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Pulmonary hypertension detection by computed tomography pulmonary transit time in heart failure with reduced ejection fraction

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Aims To evaluate the relationships between pulmonary transit time (PTT), cardiac function, and pulmonary haemodynamics in patients with heart failure with reduced ejection fraction (HFrEF) and to explore how PTT performs in detecting pulmonary hypertension (PH).

Methods and results In this prospective study, 57 patients with advanced HFrEF [49 men, 51 years ± 8, mean left ventricular (LV) ejection fraction 26% ± 8] underwent echocardiography, right heart catheterization, and cardiac computed tomography (CT). PTT was measured as the time interval between peaks of attenuation in right ventricle (RV) and LV and was compared between patients with or without PH and 15 controls. PTT was significantly longer in HFrEF patients with PH (21 s) than in those without PH (11 s) and controls (8 s) ($P < 0.001$) but not between patients without PH and controls ($P = 0.109$). PTT was positively correlated with pulmonary artery wedge pressure (PAWP) ($r = 0.74$), mean pulmonary artery pressure ($r = 0.68$), N-terminal pro-B-type natriuretic peptide ($r = 0.60$), mitral ($r = 0.54$), and tricuspid ($r = 0.37$) regurgitation grades, as well as with LV, RV, and left atrial volumes (r from 0.39 to 0.64) ($P < 0.01$). PTT was negatively correlated with cardiac index (r = -0.63) as well as with LV (r = -0.66) and RV (r = -0.74) ejection fractions. PAWP, cardiac index, mitral regurgitation grade, and RV end-diastolic volume were all independent predictors of PTT. PTT value ≥14 s best-detected PH with 91% sensitivity and 88% specificity (area under the receiver operating characteristic curve: 0.95).

Conclusion In patients with HFrEF, PTT correlates with cardiac function and pulmonary haemodynamics, is determined by four independent parameters, and performs well in detecting PH.

Keywords heart failure • computed tomography • pulmonary hypertension

Introduction

In advanced heart failure (HF) with reduced ejection fraction (HFrEF), pulmonary hypertension (PH) is common, results from increased left ventricular (LV) end-diastolic pressure transmitted to the left atrium and eventually to the pulmonary circulation, and is associated with a worse outcome.[1–3] Pre-transplant PH is also associated with increased mortality after heart transplantation.[4] As transthoracic echocardiography may be imprecise for estimating the LV filling pressures,[5–7] accurate measurement of haemodynamic parameters requires right heart catheterization (RHC).[8]

The time interval necessary for a contrast bolus to pass from the right-sided to left-sided circulation, available at computed tomography (CT) and magnetic resonance (MR), the so-called pulmonary transit time (PTT), could be a surrogate for estimating these parameters in both pre-capillary and post-capillary PH.[9–11] In HFrEF, PTT has

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been shown to correlate with LV volumes, LV ejection fraction,[11–16] and pulmonary artery wedge pressure (PAWP).[11] Hence, we hypothesized that PTT might reflect PAWP and help to detect PH in patients with HFrEF. The aims of this study were, therefore, to explore the determinants of PTT in these patients, to investigate whether PTT is associated with PAWP, and to evaluate the performance of PTT in detecting PH.

Methods

Study group

Our local ethics committee approved the protocol of this prospective investigation. Between October 2015 and January 2019, we invited 63 consecutive patients with HFrEF (LV ejection fraction <40% at echocardiography) who were scheduled for pre-transplant work-up for either non-ischaemic dilated cardiomyopathy or ischaemic heart disease to participate to this investigation provided that they were older than 30 years as well as without congenital heart disease, primary valvular disease, isolated right ventricular (RV) dysfunction, acute HF defined as rapid onset or worsening of symptoms, and/or signs of HF,[17] renal insufficiency (estimated glomerular filtration rate <40 mL/min/1.73 m^2), except under dialysis, or known as intolerant to iodinated contrast medium. Three patients declined our invitation and 60 patients accepted it and gave their written informed consent. Within the same time period, we also included 15 age- and gender-matched healthy controls who had normal coronary CT and echocardiography examinations who also gave their written informed consent.

