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ORIGINAL PAPER

Pulmonary arterial stiffness assessed by cardiovascular magnetic resonance imaging is a predictor of mild pulmonary arterial hypertension

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Abstract

Early detection of mild pulmonary arterial hypertension (PAH) based on clinical evaluation and echocardiography remains quite challenging. In addition to enhanced right ventricular (RV) assessment, cardiac magnetic resonance (CMR) imaging may accurately reflect deleterious remodeling and increased stiffness of the central pulmonary arteries based on pulsatility, or percent change of the PA during the cardiac cycle. The purpose of this study is to assess the utility of measuring PA pulsatility by CMR as a potential early maker in PAH. We hypothesize that pulsatility may help discriminate mild PAH from normal control subjects. Consecutive patients with PAH (n = 51) were prospectively enrolled to receive same day CMR and right heart catheterization (RHC). PA stiffness indices including pulsatility, distensibility, compliance, and capacitance were calculated. Comparisons were made between patients with varying severities of PAH and normal controls (n = 18). Of the 51 subjects, 20 had mild PAH, and 31 moderate-severe based on hemodynamic criteria. PA pulsatility demonstrated a progressive decline from normal controls (53%), mild PAH (22%), to moderate-severe PAH (17%; $p < 0.001$). There was no difference in RV size, function or mass between mild PAH and normal controls. PA pulsatility below 40% had an excellent ability to discriminate between mild PAH and normal controls with a sensitivity of 95% and specificity of 94%. CMR assessment of PA stiffness may noninvasively detect adverse pulmonary vascular remodeling and mild PAH, and thus be a valuable tool for early detection of PAH. Trial Registration: ClinicalTrials.gov Identifier: NCT01451255; https://clinicaltrials.gov/ct2/show/NCT01451255.

Keywords Magnetic resonance imaging · Pulmonary hypertension · Pulmonary artery pulsatility

Abbreviations

6MWT	6 min walk test
AUC	Area under the curve
BMI	Body mass index
BNP	Brain natriuretic peptide
BSA	Body surface area
CO	Cardiac output
CMR	Cardiac magnetic resonance
EDV	End diastolic volume
EF	Ejection fraction
EIPH	Exercise induced pulmonary hypertension
ESV	End systolic volume
FAC	Fractional area of change
LVEDP	Left ventricular end diastolic pressure
maxA	Maximum pulmonary artery area
MLWHFQ	Minnesota living with heart failure questionnaire
minA	Minimum pulmonary artery area
mPAP	Mean pulmonary artery pressure
NPV	Negative predictive value
PA	Pulmonary artery

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PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PP	Pulse pressure
PPV	Positive predictive value
PVH	Pulmonary venous hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
ROC	Receiver operating characteristic
RV	Right ventricle
RVEDV	Right ventricle end diastolic volume
RVEF	Right ventricle ejection fraction
RVESV	Right ventricle end systolic volume
RVSP	Right ventricle systolic pressure
SD	Standard deviation
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion
VA	Ventricular-arterial
WU	Wood's units

Introduction

The normal pulmonary circulation is a low pressure, low resistance system with highly compliant and elastic vessels [1]. Pulmonary arterial hypertension (PAH) is a devastating disease of the pulmonary vasculature characterized by increased stiffness secondary to deleterious remodeling. Higher resistance and worsened compliance causes elevated pulmonary pressures leading to excessive afterload and right ventricular (RV) dysfunction. Although pharmacologic therapy is effective in PAH, it is unfortunately often detected late in the disease with advanced vascular stiffness and RV dysfunction. It has been suggested that central loss of PA compliance can be implicated as a manifestation of progressing PAH [2–5]. While the pathophysiology remains complex, the predominant mechanisms include endothelial dysfunction and loss of pulmonary vasculature elasticity with replacement by hypertrophy and fibrosis [6, 7].

Early recognition of PAH is essential, as evidence-based therapeutic interventions are known to improve survival and functional capacity [8, 9]. Unfortunately, early diagnosis remains challenging. Doppler echocardiography (echo) has a fundamental role in screening for PAH by estimating pulmonary pressures and assessment of RV size and systolic function [8]. However, detection of RV enlargement or dysfunction and tricuspid regurgitant velocity by echo are insensitive in mild PAH [10, 11]. We evaluated pulmonary artery pulsatility by cardiac magnetic resonance imaging as an indicator of mild PAH.

Recorded as a percentage, pulsatility reflects the cross-sectional area change of the main PA and is a useful surrogate marker for central PA stiffness [2, 12–14]. Due to its high resolution, CMR is an ideal imaging modality to detect PA pulsatility [15, 16]. The ability of pulsatility to discriminate patients with high pressure, more severe, or advanced pulmonary hypertension (PH) from those without PH has been previously demonstrated [2, 12–14]. However, minimal data on the ability of pulsatility to discriminate mild or lower pressure PAH is currently available. Accordingly, the primary aim of this study was to determine if pulsatility could adequately discriminate patients with mild PAH from normal controls.

Methods

Study participants and clinical data

The study was approved by the Mayo Clinic Institutional Review Board and all patients provided written informed consent. Seventy-two consecutive subjects with known or suspected PAH were prospectively enrolled at an accredited PAH center. Eighteen control subjects without symptoms, history of cardiovascular disease, or PAH risk factors were also recruited. All control subjects had a normal examination and limited bedside echo to exclude structural heart disease or elevated right-sided pressures. In the study group, echo was performed for estimation of systolic and mean PA pressure, right atrial pressure, and markers of RV size and function (e.g. RV transverse diameter, fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and qualitative visual assessment of RV systolic function) as previously described [17, 18]. Patients with a calculated mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg or RV systolic pressure (RVSP) $\geq$ 35 mmHg on echo and clinical suspicion for PAH underwent same day CMR and right heart catheterization (RHC). Group I PAH was defined and classified by expert consensus from the 5th world health symposium on PH [19]. Participants with other causes of PH were excluded. Participants were still included if PCWP exceeded 15 mmHg provided that they were still deemed to have predominant PAH based on an elevated transpulmonary gradient, PVR, and clinical designation.

Right heart hemodynamic catheterization

Hemodynamic data were collected at end-expiration with the patient in the supine position and averaged in triplicate. Standard measurements including right atrial pressure, systolic and diastolic RV and PA pressures, and left heart filling pressure (pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP)) were obtained. Cardiac output (CO) was calculated using the Fick method and indexed to body surface area (BSA). Pulse pressure (PP; PA systolic-PA diastolic pressure),

mPAP ((systolic + 2*Diastolic)/3), and pulmonary vascular resistance (PVR; (mPAP-PCWP or LVEDP)/CO) were calculated. Patients were characterized as having PAH if their mPAP ≥ 25 mmHg, PCWP < 15 mmHg, and PVR ≥ 3 Wood units (WU). Patients with mixed group 1 and group 2 PH were included only if the elevation of mPAP was determined to be primarily elevated secondary to pulmonary vascular resistance (PVR) out of proportion to the wedge pressure. Subjects were arbitrarily classified as mild PAH if their mPAP was between 25 and 40 mmHg and moderate-severe PAH if their mPAP was ≥ 40 mmHg; any patient who's echo was concerning for PAH by tricuspid regurigitation but was found to have an mPAP less than 25 mmHg was labeled in a group as echo positive, catheterization negative (Echo+/Cath-).

