Pulmonary Arterial Hypertension: MR Imaging-derived First-Pass Bolus Kinetic Parameters Are Biomarkers for Pulmonary Hemodynamics, Cardiac Function, and Ventricular Remodeling[1]

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Purpose: To prospectively compare contrast material–enhanced (CE) magnetic resonance (MR) imaging–derived right-to-left ventricle pulmonary transit time (PTT), left ventricular (LV) full width at half maximum (FWHM), and LV time to peak (TTP) between patients with pulmonary arterial hypertension (PAH) and healthy volunteers and to correlate these measurements with survival markers in patients with PAH.

Materials and Methods: This HIPAA-compliant study received institutional review board approval. Written informed consent was obtained from all participants. Forty-three patients (32 with PAH [29 women; median age, 55.4 years], 11 with scleroderma but not PAH [seven women; median age, 58.9 years]) underwent right-sided heart catheterization and 3-T CE cardiac MR imaging. Eighteen age- and sex-matched healthy control subjects (12 women; median age, 51.7 years) underwent only CE MR imaging. A short-axis saturation-recovery gradient-echo section was acquired in the basal third of both ventricles, and right-to-left-ventricle PTT, LV FWHM, and LV TTP were calculated. Statistical analysis included Kruskal-Wallis test, Wilcoxon rank sum test, Spearman correlation coefficient, multiple linear regression analysis, and Lin correlation coefficient analysis.

Results: Patients had significantly longer PTT (median, 8.2 seconds; 25th–75th percentile, 6.9–9.9 seconds), FWHM (median, 8.2 seconds; 25th–75th percentile, 5.7–11.4 seconds), and TTP (median, 4.8 seconds; 25th–75th percentile, 3.9–6.5 seconds) than did control subjects (median, 6.4 seconds; 25th–75th percentile, 5.7–7.1 seconds; median, 5.2 seconds; 25th–75th percentile, 4.1–6.1 seconds; median, 3.2 seconds; 25th–75th percentile, 2.8–3.8 seconds, respectively; $P < .01$ for each) and subjects with scleroderma but not PAH (median, 6.5 seconds; 25th–75th percentile, 5.6–7.0 seconds; median, 5.0 seconds; 25th–75th percentile, 4.0–7.3 seconds; median, 3.6 seconds; 25th–75th percentile, 2.7–4.0 seconds, respectively; $P < .02$ for each). PTT, LV FWHM, and LV TTP correlated with pulmonary vascular resistance index ($P < .01$), right ventricular stroke volume index ($P \leq .01$), and pulmonary artery capacitance ($P \leq .02$). In multiple linear regression models, PTT, FWHM, and TTP were associated with mean pulmonary arterial pressure and cardiac index.

Conclusion: CE MR-derived PTT, LV FWHM, and LV TTP are noninvasive compound markers of pulmonary hemodynamics and cardiac function in patients with PAH. Their predictive value for patient outcome warrants further investigation.

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In patients with pulmonary arterial hypertension (PAH), increased vascular pressure and resistance cause right ventricular (RV) dysfunction, leading to RV failure and death. Diagnosis and treatment of PAH are challenging, and overall prognosis is poor, with 15% mortality in the 1st year and mean survival of 2–3 years despite state-of-the-art therapy (1). While traditional survival predictors include right atrial pressure, pulmonary vascular resistance (PVR), and cardiac index (CI) (1,2), recent studies have identified RV stroke volume index and pulmonary vascular capacitance as predictors of scleroderma-associated PAH (3). These parameters can be assessed with right-sided heart catheterization (RHC), which is also required to make a definitive diagnosis of PAH. However, the invasive nature and associated radiation exposure of this procedure warrant alternate methods for repeated evaluation of disease progression and treatment response. Echocardiography is the noninvasive modality most commonly used to evaluate RV function and structure and estimate pulmonary pressures and resistance. Thus, it is recommended as a screening tool in the diagnosis of PAH (1,4). However, this modality has several drawbacks, including user dependency, oftentimes unfavorable echo windows, and varying accuracy in the estimation of pulmonary hemodynamics (4,5).

Cardiac magnetic resonance (MR) imaging is reliable and reproducible in the noninvasive assessment of cardiac structure and function and is considered the standard of reference in RV evaluation (6,7). Furthermore, CE MR imaging enables monitoring of the passage of a contrast material bolus through the lungs without exposing the patient to radiation. Pulmonary pressure and resistance, as well as cardiac function, are major determinants of blood flow through the pulmonary vasculature (8,9). Consequently, first-pass bolus kinetic parameters assessed with CE MR imaging, such as pulmonary transit time (PTT), left ventricular (LV) full width at half maximum (FWHM), and LV time to peak (TTP) may be altered in patients with PAH and may contain potentially valuable information for patient care. PTT describes the transit time of blood between the right and left ventricles, while FWHM and LV TTP represent the shape of the first-pass contrast material bolus in the LV cavity and contain information on bolus dispersion, which is affected by hemodynamic variables, such as PVR and stroke volume.

We hypothesized that first-pass bolus kinetic parameters reflect alterations in pulmonary pressure and vascular resistance, as well as RV function, in patients with PAH. Thus, the purpose of the present study was to prospectively compare CE MR imaging–derived right-to-left ventricle PTT, LV FWHM, and LV TTP between patients with PAH and healthy volunteers and to correlate these measurements with survival markers in patients with PAH.

