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RV Dysfunction In Pulmonary Hypertension Is Independently Related To Pulmonary Artery Stiffness

Gerin R. Stevens, MD, PHD,* Ana Garcia-Alvarez, MD, MSC,‡§‖ Sheila Sahni, MD,† Mario J. Garcia, MD,* Valentin Fuster, MD, PHD,‡§ Javier Sanz, MD‡

New York, New York; and Madrid and Barcelona, Spain

OBJECTIVES This study investigated whether right ventricular (RV) adaptation to chronic pressure overload is associated with pulmonary artery (PA) stiffness beyond the degree of severity of pulmonary hypertension (PH).

BACKGROUND Increased PA stiffness has been associated with reduced survival in PH. The mechanisms for this association remain unclear.

METHODS Right heart catheterization and cardiac magnetic resonance were performed within 1 week in 124 patients with known or suspected chronic PH. Pulmonary vascular resistance index (PVRI) and PA pressures were quantified from right heart catheterization. Cardiac magnetic resonance included standard biventricular cine sequences and main PA flow quantification with phase-contrast imaging. Indexes of PA stiffness (elasticity, distensibility, capacitance, stiffness index beta, and pulse pressure) were quantified combining right heart catheterization and cardiac magnetic resonance data. RV performance and adaptation were measured by RV ejection fraction, right ventricular mass index (RVMI), RV end-systolic volume index, and right ventricular stroke work index (RVSWI).

RESULTS All indexes of PA stiffness were significantly correlated with measures of RV performance (Spearman rho coefficients ranging from -0.20 to 0.61, $p < 0.05$). Using multivariate regression analysis, PA elasticity, distensibility, and index beta were independently associated with all measures of RV performance after adjusting PVRI ($p \leq 0.024$). PA capacitance was independently associated with RV ejection fraction, RVMI, and RVSWI ($p < 0.05$), whereas PA pulse pressure was associated with RVMI and RVSWI ($p \leq 0.027$). Compared with PVRI, PA elasticity, distensibility, capacitance, and index beta explained 15% to 68% of the variability in RV ejection fraction, RVMI, and RV end-systolic volume index. Relative contributions of PA stiffness for RVSWI were 1.2× to 18.0× higher than those of PVRI.

CONCLUSIONS PA stiffness is independently associated with the degree of RV dysfunction, dilation, and hypertrophy in PH. RV adaptation to chronic pressure overload is related not only to the levels of vascular resistance (steady afterload), but also to PA stiffness (pulsatile load). (J Am Coll Cardiol Img 2012;5:378–87) © 2012 by the American College of Cardiology Foundation

From the *Montefiore-Einstein Center for Heart and Vascular Care, Albert Einstein College of Medicine, Bronx, New York, New York; †Department of Medicine, Mount Sinai School of Medicine, New York, New York; ‡The Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York; §Centro Nacional de Investigación Cardiovascular, Madrid, Spain; and the ‖Thorax Institute, Department of Cardiology, Hospital Clinic, Barcelona, Spain. All authors have reported that they have no relationships relevant to the contents of this paper to disclose. Jeroen J. Bax, MD, PhD, served as Guest Editor for this paper.

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The importance of increased arterial stiffness and pulsatile load in the systemic circulation has been demonstrated not only for cardiovascular events (1), but also for left ventricular hypertrophy (2), dilation (3), and systolic dysfunction (4). Similarly, abnormal pulmonary artery (PA) stiffness has been documented in pulmonary hypertension (PH) (5,6). Theoretical and experimental models predict a deleterious influence of increased PA stiffness on right ventricular (RV) performance (7–10); however, its real impact on RV adaptation to pressure overload in the clinical setting remains largely unknown. Understanding the mechanisms leading to RV failure is important because this is the main cause of mortality in PH (11).

Increased PA stiffness has been associated with reduced survival in PA hypertension (12–14). We hypothesized that increased PA stiffness would be independently associated with adverse RV remodeling and performance beyond the degree of PH as determined by the levels of pulmonary vascular resistance index (PVRI), providing a potential mechanistic link between PA stiffness and clinical outcome. Stiffness can be determined from hemodynamic information derived invasively from right heart catheterization (RHC) combined with noninvasive measurements of PA dimensions and flow from cardiac magnetic resonance (CMR). RV mass and systolic function indexes can be quantified with CMR, as this is considered the noninvasive gold standard for this purpose (15).

METHODS

Population. We retrospectively studied 124 patients referred to a single center for CMR evaluation and a RHC within 7 days. Seventy-one patients (57%) had same-day studies, 24 (19%) were performed within 1 day, and the remainder were done within 2 to 7 days (24%). Hemodynamic conditions at the time of RHC and CMR were similar as demonstrated by the strong correlations between inter-test heart rates and cardiac indexes, respectively ($r = 0.735$ and $r = 0.701$; $p < 0.001$). Patient characteristics are presented in Table 1. Most patients were women (69.4%) and Caucasian (38.7%) with a median age of 52.0 years. The majority of patients were confirmed by RHC to have PH (n = 102), defined as resting mean PA pressure >25 mm Hg (11). Seven patients with normal resting mean PA pressures, but >30 mm Hg with exercise, were considered as non-PH patients according to the latest consensus recommendations (11). Estimated glomerular filtration rate was calculated using the National Kidney Foundation calculator (16) and standardized to isotope dilution mass spectrometry (n = 108). Patients with documented PH were further classified according to the recently updated World Health Organization (WHO) Dana Point criteria (17) 1) PA hypertension (n = 55); 2) left heart disease (n = 16); 3) lung disease (n = 10); 4) chronic thromboembolic disease (n = 3); and 5) miscellaneous/sarcoidosis (n = 18). The Institutional Review Board approved this study with a waiver of informed consent.