Echocardiography

Comprehensive echocardiography was performed on IE33 sonographs (Philips Medical Systems, Cleveland, OH, USA) within one day before RHC (interquartile range: 1–2 days) by experienced cardiologists (all >10 years of experience) and reviewed off-line by one experienced cardiologist (A.C.P. with 14 years' experience in echocardiography) who measured and computed LV volumes, LV ejection fraction, mitral valve inflow pattern (E and A velocity), septal mitral valve annular velocities (e'), and valvular regurgitation.[18,19] The tricuspid regurgitation gradient was computed using the peak tricuspid regurgitation velocity by continuous-wave Doppler.[8]

RHC and N-terminal pro-B-type natriuretic peptide

RHC was performed by one experienced investigator (A.C.P.) with 10 years of experience and particular expertise in HF and PH. While patients were in supine position, a 7-Fr Swan-Ganz balloon-tipped catheter was inserted into their right internal jugular vein and advanced through the right heart chambers into the pulmonary artery. Systolic, diastolic, and mean pulmonary artery pressures (PAP) and mean PAWP were measured. An 18-gauge catheter was also introduced in the left brachial artery for measurement of arterial pressure and to obtain arterial blood samples. Cardiac output was measured by the Fick method by measuring oxygen uptake (VO_2) and simultaneous radial arterial and pulmonary artery O_2 saturation. Pulmonary vascular resistance was calculated as (mean PAP minus PAWP)/cardiac output. PH due to left heart disease was defined as a mean PAP ≥25 mmHg and PAWP >15 mmHg.[8] N-terminal pro-B-type natriuretic peptide (NT-proBNP) was collected within 24 h before RHC.

CT acquisition

As part of their pre-transplant work-up, patients had a contrast-enhanced thoracoabdominal CT scan in order to rule out any disorder contraindicating heart transplantation. CT scans were performed before RHC with a short-time interval between both examinations (median 4 h; interquartile range: 4–24 h). All CT examinations were performed using a 256-detector row scanner (ICT, Philips Healthcare, Cleveland, OH, USA). To determine PTT, first-pass perfusion images were acquired on a single transversal slice through both ventricles with the following parameters: slice thickness, 10 mm; rotation time, 270 ms; tube potential, 100 kV; and tube current, 20 mA. Contrast injection protocol consisted in 40 mL of 400 mg iodine/mL iodinated contrast medium (Iomeprol, Bracco Diagnostics, Milan, Italy) injected at a flow rate of 5 mL/s through a right antecubital vein and followed by 20 mL of saline bolus chaser at 5 mL/s. First-pass perfusion began simultaneously with contrast medium injection and slices were acquired every 0.8 s for a maximum of 60 s. Five seconds after starting contrast injection, the patients were asked to suspend their breath as long as possible and then to breath gently. The acquisition was discontinued as soon as the contrast density visually decreased in the aorta. After the first-pass perfusion, a second acquisition consisted of a retrospective electrocardiogram-gated cardiac CT after injection of 60 mL of contrast medium at 2 mL/s. The acquisition parameters were: collimation, 128 × 0.625 mm; rotation time, 270 ms; tube potential from 100 to 120 kV depending on patient's weight; and tube current from 300 to 800 mAs depending on automatic tube current modulation. The effective radiation dose of CT was calculated as follows: dose-length product provided by the scanner × conversion factor of 0.017.[20] The average radiation exposure was 1.7 mSv ± 0.6 and 11.1 mSv ± 1.4 for the first-pass perfusion and cardiac images, respectively.

PTT and cardiac function

First-pass perfusion images were analysed with commercially available software (Functional CT, Philips Healthcare, Cleveland, OH, USA). CT parameters were analysed by Observer Nr1 (G.C.) with 6 years of experience in cardiac imaging blinded to RHC results. Circular regions of interest (ROI) of at least 250 mm^2 were placed over the RV and the LV (*Figure 1A*). Time-attenuation curves were generated through both ROI. PTT was calculated by subtracting the time to peak (maximal attenuation) of the RV curve from that of the LV curve (*Figure 1B*), as proposed in MR studies,[11] and was expressed in seconds. Normalized PTT was calculated as PTT/RR interval in seconds and expressed in cardiac cycles.[11,15] From CT images, LV and RV end-diastolic volumes, end-systolic volumes, and ejection fractions were calculated from short-axis views according to Simpson technique using semi-automated software (Comprehensive Cardiac CT, Philips Healthcare). Left atrial maximal volume was also calculated with this software with a semi-automated method including 3D detection of the left atrial lumen of each cardiac phase, with manual correction if necessary. All values were normalized to body surface area. CT-derived cardiac output and cardiac index were calculated by multiplying RV stroke volume and RV stroke volume index by the heart rate, respectively. In order to assess interobserver agreement, PTT was independently calculated by Observer Nr2 (B.G.) with 26 years of experience in cardiothoracic imaging. In order to assess intraobserver agreement, the Observer Nr1 (G.C.) redid all measurements and computations for more than 1 month thereafter. Post-processing time to obtain PTT was measured for each observer.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median with interquartile range for NT-proBNP and as count and