Advances in Knowledge

- MR imaging–derived first-pass contrast bolus parameters (pulmonary transit time [PTT], left ventricular [LV] full width at half maximum [FWHM], and LV time to peak [TTP]) are significantly prolonged in patients with pulmonary arterial hypertension (PAH) compared with those in age- and sex-matched healthy control subjects and patients with scleroderma but not PAH.
- PTT, LV FWHM, and LV TTP correlate significantly with known invasive and noninvasive survival markers in patients with PAH.
- PTT, LV FWHM, and LV TTP are associated with pulmonary hemodynamics and right ventricular function.

Implication for Patient Care

- MR imaging–derived PTT, LV FWHM, and LV TTP are noninvasive biomarkers used in the combined evaluation of pulmonary hemodynamics and cardiac function in patients with PAH, and their predictive value with regard to patient survival warrants further evaluation.

Materials and Methods

Study Design and Patient Population

This prospective study was approved by the Johns Hopkins University institutional review board and adhered to Health Insurance Portability and Accountability Act requirements. Written informed consent was obtained from all study participants.

Between January 2008 and October 2010, we enrolled 43 consecutive patients (36 women; median age for all patients, 58.7 years; 25th–75th percentile range, 50.2–66.6 years) who were known to have or who were suspected of having

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Abbreviations:
CE = contrast material–enhanced
CI = cardiac index
FWHM = full width at half maximum
LV = left ventricular
PAH = pulmonary arterial hypertension
PAP = pulmonary arterial pressure
PCWP = pulmonary capillary wedge pressure
PP = pulse pressure
PTT = pulmonary transit time
PVR = pulmonary vascular resistance
RHC = right-sided heart catheterization
RV = right ventricular
TTP = time to peak

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Guarantors of integrity of entire study, J.A.C.L., P.M.H., J.V.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.S., M.L.S., S.M., N.L., J.A.C.L., P.M.H., J.V.; clinical studies, J.S., S.M., R.E.G., J.O.M., J.A.C.L., P.M.H., J.V.; statistical analysis, J.S., M.L.S., S.M., D.B., N.L., P.M.H., J.V.; and manuscript editing, J.S., M.L.S., S.M., R.E.G., J.O.M., D.B., N.L., J.A.C.L., D.A.B., P.M.H., J.V.

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Potential conflicts of interest are listed at the end of this article.

PAH and who were referred from our pulmonary hypertension clinic. Patients underwent clinically indicated RHC and cardiac MR imaging on the same day. Contraindications to gadolinium chelates (including hypersensitivity to the contrast agent or a glomerular filtration rate <30 mL/min) or to MR imaging in general (ferromagnetic material, claustrophobia) served as exclusion criteria. All patients were assessed for functional capacity according to New York Heart Association criteria, and a 6-minute walk test was performed.

We also included 18 age- and sex-matched healthy control subjects (12 women; median age for all subjects, 51.7 years; 25th–75th percentile range, 48.2–57.7 years) who were free of known causes of PAH. A lipid profile was obtained for each subject, and the Framingham risk score was calculated (10). A 10-year risk score of more than 10% or contraindications to gadolinium chelates (the same as for patients) were the exclusion criteria in this group.

RHC Performance

RHC was performed by one of two experienced investigators (R.E.G., 3 years of experience with more than 200 RHCs performed; J.O.M., 5 years of experience with more than 500 RHCs performed) with expertise in pulmonary hypertension. A dual-lumen catheter was inserted through the right internal jugular vein and advanced to the right side of the heart. Cardiopulmonary hemodynamic parameters, including systolic, diastolic, and mean pulmonary arterial pressure (PAP); pulse pressure (PP) (calculated by subtracting the diastolic PAP from the systolic PAP); mean right atrial pressure; pulmonary capillary wedge pressure (PCWP); and thermodilution cardiac output were assessed. The following indexes were calculated: Stroke volume was calculated by dividing cardiac output by heart rate. Stroke volume index was calculated by dividing stroke volume by body surface area. CI was calculated by dividing thermodilution cardiac output by body surface area. PVR index (PVRI) was calculated with the following equation: PVRI = 80 × (mPAP−PCWP)/CI, where mPAP is mean PAP. Pulmonary artery capacitance was calculated by dividing stroke volume by PP.

In accordance with standard international definitions and on the basis of RHC results, patients were divided into two groups: those with PAH (mean PAP > 25 mm Hg, PCWP ≤ 15 mm Hg) and those without PAH (mean PAP ≤ 25 mm Hg) (1).

Cardiac MR Protocol

Each study participant underwent MR imaging with a 3-T unit (Magnetom Trio; Siemens Medical Systems, Erlangen, Germany). Prior to the examination, a 20-gauge intravenous catheter was inserted into an antecubital vein and connected to a power injector (MR Spectris; Medrad, Pittsburgh, Pa).