Data acquisition and analysis. RHC was performed using standard methodology by experienced personnel (18). Heart rate and systemic blood pressure measured by sphygmomanometer were monitored during the procedure. Invasive data included measurements of right-sided pressures, pulmonary capillary wedge pressure, cardiac index (cardiac output by thermodilution/body surface area), PVRI (mean PA pressure − pulmonary capillary wedge pressure / cardiac index), and PA oxygen saturation. Transpulmonic gradient was quantified as mean PA pressure minus pulmonary capillary wedge pressure, and the PA pulse pressure as systolic minus diastolic PA pressure. Right ventricular stroke work index (RVSWI) was calculated as: $0.0136 \times$ (mean PA pressure − right atrial pressure) $\times$ cardiac index / heart rate (19,20).

CMR was performed using a 1.5-T magnet (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany) and a dedicated surface coil with retrospective electrocardiographic gating, as previously described (21,22). Contiguous cine short-axis views were acquired using steady-state free precession imaging at end-expiratory breath-holds. Biventricular end-diastolic and end-systolic volumes, ejection fractions, and masses were obtained according to Simpson method using specialized software (Argus, Siemens Medical Solutions) and indexed to body surface area (23). RV trabeculations were excluded from RV mass tracings. Phase-contrast imaging was performed in a plane perpendicular to the PA trunk for measuring cross-sectional areas and average blood flow velocity. The RV stroke volume was calculated from the integration of PA flow velocity and area. PA elasticity was defined as the relative change in luminal area during the cardiac cycle (maximal area − minimal area /

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CMR = cardiac magnetic resonance
PA = pulmonary artery
PH = pulmonary hypertension
PVRI = pulmonary vascular resistance index
RHC = right heart catheterization
RV = right ventricle
RVEF = right ventricular ejection fraction
RVESVI = right ventricular end-systolic volume index
RVMI = right ventricular mass index
RVSWI = right ventricular stroke work index
WHO = World Health Organization

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Table 1. Patient Characteristics

Age, yrs (range)	52.0 (16.0–88.0)
Women	86 (69.4)
Body mass index, kg/m^2	26.6 (22.5–30.9)
PH	102 (82)
Serum creatinine, mg/dl*	0.9 (0.7–1.1)
Estimated glomerular filtration rate, ml/min/1.73 m^2*	81 (61–97.8)
Race	
Caucasian	48 (38.7)
African American	40 (32.3)
Hispanic	22 (17.7)
Asian	4 (3.2)
Other/Unknown	10 (8.1)
Indication for testing	
Left heart disease	25 (20.2)
Connective tissue disease	18 (14.5)
Rheumatoid arthritis	1 (0.8)
Scleroderma	12 (9.6)
Systemic lupus erythematosus	5 (4)
Sarcoidosis	18 (14.5)
Lung disease	14 (11.3)
Idiopathic PAH	14 (11.3)
Human immunodeficiency virus	13 (10.5)
Liver disease	8 (6.5)
Thromboembolic disease	5 (4.0)
Congenital heart disease	4 (3.2)
Shortness of breath	3 (2.4)
Sickle cell disease	2 (1.6)

Values are median (interquartile range) or n (%). *n = 108.
PAH = pulmonary artery hypertension; PH = pulmonary hypertension.

minimal area) and expressed as a percentage. Images were interpreted by 2 experienced readers blinded to the results of the RHC testing.

RV performance and adaptation were measured by right ventricular ejection fraction (RVEF), right ventricular mass index (RVMI), right ventricular end-systolic volume index (RVESVI), and RVSWI. PA distensibility was defined as the relative change in luminal area during the cardiac cycle for a given change in PA pressure (PA elasticity / PA pulse pressure) obtained by RHC and expressed as a percentage per mm Hg. PA capacitance was defined as the change in volume, as quantified with phase-contrast imaging, for a given change in PA pressure (RV stroke volume / PA pulse pressure) expressed as mm^3 per mm Hg. Finally, stiffness index beta was quantified as the natural logarithm of the ratio of PA systolic to PA diastolic pressures divided by PA elasticity (14,24).

