

Pulmonary Capillary Wedge Pressure Augments Right Ventricular Pulsatile Loading

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Background—Right ventricular 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, or interstitial fibrosis and that this relation may be changed by elevated pulmonary capillary wedge pressure, augmenting right ventricular 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 pulmonary hypertension, pulmonary fibrosis, patient age, and varying pulmonary capillary wedge pressure. Patients with suspected or documented pulmonary hypertension ($n=1009$) and normal pulmonary capillary wedge pressure 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 (0.48 ± 0.17 seconds). In the same patients, the systemic resistance-compliance product 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 but statistically significant change in the relation. However, elevation of the pulmonary capillary wedge pressure ($n=8142$) had a larger impact, significantly lowering C_{PA} for any R_{PA} and negatively correlating with the resistance-compliance product ($P<0.0001$).

Conclusions—Pulmonary hypertension and pulmonary fibrosis do not significantly change the hyperbolic dependence between R_{PA} and C_{PA} , and patient age has only minimal effects. This fixed relationship helps explain the difficulty of reducing total right ventricular afterload by therapies that have a modest impact on mean R_{PA} . Higher pulmonary capillary wedge pressure appears to enhance net right ventricular afterload by elevating pulsatile, relative to resistive, load and may contribute to right ventricular dysfunction. (*Circulation*. 2012;125:289-297.)

Key Words: heart failure ■ heart ventricles ■ hemodynamics ■ hypertension, pulmonary ■ pulmonary circulation ■ pulmonary wedge pressure ■ vascular resistance

When the left side of the 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 in understanding how the load of the left side of the heart varies with aging and disease. With aging, aortic stiffening and faster flow transmission to the periphery (enhancing wave reflection) result in systolic hypertension with less change in resistance.¹⁻³ Increases in resistance with resulting elevation of mean pressure also reduce overall arterial

compliance (eg, essential hypertension in a young patient), although not as much as with primary stiffening of the thoracic aorta.

Clinical Perspective on p 297

The pulmonary circulation is very different, although this disparity has been highlighted only recently as pulmonary hypertension (PH) and disease of the right side of the heart 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 (R_{PA}) and pulmonary arterial compliance (C_{PA})

Received June 22, 2011; accepted November 17, 2011.

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Guest Editor for this article was Robyn J. Barst, MD.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.051540/-/DC1>.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.051540

are consistently inversely related.^{4–6} More recently, Bonderman et al⁷ reported similar findings in patients after pulmonary endarterectomy. As a consequence, the product of resistance and compliance (RC time) is nearly constant, and C_{PA} can be predicted with knowledge of R_{PA} . This means that the vessels responsible for pulmonary resistance and compliance are more or less the same (eg, 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 function, at 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 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 deidentified 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 4 different databases.

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 (SPH) or known PH between 2000 and 2010. Patients receiving an 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 mm Hg (ie, World Health Organization group II PH) were also excluded from this analysis. A total of 1009 patients with a PCWP ≤15 mm Hg were identified with adequate hemodynamic data. This cohort included patients with World Health Organization group I, III, IV, and V PH.

Cohort B: Interstitial Lung Disease

We queried the New York Presbyterian Interstitial Lung Disease Program database at Columbia University, identifying 86 patients with idiopathic pulmonary fibrosis and 3 patients with fibrosis resulting from chronic eosinophilic pneumonia who had complete hemodynamic data and PCWP ≤15 mm Hg. PCWP tracings were independently interpreted by 2 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 SPH or as a routine component of lung transplant evaluation. Carbon monoxide diffusion capacity analysis was obtained in 95% of the patients, all of whom had carbon monoxide diffusion capacity <41% of predicted.

Cohort C: General RHC Analysis

The Johns Hopkins Hospital Cardiac Catheterization Database was queried for all patients receiving an isolated RHC between 2000 and 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 2 clinical cardiac catheterizations at distinct time points: at PCWP ≤10 mm Hg and at PCWP ≥20 mm Hg. Multiple catheterizations were done either for ongoing management of heart failure or as part of a cardiac transplantation/left ventricular assist device evaluation or posttransplantation/left ventricular assist device follow-up.

Cohort D: Early-Stage Heart Failure With Preserved Ejection Fraction

Rest and supine exercise hemodynamic data from 24 patients with early-stage heart failure with preserved ejection fraction 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 having early-stage heart failure with preserved ejection fraction if their resting PCWP was ≤15 mm Hg and peak exercise PCWP was ≥25 mm Hg. Resting and exercise pressures were reported at end expiration. A detailed description of this protocol has previously been 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 2 cardiologists (RJT, OHC), averaged their values, and then compared them with the recorded clinical entry using Bland-Altman analysis (Figure 1 in the online-only Data Supplement). The results show excellent agreement (95% limits of agreement, −5.9 to 2.6 mm Hg), with slight underestimation (−1.7 mm Hg) in the clinical recorded database.

Calculations of Resistance, Compliance, and RC Time

R_{PA} is calculated mean pulmonary artery [PA] pressure minus PCWP divided by cardiac output, expressed as mm Hg · s · mL^{−1}. C_{PA} is estimated by stroke volume divided by PA pulse pressure (mL · mm Hg^{−1}), as validated by several studies.^{1,4,9} Systemic arterial resistance (R_{SA}) is calculated as mean systemic arterial pressure minus mean right atrial pressure divided by cardiac output. Systemic arterial compliance (C_{SA}) is determined from stroke volume divided by systemic arterial pulse pressure. The RC time (product of resistance and compliance) is therefore expressed as units of seconds.

Statistics

Data are presented as mean±SD. Curve fits (linear or nonlinear) were generated and statistical analysis was performed with SigmaPlot version 11.0/Systat version 10.2. SigmaPlot uses the Marquardt-Levenberg algorithm for nonlinear regression curve fits. Comparison of various patient cohorts was performed with either the unpaired Student *t* test or the Mann-Whitney rank-sum test as appropriate or, for multiple groups, by 1-way ANOVA or ANOVA on ranks. The Holm-Sidak or Dunn method was used for post hoc multiple comparisons. The Pearson χ^2 test was performed for 2-way cross-tabulation. An *F* test was used to compare variances of pulmonary and systemic RC times. Other analyses such as multiple linear regressions are indicated when appropriate. A value of *P*<0.05 was considered statistically significant.