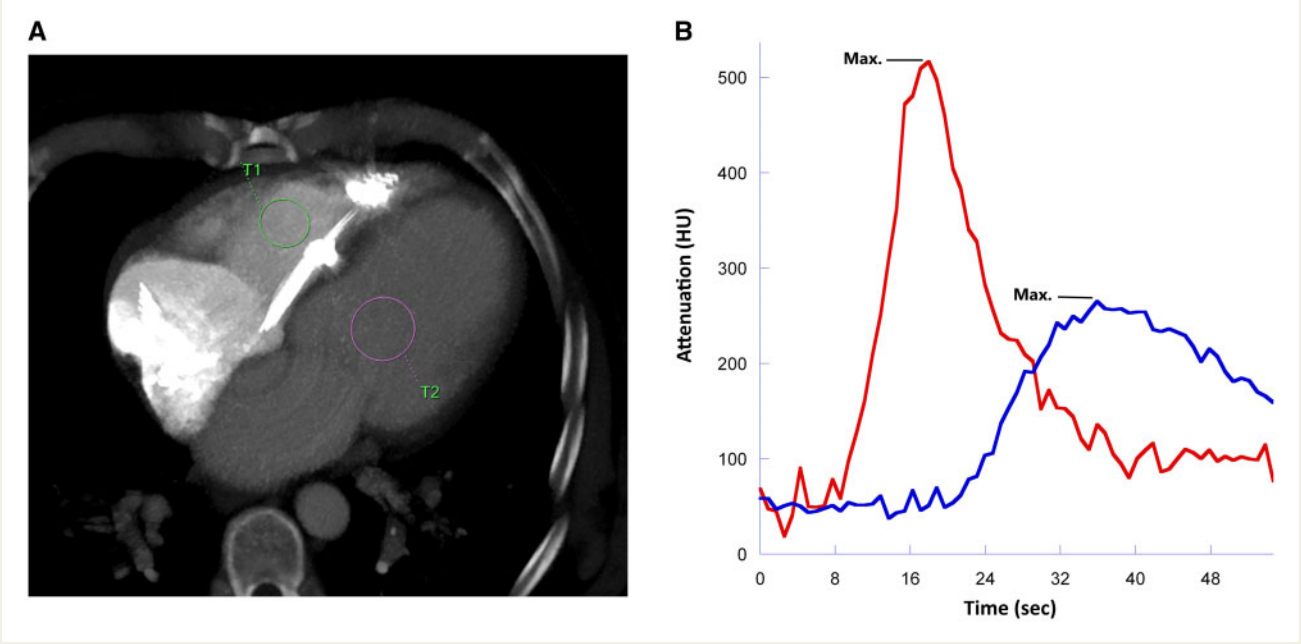

Figure 1 Pulmonary transit time technique. A 57-year-old man with non-ischaemic dilated cardiomyopathy and severe left ventricular systolic dysfunction and moderate mitral regurgitation. (*A*) First-pass perfusion scan after injection of 40 mL of contrast medium and placement of region of interest on the right (T1, green circle) and left (T2, purple circle) ventricles. (*B*) Time-attenuation curves in the right (red curve) and left (blue curve) ventricles allow calculation PTT here increased at 18 s (> cut-off value of 14 s). Elevated pulmonary pressures and decreased cardiac index were measured at RHC (mean PAP: 42 mmHg, mean PAWP: 32 mmHg, cardiac index: 1.8 L/min/m^2).

proportion for categorical variables. Analysis of variance with Bonferroni-adjusted *post hoc* pairwise comparisons was used to compare means among controls and HFrEF patients with or without PH. Non-parametric tests (Kruskal–Wallis) was used to compare the median values of NT-proBNP and χ^2 test for categorical variables. Intraobserver and interobserver agreements were assessed by calculating intraclass correlation coefficient. The Pearson correlation coefficient with Bonferroni correction was used to assess the relationship of PTT with cardiac function and haemodynamics. A *P*-value <0.05 was considered as statistically significant.

Stepwise multivariable regression analysis was performed to estimate the relationship between PTT and clinical, haemodynamic, and cardiac function parameters. Because of multicollinearity between LV and RV ejection fractions and their corresponding end-diastolic volumes, multivariable analysis using backward elimination was performed with all variables associated with PTT in univariable analysis ($P < 0.10$) except LV, RV, and left atrial volumes. Subsequently, LV end-diastolic volume, RV end-diastolic volume, and left atrial maximal volume were entered in addition to the preliminary model. The absence of multicollinearity was tested by calculating the variance inflation factor. The value of the PTT for discriminating abnormally elevated PAWP (i.e. >15 mmHg) and PH was assessed through the area under the receiver operating characteristic (ROC) curve. Optimal cut-off values were identified through the Youden index. All statistical analyses were performed using SPSS (IBM Inc., Chicago, IL, USA).