Statistical analysis. Continuous variables are expressed as median (25th to 75th percentiles). The correlations between RHC and CMR data were assessed using Spearman rho (r) coefficient. Univariate associations were explored with scatterplots to identify the type of relationship (e.g., linear, exponential). Natural logarithmic transformation was applied in the independent and/or dependent variable to linearize the association and fulfill log-linear criteria for multiple regression analysis. As PA stiffness variables were highly correlated, a different model was built for each variable and outcome. Initially, the associations between PA stiffness variables and RV performance measures were adjusted for age, sex, and ethnicity. Subsequently, PVRI or mean PA pressure was added to the models. Our final multivariate models satisfied all necessary criteria of linear regression analysis: 1) normality of the residuals tested by the Shapiro-Wilk and/or Kolmogorov-Smirnov tests; 2) linearity and homoscedasticity by inspection of residual plots; 3) independence of observations using the Durbin-Watson coefficient; 4) absence of multicollinearity by calculating the variance inflation factor; and 5) lack of serious outlier influence by assessment of DFBETA and DFFITS statistics. Interpretation of regression coefficients was performed as recommended (25). Consequently, when the independent variable was log-transformed, the regression coefficient multiplied by ln(1.01) was interpreted as the change in the outcome variable for every 1% increase in the predictor. Similarly, if both predictor and outcome were log-transformed, then 100 ($e^{\beta \ln(1.01)-1}$) was interpreted as the change in the outcome variable for every 1% increase in the predictor. Standardized regression coefficients using ordinary SDs were used to illustrate the relative contributions of PA stiffness and PVRI to the variance of each RV variable and were represented graphically as bar diagrams. Statistical analyses were performed with SPSS version 15 (SPSS Inc., Chicago, Illinois).

RESULTS

Hemodynamic and CMR characteristics. Hemodynamic characteristics of the subjects are displayed in Table 2. Right-sided pressures were elevated with high transpulmonic gradients and PVRI. Both cardiac index and PA oxygen saturation were preserved with an increased RVSWI. Table 3 shows CMR cine and phase-contrast data. Right-sided volume indexes and RVMI were elevated with reduced RVEF. Left-sided parameters were within normal limits (26). PA elasticity, distensibility, and capacitance were reduced compared with previously published normal values, whereas pulse pressure and

Table 2. Patient Hemodynamic Characteristics

Right atrial pressure, mm Hg	6.0 (3.0–12.0)
Systolic PA pressure, mm Hg	64.5 (45.5–80.0)
Mean PA pressure, mm Hg	40.0 (29.3–50.0)
PA pulse pressure, mm Hg	39.0 (26.0–50.0)
Pulmonary capillary wedge pressure, mm Hg	10.0 (7.0–13.0)
Transpulmonic gradient, mm Hg	27.0 (17.3–40.0)
PVRI, Wood units·m^2	8.7 (5.0–14.2)
Cardiac index, l/min·m^2	3.4 (2.5–3.8)
RVSWI, g·m/m^2/beat	16.7 (10.5–22.8)
PA oxygen saturation, %	66.0 (57.0–71.0)
Heart rate, beats/min	79.0 (70.0-91.0)
Mean systemic arterial pressure, mm Hg	88.0 (80.0-99.8)

Values are median (interquartile range).
PA = pulmonary artery; PVRI = pulmonary vascular resistance index; RVSWI = right ventricular stroke work index.

index beta were increased and similar to those found in other studies of PH patients (13,14,24,27,28). There were no statistically significant differences in PA stiffness or RV performance in patients with PAH (WHO Group 1) versus other etiologies of PH (WHO Groups 2 to 5) after adjusting for mean PA pressure, except for RVSWI, which was higher in WHO Group 1 (20.9 [95% confidence (CI): 18.8 to 23.0] vs. 17.2 [95% CI: 14.7 to 19.7], $p = 0.028$).

The scatterplots in Figure 1 show the curvilinear relationships between PA elasticity, distensibility, and capacitance with, respectively, RVEF (Spearman $r = 0.56, 0.61, 0.56$; $p < 0.001$), RVMI (Spearman $r = -0.39, -0.51, -0.47$; $p < 0.001$), RVESVI (Spearman $r = -0.40, -0.49, -0.40$; $p < 0.001$), and RVSWI (Spearman $r = -0.20$, $p = 0.035$; -0.42, $p < 0.001$; -0.29, $p = 0.002$). The PA pulse pressure and index beta, though, demonstrated linear correlations, respectively, with RVEF (Spearman $r = 0.49, 0.40$; $p < 0.001$), RVMI (Spearman $r = 0.48$, $p < 0.001$; 0.28, $p = 0.002$), RVESVI (Spearman $r = 0.43$, $p < 0.001$; 0.27, $p = 0.002$), and RVSWI (Spearman $r = 0.59$, $p < 0.001$; 0.23, $p = 0.012$) (Fig. 2). Distensibility showed the strongest associations with RVEF, RVMI, and RVESVI, whereas PA pulse pressure correlated best with RVSWI.