To assess PTT, a 1:10 diluted bolus (0.0025 mmol per kilogram of body-weight) of gadopentetate dimeglumine (Magnevist; Bayer Healthcare, Wayne, NJ) was injected intravenously and followed by 20 mL of normal saline, both at a rate of 5 mL/sec. One diastolic short-axis section was acquired in the basal third of both ventricles by using an electrocardiographically gated saturation-recovery gradient-echo turbo fast low-angle shot sequence with the following parameters: repetition time msec/echo time msec, 2.1/1.05; flip angle, 12°; minimal field of view; matrix, 192 × 116; in-plane spatial resolution range, 1.7 × 2.1 to 2.1 × 2.5 mm; acquisition duration, 175 msec; section thickness, 10 mm; and acceleration factor (generalized autocalibrating partially parallel acquisition), two. Imaging was performed over a period of 40 heartbeats with a 1 R wave to R wave temporal resolution. Subjects were instructed to hold their breath at a midinspirational level.

For biventricular functional and structural assessment, short-axis images were obtained during breath holds from base to apex by using a retrospectively electrocardiographically gated turbo fast low-angle shot segmented gradient-echo cine sequence. Typical imaging parameters were as follows: 6.5/3.2; flip angle, 15°; bandwidth, 260 Hz per pixel; acceleration factor (generalized autocalibrating partially parallel acquisition), two; minimal field of view; matrix, 256 × 192; spatial resolution, 1.4 × 1.4 mm; section thickness, 8 mm; section gap, 2 mm; and 30 reconstructed cardiac phases with an acquired temporal resolution of 30–40 msec.

Image Analysis

All images were analyzed with custom in-house software by an investigator (J.S.) with 2.5 years of cardiac MR imaging experience who was blinded to participants' diagnoses and RHC results. To measure interobserver variability of bolus kinetic parameters, a second blinded observer (M.L.S., 4.5 years of cardiac MR imaging experience) evaluated 28 study participants (13 control subjects, 15 patients). Post-processing times for the first investigator (J.S.) were measured as the time from when the images were loaded into our analysis software to when the results were copied into our database. They were assessed for each study participant and parameter separately.

First-pass bolus kinetic parameters were determined on the short-axis saturation-recovery gradient-echo images. After correcting for possible breathing motion, two regions of interest were placed in the RV and LV cavities, including as much blood pool as possible without extending into the myocardium, papillary muscles, or trabeculations (Fig E1 [online]). Time-intensity curves were generated for passage of the contrast material bolus through the regions of interest by using average signal intensity (Fig 1). First-pass bolus kinetic parameters were derived from these curves: Right-to-left ventricle PTT was calculated by subtracting the time of peak enhancement in the right ventricle from that in the left ventricle. TTP was calculated as the interval from the first appearance of the contrast material bolus to its peak signal intensity, where *first appearance* was defined as the time of 20% peak signal intensity. FWHM was defined as width of the time-intensity curve at half its maximum signal intensity (Fig 1). Although both LV and RV dispersion parameters

were assessed, only LV parameters were used to account for the influence of the lung on these parameters. For all measurements, signal intensities were baseline corrected.

Biventricular mass and function were assessed on the short-axis cine MR images. We used dedicated software (QMass 6.1; Medis, the Netherlands) to manually contour the endo- and epicardial borders of both ventricles during end diastole and end systole, defined by their respective smallest and largest volumes. The following parameters were quantified: end-diastolic volume, end-systolic volume, end-diastolic mass, ejection fraction, stroke volume, and cardiac output. All parameters were indexed to the body surface area. The ventricular mass index was calculated by dividing RV mass by LV mass.

Echocardiography

To evaluate the potential influence of valvular insufficiencies on the shape of the contrast material bolus, we reviewed results from clinical echocardiographic studies performed within 12 months of the CE MR examination. The degree of regurgitation was graded in accordance with recommendations by the American Society of Echocardiography. A score of 0 indicated no regurgitation; a score of 1, mild regurgitation; a score of 2, moderate regurgitation; and a score of 3, severe regurgitation. To evaluate overall regurgitant valve disease, all four individual valve scores in a study participant were added to yield a composite valvular regurgitation score (0–12, higher scores indicated more-severe disease) (11).

Statistical Analysis

Statistical analysis was performed by using Stata statistical software (version 10; Stata, College Station, Tex). Data are presented as the median, with the accompanying 25th and 75th percentiles. A P value of less than .05 was considered indicative of a significant difference. A Shapiro-Wilk test was first used to evaluate for normal distribution of values in the participant groups. Since many of the tested variables were not normally distributed, nonparametric tests were used. For comparisons between all three groups, a global test of significance (Kruskal-Wallis test with Bonferroni correction accounting for the number of comparisons) was performed to determine differences between median values. If a difference was significant, all three pairs of groups were assessed individually by using a two-sided Wilcoxon rank sum test (12,13). Correlation of bolus kinetic parameters with biventricular mass and function, as well as correlation with pulmonary hemodynamic parameters, was tested by using the Spearman correlation coefficient (ρ) with Bonferroni correction. Interobserver agreement for PTT, FWHM, and TTP was tested by using Lin concordance correlation coefficients (14). Multiple linear regression analysis was implemented to estimate the relationship of PTT, FWHM, and TTP with age, composite valvular regurgitation score, mean PAP, and RV CI.