Cardiac magnetic resonance imaging

CMR was performed on a 1.5T Siemens scanner (Erlanger, Germany) using a phased-array surface coil with patients lying supine and images obtained at end-expiration. Standard long- and short-axis cine images were acquired using steady-state with free precession imaging sequence, as previously described [20]. A stack of short-axis slices covering the heart was acquired using a slice thickness and slice gap of 8 and 2 mm, respectively, to measure systolic and diastolic ventricular volumes. To obtain cross-sectional imaging of the main PA, a plane parallel to the PA on axial imaging was performed. An orthogonal view was prescribed, followed by a cross-sectional image approximately 1–2 cm beyond the pulmonary valve (Fig. 1). Phase-contrast imaging was performed perpendicular to the main PA using a gradient echo sequence (TR 57.9 ms, TE 2.77 ms, flip angle 30°, slice thickness 5.5 mm, field of view 400; 20 reconstructed phases), with velocity encoding at 150 cm/s (which was increased as necessary to avoid velocity aliasing).

The endocardium and epicardium from short- and long-axis cine images were manually traced for left and right ventricular volumes in systole and diastole to measure end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and mass using dedicated software (Circle 42; Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The observer was blinded to all clinical data. Phase-contrast images were manually traced for measurement of maximal (maxA) and minimal (minA) PA area for the calculation of multiple parameters of PA stiffness, as shown in Table 1. Three patients (2 mild PAH, 1 moderate-severe) with PAH were excluded from analysis due to uninterpretable image quality from gating artifacts.

Statistical analysis

Continuous variables were represented by the sample median and range and categorical variables were expressed as number and percentage of patients. Baseline patient characteristics, medications, laboratory test results, echo

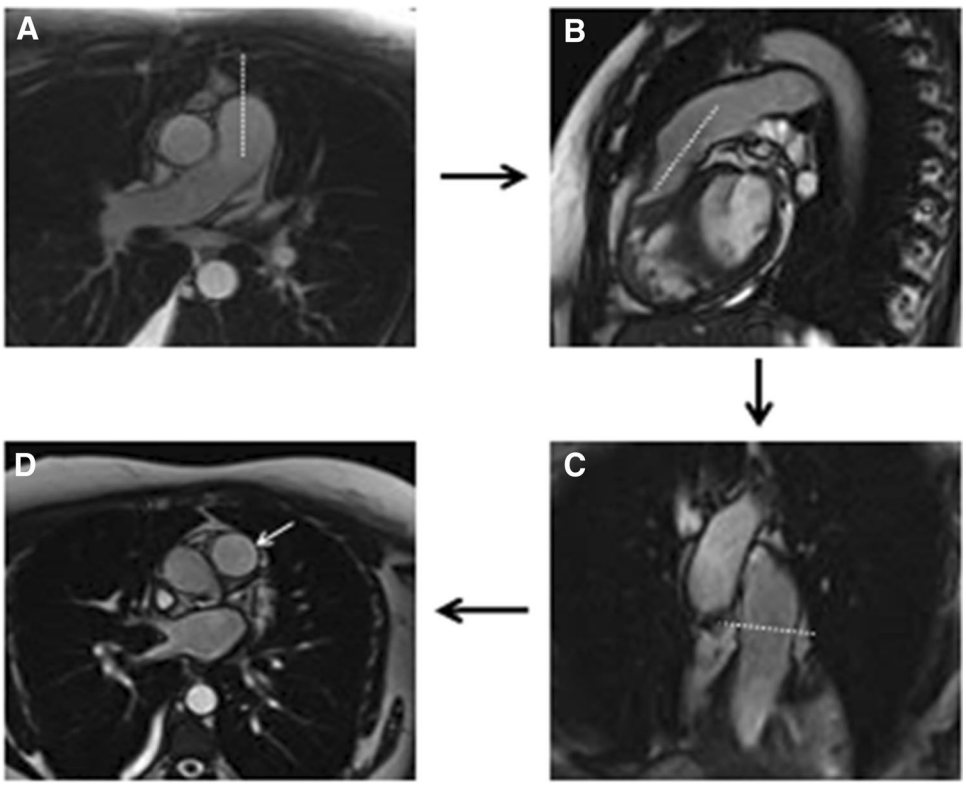

Fig. 1 CMR cross-sectional image of the main pulmonary artery. From the axial image, prescribing a plane parallel to the main PA (dashed line; **a**) results in image (**b**). From this view (**b**), an orthogonal image is prescribed which results in image (**c**). By prescribing a perpendicular sequence 1–2 cm above the pulmonary valve, a circular main PA (arrow) is obtained for calculation of pulsatility (**d**)

Table 1 Pulmonary artery stiffness indices

Index	Formula
Pulsatility (%)	[(maxA–minA)/minA]
Compliance (cm^2/mmHg)	[(maxA–minA)/PP]
Capacitance (ml/mmHg)	SV/PP
Distensibility (%/mmHg)	[(maxA − minA)/ PP * minA] * 100

maxA maximum pulmonary artery area; *minA* minimum pulmonary artery area; *PP* pulse pressure; *SV* stroke volume

measures, and invasive hemodynamics were compared between the four patient groups using Fisher's exact test or a Kruskal–Wallis rank sum test. For the ability of CMR measures to predict severity of PAH, the two comparisons were of interest: (1) normal versus the combined group of mild PAH and moderate-severe PAH patients, (2) normal versus mild PAH patients. Comparisons of PA pulsatility as well as other measures between these three sets of patient groups were made using a Wilcoxon rank sum test and also by estimating area under the receiver operating characteristic (ROC) curve (AUC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. All statistical analysis was performed using SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean time from echo to CMR was 36 ± 49 SD days, and that of CMR and RHC was 3.5 ± 0.2 SD hours. Ninety (including controls) participants were prospectively enrolled. Despite careful clinical and Doppler echo assessment, 14 subjects were excluded as hemodynamic assessment on RHC did not meet criteria for PH and subsequently labeled in the Echo+/Cath- group. Four patients were reclassified as having predominant pulmonary venous hypertension and thus excluded. In total, 18 normal controls, 20 mild PAH, and 31 moderate-severe PAH and 14 Echo+/Cath- subjects were grouped for comparison (Fig. 2).

Baseline patient characteristics for each of the patient groups are displayed in Table 2. There was a difference in age between the three groups ($P < 0.001$), with a younger age observed in normal controls (median = 43 years) compared to mild PAH (median = 63 years), and moderate-severe PAH (median = 56 years) patients. Most subjects were female which was consistent between groups ($P = 0.34$). As expected, there was a marked difference between groups in WHO ($P = 0.014$) and 6MWT ($P = 0.004$) with the moderate-severe PAH group having shorter 6MWT and a higher proportion of WHO III and IV symptomatology. There was no significant difference between PH groups with respect to PAH therapy. Brain natriuretic peptide differed significantly across groups ($P < 0.001$) and were highest in the moderate-severe group and lowest in normal control subjects. With respect to RV function, CMR found no difference between the mild PAH group and the normal controls (RVEF 48% in normals, 52% in mild). Specifically, no difference was observed in RVEDV, RVEF, or RV mass (All $P > 0.29$; Fig. 3). However, comparisons between the mild PAH group and moderate-severe group noted significant differences between these variables, as expected.