Regression analysis. Table 4 shows the results of the regression analysis. In the initial model, PA elasticity, distensibility, capacitance, pulse pressure, and index beta remained strongly associated with all 4 outcome variables despite adjustment for age, sex, and ethnicity. There was no effect modification by sex in the associations between PA stiffness and RV performance with the exception of distensibility and RVESVI (B coefficient for the interaction, selecting men as the reference category: −0.223 [95% CI: −0.440 to −0.006]). However, PA distensibility remained significantly associated with RVESVI after including the interaction term (B = −0.180; 95% CI: −0.360 to −0.001). The majority of the associations remained significant after adjusting for PVRI in the second analysis; however, PA capacitance was no longer associated with RVESVI. In addition, associations between PA pulse pressure and RVEF or RVESVI lost significance. Conversely, most, but not all, of the associations between measures of PA stiffness and RV performance indexes failed to reach statistical significance when adjusting for mean PA pressure in the third analysis (Table 4). None of the associations remained significant for RVMI and only the PA elasticity reached significance for RVESVI. PA distensibility and pulse pressure remained significantly associated with RVSWI when accounting for mean PA pressure. Finally, except for pulse pressure, all stiffness indexes remained associated with RVEF. Addition of the PA stroke volume index or the heart rate to the multivariate analysis did not significantly modify the associations between PA stiffness and RV performance when adjusting for either PVRI or mean PA pressure (data not shown). Regression coefficients adjusted by age, sex, and ethnicity can be interpreted as follows: for each 1% increase in elasticity, average RVEF increases 0.15%; RVSWI decreases 0.04 g·m/m^2/beat; average RVMI decreases 0.33 g; and RVESVI decreases 0.46 ml. All other coefficients can be similarly interpreted. The relative strengths (as determined by standardized beta coefficients) of the associations

Table 3. Patient CMR Characteristics

Cine	
RV end-diastolic volume index, ml/m^2	101.3 (79.3–142.6)
RV end-systolic volume index, ml/m^2	56.1 (38.8–86.5)
RV ejection fraction, %	42.0 (30.6–53.0)
RV mass index, g/m^2	26.0 (17.3–31.6)
LV end-diastolic volume index, ml/m^2	66.7 (53.2–78.3)
LV end-systolic volume index, ml/m^2	26.0 (17.3–31.6)
LV ejection fraction, %	61.2 (52.9–68.6)
LV mass index, g/m^2	51.2 (44.4–61.6)
Phase-contrast	
PA elasticity, %	20.3 (16.1–30.7)
PA distensibility, %/mm Hg	0.49 (0.36–1.07)
PA capacitance, mm^3/mm Hg	1.83 (1.28–3.01)
PA stiffness index beta, a/u	4.49 (2.96–6.35)

Values are median (interquartile range).
a/u = arbitrary units; CMR = cardiac magnetic resonance; LV = left ventricular; PA = pulmonary artery; RV = right ventricular.

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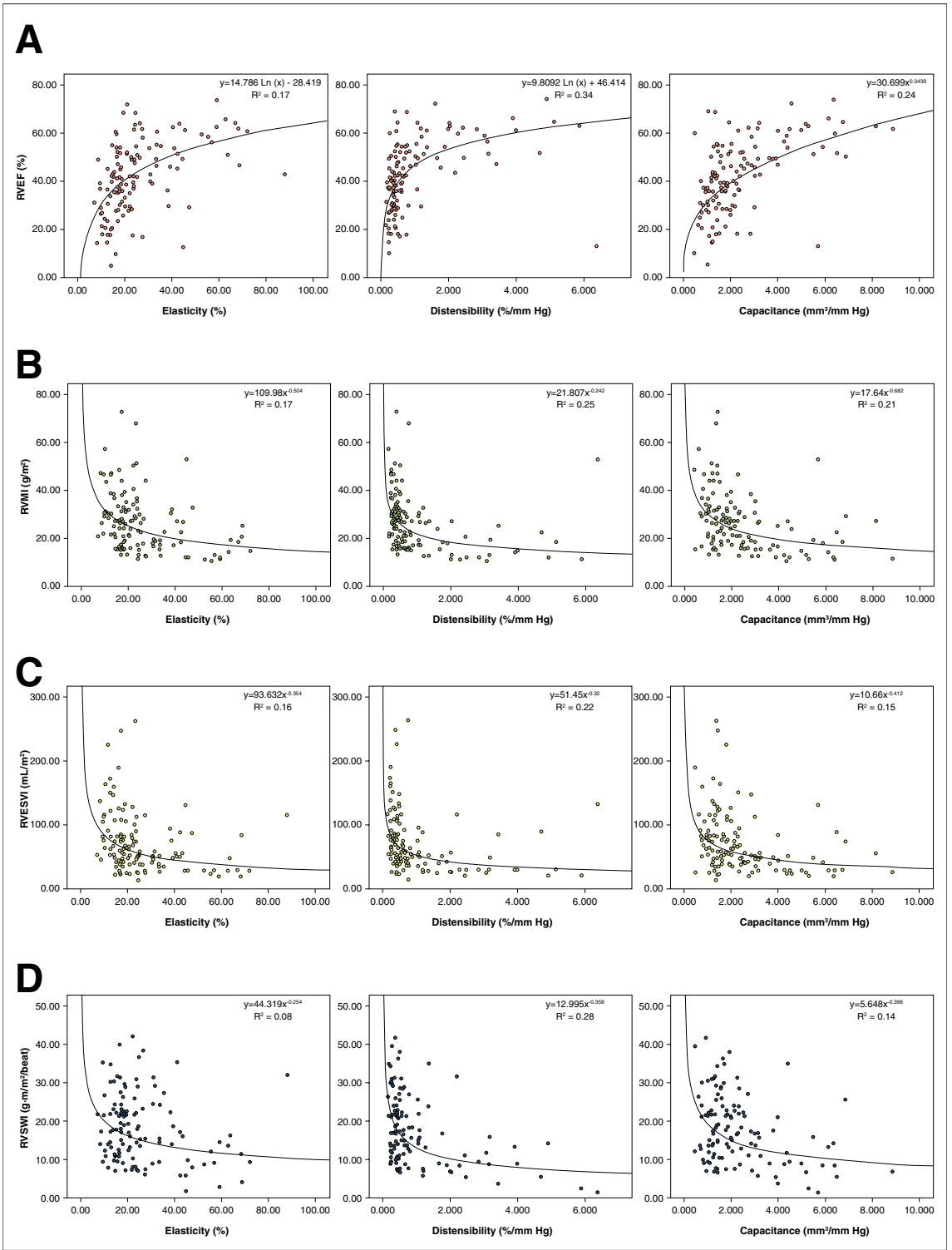