Results

Of the 60 enrolled HFrEF patients, three patients were excluded because of poor intravascular enhancement due to an unsuspected superior vena cava stenosis, unsatisfactory cardiac CT gating resulting in incomplete data, or failure of venous puncture for contrast injection. Finally, our results were based on 57 patients, 49 men, mean age 51 years ± 8, mean LV ejection fraction measured at echocardiography 26% ± 8 who underwent cardiac CT and RHC without adverse event. Thirty patients (53%) had previous myocardial infarction and ischaemic heart disease. Thirty-five patients (63%) had a pacemaker/defibrillator. PH due to left heart disease was present in 32/57 (56%) patients. PAWP and mean PAP were highly correlated ($r = 0.91$, $P < 0.001$).

Comparisons of subject's characteristics, echocardiography, cardiac CT, haemodynamics, and PTT between controls and patients, respectively with and without PH, are listed in *Table 1*. Correlations between PTT, as well as normalized PTT, and the above-mentioned parameters are listed in *Table 2*. Importantly, the strongest univariable correlates of PTT were PAWP ($r = 0.74$, $P < 0.001$) and RV ejection fraction ($r = -0.74$, $P < 0.001$) (*Figure 2*). PTT was also correlated to CT-derived LV ejection fraction ($r = -0.66$, $P < 0.001$) and cardiac index ($r = -0.63$, $P < 0.001$). As compared to PTT, normalized PTT did not modify substantially any correlation with cardiac function or pulmonary haemodynamics. The independent determinants of PTT are listed in *Table 3*.

Performance of PTT for detecting abnormally elevated PAWP and PH

The area under the ROC curve for detecting abnormally elevated PAWP (i.e. >15 mmHg) by PTT was 0.94. The corresponding optimal cut-off value of PTT was 14 s with sensitivity, specificity, positive

Table 1 Comparisons of subject's characteristics, echocardiography, cardiac CT, haemodynamics, and pulmonary transit time

	Controls ($n = 15$)	Patients without PH ($n = 25$)	Patients with PH ($n = 32$)	*P*-value
Subjects characteristics				
Age (years)	56 ± 12	51 ± 6	51 ± 10	0.173
Male sex	12 (80)	20 (80)	29 (91)	0.461
Body surface area (m^2)	1.93 ± 0.17	1.90 ± 0.18	1.97 ± 0.22	0.376
Body mass index (kg/m^2)	27 ± 4	28 ± 5	27 ± 4	0.762
Systolic blood pressure (mmHg)	133 ± 15	114 ± 13	104 ± 15	<0.001[a,b,c]
Atrial fibrillation	0 (0)	1 (4)	4 (13)	0.225
Ischaemic heart disease	0 (0)	16 (64)	14 (44)	<0.001[b,c]
NYHA Class III or IV	0 (0)	8 (32)	12 (38)	0.023[b,c]
Echocardiography parameters				
LV ejection fraction (%)	62 ± 8	29 ± 8	23 ± 6	<0.001[a,b,c]
Mitral *E/A*	1.1 ± 0.3	1.2 ± 0.6	2.7 ± 0.9	<0.001[a,b]
Septal *E*/e'	8 ± 1	11 ± 5	15 ± 6	<0.001[a,b]
Mitral regurgitation grade (0–3)	0.6 ± 0.5	1.1 ± 0.3	1.6 ± 0.7	<0.001[a,b,c]
TR grade (0–3)	0.7 ± 0.5	1.0 ± 0.4	1.4 ± 0.56	0.001[a,b]
TR gradient (mmHg)	11 ± 8	19 ± 11	35 ± 13	<0.001[a,b,c]
Cardiac CT parameters				
LV EDV (mL/m^2)	85 ± 16	163 ± 45	211 ± 71	<0.001[a,b,c]
LV ejection fraction (%)	62 ± 4	30 ± 8	19 ± 6	<0.001[a,b,c]
RV EDV (mL/m^2)	94 ± 14	100 ± 30	161 ± 47	<0.001[a,b]
RV ejection fraction (%)	50 ± 4	43 ± 10	21 ± 9	<0.001[a,b,c]
Left atrial volume (mL/m^2)	54 ± 18	71 ± 23	104 ± 33	<0.001[a,b,c]
Cardiac output (L/min)	6.2 ± 1.9	4.9 ± 1.3	4.4 ± 0.9	<0.001[b,c]
Cardiac index ($L/min/m^2$)	3.2 ± 0.8	2.6 ± 0.7	1.8 ± 0.5	<0.001[a,b,c]
Heart rate (bpm)	64 ± 8	64 ± 13	75 ± 12	<0.001[a,b]
Haemodynamics and NT-proBNP				
Systolic PAP (mmHg)		25 ± 6	51 ± 10	<0.001[a]
Diastolic PAP (mmHg)		12 ± 4	28 ± 6	<0.001[a]
Mean PAP (mmHg)		17 ± 4	37 ± 6	<0.001[a]
Mean PAWP (mmHg)		10 ± 5	25 ± 4	<0.001[a]
Cardiac output (L/min)		4.7 ± 1.4	3.6 ± 1.1	<0.001[a]
Cardiac index ($L/min/m^2$)		2.6 ± 0.7	1.8 ± 0.5	<0.001[a]
Heart rate (bpm)		66 ± 11	75 ± 13	0.003[a]
Stroke volume index (mL/m^2)		40 ± 11	25 ± 9	<0.001[a]
PVR (Wood units)		1.7 ± 0.7	3.5 ± 2.0	<0.001[a]
Oxygen saturation in PA (%)		63 ± 6	52 ± 10	<0.001[a]
NT-proBNP (pg/mL)		1160 (434–1742)	5186 (2601–10985)	<0.001[a]
Pulmonary transit time				
PTT (s)	8 ± 2	11 ± 3	21 ± 7	<0.001[a,b]
Normalized PTT (cardiac cycles)	8 ± 2	11 ± 3	27 ± 11	<0.001[a,b]