Results

Population

All study participants completed the RHC and MR examinations without serious adverse events. Of the 43 enrolled patients, we used RHC to confirm that 32 had PAH (29 women; median age, 55.4 years; 25th–75th percentile range, 50.2–66.8 years; median mean PAP, 40 mm Hg; 25th–75th percentile range, 29–49 mm Hg), including 21 patients with scleroderma-associated PAH and 11 patients with idiopathic PAH. The remaining 11 patients had underlying scleroderma but did not have PAH (seven women; median age, 58.9 years; 25th–75th percentile range, 52.8–66.1 years; mean PAP, 17 mm Hg; 25th–75th percentile range, 15–20 mm Hg). There were no differences in height, weight, or body surface area between the groups (Table E1 [online]).

First-Pass Bolus Kinetic Parameters

Because of severe motion artifacts in one patient with PAH, FWHM and TTP could not be analyzed. In a second patient with PAH, the circulation time was so slow that the downslope of the time-intensity curve was not captured long enough to enable us to calculate FWHM. In the remaining patients with PAH, right-to-left-ventricle PTT (median, 8.2 seconds; 25th–75th percentile range, 6.9–9.9 seconds), LV FWHM (median, 9.0 seconds; 25th–75th percentile range, 6.6–12.3 seconds), and LV TTP (median, 4.8 seconds; 25th–75th percentile range, 3.9–6.5 seconds) were significantly longer than those in patients with scleroderma but without PAH (median, 6.5 seconds; 25th–75th percentile range, 5.6–7.0 seconds; P = .006; median, 5.9 seconds; 25th–75th percentile range, 5.2–8.5 seconds; P = .01; and median, 3.6 seconds; 25th–75th percentile range, 2.7–4.0 seconds; P = .02, respectively) and control subjects (median, 6.4 seconds; 25th–75th percentile range, 5.7–7.1 seconds; P = .0003; median, 5.7 seconds; 25th–75th percentile range, 5.3–7.9 seconds; P = .0002; and median, 3.2 seconds; 25th–75th percentile range, 2.8–3.8 seconds; $P < .0001$, respectively) (Fig 2). There were no significant differences between control subjects and patients with scleroderma but not PAH (Table 1). In the entire study population (n = 61),

Figure 1

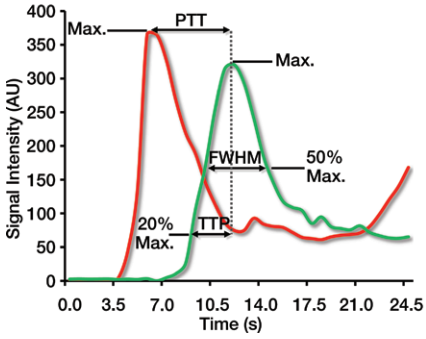

Figure 1: Time-intensity curves show passage of the contrast material bolus through the regions of interest in the right (red) and left (green) ventricular cavities and signify the calculated first-pass bolus kinetic parameters: peak-to-peak PTT, FWHM, and TTP. *Max* = maximum baseline-corrected signal intensity.

Table 1

Cardiac Function, Pulmonary Hemodynamics, and First-Pass Bolus Kinetic Parameters

Parameter	PAH ($n = 32$)	Scleroderma without PAH ($n = 11$)	Control Subjects ($n = 18$)	*P* Value
RHC				
Mean PAP (mm Hg)	40* (29–49)	17* (15–20)	NA	<.0001*
Systolic PAP (mm Hg)	65* (47.5–84.5)	29* (27–35)	NA	<.0001*
Mean right arterial pressure (mm Hg)	7.0 (3.0–8.0)	4.0 (3.0–6.0)	NA	.08
PVR index (Dyne sec/cm^5/m^2)	964* (605–1428)	244* (214–370)	NA	<.0001*
PCWP (mm Hg)	9.5 (7–11)	7 (6–8)	NA	.06
RV stroke volume index (mL/m^2)	35.8* (28.8–41.6)	43.6* (38.0–52.4)	NA	.004*
CI (l/min/m^2)	2.76 (2.19–3.16)	2.75 (2.61–3.40)	NA	.30
Pulmonary artery capacitance (mL/mm Hg)	1.45* (0.95–2.62)	3.73* (2.73–4.39)	NA	<.0001*
LV function (MR imaging)				
End-diastolic volume index (mL/m^2)	53.7†‡ (44.2–63.6)	60.8† (57.9–68.4)	68.4‡ (56.2–72.4)	.03§
End-systolic volume index (mL/m^2)	19.9 (14.9–22.6)	18.7 (17.8–27.7)	22.9 (17.2–28.3)	.49
Stroke volume index (mL/m^2)	34.4‡ ([26.9–43.0)	40.5 (36.1–42.4)	42.9‡ (37.6–47.2)	.02§
CI (L/min/m^2)	2.74 (2.00–3.13)	2.97 (2.44–3.28)	3.01 (2.63–3.29)	.63
Ejection fraction (%)	65.3 (59.1–68.8)	67.8 (57.0–70.0)	66.0 (59.8–70.4)	<.99
End-diastolic mass index (g/m^2)	62.7‡ (55.8–72.2)	71.3 (61.5–74.6)	70.2‡ (65.4–81.2)	.08
RV function (MR imaging)				
End-diastolic volume index (mL/m^2)	81.8 (75.2–92.9)	71.4 (62.3–85.2)	73.4 (60.8–84.0)	.43
End-systolic volume index (mL/m^2)	42.2†‡ (34.6–59.4)	32.1† (22.3–44.8)	31.8‡ (21.5–39.7)	.003§
Stroke volume index (mL/m^2)	34.3‡ (27.1–42.8)	40.6 (35.7–42.3)	42.3‡ (38.2–46.8)	.04§
CI (L/min/m^2)	2.9 (2.0–3.2)	3.0 (2.4–3.3)	2.9 (2.6–3.3)	<.99
Ejection fraction (%)	45.0*‡ (29.9–51.1)	55.5* (48.5–61.0)	58.4‡ (53.3–64.2)	<.0003§
End-diastolic mass index (g/m^2)	36.5*‖ (22.8–52.3)	21.8* (19.5–28.4)	26.0‖ (23.8–29.7)	.02§
Ventricular mass index	0.49*‡ (0.39–0.72)	0.35* (0.31–0.38)	0.34‡ (0.31–0.40)	<.0003§
First-pass bolus kinetic parameters				
PTT (sec)	8.2*‡ (6.9–9.8)	6.5* (5.6–7.0)	6.4‡ (5.9–7.1)	.0003§
LV FWHM (sec)	9.0*‡ (6.6–12.3)	5.9* (5.2–8.5)	5.7‡ (5.3–7.9)	.0015§
LV TTP (sec)	4.8*‡ (3.9–6.5)	3.6* (2.7–4.0)	3.2‡ (2.8–3.8)	.0003§