Figure 1. Regression Analyses Demonstrating Associations Between PA Stiffness Indexes and RV Performance Measures

Relationships are curvilinear between pulmonary artery (PA) elasticity, PA distensibility, and PA capacitance with right ventricular ejection fraction (RVEF), right ventricular mass index (RVMI), right ventricular end-systolic volume index (RVESVI), and right ventricular stroke work index (RVSWI). RV = right ventricle.

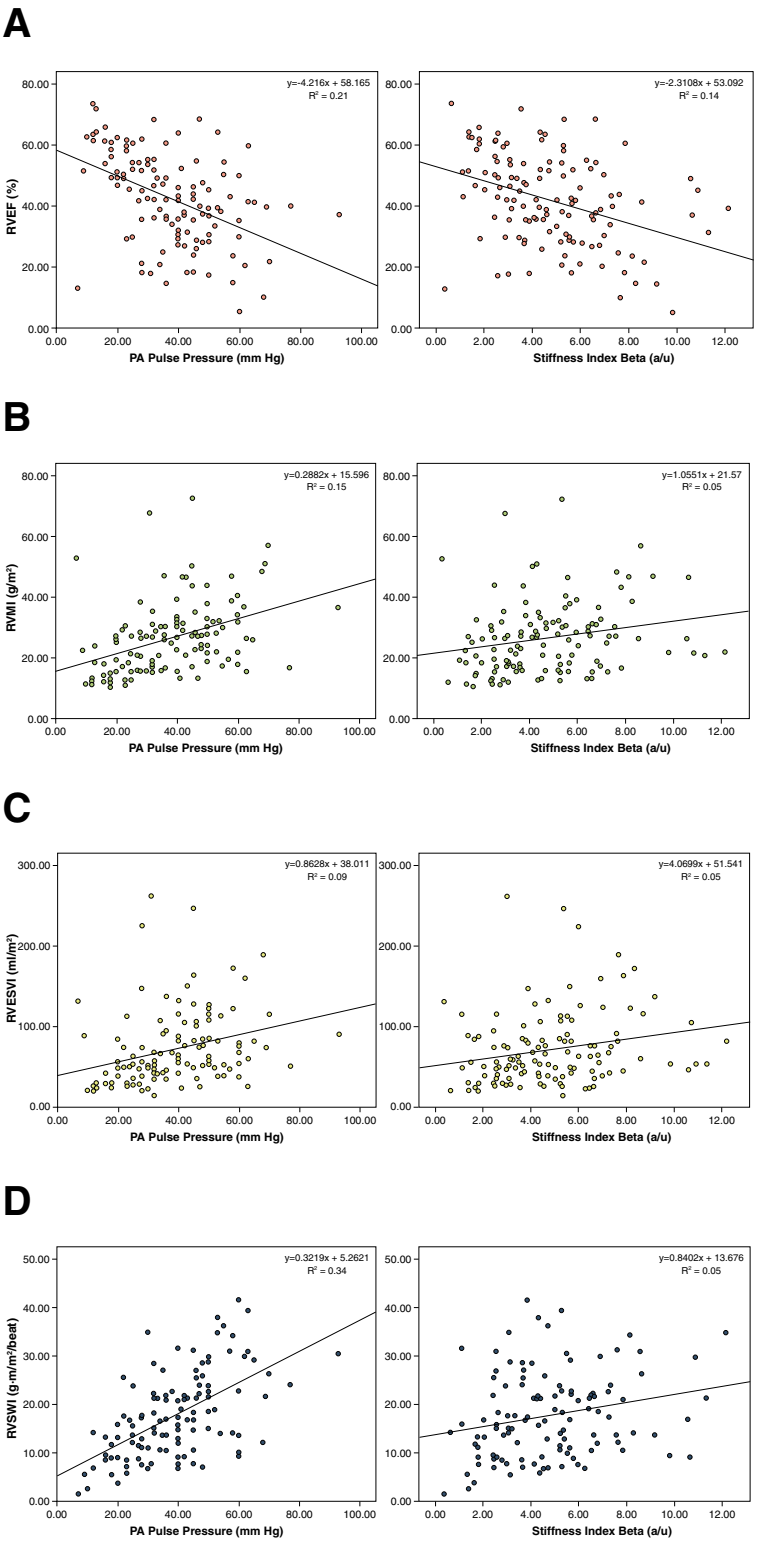

Figure 2. Scatterplots Demonstrating Linear Relationships Between PA Pulse Pressure and Stiffness Index Beta With RVEF, RVMI, RVESVI, and RVSWI

Abbreviations as in Figure 1.