Results

R_{PA} - C_{PA} Dependence in Patients With SPH/PH

Demographic and hemodynamic data for all cohorts are summarized in the Table. Figure 1A displays the scatterplot of R_{PA} versus C_{PA} from the 1009 patients in cohort A. There

Table. Clinical Characteristics and Hemodynamics

	Cohort A, SPH/PH (n=1009)	Cohort B, ILD (n=89)	Cohort C, All RHC (n=8142)	Cohort C, High PCWP (n=207)	Cohort C, Low PCWP (n=207)	Cohort D, HFpEF Rest (n=24)	Cohort D, HFpEF Exercise (n=24)
Sex, n (%)							
Male	387 (38)	69 (78)	5243 (64)	149 (72)	149 (72)	9 (37)	9 (37)
Female	622 (62)	20 (22)	2898 (36)	58 (28)	58 (28)	15 (63)	15 (63)
Unknown	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Race, n (%)							
White	707 (70)	81 (91)	5751 (71)	139 (67)	139 (67)	21 (88)	21 (88)
Black	250 (25)	4 (4)	2004 (25)	54 (26)	54 (26)	0 (0)	0 (0)
Asian/Pacific Islander	9 (1)	4 (4)	61 (1)	2 (1)	2 (1)	2 (8)	2 (8)
Hispanic	9 (1)	0 (0)	59 (1)	2 (1)	2 (1)	1 (4)	1 (4)
American Indian/Eskimo	0 (0)	0 (0)	5 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Other	14 (1)	0 (0)	170 (2)	6 (3)	6 (3)	0 (0)	0 (0)
Unknown	20 (2)	0 (0)	92 (1)	3 (1)	3 (1)	0 (0)	0 (0)
Age at catheterization, y	56±13	63±7	53±14	51±14	51±14	68±12	68±12
Mean PAP, mm Hg	33±16	22±8	24±11	32±6	16±4	20±4	43±9
Systolic PAP, mm Hg	55±27	38±12	38±19	47±10	26±7	31±7	60±13
Diastolic PAP, mm Hg	20±10	13±6	17±15	24±5	10±4	13±2	32±8
Pulmonary pulse pressure, mm Hg	35±19	25±8	21±12	24±7	16±5	18±6	29±12
Cardiac output, L/min	5.0±1.6	4.8±1.2	4.9±1.5	4.4±1.6	5.1±1.3	5.3±1.2	9.0±2.5
Stroke volume, mL	63±22	67±18	60±20	53±20	59±17	77±16	88±20
Heart rate, bpm	81±15	74±15	85±15	87±16	87±15	69±9	103±17
Right atrial pressure, mm Hg	7±4	4±3	8±5	12±5	4±3	6±2	13±4 (n=7)
PCWP, mm Hg	10±3	8±4	14±7	23±4	6±2	11±2	31±6
Pulmonary vascular resistance, mm Hg · s · mL ⁻¹	0.33±0.30	0.19±0.13	0.15±0.15	0.14±0.10	0.12±0.06	0.10±0.04	0.11±0.14
Pulmonary vascular compliance, mL · mm Hg ⁻¹	2.5±1.6	3.0±1.2	3.5±1.7	2.4±1.2	4.0±1.5	5.2±2.8	3.5±1.3
Mean systemic arterial pressure, mm Hg	91±14	96±12	92±15	88±17	89±15	99±16 (n=17)	119±21 (n=17)

SPH indicates suspected pulmonary hypertension; PH, pulmonary hypertension; ILD, interstitial lung disease; RHC, right heart catheterization; PCWP, pulmonary capillary wedge pressure; HFpEF, heart failure with preserved ejection fraction; and PAP, pulmonary arterial pressure. Values are mean±SD when appropriate.

was a consistent inverse dependence fit by the first-order (with offset) hyperbolic decay ($r^2=0.74$): $R_{PA}=0.564/(0.047+C_{PA})$. In 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 in the numerator of one and denominator of the other. Removing stroke volume from C_{PA} (ie, $1/PA$ pulse pressure) and cardiac output from R_{PA} ($PA_{mean}-PCWP$) yielded a similar relation (Figure IIA in the online-only Data Supplement). 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 seconds) but was highly variable in the systemic arteries for any mean pressure (variance=0.027 versus 0.163; $P<10^{-5}$). Lastly, we tested whether the $R_{PA}-C_{PA}$ dependence was changed by lung interstitial stiffness in cohort B, comprising patients with

severe pulmonary fibrosis. A nearly identical dependence was observed (Figure 1D) with the mean RC time (0.48 ± 0.16 seconds; Figure IIB in the online-only Data Supplement).

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 the youngest tertile dominating the upper left region. Figure 2B depicts this in graphic form, showing the percentage of patients within each age tertile who lay within each compliance or resistance tertile for the 2 circulations. In the systemic circulation, there was a marked age-dependent shift from higher to lower compliance and

