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Cardiac Magnetic Resonance Imaging-Derived Pulmonary Artery Distensibility Index Correlates With Pulmonary Artery Stiffness and Predicts Functional Capacity in Patients With Pulmonary Arterial Hypertension

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Background: Increased stiffness of the pulmonary vascular bed is known to increase mortality in patients with pulmonary arterial hypertension (PAH); and pulmonary artery (PA) stiffness is also thought to be associated with exercise capacity. The purpose of the present study was to investigate whether cardiac magnetic resonance imaging (CMRI)-derived PA distensibility index correlates with PA stiffness estimated on right heart catheterization (RHC) and predicts functional capacity (FC) in patients with PAH.

Methods and Results: Thirty-five consecutive PAH patients (23% male, mean age, 44±13 years; 69% idiopathic) underwent CMRI, RHC, and 6-min walk test (6MWT). PA distensibility indices were derived from cross-sectional area change (%) in the transverse view, perpendicular to the axis of the main PA, on CMRI [(maximum area–minimum area)/minimum area during cardiac cycle]. Among the PA stiffness indices, pulmonary vascular resistance (PVR) and PA capacitance were calculated using hemodynamic dataset from RHC. CMRI-derived PA distensibility was inversely correlated with PVR (R^2=0.34, P<0.001) and directly correlated with PA capacitance (R^2=0.35, P<0.001), and the distance in the 6MWT (R^2=0.61, P<0.001). Furthermore, PA distensibility <20% predicted poor FC (<400 m in 6MWT) with a sensitivity of 82% and a specificity of 94%.

Conclusions: Non-invasive CMRI-derived PA distensibility index correlates with PA stiffness and can predict FC in patients with PAH. (*Circ J* 2011; **75:** 2244–2251)

Key Words: Cardiac magnetic resonance imaging; Pulmonary arterial hypertension; Pulmonary artery distensibility

Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by abnormally elevated blood pressure of the pulmonary circulation that primarily results from extensive pulmonary vascular remodeling over time. Increased stiffness of the pulmonary artery (PA) leading to a higher right ventricle (RV) workload enhances energy transmission to small pulmonary vessels, resulting in further vascular damage.[1–4] So far, invasively calculated hemodynamic indices have been used for measurement of PA stiffness and treatment of response, which has been reported to be associated with mortality in PAH.[5–8] Non-invasive imaging modalities have also been used to measure PA distensibility for the assessment of PA stiffness and risk stratification in patients with pulmonary hypertension (PH). Recently, cardiac magnetic resonance imaging (CMRI) has been reported as a promising non-invasive tool for the evaluation of patients with PH and, in combination with right heart catheterization (RHC)-derived pressure quantification, showed strong correlation with PA stiffness.[1,4,9–11] Poor functional capacity (FC), represented by reduced 6-min walk distance (6WMD), was previously confirmed to be a strong independent parameter associated with mortality.[12–15] There is little information, however, relating PA stiffness to FC in PAH. Therefore, we explored whether a CMRI-derived PA distensibility index correlates with PA stiffness estimated by RHC and whether it can be used to predict FC in patients with PAH.