Values are expressed as *n* (%), mean ± standard deviation, or median (interquartile range) for NT-proBNP.
CT, computed tomography; EDV, end-diastolic volume; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; NYHA, New York Heart Association; PA, pulmonary artery; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricular; SD, standard deviation; TR, tricuspid regurgitation.
[a]Statistically significant between PH vs. without PH.
[b]Statistically significant between PH vs. controls.
[c]Statistically significant between without PH vs. controls.

predictive value, and negative predictive value of 83%, 90%, 94%, and 76%, respectively. For detecting PH, the area under the ROC curve was 0.95 (*Figure 3*). The corresponding optimal cut-off value of PTT was also 14 s with sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 88%, 91%, and 88%, respectively. Overall, this cut-off value correctly discriminated 49 of 57 (86%)

Table 2 Correlations between pulmonary transit time and subjects characteristics, echocardiography, cardiac CT, and haemodynamics

	PTT		Normalized PTT for RR interval	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Subjects characteristics				
Age (years)	-0.01	0.923	-0.10	0.477
Male sex	0.21	0.117	0.15	0.275
Body surface area (m^2)	0.05	0.695	-0.01	0.961
Echocardiographic parameters				
LV ejection fraction (%)	-0.38	0.003	-0.38	0.003
Mitral *E/A* (*n* = 46)	0.51	<0.001[a]	0.49	<0.001[a]
Septal *E*/e'	0.31	0.019	0.34	0.012
Mitral regurgitation grade (0–3)	0.54	<0.001[a]	0.55	<0.001[a]
TR grade (0–3)	0.37	0.004	0.39	0.003
TR gradient (mmHg)	0.51	<0.001[a]	0.51	<0.001[a]
Cardiac CT parameters				
LV EDV (mL/m^2)	0.39	0.003	0.39	0.003
LV ejection fraction (%)	-0.66	<0.001[a]	-0.67	<0.001[a]
RV EDV (mL/m^2)	0.64	<0.001[a]	0.65	<0.001[a]
RV ejection fraction (%)	-0.74	<0.001[a]	-0.77	<0.001[a]
Left atrial volume (mL/m^2)	0.53	<0.001[a]	0.50	<0.001[a]
Cardiac output ($L/min/m^2$)	-0.36	0.007	-0.24	0.073
Cardiac index ($L/min/m^2$)	-0.41	0.002	-0.26	0.054
Heart rate (bpm)	0.35	0.007	0.61	<0.001[a]
Haemodynamics and NT-proBNP				
Mean PAP (mmHg)	0.68	<0.001[a]	0.66	<0.001[a]
Mean PAWP (mmHg)	0.74	<0.001[a]	0.72	<0.001[a]
Cardiac output (L/min)	-0.58	<0.001[a]	-0.54	<0.001[a]
Cardiac index ($L/min/m^2$)	-0.63	<0.001[a]	-0.58	<0.001[a]
Stroke volume index (mL/m^2)	-0.65	<0.001[a]	-0.68	<0.001[a]
Heart rate (bpm)	0.36	0.006	0.54	<0.001[a]
PVR (Wood Units)	0.48	<0.001[a]	0.45	<0.001[a]
Oxygen saturation in PA (%)	-0.70	<0.001[a]	-0.69	<0.001[a]
NT-proBNP (log)	0.60	<0.001[a]	0.53	<0.001[a]