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Table 4. Regression Analysis

	Age, Sex, Ethnicity Adjusted		Age, Sex, Ethnicity, PVRI Adjusted		Age, Sex, Ethnicity, mPAP Adjusted	
	Beta (95% CI)	p Value	Beta (95% CI)	p Value	Beta (95% CI)	p Value
RVEF						
PA elasticity	14.661 (10.453–18.869)	<0.001	8.711 (4.931–12.492)	<0.001	7.868 (3.602–12.134)	<0.001
PA distensibility	9.956 (7.564–12.349)	<0.001	5.042 (2.384–7.700)	<0.001	4.848 (1.433–8.263)	0.006
PA capacitance	13.943 (10.596-17.291)	<0.001	5.682 (1.377–9.987)	0.010	6.713 (1.849–11.577)	0.007
PA stiffness index beta	−2.423 (−3.423 to −1.423)	<0.001	−1.565 (−2.352 to −0.778)	<0.001	−1.322 (−2.188 to −0.456)	0.003
PA pulse pressure	−0.441 (−0.584 to −0.299)	<0.001	−0.078 (−0.237–0.082)	0.337	0.058 (−0.158–0.275)	0.594
RVMI*						
PA elasticity*	−0.334 (−0.467 to −0.202)	<0.001	−0.174 (−0.302 to −0.046)	0.008	−0.118 (−0.254–0.017)	0.087
PA distensibility*	−0.248 (−0.320 to −0.175)	<0.001	−0.138 (−0.221 to −0.054)	0.002	−0.086 (−0.189–0.018)	0.103
PA capacitance*	−0.337 (−0.439 to −0.235)	<0.001	−0.138 (−0.276 to −0.001)	0.048	−0.091 (−0.240–0.057)	0.227
PA stiffness index beta	0.048 (0.019–0.078)	0.002	0.029 (0.004–0.055)	0.024	0.017 (−0.009–0.043)	0.204
PA pulse pressure	0.013 (0.009–0.017)	<0.001	0.005 (0.001–0.010)	0.027	0.001 (−0.006–0.007)	0.829
RVESVI*						
PA elasticity*	−0.457 (−0.637 to −0.277)	<0.001	−0.251 (−0.429 to −0.074)	0.006	−0.204 (−0.393 to −0.015)	0.035
PA distensibility*	−0.331 (−0.434 to −0.228)	<0.001	−0.169 (−0.291 to −0.047)	0.007	−0.135 (−0.284–0.014)	0.075
PA capacitance*	−0.403 (−0.553 to −0.254)	<0.001	−0.070 (−0.268–0.127)	0.482	−0.044 (−0.259–0.170)	0.682
PA stiffness index beta	0.071 (0.029–0.112)	0.001	0.042 (0.006–0.079)	0.024	0.031 (−0.007–0.069)	0.109
PA pulse pressure	0.904 (0.420–1.387)	<0.001	0.014 (−0.576–0.604)	0.963	−0.242 (−1.026–0.542)	0.543
RVSWI						
PA elasticity*	−4.111 (−7.030 to −1.192)	0.006	−4.200 (−7.379 to −1.020)	0.010	−0.110 (−3.113–2.894)	0.947
PA distensibility*	−4.861 (−6.445 to −3.276)	<0.001	−6.513 (−8.377 to −4.650)	<0.001	−2.664 (−4.962 to −0.366)	0.024
PA capacitance*	−4.782 (−7.193 to −2.371)	<0.001	−7.521 (−10.772 to −4.271)	<0.001	1.242 (−2.194–4.678)	0.475
PA stiffness index beta	1.039 (0.412–1.666)	0.001	1.017 (0.378–1.657)	0.002	0.552 (−0.035–1.138)	0.065
PA pulse pressure	0.321 (0.242–0.401)	<0.001	0.478 (0.388–0.567)	<0.001	0.303 (0.167–0.439)	<0.001

*Variables that were natural log-transformed. Beta coefficients expressed as calculated value (95% CI).
mPAP = mean pulmonary artery pressure; RVEF = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index; RVMI = right ventricular mass index; other abbreviations as in Table 2.

of PA stiffness variables and PVRI with RV performance measures are represented in Figure 3. Compared with PVRI, PA elasticity, distensibility, capacitance, and index beta explained 15% to 67% of the variability in RVEF, RVMI, and RVESVI. Relative contributions of PA stiffness variables, including PA pulse pressure, for RVSWI, as determined by standardized beta coefficients, were 1.8× to 18.0× higher than those of PVRI (Fig. 3).