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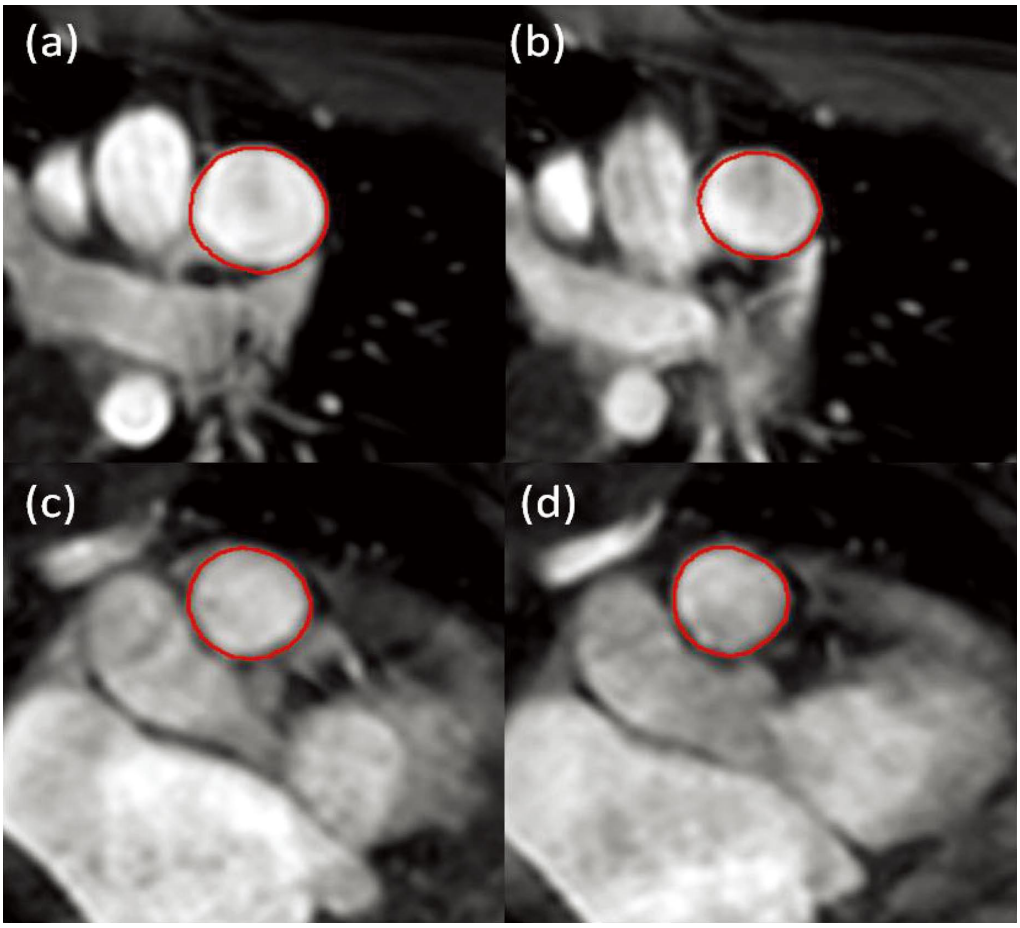

Figure 1. Image of pulmonary artery (PA) in the horizontal plane calculated for PA distensibility (%). Marked area, cross-sectional area (CSA) of PA in 2 patients: (**a**,**b**) patients who had optimal functional capacity (FC; 567 m); (**c**,**d**) patients who had poor FC (240 m). Maximum CSA: (**a**) 12.5 mm^2; (**c**) 9.9 mm^2; minimum CSA: (**b**) 9.2 mm^2; (**d**) 9 mm^2. PA distensibility (%) of each patient was 35.8 and 10.

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Methods

Subjects

Fifty-five consecutive patients who were diagnosed with PAH at Severance Cardiovascular Hospital in South Korea were prospectively recruited between March 2009 and July 2010. PAH was defined as mean PA pressure >25 mmHg and a normal pulmonary capillary wedge pressure <15 mmHg at rest, which was confirmed on RHC. Secondary causes were defined on the basis of clinical examination, laboratory tests, chest radiography, computed tomography, and echocardiography, when necessary.[16] The patients who underwent a 6-min walk test (6MWT), CMRI, echocardiography, and RHC within 72 h without any change in clinical status or medical intervention were included in the study. Twenty patients who had coexisting coronary artery disease or who did not undergo the aforementioned examinations within 72 h were excluded from the study. Thirty-five of these 55 patients were included in the final analysis. All patients gave written informed consent and the study protocol was reviewed and approved by the institutional review board.

6MWT Protocol

The 6MWT was carried out by a trained technician on a 20-m corridor with no prior practice walks. Patients were instructed to walk and cover as much ground as possible in 6 min. Standardized encouragement at 1-min intervals was given as described in the American Thoracic Society guidelines.[13]

RHC

All patients underwent RHC with a balloon-tipped, 7-Fr Swan-Ganz CCombo PA catheter (Baxter, Irvine, CA, USA) through the right or left femoral vein. The patient was in a stable condition, lying supine, and breathing room air at the time of catheterization. Hemodynamic data were collected at rest. The following hemodynamic variables were measured: systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), mean PA pressure (mPAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) using the thermodilution method and cardiac index (CO divided by body surface area). Pulmonary vascular resistance (PVR) was calculated using mPAP, PCWP, and CO, and stroke volume (SV) was calculated using CO and

