JACC: CARDIOVASCULAR IMAGING VOL. 2, NO. 3, 2009

ISSN 1936-878X/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2008.08.007

Evaluation of Pulmonary Artery Stiffness in Pulmonary Hypertension With Cardiac Magnetic Resonance

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OBJECTIVES This study sought to evaluate indexes of pulmonary artery (PA) stiffness in patients with pulmonary hypertension (PH) using same-day cardiac magnetic resonance (CMR) and right heart catheterization (RHC).

BACKGROUND Pulmonary artery stiffness is increased in the presence of PH, although the relationship to PH severity has not been fully characterized.

METHODS Both CMR and RHC were performed on the same day in 94 patients with known or suspected PH. According to the RHC, patients were classified as having no PH (n = 13), exercise-induced PH (EIPH) only (n = 6), or PH at rest (n = 75). On CMR, phase-contrast images were obtained perpendicular to the pulmonary trunk. From CMR and RHC data, PA areas and indexes of stiffness (pulsatility, compliance, capacitance, distensibility, elastic modulus, and the pressure-independent stiffness index β) were measured at rest.

RESULTS All quantified indexes showed increased PA stiffness in patients with PH at rest in comparison with those with EIPH or no PH. Despite the absence of significant differences in baseline pressures, patients with EIPH had lower median compliance and capacitance than patients with no PH: 15 (interquartile range: 9 to 19.8) mm^2/mm Hg versus 8.4 (interquartile range: 6 to 10.3) mm^2/mm Hg, and 5.2 (interquartile range: 4.4 to 6.3) mm^3/mm Hg versus 3.7 (interquartile range: 3.1 to 4.1) mm^3/mm Hg, respectively ($p < 0.05$). The different measurements of PA stiffness, including stiffness index β, showed significant correlations with PA pressures ($r^2 = 0.27$ to 0.73). Reduced PA pulsatility (<40%) detected the presence of PH at rest with a sensitivity of 93% and a specificity of 63%.

CONCLUSIONS Pulmonary artery stiffness increases early in the course of PH (even when PH is detectable only with exercise and before overt pressure elevations occur at rest). These observations suggest a potential contributory role of PA stiffness in the development and progression of PH. (J Am Coll Cardiol Img 2009;2:286–95) © 2009 by the American College of Cardiology Foundation

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Manuscript received June 6, 2008; revised manuscript received August 4, 2008, accepted August 20, 2008.

Alterations in the elastic properties of the pulmonary artery (PA) have been documented in pulmonary hypertension (PH), both in the experimental setting (1–4) and in humans (5–9). The PA plays an important role in facilitating the transition from right ventricular (RV) pulsatile flow to the nearly steady flow at the capillary level with minimal energy expenditure. The preservation of this RV-PA coupling is fundamental to the maintenance

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of right heart hemodynamics and of pressure function relationships throughout the pulmonary vascular tree (10). The PA elasticity is an important factor governing this relationship, with increased stiffness leading to higher RV pulsatile workload, decreased contractile performance, and enhanced energy transmission to smaller pulmonary vessels, resulting in further vascular damage (3,4,7,11). It is unclear whether the increased stiffness observed in PH is exclusively secondary to elevated distending pressures (4,12), to pressure-independent structural changes in the vascular wall (7,13), or both. Regardless of the underlying causal mechanism, it can be hypothesized that mechanical alterations play a pathophysiological role in the clinical progression of the disease. This concept is supported by preliminary data suggesting that reduced elasticity is associated with impaired prognosis (14–16).

Strain–stress relationships can be used to study arterial elastic properties (17,18). The PA strain has been quantified using invasive approaches (5–9,14,19,20) as well as noninvasive modalities such as echocardiography (21). Cardiac magnetic resonance (CMR) is increasingly used to evaluate cardiopulmonary abnormalities in PH, including PA dimensions (12,22–25). Although previous studies have assessed PA elasticity with CMR, they either lacked information regarding pulmonary pressures (26–33), did not measure pressures on the same day (16), or evaluated small numbers of patients (12,34). The aim of this investigation was to characterize PA stiffness with CMR in a large series of patients with PH of various etiologies and degrees of severity and to provide preliminary insights into elastic alterations in a subset of patients with exercise-induced PH (EIPH) but normal pressures at rest.