DISCUSSION

Our data demonstrate an independent relationship between the pattern of RV adaptation to chronic pressure overload and PA stiffness. Elevated PA stiffness was associated with lower RVEF, increased RV hypertrophy and dilation, and higher workload on the RV as determined by the RVSWI. In a prior study of 33 patients with atrial septal defect, an ultrasound-derived index of stiffness correlated better with the RV Tei index than with PA pressures (29). To the best of our knowledge, this is the first demonstration in the clinical setting of independent associations of PA stiffness with RV dysfunction, hypertrophy, and dilation, as measured by CMR, in a large series of patients with PH. Using multivariate analyses, PA elasticity, distensibility, capacitance, and index beta were, in general, independently associated with RVEF, RVMI, RVESVI, and RVSWI after adjusting for age, sex, ethnicity, and PVRI. Demonstration of an association does not establish causality; for example, elevated PA pulse pressure may cause increased RVSWI or vice versa. Moreover, RV dysfunction could contribute to renal insufficiency, which in turn could influence arterial stiffness. However, renal function was largely preserved in our sample. In addition, our results are in agreement with pathophysiologic concepts (7–10), as well as with experimental data in rats indicating that the PA pulse pressure is a more important determinant of RV hypertrophy than mean PA pressure is (30). Moreover, based on the results in Figure 1, alterations in PA elastic properties appear to occur much earlier than changes in RV performance, thus supporting the hypothesis that PA stiffness in-

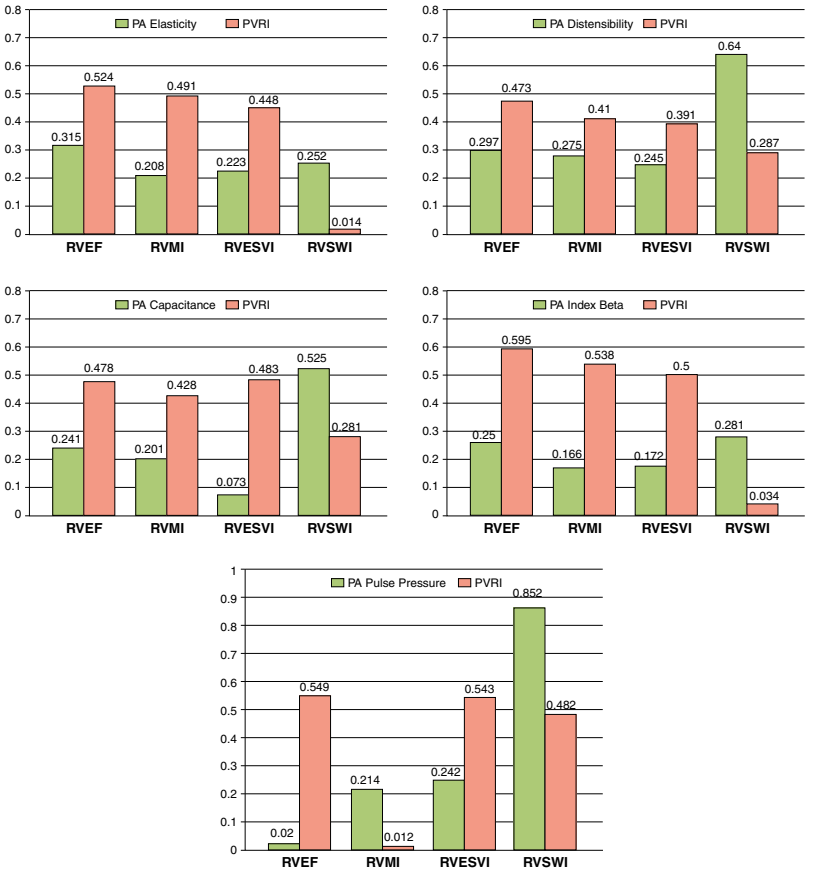

Figure 3. Relative Influence of PA Stiffness Indexes, PA Pulse Pressure, and PVRI on RVEF, RVMI, RVESVI, and RVSWI Outcomes

Standardized regression coefficients (absolute values) representing the change in the average value of the outcome (in SD units) per SD change in the predictor variable are represented. SDs for predictive values are: pulmonary vascular resistance index (PVRI) = 7.04 Wood Units·m^2, ln-transformed PA elasticity = 0.53%; ln-transformed PA distensibility = 0.88%/mm Hg; ln-transformed PA capacitance = 0.62 mm^3/mm Hg; PA pulse pressure = 16.05 mm Hg; PA index Beta = 2.43 arbitrary units. Abbreviations as in Figure 1.

deed contributes to RV adaptation in PH. Our data, therefore, provide a mechanistic link between the prognostic implications of PA stiffness in pulmonary hypertension (12–14) and RV failure as the main cause of death in PH of different etiologies.