Table 1. Baseline Demographics and Clinical Characteristics

Parameters	N=35
Age (years)	44±13
Male, n (%)	8 (23)
Etiology	
Idiopathic PAH, n (%)	24 (69)
PAH associated with CHD	7 (20)
PAH associated with PH	2 (6)
PAH associated with CTD	2 (6)
Body surface area (m^2)	1.63±0.21
Creatinine (mg/dl)	0.87±0.19
Total bilirubin (mg/dl)	0.9±0.8
Uric acid (mg/dl)	6.13±2.3
NT-proBNP (pg/ml)	897±652
Function class I·II/III·IV	17/18 (49/51)
6MWD (m)	398±101
Medications, n (%)	
Calcium channel blocker	2 (6)
Bosentan	20 (57)
Sildenafil	11 (31)
Iloprost	6 (17)
Diuretics	20 (57)
Warfarin	16 (46)

Data given as n (%) or mean±SD.
PAH, pulmonary arterial hypertension; CHD, congenital heart disease; PH, portal hypertension; CTD, connective tissue disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWD, 6-min walk distance.

Table 2. CMRI and RHC Data

Parameters	N=35
CMRI	
LV ejection fraction (%)	60±8
RV end diastolic volume (ml)	203±68
RV end systolic volume (ml)	129±67
RV ejection fraction (%)	39±14
PA distensibility (%)	19±11
RHC	
Mean RA pressure (mmHg)	11±10
Systolic PA pressure (mmHg)	79±29
Diastolic PA pressure (mmHg)	32±16
Mean PA pressure (mmHg)	50±19
Stroke volume (ml)	61±24
Heart rate (beats/min)	77±14
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.8±1.1
PVR ($dyne \cdot s/cm^5$)	802±517

Data given as mean±SD.
CMRI, cardiac magnetic resonance imaging; RHC, right heart catheterization; LV, left ventricle; RV, right ventricle; RA, right atrium; PA, pulmonary artery; PVR, pulmonary vascular resistance.

heart rate during the RHC.

CMRI Protocol

All CMRI was performed with a 1.5-T MR scanner (Achieva 1.5T; Philips Medical Systems, The Netherlands) using a 16-channel phased-array surface coil. After acquisition of localizer images, axial, sagittal, and coronal images were obtained to evaluate general thoracic vascular anatomy using a balanced fast field echo sequence (bFFE; typical repetition time/echo time [TR/TE], 3.6/1.8 ms; flip angle, 80°; field of view [FOV], 380 mm; matrix, 256; slice thickness, 5 mm; number of signal average [NSA], 1) during expiratory breath holding. Cine imaging was performed in the cardiac short axis using bFFE sequence (typical TR/TE, 2.8/1.4 ms, flip angle, 50°; FOV, 380 mm, matrix, 256; slice thickness, 10 mm; NSA, 1; sensitivity encoding [SENSE] factor, 2; 25 phases per cardiac cycle) with retrospective electrocardiogram (ECG) gating during expiratory breath holding. The cardiac short-axis slices encompassed the entire left and right ventricle without any gaps (8–12 slices). Phase contrast (PC)-CMRI was performed with a 2D-PC sequence (typical TR/TE, 4.8/2.8 ms; flip angle, 15°; FOV, 380 mm; matrix, 256; slice thickness, 8 mm; NSA, 3; 60 phases per cardiac cycle; SENSE factor, 2) using retrospective ECG gating. Each patient was urged to perform shallow breathing during PC data acquisition without breath holding. Image sections of PC-CMRI for flow measurement were planned in a double oblique section perpendicular to the main PA and 2 cm above the pulmonary valve. The encoding velocity for flow measurement was adjusted to 200 cm/s without aliasing.

CMRI Analysis

Ventricular volumes, ejection fraction, and mass were measured from the cine short-axis views using dedicated CMRI analysis software (ViewForum, version 4.1, Philips Medical Systems, The Netherlands) and computed by semi-automatically depicting the endocardial and epicardial borders in the short-axis cine images. Measurements of the flow velocities through the main PA and cross-sectional area (CSA) of the main PA during the cardiac cycle were performed by detecting the vessel's border semi-automatically using the same software (ViewForum, version 4.1). Two expert radiologists blinded to the results of the hemodynamic measurements independently measured the CSA of the main PA during the cardiac cycle for the evaluation of inter-observer variability. One of them repeated the measurement after an interval of at least 4 weeks for the evaluation of intra-observer variability.