All of the stiffness indices were significantly correlated with mPAP (all $P < 0.001$). Pulsatility was associated with a Spearman's r of − 0.62 (Fig. 4A). The strongest correlation with mPAP was observed for distensibility $r = -0.83$ (Fig. 4B). Correlations between PA stiffness indices and PVR were noted as well (all $P < 0.001$). Specifically, PVR was significantly correlated with PA pulsatility ($r = -0.57$), distensibility ($r = -0.76$), compliance ($r = -0.76$) and capacitance ($r = -0.78$). While these correlations were significant and in some cases strongly correlated, each stiffness index had a curvilinear relationship with mPAP, whereby beyond a certain pulmonary pressure there was no significant change in PA stiffness.

The evaluation of our primary CMR measure of PA pulsatility noted significant differences among the various groups (Table 3). Pulsatility values were highest for normal patients (53%, Range = 34–91%), followed by a sharp decline in mild PAH patients (22%, Range = 7–43%), and moderate-severe PAH participants (17%, Range = 2–27%; $P < 0.001$). Despite no difference in RV function between the normal controls and mild PAH, there were significant differences in PA pulsatility (Figs. 3, 5).

The sensitivity and specificity estimates for pulsatility in detecting PAH are shown in Table 4. In comparing patients without PAH to those with mild PAH, a PA pulsatility of ≤ 40% resulted in a sensitivity of 95.0% and a specificity of 94.4% for detection of PAH. The utility of CMR measures for distinguishing between patients with varying degrees of PAH is shown in Table 3. Specifically, pulsatility successfully discriminated patients with confirmed PAH (the combined group of mild and moderate-severe PAH patients) and those without PAH an AUC of 0.99 and $P < 0.001$. When excluding the moderate-severe PAH patients and comparing the combined group of normal subjects to mild PAH patients, the diagnostic utility of pulsatility remained highly evident with a maintained AUC of 0.99, $P < 0.001$ (Fig. 6).

There was a difference in age between the three study groups. Thus, additional comparisons of PA pulsatility were performed stratifying by median age in the study cohort (≤ 56 years and > 56 years). With age-stratified analyses, there remained excellent ability for pulsatility to discriminate

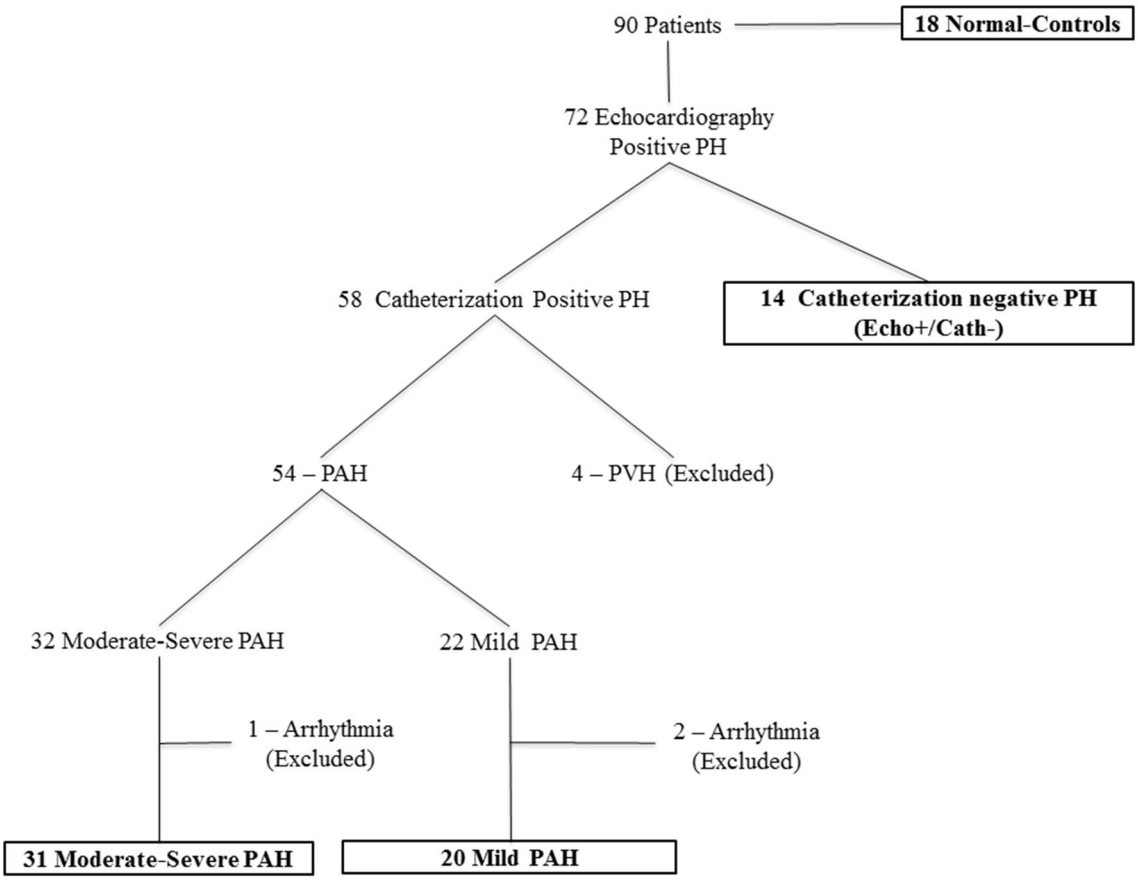

Fig. 2 Flow diagram. A breakdown of the various groups including normal controls, mild PAH, and moderate-severe PAH (*PH* pulmonary hypertension; *RHC* right heart catheterization; *CMR* cardiac magnetic resonance; *PAH* pulmonary arterial hypertension)

between patients with and without confirmed PAH (≤56 years: AUC = 0.99; >56 years: AUC = 0.91). Further age-stratified analysis between the mild PAH and the normal patients remained consistent (≤56 years: AUC = 0.97).

For the primary analysis, participants in the Echo+/Cath- group were excluded. Although their mPAP did not exceed 25 mmHg, these participants had multiple co-morbidities and in some cases well-treated PAH and thus would be inappropriate to classify in the normal control group. However, when the Echo+/Cath- group was included with the control group and compared to all those with PAH or in those with only mild PAH, the AUC fell slightly to 0.96 and 0.93, respectively ($P < 0.001$ for both). Thus, a PA pulsatility < 40% was highly associated with PAH regardless of whether the Echo+/Cath- group was included.

Discussion

In contrast to right ventricular dysfunction and enlargement, which occurred in advanced PAH, we found abnormal PA stiffness in patients with mild PAH, and it was significantly reduced when compared to normal controls. A pulsatility index ≤ 40% demonstrated excellent ability to predict low pressure, mild PAH with a sensitivity of 95.0%, and a specificity of 94.4%. With a NPV of 94.4%, a pulsatility > 40% would appear to be an acceptable marker to exclude mild PAH. This finding suggests that this measurement could be utilized in the noninvasive detection of mild PAH.