Note.—Unless otherwise indicated, data are medians, and data in parentheses are 25th–75th percentile ranges. NA = not applicable.

* $P < .01$ for patients with PAH vs those with scleroderma but not PAH.

† $P < .05$ with the two-sided Wilcoxon rank-sum test.

‡ $P < .01$ for patients with PAH vs control subjects.

§ $P < .05$ with the Kruskal-Wallis test with Bonferroni correction.

‖ $P < .05$ for patients with PAH vs control subjects.

PTT was directly correlated with LV FWHM ($r = 0.78$, $P < .0001$) and LV TTP ($r = 0.68$, $P < .0001$); FWHM and TTP were also correlated with each other ($r = 0.84$, $P < .0001$).

RV and LV Function, Remodeling, and Pulmonary Hemodynamics

RHC and cardiac MR imaging data are given in Table 1. PTT, LV FWHM, and LV TTP were linearly correlated with biventricular dysfunction and remodeling, as well as pulmonary hemodynamics (Table 2), including established RHC-derived survival predictors (Fig 3), with the exception of mean right atrial pressure. After Bonferroni correction, most correlations remained significant. No significant correlations with age, height, BSA, or heart rate were observed.

Predictors of First-Pass Bolus Kinetic Parameters

PVR index, which contains information on pulmonary hemodynamics (mean PAP) and cardiac function (CI), showed the highest univariate correlations with first-pass bolus kinetic parameters. To determine whether mean PAP or CI have a larger influence on first-pass bolus parameters, a multivariate model was implemented, including mean PAP and CI as independent parameters. Mean PAP was an independent predictor for PTT, LV FWHM, and LV TTP. CI was an independent predictor for PTT and LV TTP. In a second step, the model was also adjusted for age. In this second model, only mean PAP remained an independent predictor for all three bolus kinetic parameters; age independently predicted PTT

Table 2

Correlations of PTT, LV FWHM, and LV TTP with Biventricular Function and Remodeling and Pulmonary Hemodynamics

	PTT (n = 43)			LV FWHM (n = 41)			LV TTP (n = 42)		
Parameter	r Value	P Value with Spearman Correlation	P Value after Bonferroni Correction	r Value	P Value with Spearman Correlation	P Value after Bonferroni Correction	r Value	P Value with Spearman Correlation	P Value after Bonferroni Correction
Age	0.23	.13	NS	0.10	.54	NS	0.04	.80	NS
Weight	0.15	.35	NS	0.02	.89	NS	0.14	.37	NS
Body surface area	0.12	.43	NS	0.04	.78	NS	0.15	.34	NS
Heart rate	0.03	.84	NS	0.08	.61	NS	−0.07	.66	NS
Six-minute walk distance	−0.35	.03	NS	−0.22	.18	NS	−0.32	.05	NS
Mean right atrial pressure	0.20	.20	NS	0.16	.32	NS	0.22	.16	NS
Mean PAP	0.56	<.0001	<.002	0.48	.001	.02	0.47	.002	.04
PA capacitance	−0.60	<.0001	<.002	−0.57	.0001	.002	−0.50	.0008	.02
PCWP	0.24	.13	NS	0.06	.73	NS	0.21	.18	NS
PVR index	0.64	<.0001	<.002	0.55	.0002	.004	0.54	.0002	.004
CI	−0.48	.001	.02	−0.39	.01	NS	−0.43	.004	NS
RV stroke volume index	−0.56	<.0001	<.002	−0.52	.0005	.01	−0.52	.0004	.01
LV end-diastolic volume index	−0.42	.006	NS	−0.35	.02	NS	−0.29	.06	NS
LV end-systolic volume index	−0.23	.14	NS	−0.06	.70	NS	0.04	.79	NS
LV ejection fraction	−0.16	.32	NS	−0.37	.02	NS	−0.40	.008	NS
LV mass index	−0.10	.53	NS	−0.25	.10	NS	−0.09	.59	NS
RV ED volume index	0.22	.16	NS	0.16	.31	NS	0.15	.35	NS
RV ES volume index	0.37	.02	NS	0.37	.02	NS	0.33	.03	NS
RV ejection fraction	−0.54	<.0001	<.002	−0.54	.0002	.004	−0.52	.0004	.008
RV mass index	0.47	.001	.03	0.24	.12	NS	0.30	.05	NS
Ventricular mass index	0.54	<.0001	<.002	0.42	.006	NS	0.40	.009	NS