Calculation of PA Stiffness and Distensibility Indices

RHC-derived stiffness indices including PA pulse pressure (PP), PVR, and PA capacitance were calculated as follows: PP (mmHg)=[sPAP−dPAP]; PVR ($dynes \cdot s/cm^5$)=[80×(mPAP−PCWP)/CO]; PA capacitance (mm^3/mmHg)=[SV/PP].[6,7,17] CMRI-derived PA distensibility index (%) was defined as [(maximum CSA−minimum CSA)/minimum CSA] (Figure 1).[4] RHC-CMRI-derived stiffness indices were also calculated as follows: PA stiffness index β=[(sPAP/dPAP)/(maximum CSA−minimum CSA/minimum CSA)] and elastic modulus (ml/mmHg)=[(PP×minimum CSA)/(maximum CSA−minimum CSA)].[11]

Statistical Analysis

Variables are presented as mean±SD or number (%). Comparison of the continuous variables between groups was conducted using Student's t-test. Bland–Altman analysis was performed for intra-observer and inter-observer variability of CMRI-derived PA distensibility index. The correlation between hemodynamic variables and CMRI measurements was assessed using Pearson's correlation coefficient. Correlation coefficients between PA distensibility and other variables were determined by linear regression analysis. To determine whether CMRI-derived PA distensibility index has an independent predictive value, univariate and multivariate logistic analysis was per-