Although abnormal measurements of PA pulsatility have previously been described in PAH, only minimal data regarding PA stiffness in patients with mild, low pressure PAH have been published, as prior studies predominantly included more advanced PH [2, 12–14, 21–31]. Sanz et al. retrospectively analyzed 42 PAH patients comparing those without PH (n = 17) to PAH patients with an average mPAP of 49 mmHg. Patients with PAH were shown to have markedly reduced pulsatility (17.4 vs 49.1%) [24]. A subgroup of patients with exercise-induced PH (EIPH; n = 6) in the aforementioned study by Sanz et al. demonstrated that despite normal invasive hemodynamics at rest, those patients had lower PA compliance (8.4 vs. 15 mm^2/mmHg) and capacitance (3.7 vs. 5.2 mm^3/mm Hg) but not pulsatility (38.8 vs. 55.2%) [13]. In a well-designed study from Swift and

Table 2 Patient characteristics

Variable	Normal (N = 18)	Mild PAH (N = 20)	Mod-Sev PAH (N = 31)	P-value
Patient characteristics				
Age (years)	43 (35, 57)*	63 (38, 81)	56 (32, 79)	< 0.001
Gender (% male)	5 (27.8%)	5 (25.0%)	10 (32.3%)	0.52
WHO class				< 0.001
I		2 (10.0%)*	2 (6.5%)	
II		5 (25.0%)*	4 (12.9%)	
III		11 (55.0%)	20 (64.5%)*	
IV		2 (10.0%)	5 (16.1%)*	
Associated PAH	0 (0.0%)	11 (55.0%)*	4 (12.9%)	0.001
Congenital	0 (0.0%)	0 (0.0%)	1 (3.2%)	1.00
Systemic hypertension	0 (0.0%)	10 (50.0%)	16 (51.6%)	< 0.001
BMI (kg/m^2)	26.3 (18.4, 46.8)	29.2 (17.2, 52.3)	28.0 (18.1, 47.0)	0.26
MLWHF questionnaire		50 (4, 94)	49 (2, 95)	0.86
6-min walk distance (m)		352 (107, 541)	293 (138, 480)*	0.03
PAH therapy		6 (20.0%)	14 (45.2%)	0.29
Dual PAH therapy		3 (15.0%)	10 (32.3%)	0.13
Laboratory				
Creatinine (mg/dl)	0.8 (0.6, 1.1)	0.8 (0.6, 2.2)	0.9 (0.5, 4.9)*	0.02
BNP (pg/ml)	25 (5, 56)*	71 (13, 761)*	223 (9, 903)*	< 0.001
Echocardiogram				
RVSP (mmHg)		41 (24, 61)	73 (39, 128)*	< 0.001
PA mean (mmHg)		32 (19, 43)	52 (34, 86)*	< 0.001
TAPSE (mm)		22 (9, 28)	17 (10, 28)*	< 0.001
RV area diastole (cm^2)		18 (12.0, 29.0)	30.0 (11.6, 77.0)*	< 0.001
FAC (%)		37.3 (7.9, 61.8)	34.6 (15.6, 69.8)	0.38
RHC				
Heart rate (bpm)		77 (49, 117)	78 (51, 116)	0.19
Systolic BP (mmHg)		130 (88, 193)	122 (87, 160)	0.06
RA pressure (mmHg)		6 (0, 12)	9 (1, 29)*	0.018
$PA_{systolic}$ pressure (mmHg)		52 (40, 63)	89 (61, 130)*	< 0.001
$PA_{diastolic}$ pressure (mmHg)		23 (15, 30)	37 (23, 57)*	< 0.001
mPAP (mmHg)		32 (25, 40)	55 (37, 78)*	< 0.001
PCWP or LVEDP (mmHg)		12 (3, 16)	14 (5, 36)	0.06
PVR (dynes-sec-cm^{-5})		285 (130, 455)	736 (176, 1840)*	< 0.001
PA pulse pressure (mmHg)		30 (14, 43)	55 (34, 88)*	< 0.001
Cardiac output (L/min)		4.94 (2.44, 9.21)	4.25 (1.70, 9.89)	0.13
Cardiac index ($L/min/m^2$)		2.81 (1.45, 4.63)	2.34 (1.03, 4.32)	0.12
CMR				
PA pulsatility (%)	53 (34, 91)*	22 (7, 43)*	17 (2, 27)*	< 0.001
RVEDV (ml)	113 (55, 218)	123 (53, 163)	146 (70, 356)*	< 0.001
RVEDV Index (ml/m^2)	63.2 (34.4, 109)	62.6 (27.9, 116)	81.4 (35.5, 155)*	< 0.001
RVESV (ml)	60 (31, 115)	56 (31, 132)	90 (33, 266)*	< 0.001
RVESV Indexed (ml/m^2)	33 (16, 58)	31 (16, 67)	51 (15 118)*	< 0.001
RVEF (%)	48 (34, 67)	52 (7, 71)	42 (15, 75)*	< 0.001
RV Mass (grams)	25 (11, 43)	29 (16, 56)	47 (16, 90)*	< 0.001

The sample median (minimum, maximum) is given for continuous variables. * Represents statistical significance between groups. P-values result from a Kruskal–Wallis rank sum test or Fisher's exact test and test for overall differences between groups. *WHO* World Health Organization; *PAH* pulmonary arterial hypertension; *BMI* body mass index; *MLWHF* Minnesota living with heart failure; *BNP* brain natriuretic peptide; *RVSP* right ventricular systolic pressure; *PA* pulmonary artery; *TAPSE* tricuspid annular plane systolic excursion; *FAC* fractional area change; *BP* blood pressure; *RA* right atrial; *mPAP* mean pulmonary arterial pressure; *PCWP* pulmonary capillary wedge pressure; *LVEDP* left ventricular end-diastolic pressure; *PVR* pulmonary vascular resistance; *RVEDV* right ventricular end diastolic volume; *RVESV* right ventricular end systolic volume; *RVEF* right ventricular ejection fraction; *RV* right ventricular