[a]Significant after Bonferroni correction for multiples testing.
CT, computed tomography; EDV, end-diastolic volume; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; NT-pro-BNP, N-terminal-pro-B-type natriuretic peptide; PA, pulmonary artery; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PTT, pulmonary transit time; PVR, pulmonary vascular resistance; RV, right ventricular; TR, tricuspid regurgitation.

patients between those with normal vs. elevated PAWP, and 51 of 57 (89%) patients between those with PH vs. without PH. Normalized PTT ≥16 cardiac cycles detected PH with a sensitivity of 88%, a specificity of 92%, a positive predictive value of 93%, and a negative predictive value of 85%. The area under the ROC curve was 0.96 (*Figure 3*).

Reproducibility of and time needed for PTT measurement

With intraclass correlation coefficients of respectively 0.98 and 0.96, intraobserver and interobserver agreements were excellent. Median post-processing time needed for PTT computation was 38 s (interquartile range: 29–64 s) for observer Nr1 and 36 s (interquartile range: 31–46 s) for observer Nr2.

Discussion

This study shows the following findings. First, HFrEF patients with PH have significantly longer PTT than those without PH and controls; higher the PAWP and mean PAP, longer the PTT. Second, high PAWP, low cardiac index, dilated RV, and high mitral valve regurgitation grade are all associated with prolonged PTT. Third, PTT performs well in detecting PH in patients with HFrEF with an area under the ROC curve of 0.95. These findings deserve further discussion.

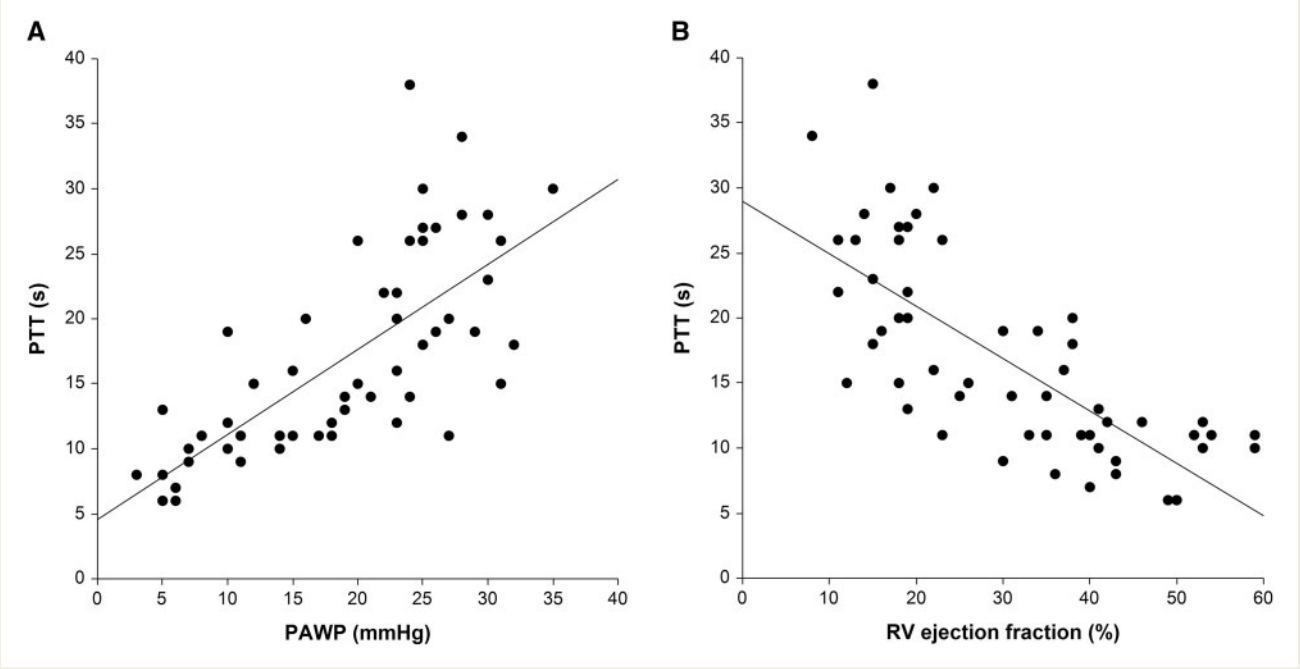

Figure 2 Correlations between PTT and PAWP ($r = 0.74$, $P < 0.001$) (*A*) and between PTT and RV ejection fraction ($r = -0.74$, $P < 0.001$) (*B*).