METHODS

Population. We studied 95 consecutive patients referred for CMR evaluation of known or suspected chronic PH and who underwent right heart catheterization (RHC) on the same day. After exclusion of 1 individual with a final diagnosis of pulmonary valve stenosis, 94 patients were included. The etiologic diseases responsible for the established or presumed diagnosis of PH were determined after comprehensive diagnostic evaluation (35,36). They included collagen vascular disease in 23 subjects, left heart disease in 15 subjects, lung disease in 12 subjects, sarcoidosis in 10 subjects, human immunodeficiency virus infection in 9 subjects, congenital systemic-to-pulmonary shunt in 4 subjects, portopulmonary syndrome in 3 subjects, hyperthyroidism in 2 subjects, chronic thromboembolic disease in 1 subject, and sickle cell disease in 1 subject. No specific etiology was found in 14 patients (11 finally diagnosed with idiopathic PH and 3 with no PH). The institutional review board approved the study, and all individuals or their legal representatives consented to the procedures.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance
dPAP = diastolic pulmonary artery pressure
EIPH = exercise-induced pulmonary hypertension
mPAP = mean pulmonary artery pressure
PA = pulmonary artery
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
RHC = right heart catheterization
RV = right ventricle/ventricular
ROC = receiver-operating characteristic
sPAP = systolic pulmonary artery pressure

Data acquisition. CMR preceded the RHC in all but 2 patients, with a mean interval between the tests of 3.7 ± 1.4 h. CMR was performed in a 1.5-T magnet (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany), using a dedicated surface coil and retrospective electrocardiographic gating. Phase-contrast images perpendicular to the pulmonary trunk were obtained using a segmented fast gradient echo sequence (repetition time 7.5 ms, echo time 3.1 ms, slice thickness 6 mm, matrix = 256 × 96, 5 to 7 segments, 20 reconstructed cardiac phases, velocity encoding 100 cm/s), as previously described (25). Images were acquired in end-expiration preceded by brief hyperventilation. Patients received contrast agent (25 to 35 ml) and a saline bolus (20 ml) for pulmonary angiography if clinically indicated.

RHC was performed using a Swan-Ganz catheter and standard methodology. Patients were instructed to fast for 6 to 8 h before the procedure. Hemodynamic measurements included right atrial pressure, systolic PA pressure (sPAP), mean PA pressure (mPAP), diastolic PA pressure (dPAP), pulmonary capillary wedge pressure, cardiac index (cardiac output by thermodilution divided by body surface area), pulmonary vascular resistance (PVR) index (calculated as mPAP minus capillary wedge pressure divided by the cardiac index), and PA oxygen saturation. The pulmonary pulse pressure

Table 1. Indexes of PA Stiffness

Parameter	Units	Formula	Definition
Pulsatility	%	maxA − minA/minA × 100	Relative change in lumen area during the cardiac cycle
Compliance	mm^2/mm Hg	[(maxA − minA)/PP]	Absolute change in lumen area for a given change in pressure
Capacitance	mm^3/mm Hg	SV/PP	Change in volume associated with a given change in pressure
Distensibility	%/mm Hg	[(maxA − minA)/PP × minA] × 100	Relative change in lumen area for a given change in pressure
Elastic modulus	mm Hg	PP × minA/(maxA − minA)	Pressure change driving a relative increase in lumen area
Stiffness index β	N/A	*Ln*(sPAP/dPAP)/[(maxA − minA)/minA]	Slope of the function between distending arterial pressure and arterial distension

dPAP = diastolic pulmonary artery pressure; maxA = maximal area; minA = minimal area; N/A = not applicable; PA = pulmonary artery; PP = pulse pressure; sPAP = systolic pulmonary artery pressure.

was quantified as sPAP minus dPAP. In those patients with normal pressures at rest, isotonic upper extremity exercise was performed to achieve an increment in heart rate and output ≥30% than baseline, at which time measurements were repeated. For the purpose of analysis, patients were subdivided in 3 groups: patients with no PH, patients with EIPH only (defined as mPAP >30 mm Hg with exercise), and patients with PH at rest (mPAP >25 mm Hg) (35).

Data analysis. CMR images were analyzed using specialized software (Argus, Siemens Medical Solutions). The contours of the main PA cross section were traced in each phase, and the maximal and minimal PA areas were recorded. Tracings were performed on the magnitude images, using the velocity images as a reference. The reproducibility of these measurements in our laboratory has already been reported (25). The RV stroke volume and cardiac index were quantified from the PA flow data. Various indexes of stiffness (16–18,20) were calculated from CMR and RHC, as shown in Table 1.