Note.—NS = not significant.

with borderline significance. In a third model, composite valvular regurgitation score, mean PAP, and CI were included to estimate the influence of valvular insufficiency on the shape of the contrast material bolus. Again, only mean PAP was an independent predictor for bolus kinetic parameters (Table 3).

Echocardiography

Of the 29 patients with PAH who were evaluated with echocardiography, 24 had tricuspid regurgitation (82.8%, 20 mild cases, three moderate cases, one severe case), 14 had pulmonary regurgitation (48.3%, 12 mild cases, two moderate cases), 16 had mild mitral regurgitation (55.2%), and five had mild aortic regurgitation (17.2%). Of the 11 evaluated patients with scleroderma but not PAH, eight had mild tricuspid regurgitation (72.7%), three had mild pulmonary regurgitation (27.3%), five had mitral regurgitation (45.5%, four with mild regurgitation, one with moderate regurgitation), and two had mild aortic regurgitation (18.2%). There was no significant correlation between higher regurgitation score and longer bolus kinetic parameters for either group separately or for both groups combined.

Interobserver Variability

Correlation coefficients for interobserver concordance regarding PTT, FWHM, and TTP were 0.99, 0.999, and 0.97, respectively ($P < .0001$ each).

Postprocessing time for PTT (median, 98 seconds; 25th–75th percentile range, 75.5–133.0 seconds) was significantly shorter than that for FWHM (median, 234.5 seconds; 25th–75th percentile range, 202.75–290.75 seconds; $P = .0002$) and TTP (median, 139.5 seconds; 25th–75th percentile range, 115.75–179.75 seconds; $P = .03$). Analysis of TTP was significantly faster than that of FWHM ($P = .001$).

Discussion

In the present study, patients with PAH had significantly prolonged CE MR imaging–derived right-to-left ventricle PTT, LV FWHM, and LV TTP when compared with healthy volunteers and patients with scleroderma but not PAH. All three bolus kinetic parameters were correlated with RHC-derived pulmonary hemodynamics, RV dysfunction, and remodeling. In multiple linear regression analyses, pulmonary hemodynamics and RV function were independently associated with first-pass bolus kinetic parameters. After adjustment for age, only mean PAP remained an independent predictor of PTT, FWHM, and TTP.

Table 3

Multiple Linear Regression Models to Estimate the Relationship of mean PAP, CI, Composite Valvular Regurgitation Score, and Age with PTT, LV FWHM, and LV TTP

A: Model 1

	Mean PAP			CI		
Parameter	β	95% Confidence Interval	*P*	β	95% Confidence Interval	*P*
PTT	0.063	0.029, 0.098	.0007*	−0.97	−1.82, −0.11	.03*
LV FWHM	0.158	0.062, 0.254	.002*	…	…	NS
LV TTP	0.053	0.004, 0.101	.04*	−1.27	−2.47, −0.74	.04*

B: Model 2

	Mean PAP			Age		
Parameter	β	95% Confidence Interval	*P*	β	95% Confidence Interval	*P*
PTT	0.070	0.036, 0.104	.0002*	0.052	0.003, 0.102	.04*
LV FWHM	0.178	0.082, 0.274	.0008*	…	…	NS
LV TTP	0.056	0.006, 0.106	.03*	…	…	NS

C: Model 3

	Mean PAP			Valvular Regurgitation Score		
Parameter	β	95% Confidence Interval	*P*	β	95% Confidence Interval	*P*
PTT	0.058	0.037, 0.078	.008*	…	…	NS
LV FWHM	0.134	0.090, 0.179	.005*	…	…	NS
LV TTP	0.063	0.042, 0.085	.007*	…	…	NS

Note.—NS = not significant.

*$P < .05$ with multiple linear regression analysis.

In patients with PAH, multiple factors lead to an increase in PVR and pressure (15), which in turn causes progressive RV dysfunction. Blood flow through the lungs is mainly determined by pulmonary hemodynamics and cardiac function (8,9). Thus, changes in these parameters affect the pulmonary transit of a contrast material bolus. In the present study, this is reflected in the significantly prolonged first-pass contrast material bolus kinetic parameters.

Patients with scleroderma but not PAH had values comparable with those of healthy control subjects, suggesting that the observed changes were due to the altered pulmonary hemodynamics and cardiac function and were not due to underlying scleroderma, which was present in the majority of the patients with PAH.