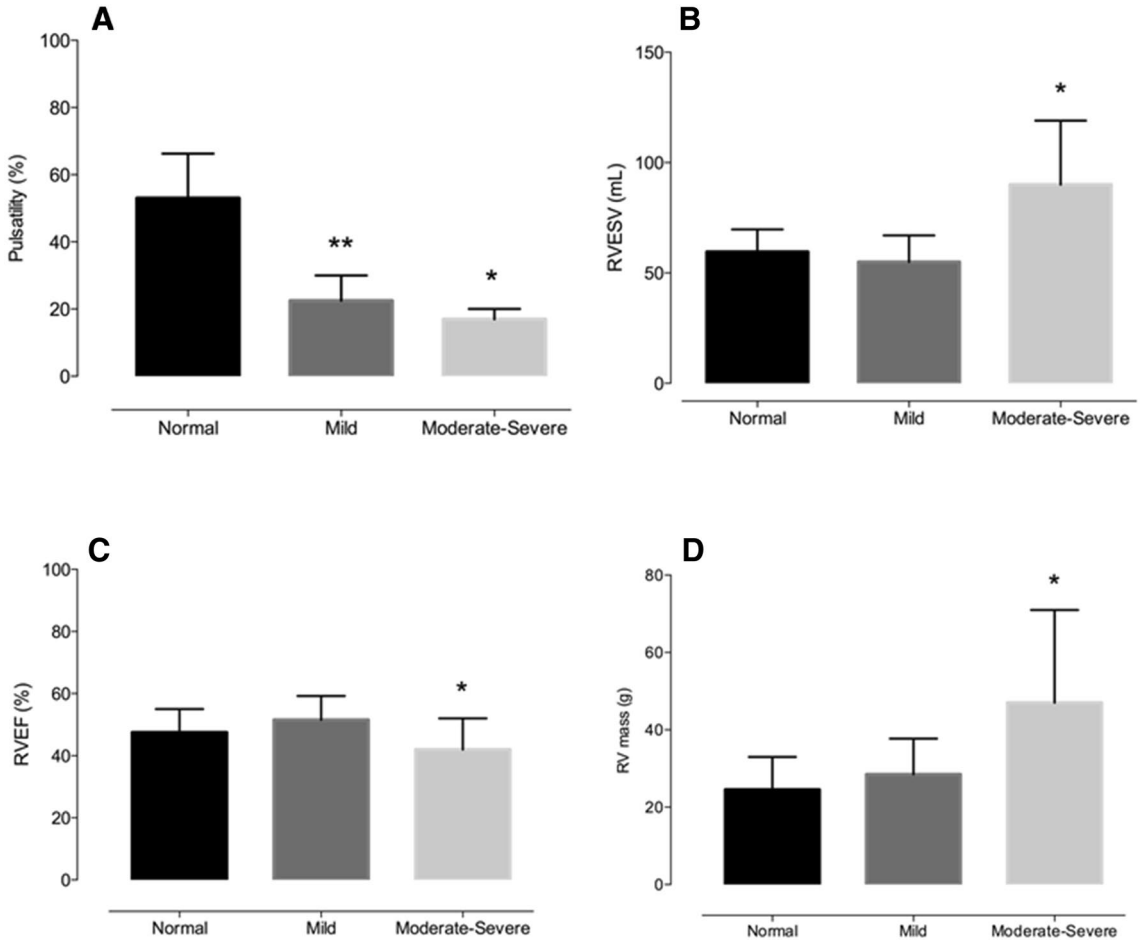

Fig. 3 PA pulsatility and RV parameters. Column graphs representing the median values between groups. **a** PA pulsatility was significantly reduced in the mild and moderate-severe patients compared to controls. Right ventricular size (right ventricular end-systolic volume, RVESV; (**b**), RV ejection fraction (**c**), and RV mass (**d**) were all worse in the moderate-severe group compared to normal controls. There was no difference in those parameters between the mild PAH subjects and normal controls. $P < 0.05$ for normal controls versus mild PAH (*) and normal controls versus moderate-severe PAH (**)

colleagues, subjects with PAH and a PVR < 4 Wood units (n = 37; average mPAP 31 mmHg) had reduced PA pulsatility of 13.0% [23]. The current study compliments these previous findings while designed to focus on low pressure mild PAH. The current data seems to reinforce and confirm the fact that PA pulsatility even in lower pressure disease states is an early marker of disease. The similar ranges of values of normal and abnormal from prior studies and the current investigation also suggests that the measurement is likely generalizable between centers.

Whether the changes in main PA stiffness represent a marker of disease or independently contribute to the pathogenesis of RV dysfunction remains an area of active investigation [32]. Strong evidence implicates distal small pulmonary vasculature in the pathogenesis of PAH due to smooth muscle hypertrophy, medial thickening, endothelial proliferation, and vasoconstriction, ultimately leading to increased resistance [8, 33, 34]. These changes are coupled to alterations in the more central pulmonary vasculature which includes loss of elastin and a transition to stiffer collagen fibers [35]. Thus, as demonstrated in our study, the main PA becomes larger and more rigid. These changes of the central PA have two major consequences. First, adverse ventriculo-arterial coupling precludes RV systolic elastance to match the increasing arterial resistance (e.g. arterial elastance), initially largely contributed to by decreased central arterial compliance and pulsatile load [4]. Second, the lack of a compliant, pulsatile PA causes more rapid transmission of the pressure pulse to the distal vasculature, thereby worsening small vessel injury. Some investigators have postulated that changes to the main PA are directly related to alterations in PVR while others have shown independent changes [2, 36–38].