Categorical values are expressed as percentages, and continuous variables as mean ± standard deviation or median (interquartile range). Departures from normality were detected with the Shapiro-Wilk statistic. Differences between patient groups were evaluated with chi-square, 1-way analysis of variance, or the Kruskal-Wallis test (with the post-hoc Wilcoxon rank sum test for multiple comparison adjustment) as appropriate. The agreement in cardiac index between RHC and CMR was evaluated with the Bland-Altman method. The associations between pulmonary pressures/resistance and PA stiffness were explored using the Spearman rho (r) coefficient, regression analysis, and curve fitting (different fitting models were tested and compared with the F and R^2 statistics). Multivariate linear regression analyses were used to assess whether the associations between pulmonary pressures/resistance and PA stiffness were maintained after adjusting for age, gender, and history of collagen vascular disease. The ability of PA pulsatility to detect the presence of PH was tested using receiver-operating characteristic (ROC) curves and expressed as sensitivity/specificity with 95% confidence intervals (CI). All tests were 2-tailed, and a p value <0.05 was considered statistically significant. Statistical analyses were performed with the statistical packages SAS (version 9.1, SAS Institute Inc., Cary, North Carolina) and SPSS for Windows (version 15.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patients' demographic and resting hemodynamic data are summarized in Table 2. As expected, right atrial pressure, pulmonary pressures, and PVR index were higher and PA oxygen saturation was lower in the subjects with PH at rest. Cardiac index was also lower, although only statistically different from subjects with no PH. There were no significant hemodynamic differences at rest between patients with no PH and those with EIPH. For the entire sample, the median cardiac index as quantified by phase-contrast CMR was 2.8 (2.3 to 3.6) l/min/m^2. The correlation coefficient between RHC and CMR for quantification of cardiac index was 0.77 ($p < 0.0001$), and the mean bias and 95% CI were 0.4 (1.9 to −1.1) l/min/m^2. The mean difference in heart rate at the times of the RHC and CMR was 3 ± 9 beats/min ($r = 0.81$, $p < 0.0001$).

As shown in Table 3, PA dimensions and indexes of stiffness were increased in the patients with PH at rest in comparison with the other 2 subgroups. Despite similar pulmonary pressures and resistance, subjects with EIPH had lower compliance and capacitance ($p < 0.01$ for both, adjusted for multiple comparisons) than patients with no PH. A trend for increases in all other indexes of stiffness was also noted in the presence of EIPH versus no PH (Fig. 1), although without reaching statistical significance.

Table 2. Demographic and Resting Hemodynamic Data

	Total (n = 94)	No PH (n = 13)	EIPH (n = 6)	PH at Rest (n = 75)
Age (yrs)	53 ± 16	50 ± 13	60 ± 15	53 ± 17
Female	73 (78%)	10 (77%)	6 (100%)	57 (76%)
Right atrial pressure (mm Hg)	6 (3–12)	4 (3–6)	2 (1–4)	8 (4–12)*†
sPAP (mm Hg)	65 (44–80)	24 (22–29)	32 (24–36)	70 (60–82)*†
mPAP (mm Hg)	40 (28–48)	15 (14–18)	15 (14–18)	43 (35–40)*†
dPAP (mm Hg)	25 (17–32)	9 (8–12)	9 (7–11)	28 (20–35)*†
Pulmonary wedge pressure (mm Hg)	9 (6–12)	6 (5–9)	6 (5–9)	10 (7–12)*†
PVR index (Wood units × m^2)	9.3 (5–15)	2.7 (1.8–4.4)	2.5 (2.2–3.5)	10.6 (6.7–17)*†
Cardiac index (l/min × m^2)	3.3 (2.4–3.7)	3.6 (2.7–3.8)	3.3 (2.5–3.6)	3.2 (2.3–3.7)*
PA oxygen saturation (%)	66 (56–70)	70 (66–75)	70 (68–78.2)	64 (54–69)*†

Data are expressed as mean ± SD or median (interquartile range). *p < 0.05 in comparison with patients with no PH. †p < 0.05 in comparison with patients with EIPH.
EIPH = exercise-induced pulmonary hypertension; mPAP = mean pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; other abbreviations as in Table 1.