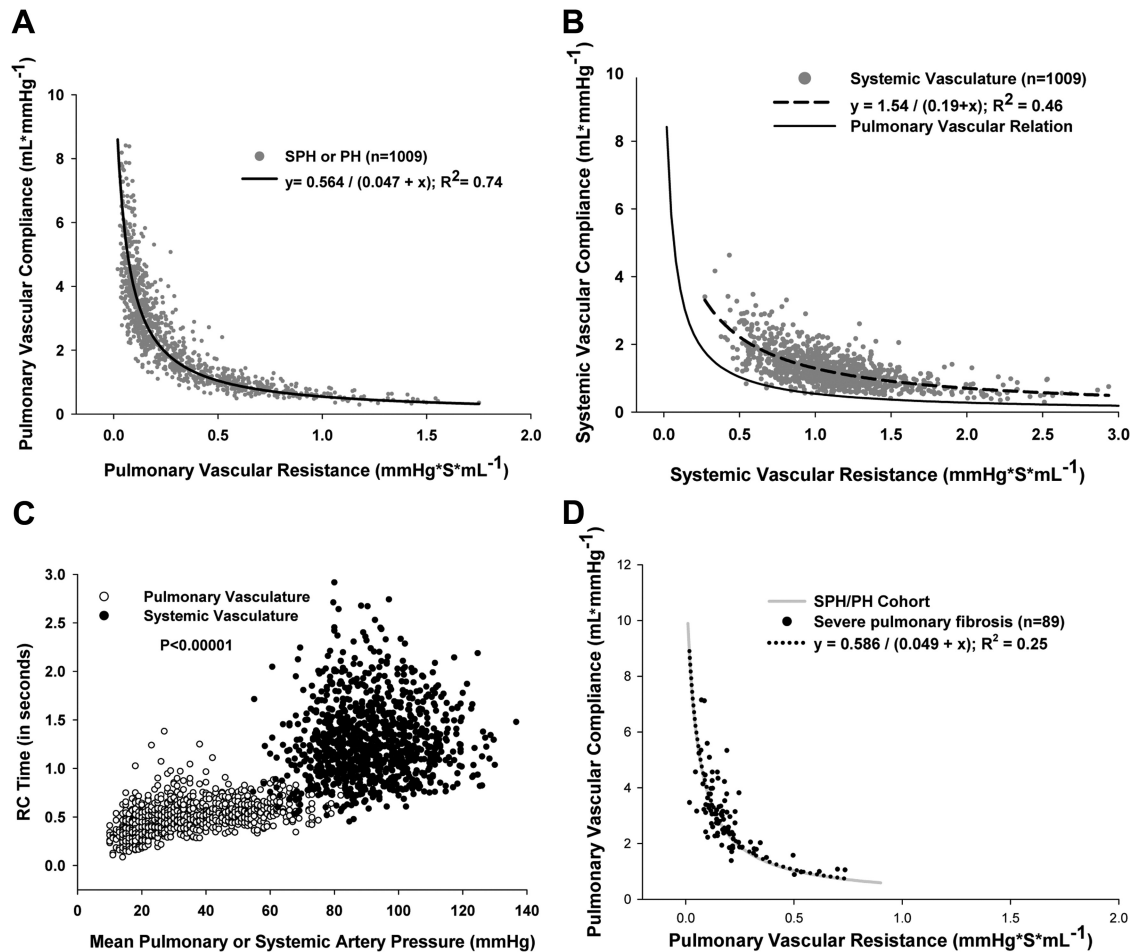


Figure 1. Pulmonary vascular resistance-compliance relationship. **A**, Pulmonary vascular resistance (R_{PA}) vs pulmonary arterial compliance (C_{PA}) in patients with known (PH) or suspected (SPH) pulmonary hypertension. The best-fit curve is given by $y = 0.564 / (0.047 + x)$. **B**, Systemic arterial resistance-compliance (R_{SA} - C_{SA}) relationship for the same patient cohort, with the curve fit for pulmonary data also shown. **C**, Resistance-compliance product for pulmonary or systemic vasculature plot vs 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 with the cohort A result (gray solid line); they were identical.

lower to higher resistance (both $P < 0.00001$; P values are for χ^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 still statistically significant. This was formally tested by log transformation of each curve and subsequent ANCOVA with age used as a categorical (and continuous) variable ($P < 0.001$; Figure III in the online-only Data Supplement). For a median R_{PA} of 3 Wood units, C_{PA} fell from 2.64 to 2.15 $\text{mL} \cdot \text{mmHg}^{-1}$ as age rose from 20 to 90 years, 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 8142 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; those patients with a PCWP ≤ 10 mm Hg (black) lay on the previously derived

curve, whereas those with PCWP ≥ 20 mm Hg had a disproportionate decline in C_{PA} (red). We again confirmed that this change was not driven by stroke volume (Figure IVA in the online-only Data Supplement). Converting the data to a log (R_{PA})-log (C_{PA}) plot (Figure 3B) showed that 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 lowered from 3.34 to 1.65 to 0.82 $\text{mL} \cdot \text{mmHg}^{-1}$ as PCWP increases from 0 to 25 to 50 mm Hg, respectively (C_{PA} range, 2.52 $\text{mL} \cdot \text{mmHg}^{-1}$). Increased PCWP therefore also resulted in a lower RC time, principally as a result of lower compliance ($RC = -0.0063 \times \text{PCWP} + 0.46$; Figure 3C; $r^2 = 0.98$; $P < 0.002$). This is also displayed in plots of RC versus mean pressure (Figure IVB in the online-only Data Supplement). 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 2 RHCs at different time points: when PCWP was ≤ 10 mm Hg and when PCWP

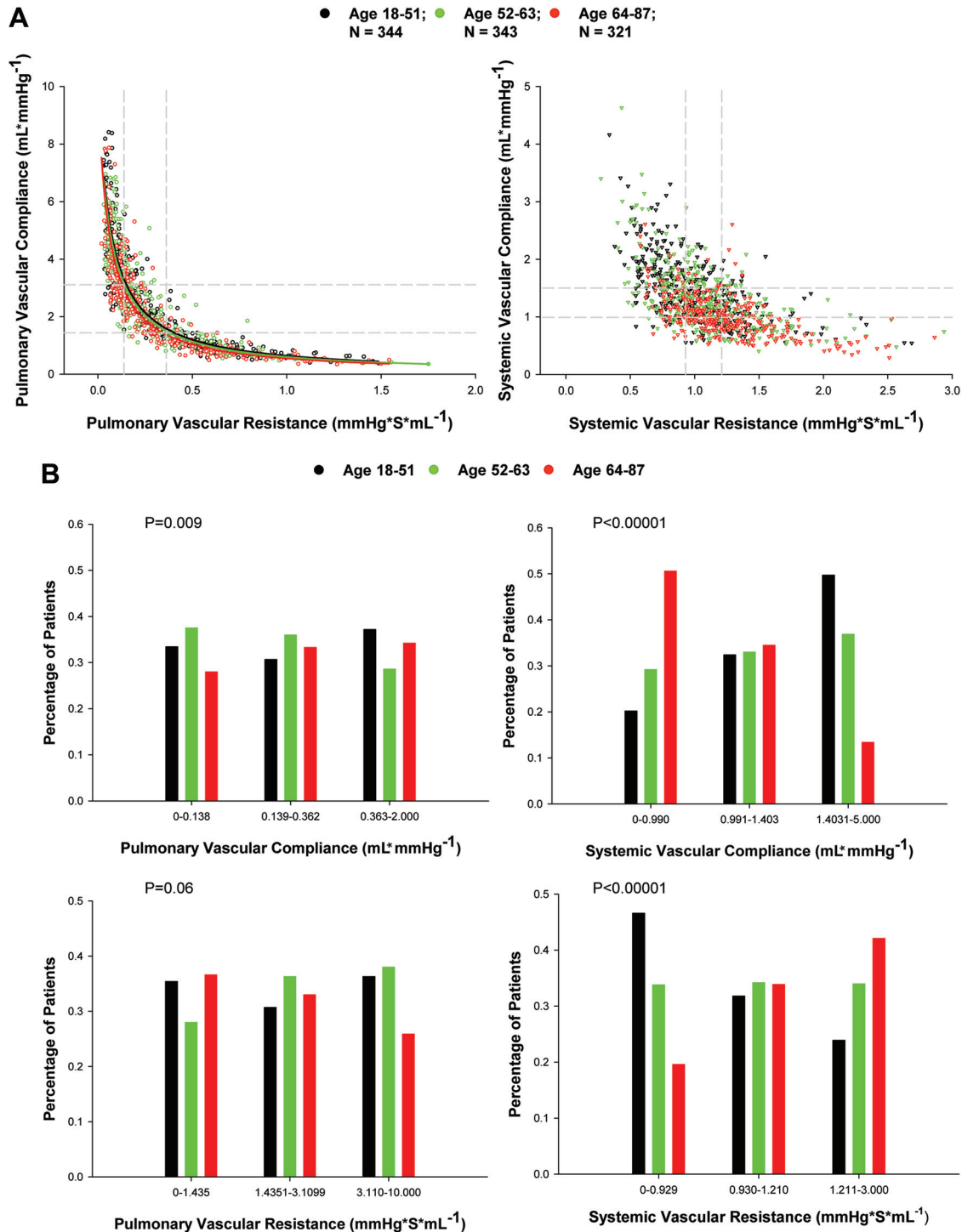


Figure 2. Age effect on pulmonary vascular resistance-compliance relationship ($R_{PA}-C_{PA}$). **A**, Left, $R_{PA}-C_{PA}$ relationship; right, systemic arterial resistance-systemic arterial compliance ($R_{SA}-C_{SA}$) relationship. Data are subgrouped (color coding) into 3 age tertiles. Dashed lines 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, χ^2 test. See text for details.