Table 3 Independent determinants of the pulmonary transit time

Parameter	β (95% CI)	*P*-value
Cardiac index (L/min/m^2)	-4.2 (-5.9 to -2.5)	<0.001
PAWP (mmHg)	0.30 (0.14–0.46)	<0.001
RV end-diastolic volume (mL/m^2)	0.04 (0.01–0.07)	0.004
Mitral regurgitation grade (0–3)	2.6 (0.6–4.5)	0.010

CI, confidence interval; PAWP, pulmonary artery wedge pressure; RV, right ventricular.

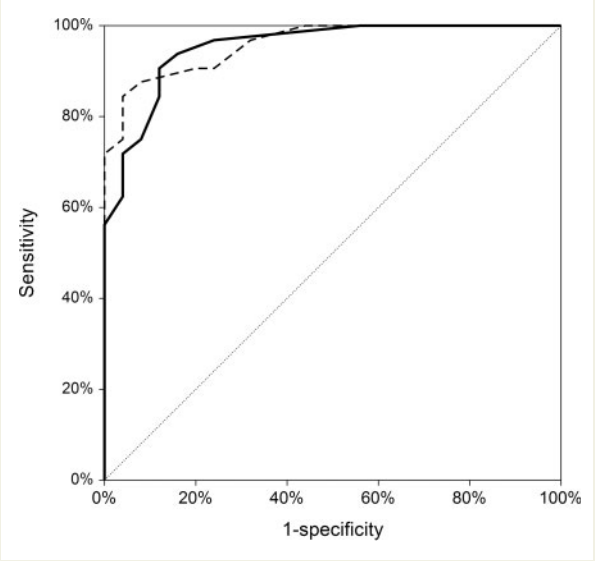

Figure 3 Receiver operating characteristic curve shows the relationship between sensitivity and specificity of PTT (continuous line) and normalized PTT (discontinuous line) for detecting PH among HFrEF patients. The area under the curve is 0.95 and 0.96, respectively.

In HFrEF patients with PH, this study suggests that PAWP independently contributes to increase PTT. It has been well established that PTT is increased in patients with HF.[12,21] In these patients, recent magnetic resonance imaging (MRI) and echocardiography-based studies have shown that PTT negatively correlated with LV ejection fraction[11–16] but most of these studies did not investigate possible correlations between PTT and RHC-derived PAWP and mean PAP. On the one hand, our study confirms the negative correlations between PTT and LV ejection fraction ($r = -0.66$)—fairly close to those previously reported (r ranging from -0.64 to -0.74)[11,12,14,16]—as well as between PTT and RV ejection fraction with coefficient correlation similar to that previously reported ($r = -0.74$).[11] On the other hand, by showing a positive correlation between PTT and PAWP, our study suggests that pulmonary haemodynamic contributes to increase PTT. At least in acute HF, PTT indeed dramatically increases for decreasing after depletive treatment.[22] Recently, Cao *et al.*[11] also reported a positive and significant correlation ($r = 0.68$) between PTT and PAWP in a study group of 28 patients with either HFrEF or HF with preserved ejection fraction. However, the physiological substratum of the relationships between PTT and PAWP remains unclear as PTT could be influenced by non-elucidated mechanisms induced by

increased PAWP that might affect vascular enhancement and contrast medium circulation time. Among others, these mechanisms include the enlargement of the vascular bed, the heterogeneity in the lung perfusion, and the diffusion of the contrast medium out of the vessels into the interstitial space.[22–25] All these factors may lead to increased pulmonary blood volume and PTT provided that PTT measured by peripheral intravenous injection of contrast medium is equal to pulmonary blood volume divided by cardiac output according to indicator dilution and transit time equations.[26]

Based on the multivariable analysis, this study suggests also that beside PAWP, cardiac index, RV volume, and mitral regurgitation grade independently contribute to PTT. Despite these cofactors, PTT performs well in detecting PH as the area under the ROC curve reaches 0.95, 14 s being the best compromise cut-off value. In HFrEF patients with PH, the good performance of PTT in detecting PH could be explained by low cardiac index, severe mitral regurgitation, and RV dilatation, all these factors contributing to PTT prolongation. In patients with HFrEF, subject to confirmation in large study groups in multicentre studies, PTT could be a non-invasive surrogate of LV filling pressures and a tool for PH detection. In HFrEF patients, PTT could also have a prognostic value as it depends on pulmonary pressures, RV volume, and mitral regurgitation severity, all reported as outcome predictors.[2,27] In this line, Ricci *et al.*[28] have recently shown with MRI that PTT-derived pulmonary blood volume is such a prognosticator in a group of 112 HF patients.