Except for a weak correlation with capacitance ($r = 0.23$, $p = 0.02$), there was no association between age and PA stiffness. No gender-specific differences were found (data not shown). As shown in Table 4, there were significant correlations between PA stiffness indexes and pulmonary pressures/resistance that were particularly strong for compliance, capacitance, distensibility, and the elastic modulus. After adjusting for age, gender, and presence of collagen vascular disease, all associations remained highly significant ($p < 0.01$) except for the association of stiffness index β with PVR index ($p = 0.11$). Regression curves between sPAP and the various indexes (Fig. 2) indicate that the relationship between sPAP and measures of PA stiffness is curvilinear, with the greatest impact at mild to moderate elevations in pressure.

As shown by ROC curve analysis (Fig. 3), evaluation of PA pulsatility may be useful in determining the presence or absence of PH at rest. A value of PA pulsatility <40% was associated with a mean PA pressure >25 mm Hg with a sensitivity of 93% (95% CI: 85% to 98%) and a specificity of 63% (95% CI: 39% to 84%). Alternatively, a pulsatility cutoff <24% could detect the presence of PH with moderate sensitivity (77%) (95% CI: 66% to 86%) but high specificity (95%) (95% CI: 74% to 99%).

DISCUSSION

This study in a large series of patients with PH of various etiologies shows strong exponential relationships between most indexes of PA stiffness and PH severity. Alterations in PA elasticity are observed early in the course of the disease, even before overt pressure elevations. Moreover, higher distending pressures do not fully account for the increased stiffness (as indicated by the elevated stiffness index β), suggesting a role of altered PA intrinsic elastic properties.

Noninvasive evaluation of simple changes in PA dimensions with CMR reveals alterations in PA stiffness in chronic PH. In our study, PA pulsatility was decreased (17%) in subjects with PH at rest in comparison with patients with EIPH or no PH (39% and 55%, respectively), values comparable to

Table 3. PA Stiffness Data

	Total	No PH	EIPH	PH at Rest
Maximal PA area (cm^2)	9.7 (8.44–12)	7.1 (5.2–8.2)	6.2 (4.7–8)	10.7 (9–12.3)*†
Minimal PA area (cm^2)	8.1 (6.6–10.1)	4.5 (3.9–5.8)	4.8 (3.3–5.7)	8.5 (7.5–10.5)*†
Pulsatility (%)	19.7 (15.1–33.3)	55.2 (27.3–64.6)	38.8 (27.4–49)	17.2 (14.1–22.7)*†
Compliance (mm^2/mm Hg)	4.4 (3.2–7.9)	15 (9–19.8)	8.4 (6–10.3)*	3.9 (2.8–5.5)*†
Capacitance (mm^3/mm Hg)	1.9 (1.2–3.1)	5.2 (4.4–6.3)	3.7 (3.1–4.1)*	1.5 (1.2–2.3)*†
Distensibility (%/mm Hg)	0.5 (0.3–1.2)	3.1 (2–4.3)	1.9 (1.2–2.6)	0.4 (0.3–2.6)*†
Elastic modulus (mm Hg)	205.8 (84.2–290.2)	32.6 (23.2–51.4)	52.7 (39.2–83.9)	246.9 (155.8–321.6)*†
Stiffness index β	4.6 (2.4–4.6)	1.8 (1.5–3.3)	2.8 (2.4–4.6)	5.2 (4.7–6)*†

Data expressed as median (interquartile range). *p < 0.05 in comparison with patients with no PH at rest. †p < 0.05 in comparison with patients with no EIPH.
Abbreviations as in Tables 1 and 2.