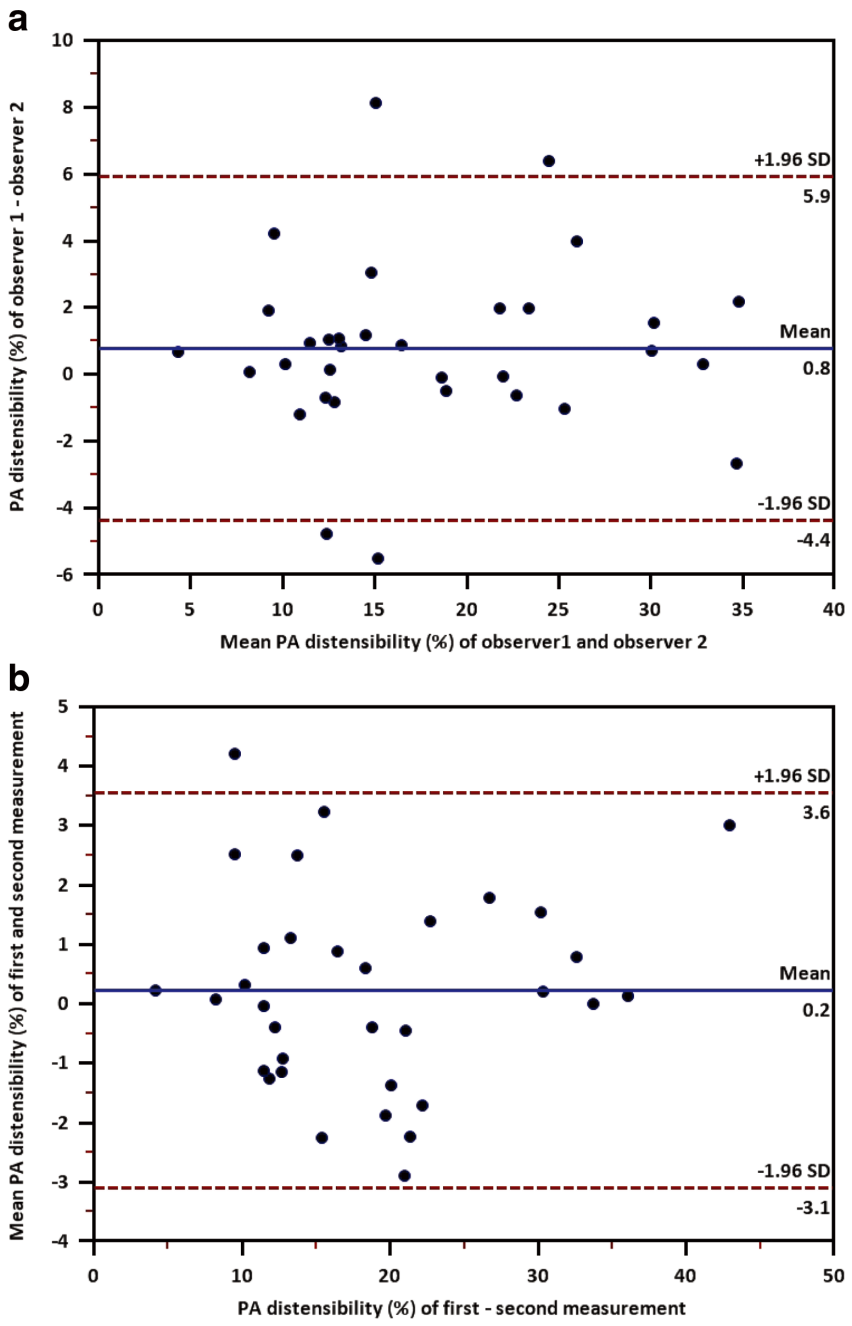

Figure 2. Bland–Altman plots showing (**a**) inter-observer variability and (**b**) intra-observer variability of cardiac magnetic resonance imaging-derived pulmonary artery (PA) distensibility.

formed. To test the function of CMRI-derived PA distensibility index to predict the FC, we used receiver operating characteristic (ROC) curve analysis, which was generated by plotting sensitivity against 1–specificity for all possible cut-off values using Youden's index. Statistical analysis was performed using SPSS (SPSS, Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Demographics and clinical characteristics are given in Table 1. The majority of patients were female, and the mean age was 44 years. Twenty-four patients (69%) were diagnosed with idiopathic PAH. In the remaining patients, PAH was associated with congenital heart diseases (n=7, 20%; atrial septal defect in 6 patients and patent ductus arteriosus in 1 patient), portal hypertension (n=2, 6%), and connective tissue disease (n=2, 6%, systemic lupus erythematous and systemic sclerosis each in 1 patient). Table 2 lists the CMRI and RHC data. CMRI-derived RV volumes and RV ejection fraction were reduced compared with healthy population values.[12] Mean PA pressure and PVR were elevated in RHC data.

Inter- and Intra-Observer Variability of CMRI-Derived PA Distensibility Index

Two expert radiologists who were blinded to clinical information independently measured the CMRI-derived PA distensi-