≥ 20 mm Hg. We also examined 24 patients (Cohort D) with early-stage heart failure with preserved ejection fraction, meaning a PCWP ≤ 15 mm Hg at rest, but in whom PCWP rose ≥ 25 mmHg during supine exercise. As shown in Figure 4A and 4B, 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 ± 0.15 to 0.28 ± 0.12 seconds and 0.43 ± 0.17 to 0.26 ± 0.10 seconds; both $P < 0.001$). The shift in both curves was statistically significant (Figure VA and VB in the online-only Data Supplement). Thus, unlike mechanisms involved with PH, both acute and chronic elevation of PCWP

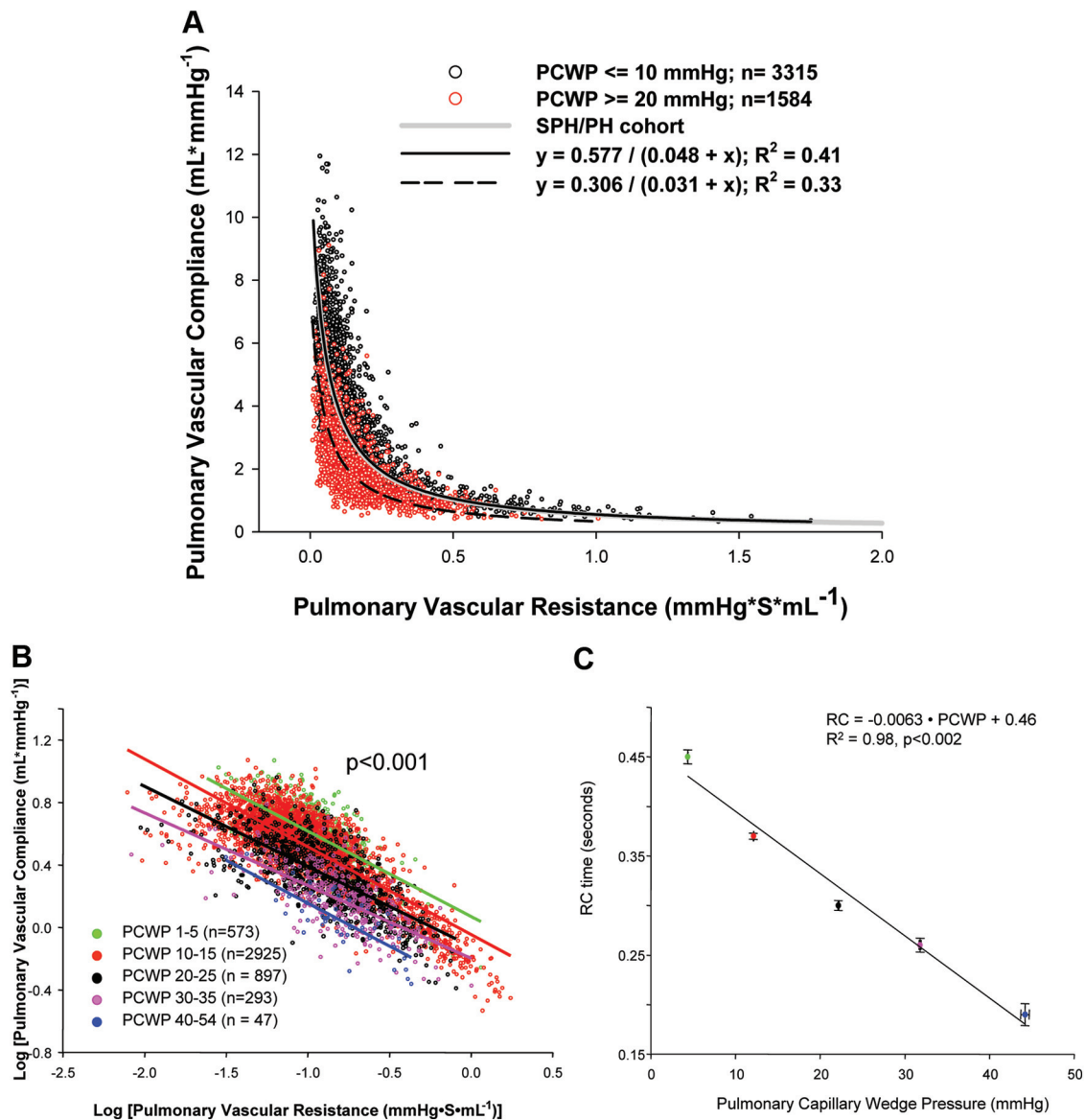


Figure 3. Effect of elevated pulmonary capillary wedge pressure (PCWP) on pulmonary vascular resistance-compliance relationship (R_{PA} - C_{PA}). **A**, R_{PA} - C_{PA} relationship from 2 subgroups of cohort C, those with normal-range or elevated PCWP. Gray line is the best-fit curve from Figure 1A (cohort A). **B**, Log(R_{PA})-log(C_{PA}) plot (n = 4735), color coded into 5 subgroups based on PCWP ($P < 0.001$). **C**, Mean resistance-compliance product (RC time) for each PCWP subgroup vs PCWP. SPH/PH indicates suspected/known pulmonary hypertension.

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 independently of one another. The pulmonary vasculature is very different, coupling resistance and compliance in a very constrained manner as long as pulmonary venous pressure is low. Increasing PCWP appears to alter this behavior to augment right heart pulsatile load. The present 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 because RV dysfunction is a major independent predictor of death resulting 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 overall predictability of the relationship 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. From 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 PA

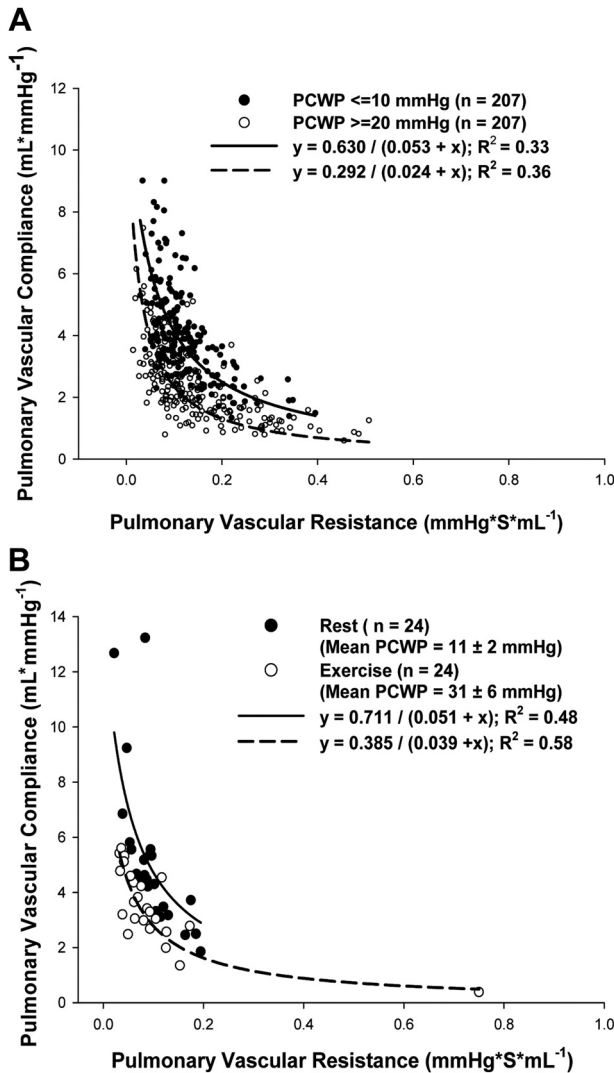


Figure 4. Effect of pulmonary vascular resistance-compliance relationship (R_{PA} - C_{PA}) relationship by change in pulmonary capillary wedge pressure (PCWP) within an individual patient. **A**, R_{PA} - C_{PA} for each patient is plotted at 2 different study times: at a low PCWP (PCWP ≤ 10 mm Hg) and at a high PCWP (PCWP ≥ 20 mm Hg). **B**, Effect of increasing PCWP during supine exercise on R_{PA} - C_{PA} in 24 patients with early heart failure with preserved ejection fraction.