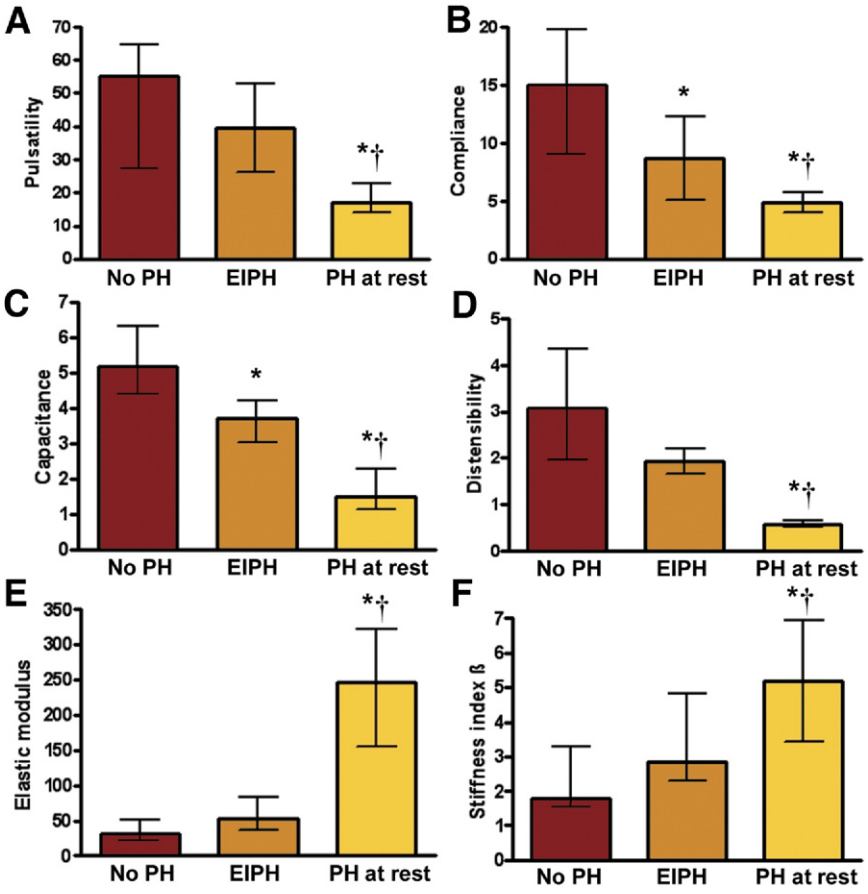

Figure 1. Indexes of PA Stiffness According to Patient Subgroups

Median values and interquartile ranges (error bars) for pulmonary artery pulsatility **(A)**, compliance **(B)**, capacitance **(C)**, distensibility **(D)**, elastic modulus **(E)**, and stiffness index β **(F)** in the different patient subgroups. $*p < 0.05$ in comparison with patients with no pulmonary hypertension (PH). $\dagger p < 0.05$ in comparison with patients with exercise-induced pulmonary hypertension (EIPH). PA = pulmonary artery.

previous studies (14,16,20,26–31). The evaluation of pulsatility may be useful in the clinical setting, where pulmonary pressures are often unknown. In this regard, we showed that a value of PA pulsatility <40% can detect the presence of PH at rest with a high sensitivity, whereas reductions below 24% carry high specificity. In addition, this index has been previously shown to provide prognostic information in patients with pulmonary arterial hypertension (16). However, because of the strong dependency of strain on underlying pressures, quantification of pulsatility alone is insufficient to fully characterize PA elastic properties (19), and other indexes need to be evaluated.

Table 4. Spearman Correlation Coefficients Between Stiffness Measures and Pulmonary Pressures/Resistance

	sPAP	mPAP	PVR Index
Maximal PA area	0.54*	0.51*	0.43*
Minimal PA area	0.61*	0.58*	0.50*
Pulsatility	−0.49*	−0.48*	−0.47*
Compliance	−0.71*	−0.63*	−0.58*
Capacitance	−0.83*	−0.75*	−0.79*
Distensibility	−0.78*	−0.70*	−0.63*
Elastic modulus	0.78*	0.70*	0.63*
Stiffness index β	0.45*	0.35	0.30

All correlations: $p < 0.05$. $*p < 0.001$.
Abbreviations as in Tables 1 and 2.

Measuring PA compliance intraoperatively, Greenfield et al. (6) reported an average change in radius of 8.7 mm/cm H_2O in normal men and 0.91 mm/cm H_2O in patients with severe PH. For a PA radius of 1.6 cm (the average in our patients), this would correspond to respective area changes of 9 and 1 mm^2/mm Hg, in good agreement with our compliance measurements. Capacitance quantifies