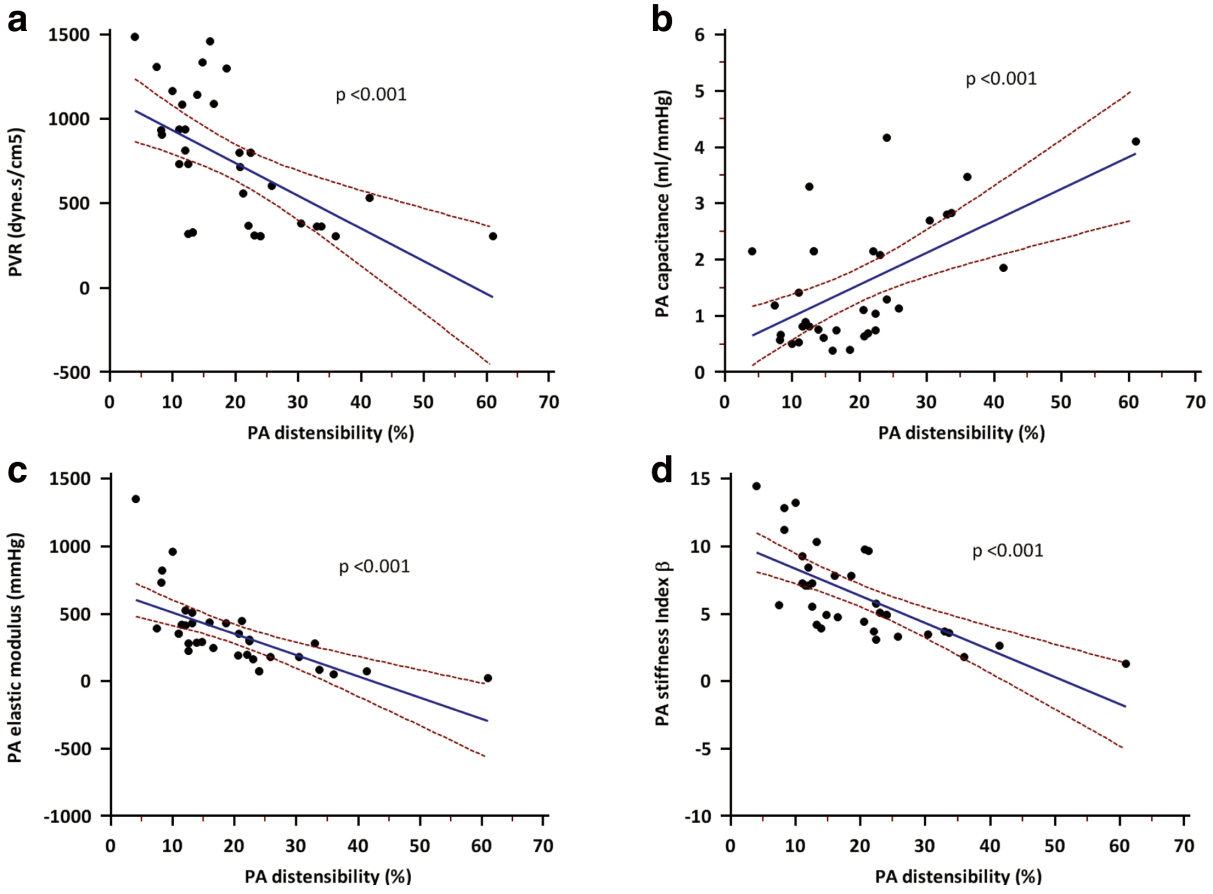

Figure 3. Pulmonary artery (PA) stiffness indices and cardiac magnetic resonance imaging (CMRI)-derived PA distensibility index: (**a**) right heart catheterization (RHC)-derived pulmonary vascular resistance (PVR) vs. CMRI-derived PA distensibility; (**b**) RHC-derived PA capacitance vs. CMRI-derived PA distensibility; (**c**) RHC- and CMRI-derived elastic modulus vs. CMRI-derived PA distensibility; and (**d**) RHC- and CMRI-derived stiffness index β vs. CMRI-derived PA distensibility.

Table 3. Logistic Regression Analysis of Predictors of Optimal Functional Capacity

Parameters	Univariate		Multivariate	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (years)	0.96 (0.91–1.01)	0.187		
NT-proBNP (pg/ml)	1.00 (0.99–1.00)	0.181		
RV end diastolic volume (ml)	0.99 (0.98–1.00)	0.073		
RV ejection fraction (%)	1.04 (0.99–1.09)	0.118		
PA distensibility (%)	1.51 (1.17–1.96)	0.002**	1.46 (1.12–1.94)	0.011**
Mean RA pressure (mmHg)	1.00 (0.95–1.05)	0.962		
Mean PA pressure (mmHg)	1.00 (0.97–1.04)	0.612		
PA capacitance (ml/mmHg)	1.96 (0.96–64.02)	0.066		
PVR (dyne·s/cm^5)	0.99 (0.99–1.00)	0.078		
Elastic modulus (mmHg)	0.99 (0.98–0.99)	0.011*	1.00 (0.99–1.01)	0.203
Stiffness index β	0.51 (0.32–0.78)	0.002**	0.58 (0.29–1.14)	0.151

*P<0.05; **P<0.01.
OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 2.