adds relatively little to overall pulmonary vascular compliance because, if the PA stiffened independently of resistance with PH, the RC time would decline. This is further supported by work of Saouti et al,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_{PA} also support this notion and are consistent with little rise in pulse-wave velocity from the main PA to the peripheral lung with aging.¹⁴

Although some change in main PA distensibility can occur with disease or age, it 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_{PA} means that resistance must decline substantially to affect net RV loading meaning-

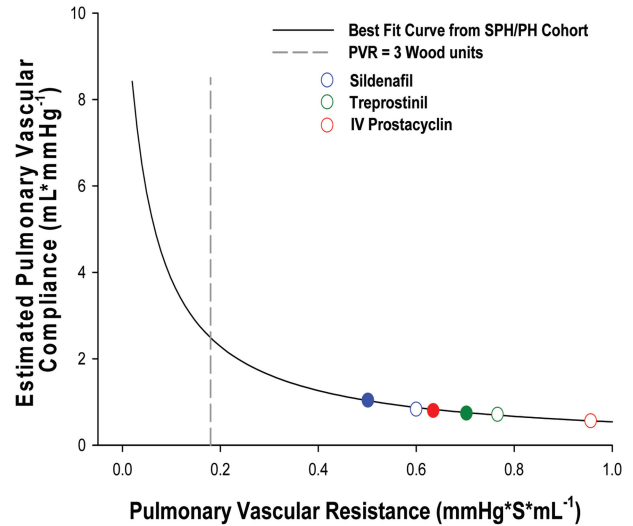


Figure 5. Effect of pulmonary hypertension (PH) treatment on pulmonary vascular resistance-compliance relationship (R_{PA} - C_{PA}) data. The curve fit from cohort A (known/suspected PPH [PH/SPH]) is shown, and superimposed on it are mean pretreatment and posttreatment R_{PA} derived from 3 PH therapeutic trials involving sildenafil, treprostinil, and prostacyclin, respectively.¹⁶⁻¹⁸ There were high resting R_{PA} and low C_{PA} and only a modest decline in R_{PA} with treatment; therefore, C_{PA} remained low and thus pulsatile load remained high after therapy.

fully because pulmonary compliance would still be quite low. This was first suggested by Lankhaar et al⁴ and may underscore why hemodynamic measurements, including R_{PA} , have been generally unreliable end points for clinical PH management.¹⁵ One can appreciate this problem by plotting the average pretreatment and posttreatment R_{PA} from 3 large therapeutic PH trials involving sildenafil, treprostinil, and prostacyclin, respectively (Figure 5).¹⁶⁻¹⁸ A high baseline R_{PA} (0.62, 0.77, and 0.96 $\text{mmHg} \cdot \text{s} \cdot \text{mL}^{-1}$, respectively) and modest decline with treatment (0.50, 0.71, and 0.63 $\text{mmHg} \cdot \text{s} \cdot \text{mL}^{-1}$, respectively) would mean little to no change in estimated compliance, thus maintaining a high RV pulsatile load. Although these therapies are used clinically, more effective treatment would need to reduce R_{PA} further or differentially enhance C_{PA} to also affect pulsatile load.

The sensitivity of R_{PA} - C_{PA} relation 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 affect parenchymal stiffness, with the lung acting more like a wet sponge than a 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 that 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 al¹⁹ recently

showed that symptoms and clinical outcomes of patients with left ventricular dysfunction correlate better with augmentation in PAP than the change in PCWP. At first glance, this may seem to be in contrast to the findings in this study. However, we would suggest that this observation could be explained by the effect of PCWP on the R_{PA} - C_{PA} relationship. Elevations in PCWP lower 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 with 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 left ventricular 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 SPH or known PH, and although 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 as 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 interobserver 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 compared favorably with such alternative approaches in smaller controlled studies.¹⁻⁴

Conclusions

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 affect pulmonary arterial and thus RV pulsatile loading offer new insight into the symptomatology of heart failure with preserved ejection fraction and other left heart failure disorders.

Sources of Funding

Funding was provided by National Institutes of Health—National Heart, Lung, and Blood Institute grants 5P50HL084946, K23 HL086714, T32-HL-07227, and KL2-RR024156; Fondation Leducq and Peter Belfer Laboratory; The Robert Wood Johnson Physician Faculty Scholars Program; and the Herbert and Florence Irving Scholar Award.

Disclosures

Dr Lederer is a consultant for Gilead and on the clinical trial steering committee for Intermune. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Right ventricular dysfunction is a major independent predictor of death in patients with elevated afterload from pulmonary hypertension. We analyzed data from >1000 right heart catheterizations to show that, unlike the systemic circulation, pulmonary vascular resistance (R_{PA}) and compliance (C_{PA}) display a highly predictable, inverse correlation and that this relationship is not significantly altered by pulmonary hypertension or severe pulmonary fibrosis and is altered only minimally by aging. This means that, unlike the proximal aorta in the systemic circulation, the main pulmonary artery contributes relatively little to overall C_{PA} and is little affected by age. The consistent R_{PA} - C_{PA} relation allows the prediction of R_{PA} decline required by a given treatment to adequately lower C_{PA} and thus reduce pulsatile and net right ventricular afterload. Current monotherapies for pulmonary hypertension are not reducing pulsatile afterload in most patients, identifying an area of clinical need. We also found that the R_{PA} - C_{PA} relationship is sensitive to changes in pulmonary venous pressure (mean pulmonary capillary wedge pressure) because elevation of this pressure lowers C_{PA} for any given R_{PA} , augmenting right ventricular pulsatile afterload. In patients with exertional dyspnea and a preserved ejection fraction who exhibit a marked rise in pulmonary capillary wedge pressure during exercise, we found a disproportionate decline in C_{PA} and thus increased pulsatile load. This identifies a novel mechanism whereby left-side diastolic dysfunction contributes to right ventricular load.