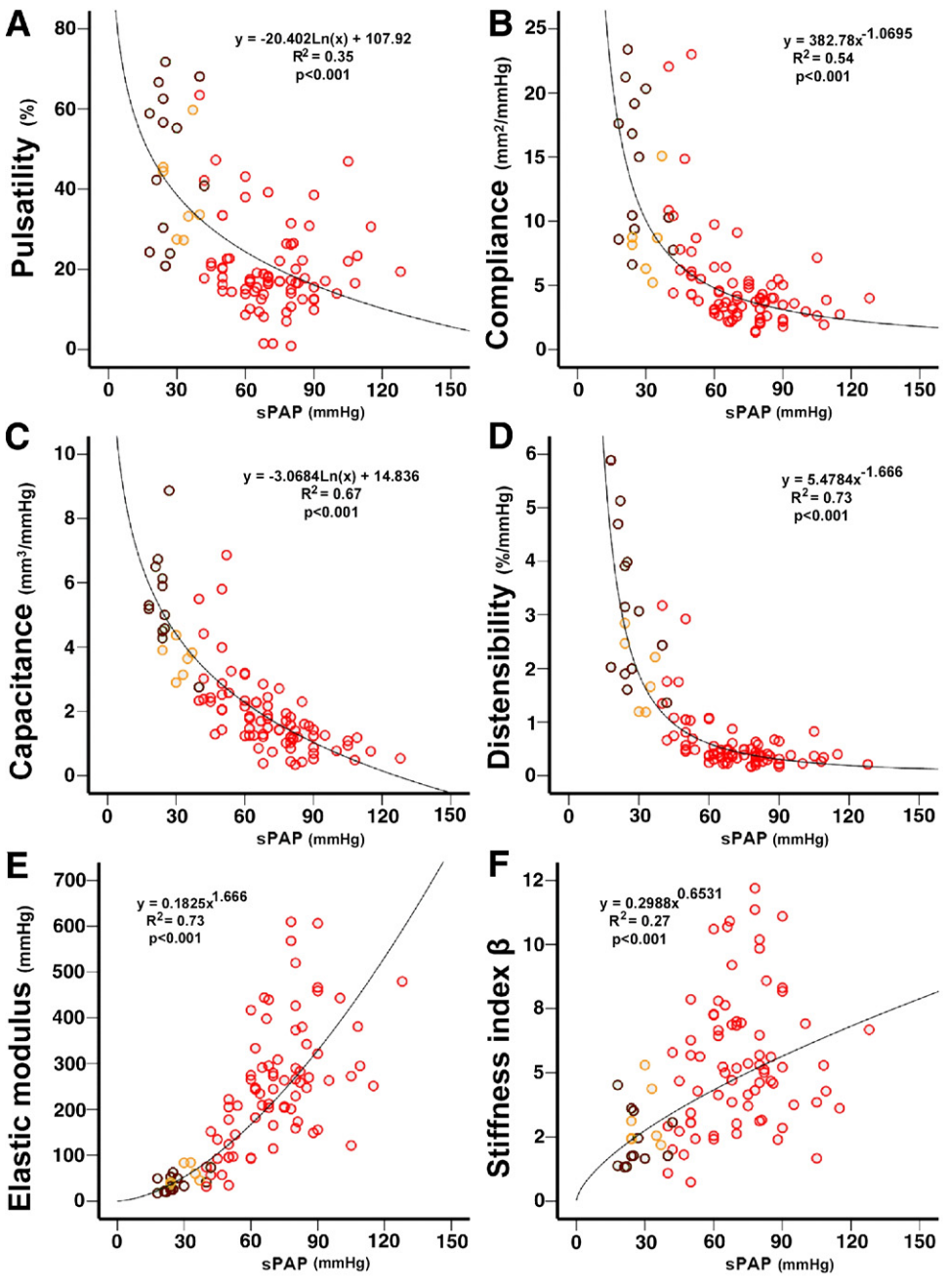

Figure 2. Relationship Between sPAP and PA Stiffness

Regression analysis of the relationships between systolic pulmonary artery pressure (sPAP) and pulmonary artery pulsatility **(A)**, compliance **(B)**, capacitance **(C)**, distensibility **(D)**, elastic modulus **(E)**, and stiffness index β **(F)**. **Brown circles** = patients with no PH; **orange circles** = patients with EIPH; **red circles** = patients with PH at rest. Abbreviations as in Figure 1.

total (rather than local) arterial compliance. In our study we used the ratio of stroke volume to pulse pressure that, although known to overestimate total compliance, has been previously validated in humans (12,34) and was the strongest predictor of mortality in a recent study of idiopathic PH (15). Our measurements of capacitance in PH are comparable to the values of approximately 1 ml/mm Hg found by Lankhaar et al. (12), 1.4 ml/mm Hg reported by Mahapatra et al. (15), or 1.8 ml/mm Hg/m^2 in the work of Muthurangu et al. (34). Distensibility of the normal pulmonary circulation