Previous studies have been performed to evaluate MR imaging–derived PTT in patients with coronary artery disease, LV hypertrophy, or LV dysfunction (16,17). These patients had prolonged transit times that correlated with LV function parameters. In a recent study in patients with congestive heart failure (18), prolonged PTT was correlated with brain natriuretic peptide level, biventricular function, and systolic RV pressure.

Few studies, however, have been performed to evaluate contrast material bolus kinetic parameters in patients with RV dysfunction or altered pulmonary hemodynamics. Goldman et al (19) used CE MR imaging to examine main pulmonary artery–to–pulmonary vein transit time in 12 patients with PAH. They found correlations between transit time and systolic and mean PAP, comparable to findings in the present study. Lakoma et al (20) further evaluated pulmonary artery–to–ascending aorta PTT and FWHM in 16 patients who were to undergo a Ross procedure. PTT and bolus dispersion after the Ross procedure were longer than those in a control group and correlated with biventricular dysfunction. PTT values in the control group (mean ± standard deviation, 6.8 seconds ± 1.4) were close to those in our control group (median, 6.4 seconds; 25th–75th percentile range, 5.7–7.1 seconds). In another recent study, Sergiacomi et al (21) evaluated mean transit time and TTP in first-order pulmonary arteries of 18 patients with combined pulmonary fibrosis and emphysema by using time-resolved three-dimensional MR angiography. Patients had significantly prolonged bolus kinetic parameters compared with healthy volunteers and a significant association of mean transit time and TTP with mean PAP and PVR index, similar to our results.

Invasive hemodynamic markers, such as right atrial pressure and PVR index, are established predictors of survival in patients with PAH (2). Improvement of these parameters alone, however, does not necessarily improve clinical symptoms or patient survival (22). Rather, cardiac function and pulmonary hemodynamics need to be considered as a unit (3,4). Furthermore, it has recently been suggested that traditional predictors of survival are not sufficient for patients with PAH and connective tissue disease, including scleroderma (3,23). In these patients, decreased RV stroke volume index and pulmonary artery capacitance and increased PVR are predictive of worse outcome (3). Stroke volume index and pulmonary artery capacitance, which reflect pulsatile flow in the proximal pulmonary vasculature, are believed to be useful in the estimation of vascular compliance. Additionally, stroke volume index and pulmonary artery capacitance have been shown to be predictive of survival in patients with idiopathic PAH (24,25).

In the present study, first-pass bolus kinetic parameters were significantly correlated with RV function and remodeling, as well as with hemodynamic variables, including the aforementioned survival predictors. The strongest correlations were found with PVR index, stroke volume index and pulmonary artery capacitance, and RV

Figure 2

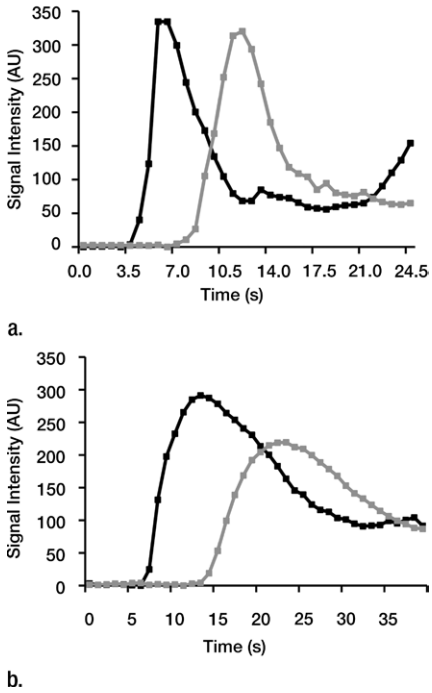

Figure 2: Time-intensity curves for RV (black) and LV (gray) bolus passage in **(a)** a 57-year-old healthy woman and **(b)** a 67-year-old woman with idiopathic PAH (mean PAP, 48 mm Hg). The curves in **a** are noticeably steeper and narrower, which is reflected in a shorter PTT (6.5 seconds), LV FWHM (4.72 seconds), and LV TTP (2.84 seconds), than those in **b** (10.9, 17.5, and 7.7 seconds, respectively).