Pulmonary Capillary Wedge Pressure Augments Right Ventricular Pulsatile Loading
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Circulation. 2012;125:289-297; originally published online November 30, 2011;
doi: 10.1161/CIRCULATIONAHA.111.051540

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
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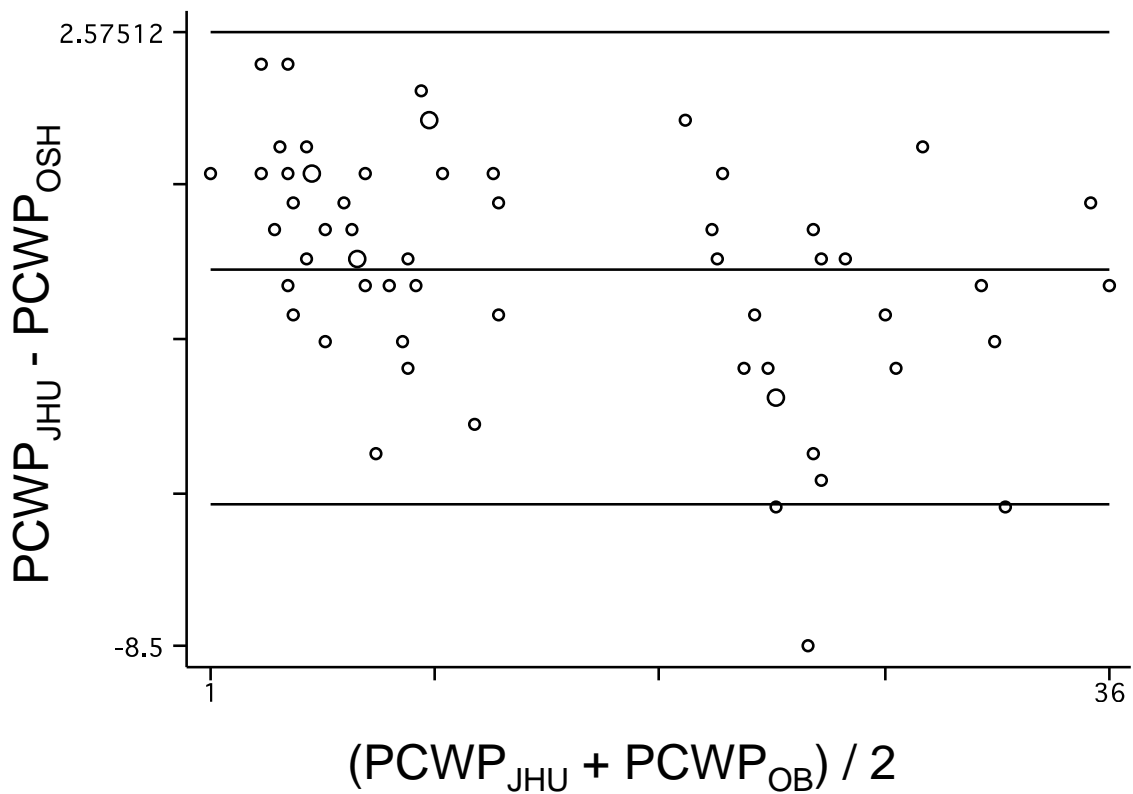
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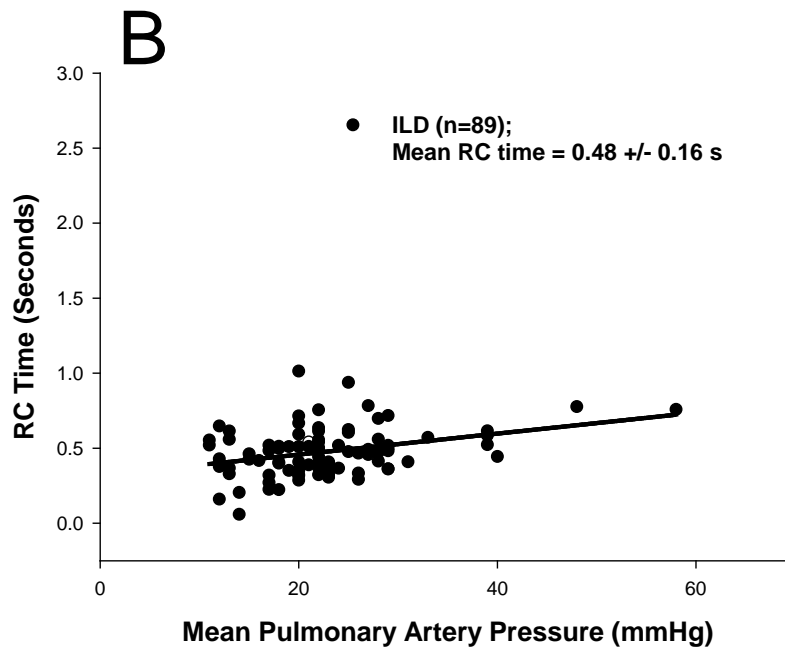
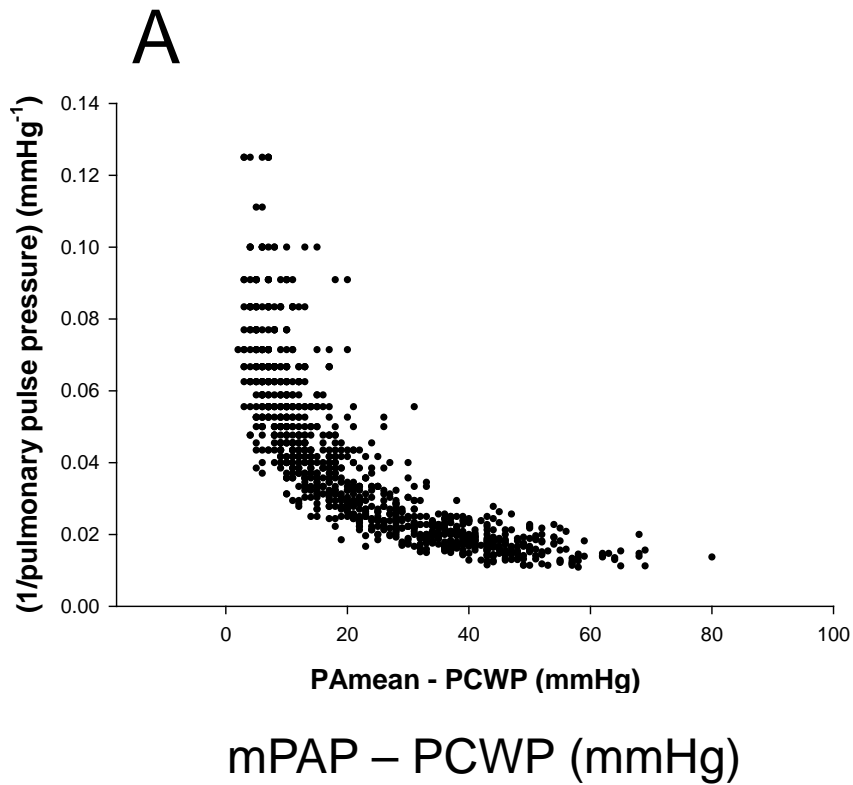
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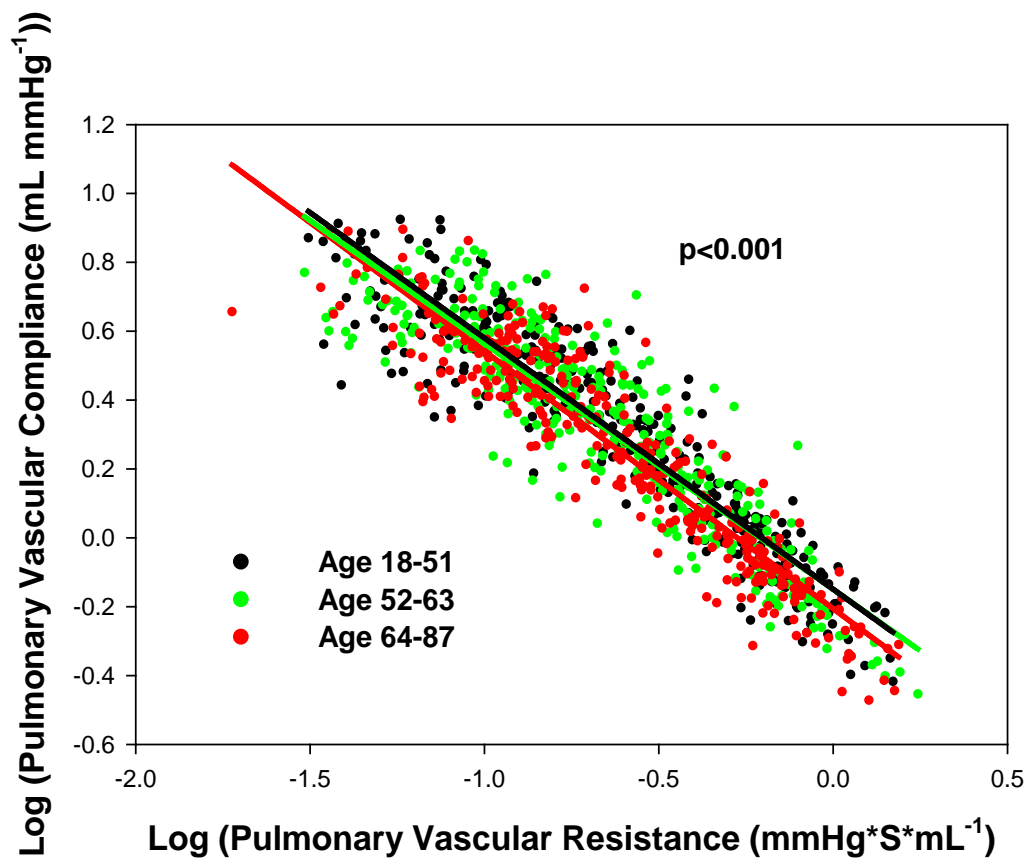
Bland-Altman Comparison of PCWP from
JHU clinical data base versus mean of two
expert independent observers (OB)