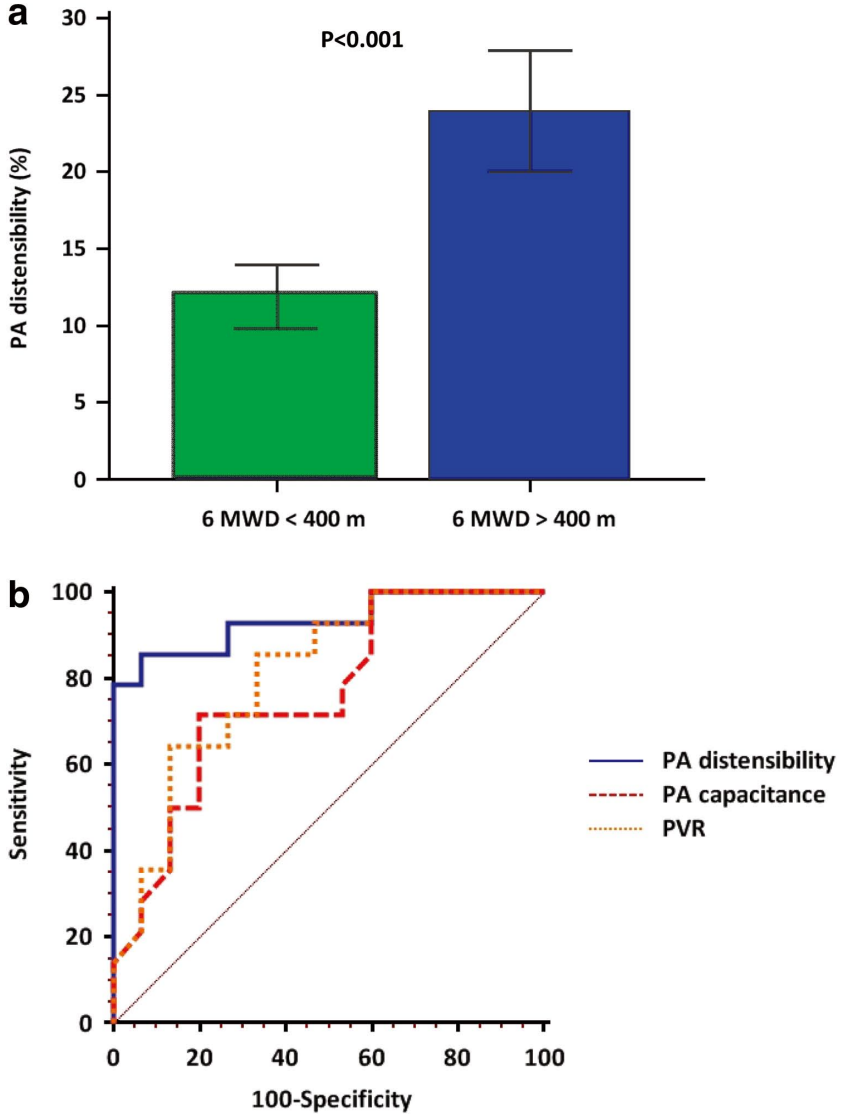

Figure 4. (**a**) Mean pulmonary artery (PA) distensibility vs. 6-min walk distance (6MWD). (**b**) Comparison of predictive abilities of difference stiffness indices for functional capacity. PVR, pulmonary vascular resistance.

bility. Inter-observer and intra-observer variability are given in Figure 2. Intraclass correlation coefficients between inter-observer and intra-observer variability were 0.94 (0.90–0.97) and 0.98 (0.96–0.99).

Correlation of CMRI-Derived PA Distensibility Index With PA Stiffness

CMRI-derived PA distensibility index was negatively correlated with PVR (R^2=0.34, P<0.001; Figure 3a) and positively correlated with PA capacitance (R^2=0.35, P<0.001; Figure 3b) on RHC. There was also an inverse exponential correlation between CMRI-derived PA distensibility index and elastic modulus (R^2=0.43, P<0.001; Figure 3c) and stiffness index β (R^2=0.47, P<0.001; Figure 3d) with statistical significance as previously reported.[11]

Prediction of FC Using CMRI-Derived PA Distensibility Index

There was a significant positive correlation between 6MWD and PA distensibility (R^2=0.61, P<0.001). Based on a study of the utility of 6MWD in predicting clinical outcome,[16,18] we divided the 35 patients into 2 groups: 1 group who walked ≥400 m in the 6MWT (optimal FC), and another group who walked <400 m (poor FC). Multivariate logistic regression analysis showed that CMRI-derived PA distensibility index is the strongest predictor of FC (odds ratio, 1.46; P=0.011; Table 3) and there was a significance difference in CMRI-derived PA distensibility index between the 2 groups (P<0.001; Figure 4a). As shown on ROC curve analysis of the predictors able to distinguish between optimal or poor FC (Figure 4b), CMRI-derived PA distensibility index had stronger predictive power (area under the curve [AUC]=0.941, 0.802–0.993) than RHC-derived PVR (AUC=0.807, 0.619–0.920) and PA capacitance (AUC=0.760, 0.566–0.898). CMRI-derived PA distensibility index <20% was associated with 6MWD<400 m with 82% sensitivity and 94% specificity.

Discussion

In the present study, CMRI-derived PA distensibility index consistently correlated with the RHC-derived PA stiffness index, PVR, and PA capacitance. Multivariate logistic regres-

sion showed that CMRI-derived PA distensibility index could be used to predict FC in patients with PAH. A cut-off for CMRI-derived PA distensibility of <20% predicted poor FC in 6MWD of <400 m with 82% sensitivity and 94% specificity. This is the first study to demonstrate the clinical availability of the CMRI-derived PA distensibility index.