The contribution of PA stiffness to impaired RV performance and remodeling is most likely through an increase in afterload. Ventricular afterload can be expressed in terms of a steady component (the opposition that the ventricle encounters to maintaining forward flow) and an oscillatory component (the opposition faced by the ventricle to the pulsatile components of flow). Whereas the first component is generally quantified as vascular resistance, pulsatile afterload is often disregarded in clinical practice because it requires complex invasive quantification of input impedance (9,10). In the systemic circulation, approximately 10% of the hydraulic power generated by the left ventricle is used to maintain pulsatile flow and pressure (9). However, in the pulmonary circulation, the RV spends approximately 30% of its power in generating pulsations (5,7,8,10). Oscillatory power is generally considered "wasted" energy dissipated through the arterial bed, although it has been suggested that increased pulsations in the pulmonary circulation are meant to transmit energy to the pulmonary veins and facilitate left ventricular filling (10). Nonetheless, recent work has shown that abnormally increased pulsatile flow secondary to proximal PA stiffness induces inflammatory gene expression, cell proliferation, and leukocyte adhesion in the endothelium of distal vessels (31). Adequate elasticity of the PA is vital for appropriate matching between the RV and its external load. With increased PA stiffness, the RV may spend as much energy on vascular pulsation as in maintaining steady forward flow (5,7–9). Moreover, an increase in PA stiffness may be more important than an equivalent elevation in resistance in terms

of power spent by the RV to maintain output (32). Increased pulse wave velocity is a major mechanism by which increased stiffness raises ventricular afterload, as earlier wave reflections arrive at the PA during systole while the RV is still ejecting instead of during diastole (5,9,33–35). As in the systemic circulation, this manifests as increased pulse pressure. Therefore, it is not surprising that in our investigation, the PA pulse pressure strongly correlated with RV workload represented by the RVSWI. From a clinical perspective, PA pulse pressure is easily quantifiable from routine RHC evaluations although it requires an invasive procedure. However, the contributions of other indexes of PA stiffness seem to be more relevant than PA pulse pressure in determining RV dysfunction, hypertrophy, and dilation. These are more comprehensive parameters that account not only for the pulse pressure but also for relative area change or stroke volume. Therefore, the combination of invasive and noninvasive data appears to provide complementary information when understanding the mechanisms of RV adaptation to chronic pressure overload. Moreover, PA elasticity can be determined by CMR in a completely noninvasive fashion, without knowledge of invasive hemodynamic data.

It is well known that stiffness is markedly dependent on underlying distending pressures (36,37). Therefore, though it is not surprising that the associations between PA stiffness and RV performance were sustained after accounting for PVRI, it was less expected that some indexes remained independently associated with RV performance (specifically RVEF) even after adjusting for the distending pressure (mean PA pressure). This suggests, contrary to prior observations (36), but in agreement with others (10,24,33), that PA intrinsic elastic properties are altered in PH independent of distending pressures. Potential mechanisms include increased wall tension as a stimulus for myocyte hypertrophy and histological changes (34) or elevated sympathetic tone (38) causing PA stiffening and increased RV oscillatory energy demands (39). Regardless of the underlying mechanisms, alterations in PA stiffness are likely to occur early in the course of the disease (24,40). However, based on the curvilinear relationships shown in Figure 1, it would appear that the influence of PA stiffness on RV status is more marked in later stages, where mild increases in stiffness would cause proportionally higher reductions in RVEF and increases in RVMI, RVESVI, or RVSWI. This may reflect a point where the PA cannot dilate much further despite continued increases in pressure (6).

Study limitations. The main limitation of this study is that CMR and RHC were not performed simultaneously, so we assumed steady conditions in the interval between tests. We tried to minimize this limitation by including patients with chronic PH and who had both tests performed within 7 days. In addition, hemodynamic conditions were similar between tests and sensitivity analyses did not show a significant influence of time interval between tests on reported associations (data not shown). Disease- or drug-specific influences on PA-RV interactions could have influenced our results and were not separately analyzed due to sample sizes and limited data availability. Additionally, it is not possible to demonstrate a causal relationship between PA stiffness and RV performance due to the study design (cross-sectional). RVEF is load-dependent and does not solely reflect RV contractility; however, it is a widely accepted index in clinical practice with known prognostic implications. Finally, indexes of PA stiffness reflect pulsatile load to some extent but not completely, as they do not account for factors such as blood inertial forces or pulse wave velocity.

CONCLUSIONS

Our data demonstrate sustained associations between indexes of PA stiffness and measures of RV adaptation to chronic pressure overload independent of the degree of PVRI elevation. These findings suggest that RV performance and remodeling are determined not only by resistance (steady afterload), but also by PA stiffness (pulsatile load). Therefore, knowledge of PA elastic properties may contribute to our understanding of RV adaptation and eventual failure in PH.

Reprint requests and correspondence: Dr. Gerin R. Stevens, Center for Advanced Cardiac Therapy, Montefiore Medical Center, Greene Medical Arts Pavilion, 3400 Bainbridge Avenue, 7th Floor, Bronx, New York, New York 10467-2490. *E-mail: gstevens@montefiore.org.*

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Key Words: cardiac magnetic resonance ■ pulmonary artery stiffness ■ pulmonary hypertension ■ right ventricular function.