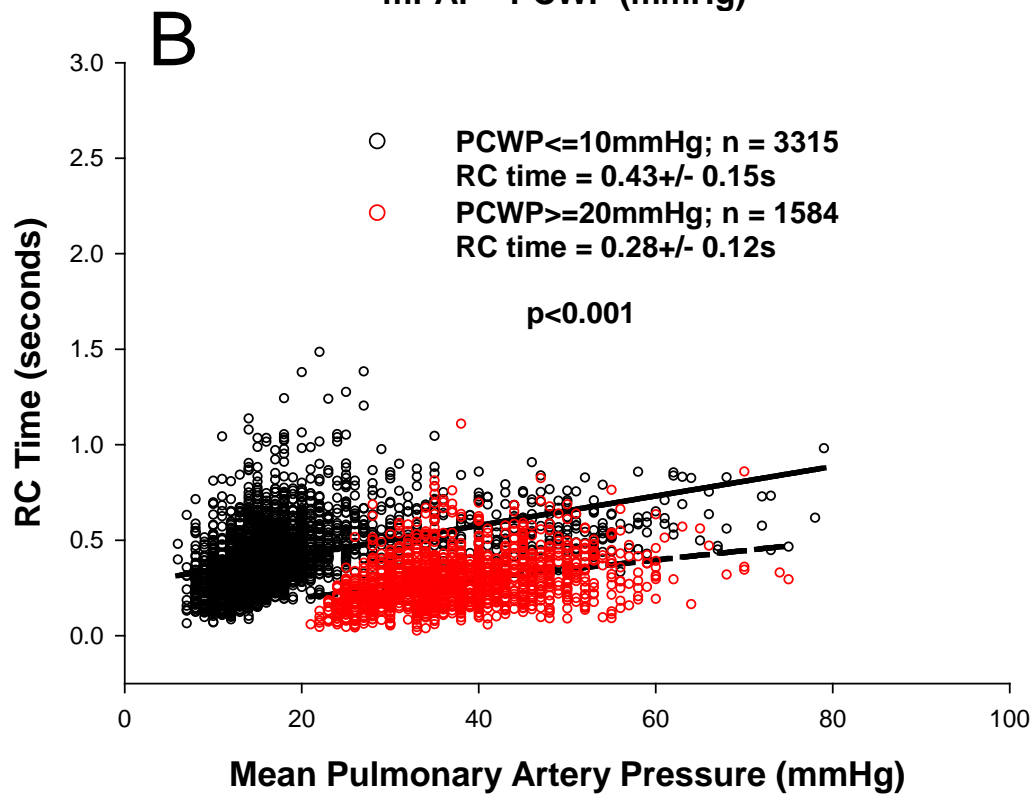
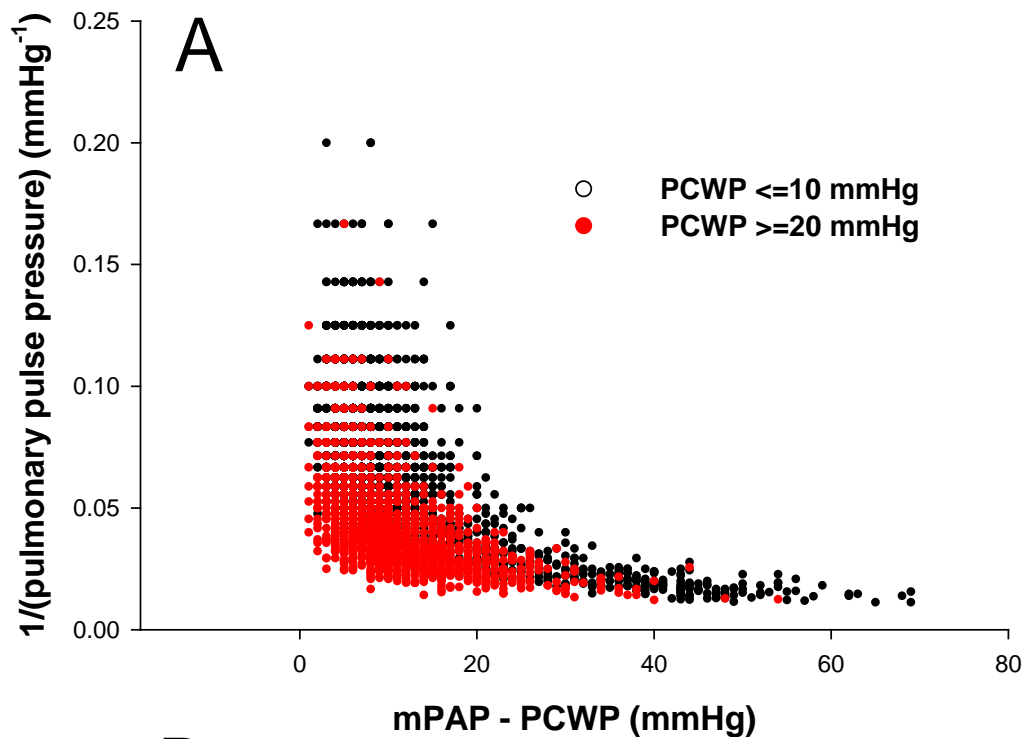
Limits of agreement: - 5.9 to 2.58 mmHg