Correlations Between PA Stiffness and CMRI-Derived PA Distensibility Index

Previous investigations showed histopathological changes in the pulmonary arteries during the progression of hypertension in pulmonary circulation that modifies the elastic properties of the pulmonary vessel wall, and that PA pressure correlated linearly with PA stiffness.[2,5,6] Invasively measured PA capacitance and PVR, which reflect PA stiffness, strongly predict survival in PAH.[6,7] More recently, PA distensibility index using non-invasive methods such as echocardiography or computed tomography were introduced to easily measure PA stiffness, but they have some limitations: reproducibility and variability using these methods were limited, and there was lack of data to compare with invasive hemodynamic parameters[9,10] In the present study, both invasively and noninvasively measured PA hemodynamic data were acquired within 72 h and the reproducibility and variability of CMRI-derived PA distensibility index were acceptable to be obtained to compare with each other. (**Figures 1**, **2**). Furthermore, the present study showed that the CMRI-derived PA distensibility index correlated with the RHC-derived PA stiffness index statistically significantly (**Figure 3**).

PA Distensibility as a Predictor of FC

As a simple objective measurement of FC, 6MWD is the only functional test modality approved by the Food and Drug Administration as an endpoint for clinical trials and which can serve as a guide for therapeutic decision-making.[12,16,19–22] Some studies have shown that 6MWD varies greatly between individuals due to physiological and pathologic factors but its prognostic ability is not inferior to that of the adjusted % predicted 6MWD,[23] and the 6MWD is reproducible and used successfully to evaluate FC in patients with PAH of various etiologies, including congenital heart disease.[24–29] Previous studies have reported a 6MWD≥400 m as an optimal FC,[30] which was associated with good clinical outcomes. Therefore, although the threshold of 6MWD for prognosis may differ slightly depending on the combination of detailed assessments of different clinical and objective characteristics, the expert consensus is that patients with 6MWD≥400 m have an optimal FC.[16,18,25,31] In terms of the present 6MWD results, the CMRI-derived PA distensibility index was significantly different for 2 groups: 1 group had optimal FC and the other group had poor FC (**Figure 4a**). Previous studies confirmed that decreased PA stiffness index and poor FC are predictors of mortality in patients with PAH,[1,6,7] but the relationship between PA stiffness and FC was not completely established. The present data showed that CMRI-derived PA distensibility index was a strong predictor of optimal FC among other well-known parameters according to multivariate logistic regression. Subsequently, by comparing the ROC curves for the differentiating threshold of FC with other invasively measured PA stiffness indices including PVR and PA capacitance, we found that CMRI-derived PA distensibility index was the most reliable parameter and that patients with PAH who have PA distensibility ≥20% have optimal FC (6MWD≥400 m), whereas those with PA distensibility <20% have poor FC (6MWD<400 m; 82% sensitivity and 94% specificity; AUC=0.941, P<0.001; **Figure 4b**). Prediction of FC using CMRI-derived PA distensibility index may be important and noteworthy in a clinical setting, because accurate non-invasive evaluation of PA distensibility index could be useful in certain circumstances in which PA stiffness and FC are unknown and difficult to measure.

Study Limitations

The small subject group and prospective manner of the study may have influenced the strength of the association. Because the disease is rare, however, the present report could be noteworthy within this field. In the 20% of the present subjects with congenital heart disease, 6MWD could be underestimated due to chronic adaptation, but in the case of atrial septal defect, compared to the most common form of Eisenmenger syndrome, a large ventricular septal defect, the response of the RV to pulmonary circulation tends to resemble that of idiopathic PAH.[32] In patients with PH, severe pulmonary regurgitation (PR) is sometimes observed. In the present study severe PR was observed in 3 patients out of 35, suggesting that the PA distensibility index would be overestimated.[33–35] PA stiffness index and CMRI-derived PA distensibility index showed a good relation between these 2 variables due to CSA difference of the items in the formula. In CMRI analysis, measurement of the CSA of the main PA on CMRI could be confounded by intra-observer and inter-observer variability, because more than 2 radiologists were involved in data interpretation.

Conclusions

There is potential for the use of CMRI to be expanded in the treatment of PAH in the clinical context. In the present study, non-invasive CMRI-derived PA distensibility index correlated with PA stiffness and predicted FC in patients with PAH. Further, large-scale study is needed, however, to establish the ability of CMRI-derived PA distensibility index to predict FC.

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