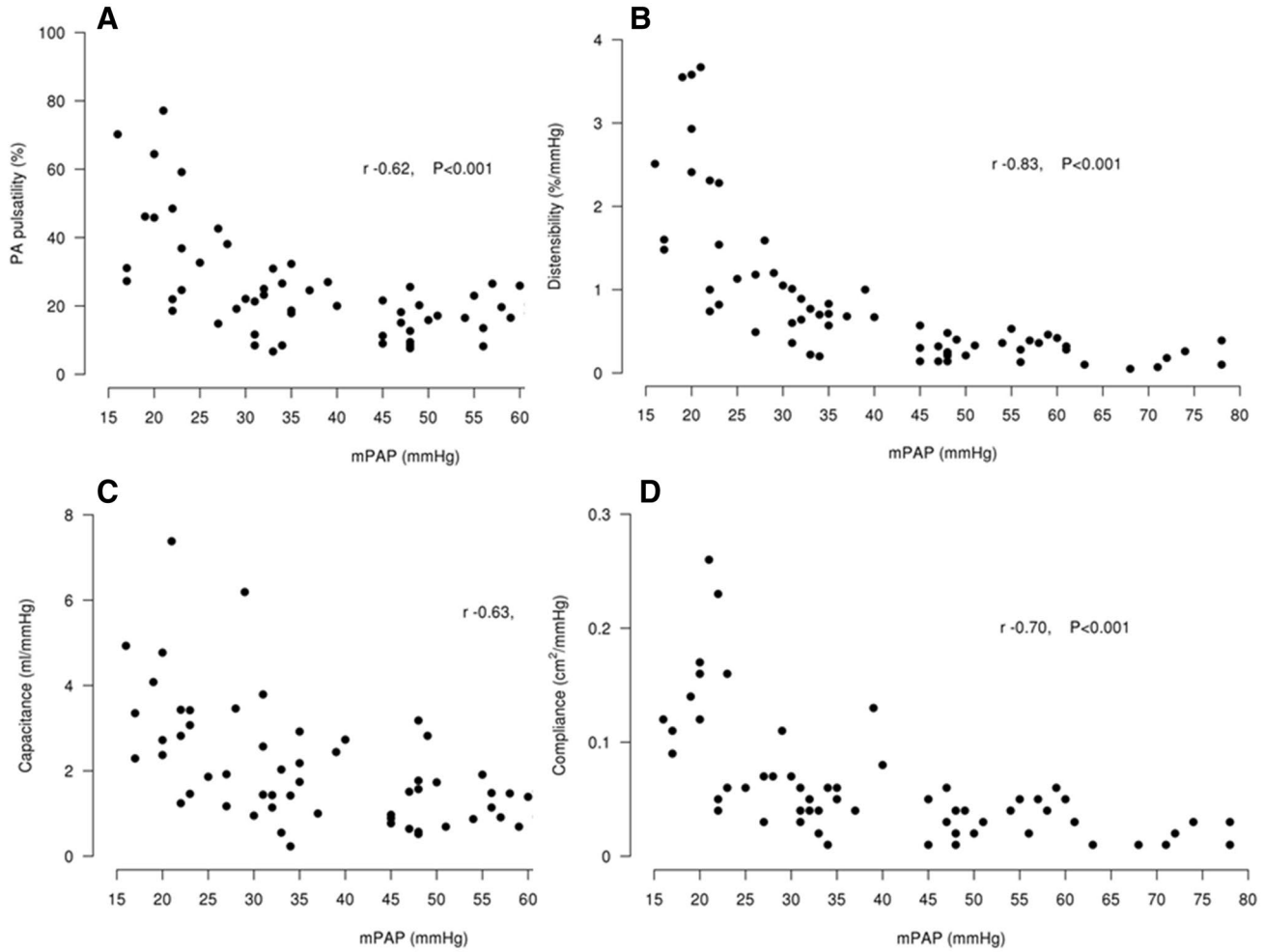

Fig. 4 Correlations of PA stiffness with pressure. Pulsatility (**a**), distensibility (**b**), capacitance (**c**), and compliance (**d**) demonstrated good correlation to mPAP based on RHC. Note the curvilinear relationship to all measurements, with sharp decline at lower pressures, but beyond a certain mPAP (≈40 mmHg), the curve becomes flattened. This suggests that beyond a particular PA pressure, there is minimal additional change in PA stiffness

Table 3 Utility of CMR for distinguishing between varying degrees of PAH

Variable	Normal (Group 1) (N = 18)	Mild PAH (Group 2) (N = 20)	Mod-Sev PAH (Group 3) (N = 31)	Groups 1 vs. Groups 2		Groups 1 vs. Group 2–3	
				AUC	P-value	AUC	P-value
PA pulsatility (%)	53 (34, 91)	22 (7, 43)	17 (2, 27)	0.99	< 0.001	0.99	< 0.001
RVEDV (ml)	113 (55, 218)	123 (53, 163)	146 (70, 356)	0.63	0.052	0.47	0.71
RVESV (ml)	60 (31, 115)	56 (31, 132)	90 (33, 266)	0.69	0.005	0.56	0.50
RVEF (%)	48 (34, 67)	52 (7, 71)	42 (15, 75)	0.68	0.007	0.56	0.46
RV Mass (grams)	25 (11, 43)	29 (16, 56)	47 (16, 90)	0.78	< 0.001	0.66	0.048

The sample median (minimum, maximum) is given. P-values result from a Wilcoxon rank sum test. *AUC* area under the receiver operating characteristic (ROC) curve; *RVEDV* right ventricular end-diastolic volume; *RVEF* right ventricular ejection fraction; *RVESV* right ventricular end systolic volume

This study included a large cohort of mild, low pressure PAH patients prospectively enrolled in the evaluation of PA stiffness. Although stringent methods for recruitment of mild PAH patients were applied, there was still a large subset with normal hemodynamics on RHC despite suggestion of PH on echocardiography (who incidentally had PA pulsatility

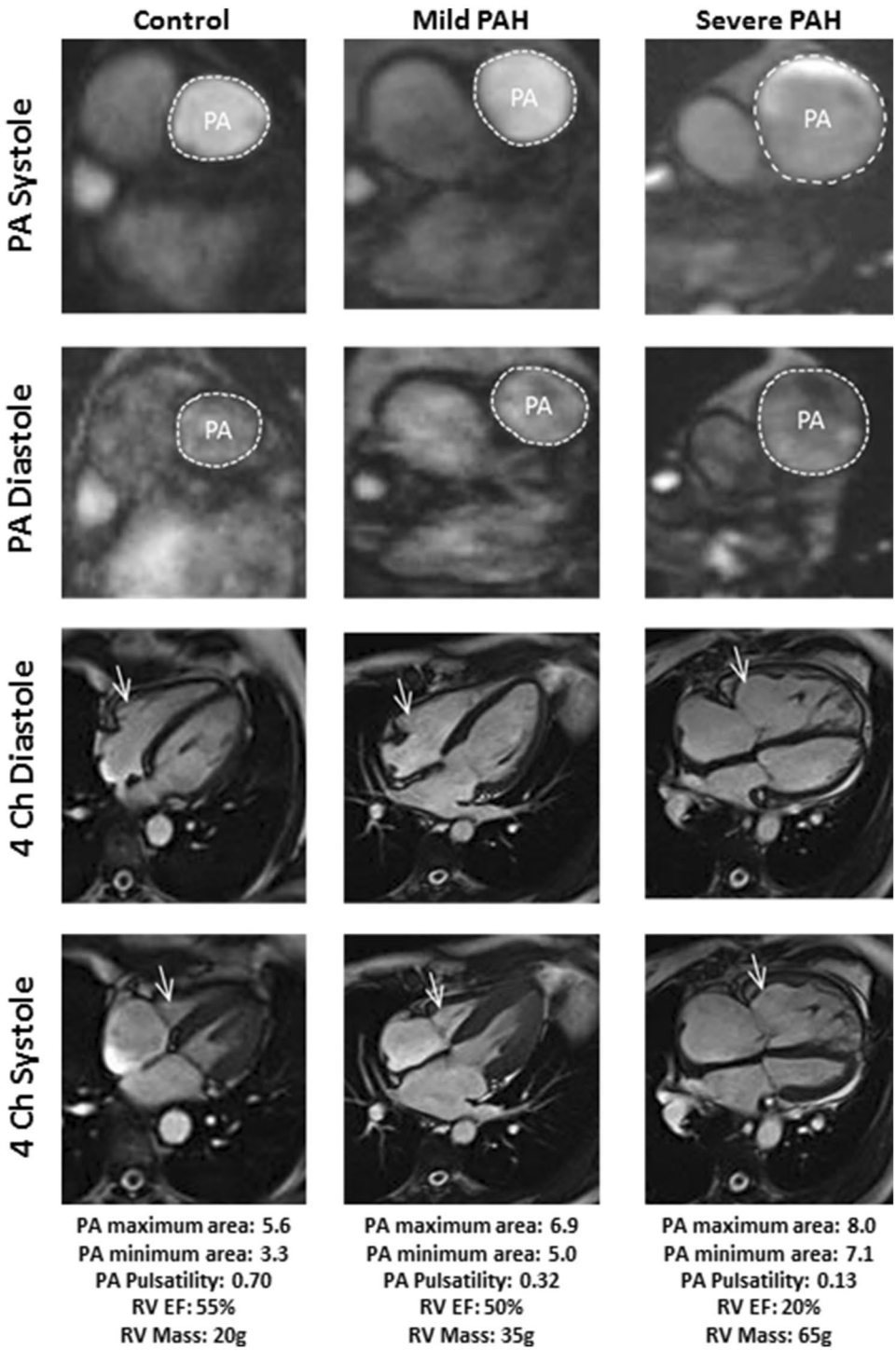

Fig. 5 CMR images of the main pulmonary artery and right ventricle. Selected CMR images from representative subjects in the various groups. Cross-sectional systolic and diastolic still-frames demonstrating PA pulsatility. Diastolic and systolic 4-chamber images reflecting right ventricular (arrow) size and function with measurements below. While pulsatility was lower in mild PAH, RV size and function were not different compared to normal controls. However, in those with moderate-severe PAH compared to mild PAH, pulsatility was lower and severity of RV size and function were worse

values which were intermediate between normal and mild PAH). This underscores the difficulty of detecting mild PAH based on clinical evaluation and Doppler echo alone. It is possible that some patients with mild PAH were not adequately captured due to inadequate Doppler assessment. The echocardiogram in this study was used as a screening tool for the control group to rule out evidence of pulmonary hypertension. Due to technical limitations and funding constraints, this group did not receive a formal echocardiogram assessment which could limit our comparison of the groups. That said, each normal control participant had a comprehensive history and physical examination as well as hand-held bedside echocardiographic screening from a board-certified echocardiographer. Further, CMR has become a standard in volume function analysis and was used for our final comparisons and thus is complementary to echo. Another limitation