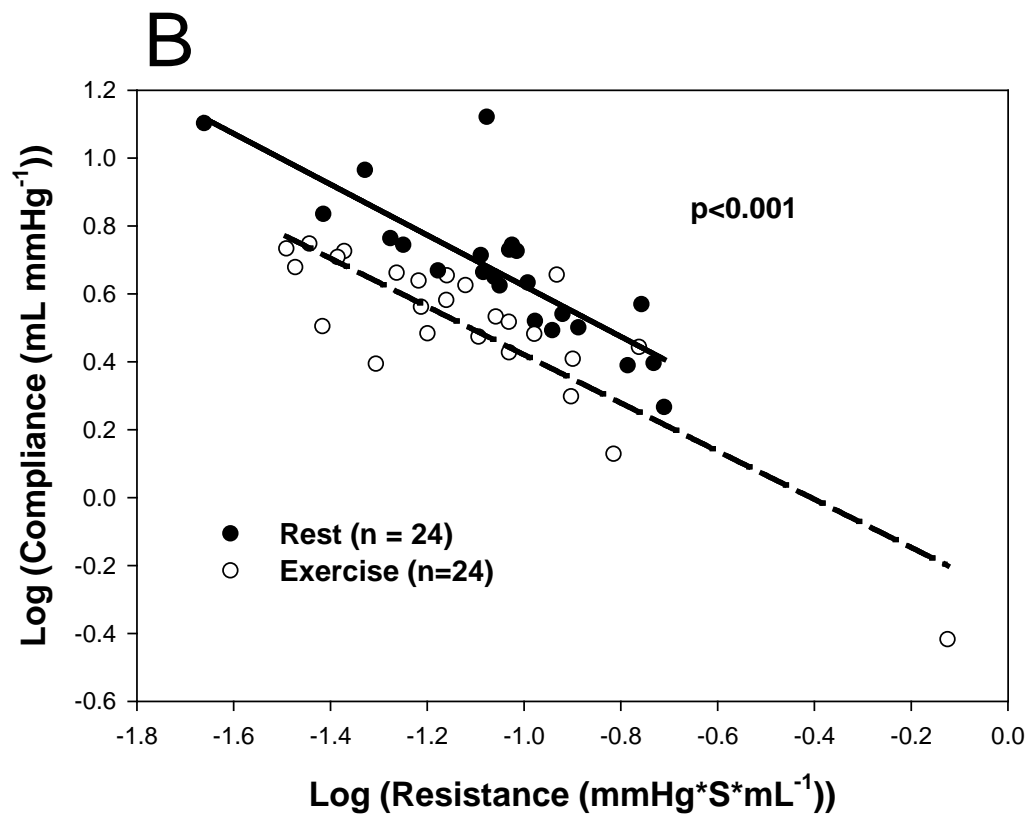
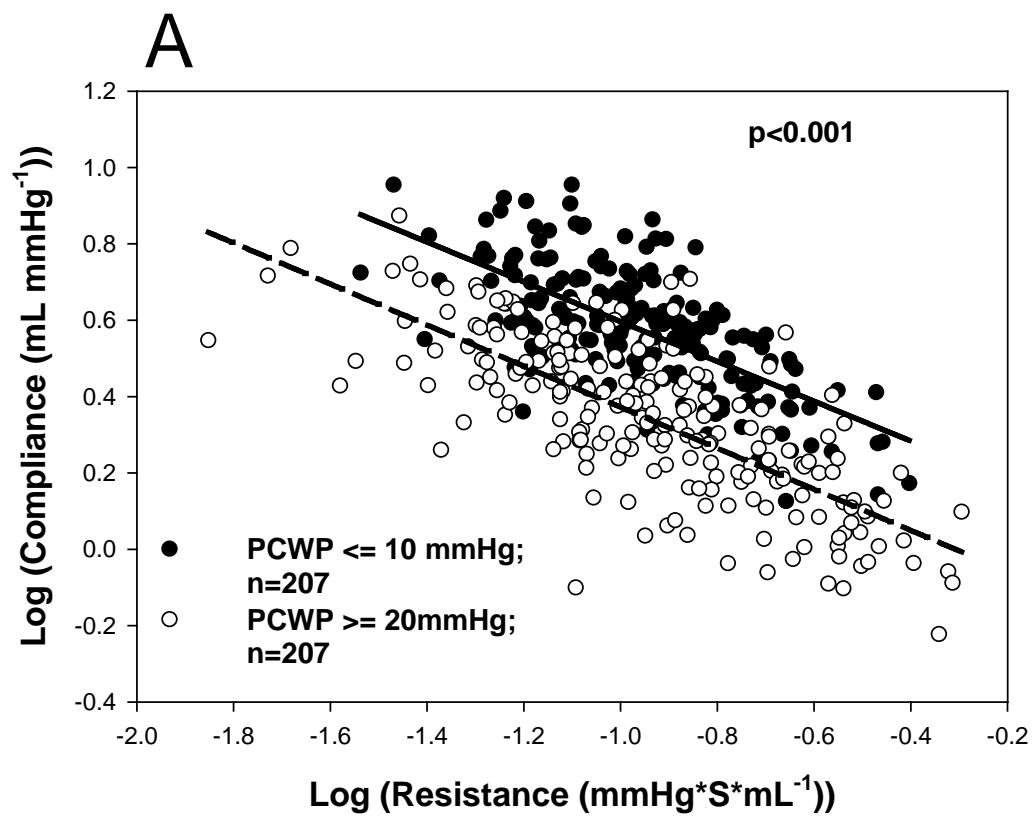
Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5

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 $1/\text{pulmonary pulse pressure}$ for the data in Cohort A. meanPA-PCWP is equal to R_{PA} multiplied by cardiac output, while $1/PP$ is equal to C_{PA} divided by SV. The inverse dependence was evident and similar to that in the plots of R_{PA} versus C_{PA} (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 $\text{Log}(R_{PA})$ versus $\text{Log}(C_{PA})$ 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 patient 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)** $\text{Log } R_{PA}$ versus $\text{log } C_{PA}$ 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).