWP >= 20 mmHg; n=1584
SPH/PH cohort

y = 0.577 / (0.048 + x); R² = 0.41
y = 0.306 / (0.031 + x); R² = 0.33

RC = -0.0063 • PCWP + 0.46
R² = 0.98, p<0.002

PCWP 1-5 (n=573)
PCWP 10-15 (n=2925)
PCWP 20-25 (n=897)
PCWP 30-35 (n=293)
PCWP 40-54 (n=47)

Log [Pulmonary Vascular Compliance (mL/mmHg)]

Log [Pulmonary Vascular Resistance (mmHg•S•mL⁻¹)]

Pulmonary Capillary Wedge Pressure (mmHg)

RC time (seconds)
Pulmonary Vascular Compliance (mL mmHg⁻¹)

Pulmonary Vascular Resistance (mmHg S mL⁻¹)

A

PCWP ≤10 mmHg (n = 207)
PCWP ≥20 mmHg (n = 207)

y = 0.630 / (0.053 + x); R² = 0.33
y = 0.292 / (0.024 + x); R² = 0.36

B

Rest (n = 24)
(Mean PCWP = 11 ± 2 mmHg)
Exercise (n = 24)
(Mean PCWP = 31 ± 6 mmHg)

y = 0.711 / (0.051 + x); R² = 0.48
y = 0.385 / (0.039 + x); R² = 0.58
Estimated Pulmonary Vascular Compliance (mL mmHg$^{-1}$) vs. Pulmonary Vascular Resistance (mmHg*S*mL$^{-1}$)

- **Best Fit Curve from SPH/PH Cohort**
- **PVR = 3 Wood units**
- Sildenafil
- Treprostinil
- IV Prostacyclin
Pulmonary Capillary Wedge Pressure Augments Right Ventricular Pulsatile Loading

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Supplemental Material
Bland-Altman Comparison of PCWP from JHU clinical data base versus mean of two expert independent observers (OB)

Limits of agreement: -5.9 to 2.58 mmHg
Supplemental Figure 2

A

\[
\text{PAmean - PCWP (mmHg)} \\
(1/\text{pulmonary pulse pressure}) \quad (\text{mmHg}^{-1})
\]

B

\[
\text{mPAP – PCWP (mmHg)}
\]

ILD (n=89); Mean RC time = 0.48 +/- 0.16 s

Mean Pulmonary Artery Pressure (mmHg)

RC Time (Seconds)
Supplemental Figure 3
Mean Pulmonary Artery Pressure (mmHg)

<table>
<thead>
<tr>
<th>RC Time (seconds)</th>
<th>PCWP &lt;=10 mmHg; n = 3315</th>
<th>RC time = 0.43 +/- 0.15s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCWP &gt;=20 mmHg; n = 1584</td>
<td>RC time = 0.28 +/- 0.12s</td>
</tr>
</tbody>
</table>

\[ p < 0.001 \]

\[ \frac{1}{\text{pulmonary pulse pressure}} \text{ (mmHg}^{-1}) \]

Supplemental Figure 4
Supplemental Figure 1  Bland-Altman Plot for consistency of pulmonary capillary wedge pressure (PCWP) analysis.  PCWP data from 50 randomly selected patients from Cohort C and 10 patients from Cohort B were retrospectively assessed by two blinded and independent cardiologists (OB), the results averaged and then compared with the value obtained from the clinical database (JHU) that had been used in the study analysis. The plot shows the average of the two observations on the abscissa, and difference on the ordinate, and found a mean difference of < 2 mmHg, with limit of agreement ranging from -5.9 to 2.6 mmHg.

Supplemental Figure 2.  A) Plot of mean PA pressure-PCWP versus 1/pulmonary pulse pressure for the data in Cohort A. meanPA-PCWP is equal to RPA multiplied by cardiac output, while 1/PP is equal to CPA divided by SV. The inverse dependence was evident and similar to that in the plots of RPA versus CPA (i.e. Figure 1).  B) Plot of RC time constant versus mean pulmonary pressure for cohort B patients with interstitial fibrosis. Cohort B subjects had a narrow range for the RC product that was very similar to that in the pulmonary hypertension cohort A.

Supplemental Figure 3.  Plot of Log(RPA) versus Log(CPA) for each age tertile for the pulmonary hypertension subjects in Cohort A. This is a log-transformed version of Figure 2A facilitating linear covariance analysis. While the data were generally overlapping with age group, there was a small statistically significant shift (to the left) with increasing age (p<0.001, by analysis of covariance).

Supplemental Figure 4.  A) Similar plot as shown in Supplemental Figure 2A, but based on the data in Cohort C. Results are color coded for patients with a low versus elevated PCWP. Comparison plot is shown in Figure 3A. This confirms that the hyperbolic relation and downward shift with higher PCWP is not due to inverse dependence of stroke volume.  B) RC produce for Cohort C patients with reduced versus elevated PCWP. There was a significant decline in the product in patients with higher wedge. The analysis of covariance showed parallel relations for RC versus mean pulmonary artery pressure, with a highly significant impact of the PCWP group (p<0.001).

Supplemental Figure 5.  A) Log RPA versus log CPA plot for data in Cohort C – with patients selected from among those with a PCWP < 10 mmHg versus > 20 mmHg (as color coded in Figure 3A). These data are then subjected to analysis of covariance, with the PCWP level as a grouping factor. There was a significant downward shift of the relation in those subjects with a high PCWP (p <0.001 for this offset), and no interaction effect.  B) Similar analysis for data from Figure 4B – patients before and during exercise. Exercise associated elevation in PCWP was coupled to a decline in the relations, with a parallel shift downward (p<0.001 for this effect, by analysis of covariance).