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value of PA pulsatility between varying degrees of PAH

PA pulsatility	Fraction (%) of patients			
	Sensitivity	Specificity	PPV	NPV
Comparison of the normal and mild PAH patient groups				
≤0.75	20/20 (100.0%)	3/18 (16.7%)	20/35 (57.1%)	3/3 (100.0%)
≤0.55	20/20 (100.0%)	8/18 (44.4%)	20/30 (66.7%)	8/8 (100.0%)
≤0.40	19/20 (95.0%)	17/18 (94.4%)	19/20 (94.4%)	17/18 (94.4%)
≤0.35	18/20 (90.0%)	17/18 (94.4%)	18/19 (94.4%)	17/19 (89.5%)
≤0.25	13/20 (65.0%)	18/18 (100.0%)	13/13 (100.0%)	18/25 (72.0%)
Comparison of the normal and combined group of mild PAH and moderate-severe PAH patients				
≤0.75	51/51 (100.0%)	3/18 (16.7%)	51/66 (77.3%)	3/3 (100.0%)
≤0.55	51/51 (100.0%)	8/18 (44.4%)	51/61 (83.6%)	8/8 (100.0%)
≤0.40	50/51 (98.0%)	17/18 (94.4%)	50/51 (98.0%)	17/18 (94.4%)
≤0.35	49/51 (96.1%)	17/18 (94.4%)	49/50 (98.0%)	17/19 (89.5%)
≤0.25	41/51 (80.4%)	18/18 (100.0%)	41/41 (100.0%)	18/28 (64.3%)

NPV negative predictive value; *PPV* positive predictive value

of the study is that CMR and RHC were not performed simultaneously as this was not possible at our institution. However, all studies were performed on the same day (mean 3.5 h apart). While all subjects were diagnosed with PAH, some were on PH-specific therapies while others were not, thus potentially affecting the degree of PA stiffness. Lastly, age differences may have also substantially impacted the data. Normal controls were younger than those with PAH, and certainly our data seem to suggest some impact on aging and central PA stiffness although others have demonstrated no association between age or gender and PA stiffness [13].

Specific pharmacological therapy for PAH has greatly enhanced functional capacity, delayed disease progression, and perhaps improved survival (compared to historical controls), but patients enrolled in these trials are symptomatic and have at least moderately elevated pressures, and often some degree of RV dysfunction [8, 39–44]. Our results demonstrate that pulsatility may aid in the detection of mild PAH, particularly in those patients who are at 'high risk' or display worrisome clinical features but in whom conventional testing is insufficient or inconclusive. In these cases, pulsatility may offer an alternative means to establish a diagnosis and perhaps allow therapy to be instituted in patients with mild disease before irreversible changes in the RV and distal pulmonary vasculature occur.

In conclusion, the examination of RV function, PA hemodynamics, and vascular wall stiffness using CMR may allow for enhanced diagnostic characterization. Noninvasive measurement of PA pulsatility could be a potential marker for detection of patients with mild PAH, thus potentially allowing for early intervention before the development of cardiac dysfunction and RV failure.

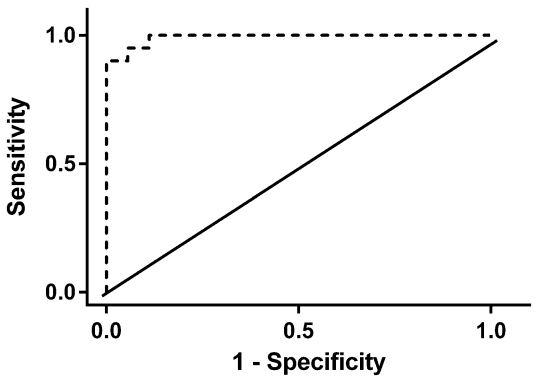

Fig. 6 ROC curve for pulsatility. PA pulsatility < 40% was highly predictive of PAH when normal controls were compared to participants with mild PAH (AUC 99%, P < 0.001)

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Compliance with ethical standards

Conflict of interest All authors involved have no conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Milnor WR, Jose AD, Mcgaff CJ (1960) Pulmonary vascular volume, resistance, and compliance in man. Circulation 22(1):130–137
2. Stevens GR, Garcia-Alvarez A, Sahni S, Garcia MJ, Fuster V, Sanz J (2012) RV dysfunction in pulmonary hypertension is independently related to pulmonary artery stiffness. JACC: Cardiovasc Imaging 5(4):378–387
3. Vanderpool RR, Pinsky MR, Naeije R, Deible C, Kosaraju V, Bunner C, Mathier MA, Lacomis J, Champion HC, Simon MA (2015) RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart 101(1):37–43. https://doi.org/10.1136/heartjnl-2014-306142
4. Sanz J, Garcia-Alvarez A, Fernandez-Friera L, Nair A, Mirelis JG, Sawit ST, Pinney S, Fuster V (2012) Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. Heart 98(3):238–243. https://doi.org/10.1136/heartjnl-2011-300462
5. Rolf A, Rixe J, Kim WK, Börgel J, Möllmann H, Nef HM, Liebetrau C, Kramm T, Guth S, Krombach GA (2014) Right ventricular adaptation to pulmonary pressure load in patients with chronic thromboembolic pulmonary hypertension before and after successful pulmonary endarterectomy-a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 16:96
6. Tuder RM, Archer SL, Dorfmuller P, Erzurum SC, Guignabert C, Michelakis E, Rabinovitch M, Schermuly R, Stenmark KR, Morrell NW (2013) Relevant issues in the pathology and pathobiology of pulmonary hypertension. J Am Coll Cardiol 62(25):D4-D12. https://doi.org/10.1016/j.jacc.2013.10.025
7. Botney MD (1999) Role of hemodynamics in pulmonary vascular remodeling: implications for primary pulmonary hypertension. Am J Respir Crit Care Med 159(2):361–364
8. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GYH, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel M-P, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 37(1):67–119. https://doi.org/10.1093/eurheartj/ehv317
9. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BKS, Sitbon O, Souza R, Torbicki A, Zeng XF, Rubin LJ, Simonneau G, Investigators S (2013) Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. New Engl J Med 369(9):809–818. https://doi.org/10.1056/Nejmoa1213917
10. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM (2009) Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. American journal of respiratory critical care medicine 179(7):615–621
11. Fisher M, Criner G, Fishman A, Hassoun P, Minai O, Scharf S, Fessler H (2007) Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 30(5):914–921
12. Stevens GR, Lala A, Sanz J, Garcia MJ, Fuster V, Pinney S (2009) Exercise Performance in Patients With Pulmonary Hypertension Linked to Cardiac Magnetic Resonance Measures. J Heart Lung Transpl 28(9):899–905. https://doi.org/10.1016/j.healun.2009.05.004
13. Sanz J, Kariisa M, Dellegrottaglie S, Prat-Gonzalez S, Garcia MJ, Fuster V, Rajagopalan S (2009) Evaluation of Pulmonary Artery Stiffness in Pulmonary Hypertension With Cardiac Magnetic Resonance. Jacc-Cardiovasc Imag 2(3):286–295. https://doi.org/10.1016/j.jcmg.2008.08.007
14. Gan CT-J, Lankhaar J-W, Westerhof N, Marcus JT, Becker A, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A (2007) Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. CHEST Journal 132(6):1906–1912
15. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, Ho VB, Jerosch-Herold M, Kramer CM, Manning WJ (2010) ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 55(23):2614–2662
16. Ibrahim E-SH, Shaffer JM, White RD (2011) Assessment of pulmonary artery stiffness using velocity-encoding magnetic resonance imaging: evaluation of techniques. Magnetic resonance imaging 29(7):966–974
17. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE (2004) Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. CHEST J 126(1_suppl):14S-34S
18. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23(7):685–713
19. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Sanchez MAG, Kumar RK, Landzberg M, Machado RF (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25):D34-D41
20. Kramer C, Barkhausen J, Flamm S (2008) Standardized CMR protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 10:35
21. Tardivon AA, Mousseaux E, Brenot F, Bittoun J, Jolivet O, Bourroul E, Duroux P (1994) Quantification of hemodynamics in primary pulmonary-hypertension with magnetic-resonance-imaging. Am J Respir Crit Care Med 150(4):1075–1080
22. Swift AJ, Rajaram S, Hurdman J, Hill C, Davies C, Sproson TW, Morton AC, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG (2013) Noninvasive estimation of PA pressure, flow, and resistance With CMR imaging derivation and prospective validation study from the ASPIRE registry. Jacc-Cardiovasc Imag 6(10):1036–1047. https://doi.org/10.1016/j.jcmg.2013.01.013
23. Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot C, Kiely DG, Wild JM (2012) Pulmonary artery relative area change detects mild elevations in pulmonary vascular resistance and predicts adverse outcome in pulmonary hypertension. Invest Radiol 47(10):571–577. https://doi.org/10.1097/RLI.0b013e31826c4341
24. Sanz J, Kuschnir P, Rius T, Salguero R, Sulica R, Einstein AJ, Dellegrottaglie S, Fuster V, Rajagopalan S, Poon M (2007) Pulmonary arterial hypertension: noninvasive detection with phase-contrast MR imaging. Radiology 243(1):70–79. https://doi.org/10.1148/radiol.2431060477