Figure 3

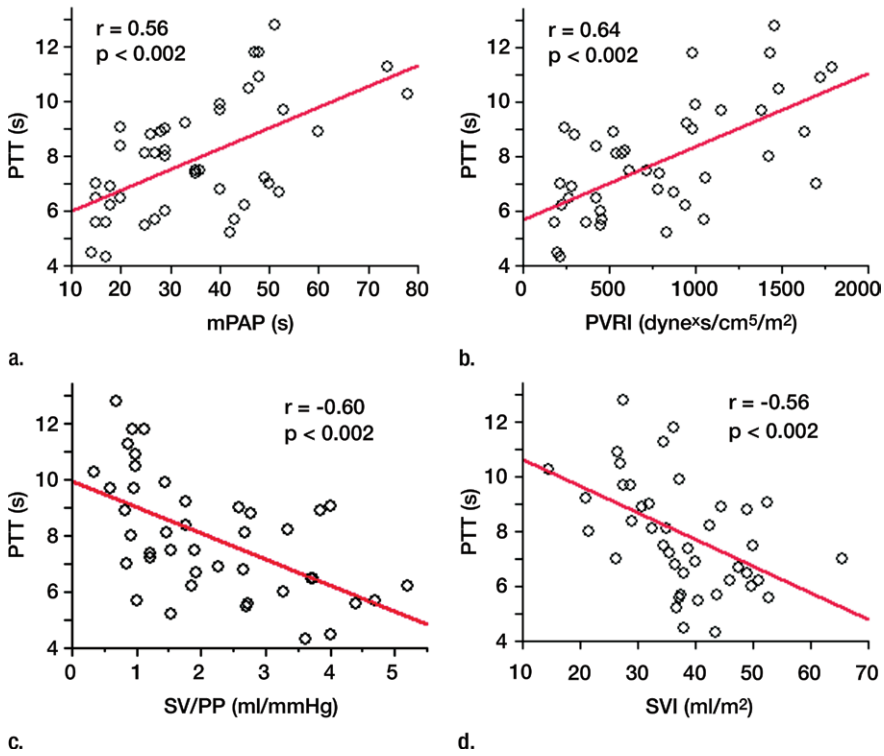

Figure 3: Graphs show correlation of PTT with **(a)** mean PAP, **(b)** PVR index *(PVRI)*, **(c)** pulmonary artery capacitance *(SV/PP)*, and **(d)** stroke volume index *(SVI)*.

stroke volume index, all of which are important survival markers in patients with scleroderma and PAH (3). Thus, PTT, LV FWHM, and LV TTP may be well suited as compound markers in the evaluation of patients known to have or suspected of having PAH.

The only survival parameter that lacked a significant correlation with bolus kinetic parameters was right atrial pressure. Despite being a well-established survival predictor, right atrial pressure recently has failed to demonstrate prognostic value in connective tissue disease–associated PAH (3,23).

Because of the risks of RHC, including invasiveness of the procedure and exposure to radiation, several authors have attempted to correlate MR imaging measurements with pulmonary hemodynamics. Parameters that showed a significant correlation with mean PAP, systolic PAP, and PVR index included several flow parameters (26–28), RV function (RV end-systolic volume and RV ejection fraction [29]), and biventricular remodeling parameters (RV wall thickness [30], ventricular mass index [31], and RV septomarginal trabeculation mass [32]). Some of these MR imaging–derived parameters, however, require extensive postprocessing and lack necessary reproducibility (5,33).

In comparison, the first-pass bolus kinetic parameters tested in the present study were quickly analyzed and had high interobserver correlation. The three first-pass bolus kinetic parameters closely correlated with each other and showed similar results regarding the correlation with survival markers, suggesting that all were well suited for evaluation of patients suspected of having PAH and noninvasive treatment monitoring. In our experience, PTT was the fastest and simplest parameter to analyze and therefore could be recommended for use in clinical practice. Furthermore, PTT was the only parameter that correlated with ventricular mass index, indicating that it also contains information pertinent to biventricular remodeling and interdependence.

In addition to the short postprocessing times, our approach of using a saturation-recovery sequence at a rate of one image per heartbeat also delivers a higher temporal resolution (median, 0.87 seconds; 25th–75th percentile range, 0.94–0.78 seconds) compared with MR angiographic techniques (1.5 seconds [21]), which may improve accuracy and detectability of smaller differences in first-pass bolus kinetic parameters.

Our study had certain limitations: First, we did not prospectively evaluate these patients for valvular heart

disease, which could have altered first-pass bolus kinetic parameters. However, we reviewed 40 clinical echocardiographic reports (29 patients with PAH and 11 patients with scleroderma but not PAH) of examinations that were performed within 12 months of MR imaging. In this retrospective review, no significant relationship between valvular regurgitation severity and the first-pass bolus kinetic parameters could be found. Second, it has been shown that varying injection durations may alter peak signal enhancement, mean transit time, and TTP (34). In the present study, injection duration varied from 0.5 second to 1.4 seconds (median, 0.8 seconds; 25th–75th percentile range, 0.6–0.9 seconds) according to body weight. However, at a temporal resolution of 0.87 seconds (25th–75th percentile range, 0.78–0.94 second), it is doubtful that these small variations had a significant effect on bolus kinetic measurements. In addition, there was no significant difference in weight, amount of administered contrast agent, or injection duration between any of the groups, and no correlation between patient weight and bolus hemodynamics could be observed. Thus, it is unlikely that the slight variance in contrast material administration significantly altered our results.

A third limitation is the need for gadolinium-containing contrast agents that have potential adverse effects, including hypersensitivity reactions and nephrogenic systemic fibrosis. However, nephrogenic systemic fibrosis occurs only in patients with advanced kidney disease (35), which was not present in any of these participants. In addition, the doses of injected contrast material were small, which may have further reduced the risk of nephrogenic systemic fibrosis.

In conclusion, PTT, LV FWHM, and LV TTP are compound markers that are useful in the noninvasive evaluation of pulmonary hemodynamics, RV function, and ventricular remodeling in patients with PAH. All three evaluated first-pass bolus hemodynamic parameters are fast and easy to analyze with high interobserver agreement. Their predictive value in regard to patient survival warrants further evaluation.

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