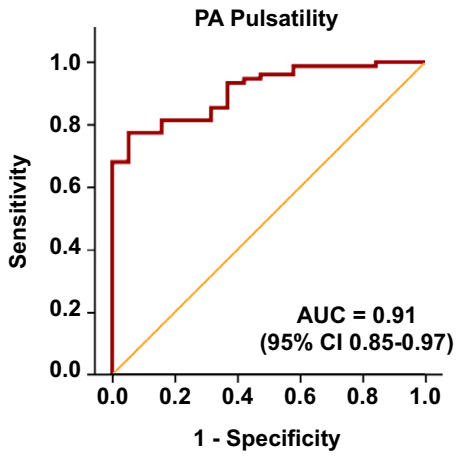

Figure 3. Diagnostic Ability of PA Pulsatility for the Presence of PH

The receiver-operating characteristic curve of the ability of PA pulsatility to detect mean PA pressure (at rest) >25 mm Hg. AUC = area under the curve; CI = confidence interval; other abbreviations as in Figure 1.

is approximately 2% increase in diameter (approximately 4% change in area) per mm Hg (37), again in agreement with our results. Similarly, the normal PA elastic modulus is approximately 140 to 160 g/cm^2, increasing to 500 to 2,000 g/cm^2 in the presence of PH (6,9,38). Using the same units, the median elastic modulus in our study would be 99 g/cm^2 in patients with no PH and 699 g/cm^2 in patients with PH at rest. Altogether, these numbers validate the use of same-day CMR-derived strains and RHC-derived pressures for PA stiffness assessment.

We found an inverse exponential relationship ($r^2 = 0.73$) between sPAP and distensibility, which suggests that at a certain level of PH and dilatation the PA approaches its elastic limit. This value seems to be in the vicinity of 40 mm Hg of mPAP (data not shown) or 60 mm Hg of sPAP (Fig. 2D), in agreement with previous invasive data (8,39). Although the reasons for this curvilinear relationship are likely complex and beyond the scope of our investigation, it has been postulated that this is related to the progressive recruitment of nondistensible collagen versus elastin fibers at increasing degrees of deformation (40).

An interesting finding in this investigation is that, despite the absence of significant hemodynamic differences at rest, compliance and capacitance were decreased in patients with EIPH when compared with subjects with no PH. As shown also in Figure 2, alterations in PA elastic properties can be noted before overt pressure elevation, suggesting that elevated distending pressures are not the only factor responsible for such abnormalities. This concept is further supported by the progressive increase in stiffness index β with escalating disease severity. Because of the logarithmic data transformation in its calculation, stiffness index β is expected to account for the curvilinear nature of strain/pressure relationships and has been proposed as a pressure-independent index in the systemic circulation (41). To the best of our knowledge, this is the first investigation quantifying this index in the pulmonary circulation. These findings are in agreement with the functional and histopathological changes in the pulmonary arteries that accompany PH, such as diffuse wall thickening, collagen and extracellular matrix deposition, smooth muscle cell proliferation, and increased vascular tone, which may modify the viscoelastic properties of the vessel wall (4,11,13,14).

The observation that early alterations in stiffness precede pressure elevation suggests a contributory role in the progression of disease. PH is associated with changes in the pattern and velocity of blood flow in the pulmonary circulation (25,42) that are expected to have significant effects on shear stress. Low and/or oscillatory shear stresses exert profound influence on endothelial cell function and promote vasoconstriction, proliferation of smooth muscle cells, and imbalance between synthesis and degradation of extracellular matrix, all of which contribute to arterial remodeling and may cause abnormal elasticity. The increase in stiffness can lead to increase in pulse pressure and further PA dilatation, which in turn favors continued alteration in shear stress, establishing a cycle that may contribute to the progressive vascular remodeling and PA pressure elevation (11,43–45) (Fig. 4).

There are several potential implications of the findings in this study. From a clinical perspective, and as mentioned before, PA pulsatility can be used as an indirect marker of the presence of PH for diagnostic purposes. In addition, combination of pressure and strain information may aid in the early identification of patients with abnormal pulmonary vasculature despite normal pressures at rest. From a research perspective, areas to explore in future studies would include the implications of different degrees of PA stiffness abnormalities in the progression of disease, as well as the influence of several therapeutic interventions on PA elastic properties.