25. Garcia-Alvarez A, Fernandez-Friera L, Mirelis JG, Sawit S, Nair A, Kallman J, Fuster V, Sanz J (2011) Non-invasive estimation of pulmonary vascular resistance with cardiac magnetic resonance. Eur Heart J 32(19):2438–2445. https://doi.org/10.1093/eurheartj/ehr173
26. Frank H, Globits S, Glogar D, Neuhold A, Kneussl M, Mlczoch J (1993) Detection and quantification of pulmonary-artery hypertension with Mr-imaging—results in 23 patients. Am J Roentgenol 161(1):27–31
27. Boerrigter B, Mauritz G-J, Marcus JT, Helderman F, Postmus PE, Westerhof N, Vonk-Noordegraaf A (2010) Progressive dilatation of the main pulmonary artery is a characteristic of pulmonary arterial hypertension and is not related to changes in pressure. CHEST J 138(6):1395–1401
28. Jardim C, Rochitte CE, Humbert M, Rubenfeld G, Jasinowodolinski D, Carvalho CRR, Souza R (2007) Pulmonary artery distensibility in pulmonary arterial hypertension: an MRI pilot study. Eur Respir J 29(3):476–481
29. Kang K-W, Chang H-J, Kim Y-J, Choi B-W, Lee HS, Yang W-I, Shim C-Y, Ha J, Chung N (2011) Cardiac magnetic resonance imaging-derived pulmonary artery distensibility index correlates with pulmonary artery stiffness and predicts functional capacity in patients with pulmonary arterial hypertension. Circ J 75(9):2244–2251
30. Lankhaar J-W, Westerhof N, Faes TJC, Tji-Joong Gan C, Marques KM, Boonstra A, van den Berg FG, Postmus PE, Vonk-Noordegraaf A (2008) Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. Eur Heart J 29(13):1688–1695. https://doi.org/10.1093/eurheartj/ehn103
31. Ley S, Mereles D, Puderbach M, Gruenig E, Schöck H, Eichinger M, Ley-Zaporozhan J, Fink C, Kauczor H-U (2007) Value of MR phase-contrast flow measurements for functional assessment of pulmonary arterial hypertension. Eur Radiol 17(7):1892–1897
32. Tan Y, Tseng P-O, Wang D, Zhang H, Hunter K, Hertzberg J, Stenmark KR, Tan W (2014) Stiffening-induced high pulsatility flow activates endothelial inflammation via a TLR2/NF-κB pathway. PLoS ONE 9(7):e102195
33. Milnor WR, Conti CR, Lewis KB, O'Rourke MF (1969) Pulmonary arterial pulse wave velocity and impedance in man. Circ Res 25(6):637–649
34. Hopkins RA, Hammon J, McHale PA, Smith PK, Anderson RW (1980) An analysis of the pulsatile hemodynamic responses of the pulmonary circulation to acute and chronic pulmonary venous hypertension in the awake dog. Circ Res 47(6):902–910
35. Linehan JH, Dawson CA, Rickaby DA, Bronikowski TA (1986) Pulmonary vascular compliance and viscoelasticity. J Appl Physiol 61(5):1802–1814
36. Lankhaar J-W, Westerhof N, Faes TJ, Marques KM, Marcus JT, Postmus PE, Vonk-Noordegraaf A (2006) Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 291(4):H1731-H1737
37. Zuckerman BD, Orton EC, Stenmark KR, Trapp JA, Murphy JR, Coffeen PR, Reeves JT (1991) Alteration of the pulsatile load in the high-altitude calf model of pulmonary hypertension. J Appl Physiol 70(2):859–868
38. Gorgulu S, Eren M, Uslu N, Ozer O, Nurkalem Z (2006) The determinants of right ventricular function in patients with atrial septal defect. Int J Cardiol 111(1):127–130
39. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W (1990) Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol): results of a randomized trial. Ann Intern Med 112(7):485–491
40. Galié N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, Zwicke D, Naeije R, Shapiro S (2005) Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 46(3):529–535
41. Rubin LJ, Badesch DB, Barst RJ, Galiè N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I (2002) Bosentan therapy for pulmonary arterial hypertension. New Engl J Med 346(12):896–903
42. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F (2001) Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebocontrolled study. The Lancet 358(9288):1119–1123
43. Galiè N, Manes A, Branzi A (2003) Prostanoids for pulmonary arterial hypertension. Am J Respirat Med 2(2):123–137
44. McGoon MD, Frost AE, Oudiz RJ, Badesch DB, Galie N, Olschewski H, McLaughlin VV, Gerber MJ, Dufton C, Despain DJ (2009) Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. CHEST J 135(1):122–129