Study limitations. The main limitation of this study is that PA pressures and dimensions were not quantified concurrently, as would have been desirable. Although simultaneous measurement with intravascular catheters in the course of a CMR study is presently feasible (34), this capability is not

available in most laboratories. We tried to overcome this limitation by studying only patients who underwent CMR and RHC within a few hours. The incremental error caused by extending the interval between tests to several hours or from hours to days is difficult to quantify, but cardiovascular stability is likely to be higher if the tests are performed on the same day because marked day-to-day changes in PA pressures occur in PH (46). Even with the short time interval used in this study, some spontaneous intra-day variations in pressures or other indexes probably occurred. Small changes in volume status between the tests (for example, related to the intravenous administration of contrast in CMR) might have influenced some hemodynamic parameters such as pulmonary wedge pressure. Moreover, CMR imaging was performed during apnea, whereas pressure measurements were obtained during free breathing. Although the response to breath-holding is variable among individuals, depending partially in changes in intrathoracic pressures, a reduction in cardiac output may occur (47). This might explain the slightly lower cardiac index measured by CMR in comparison with RHC. However, respiratory variations in PA stress–strain relationships have been reported to be minimal (6). In addition, the small differences in cardiac index and heart rate noted between the tests are reassuring in terms of the degree of hemodynamic stability. Because our results are in agreement with previously reported values measured invasively, we believe that they accurately reflect PA elastic properties.

Another limitation is the relatively small number of patients with no PH or with EIPH. These numbers reflect the expected proportions observed in the clinical setting. RHC is reserved for individuals in whom the diagnosis of PH has been made or is highly suspected. These limitations in sample size probably explain why only 2 of the evaluated indexes of stiffness differed significantly between the groups of no PH and EIPH. However, the trend for progressive impairment in elastic properties across the groups was noted for all indexes (Fig. 1), again supporting the validity of our conclusions. Some of the patients with PH at rest were already treated with calcium channel blockers, prostanoids, endothelin-receptor antagonists, or other drugs. Such medications act preferentially on distal vessels and probably have limited effects on the more proximal arteries (48,49), although we cannot exclude some influence on quantified stiffness indexes.

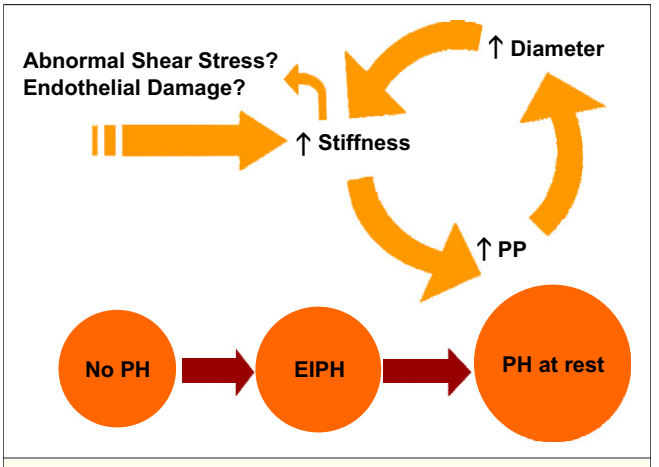

Figure 4. Proposed Role of Increased PA Stiffness in the Development and Progression of PH

In early disease stages **(top half)**, poorly identified factors that may include abnormal shear stress or endothelial injury alter PA elastic properties. This leads to increased pulse pressure (PP) and favors the development of overt PH. Elevated distending pressures result in PA dilation, causing further stiffening and shear stress abnormalities and establishing a positive feedback cycle of disease progression. The bottom half of the figure represents a cross-section of the pulmonary trunk. Initially, the PA has normal size and preserved elastic properties. In early stages, such as EIPH, there is increased stiffness of the PA wall. In advanced stages (PH at rest), stiffness continues to increase and the PA dilates. Abbreviations as in Figure 1.

We acquired images during brief breath-holds to minimize imaging time. The temporal resolution of our sequence was therefore limited (75 to 105 ms) and this might have led to small inaccuracies of PA dimension measurements.

CONCLUSIONS

Noninvasive evaluation of PA dimensions with CMR in combination with RHC-derived pressure quantification shows strong correlations between PA stiffness and PH severity. Reductions in PA elasticity take place before overt pressure elevations (as evidenced by the alterations in stiffness in EIPH), may be important in disease progression and could be useful for the early detection of PH. The increased PA stiffness is not fully accounted for by elevated distending pressures, suggesting altered intrinsic elastic properties.

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JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 3, 2009
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Key Words: hypertension ■ pulmonary ■ cardiac magnetic resonance ■ pulmonary artery.