In HFrEF patients who would have CT scan as part of their work-up, first-pass perfusion scan could be used to calculate PTT and evaluate their pulmonary haemodynamic status. In selected cases, PTT determined by CT might obviate RHC to diagnose and/or follow-up PH, particularly before heart transplantation as CT is less invasive and more easily repeatable than RHC to evaluate PH changes. In addition, combined with echocardiography parameters, PTT could contribute to improve the non-invasive estimation of PAWP. Although our results show PTT has a high ability to detect elevated PAWP and PH in this population, we acknowledge that CT has low temporal resolution and inherent limitations due to radiation exposure and contrast material.

Our study has limitations. First, haemodynamic parameters and CT were not recorded simultaneously. Although patients were clinically stable and time intervals between CT, RHC, and echocardiography were quite short, intraday variations in pulmonary pressures might have slightly influenced our results. Second, the breath-holding capability of our patients—with its possible effect on intrathoracic and pulmonary pressures—could have been variable. Indeed, our patients were asked to hold their breath whereas pulmonary pressures were measured at end of expiration during free-breathing. Also, the scan-scan repeatability of PTT has not been evaluated for radiation exposure concerns. Third, precise determination of peak enhancement might have been imprecise, especially of the LV in patients with severely increased PTT. However, PTT measurement showed overall high intra- and interobserver agreements. Finally, our results were obtained in a single institution with a small study group.

In conclusion, in HFrEF patients, PTT is longer in those with PH than without PH, is associated with elevated PAWP, low cardiac index, severe mitral valve regurgitation and RV dilatation, and performs well in detecting abnormally elevated PAWP and PH.

Conflict of interest: A.V. works as clinical scientist for Philips Healthcare. The other authors have no conflict of interest to declare.

References

1. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol* 2013;**62**(25 Suppl): D100–8.
2. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R *et al.* Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001;**37**:183–8.
3. Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry J-L. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016;**37**:942–54.
4. Butler J, Stankewicz MA, Wu J, Chomsky DB, Howser RL, Khadim G *et al.* Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. *J Heart Lung Transplant* 2005;**24**:170–7.
5. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009;**119**:62–70.
6. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A *et al.* Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017;**69**:1937–48.
7. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N *et al.* Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging* 2017;**18**: 961–8.
8. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;**37**:67–119.
9. Skrok J, Shehata ML, Mathai S, Girgis RE, Zaiman A, Mudd JO *et al.* Pulmonary arterial hypertension: MR imaging-derived first-pass bolus kinetic parameters are biomarkers for pulmonary hemodynamics, cardiac function, and ventricular remodeling. *Radiology* 2012;**263**:678–87.
10. Swift AJ, Telfer A, Rajaram S, Condliffe R, Marshall H, Capener D *et al.* Dynamic contrast-enhanced magnetic resonance imaging in patients with pulmonary arterial hypertension. *Pulm Circ* 2014;**4**:61–70.
11. Cao JJ, Li L, McLaughlin J, Passick M. Prolonged central circulation transit time in patients with HFpEF and HFrEF by magnetic resonance imaging. *Eur Heart J Cardiovascular Imaging* 2018;**19**:339–46.
12. Shors SM, Cotts WG, Pavlovic-Surjancev B, Francois CJ, Gheorghiade M, Finn JP. Heart failure: evaluation of cardiopulmonary transit times with time-resolved MR angiography. *Radiology* 2003;**229**:743–8.
13. Francois CJ, Shors SM, Bonow RO, Finn JP. Analysis of cardiopulmonary transit times at contrast material-enhanced MR imaging in patients with heart disease. *Radiology* 2003;**227**:447–52.
14. Hansch A, Heyne JP, Jung C, Wolf G, Pfeil A. Quantitative first pass perfusion in cardiovascular magnetic resonance for determination of peak ventricular transit time–a technique for evaluation of heart function. *Eur J Radiol* 2012;**81**: e996–1001.
15. de Lepper AGW, Herold IHF, Saporito S, Bouwman RA, Mischi M, Korsten HHM *et al.* Noninvasive pulmonary transit time: a new parameter for general cardiac performance. *Echocardiography* 2017;**34**:1138–45.
16. Saporito S, Herold IH, Houthuizen P, van Den Bosch HC, Den Boer JA, Korsten HH *et al.* Model-based characterization of the transpulmonary circulation by dynamic contrast-enhanced magnetic resonance imaging in heart failure and healthy volunteers. *Invest Radiol* 2016;**51**:720–7.
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129–200.
18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**: 1–39.e14.
19. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA *et al.* Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.

20. Stamm G. Collective radiation dose from MDCT: critical review of surveys studies. In: D Tack, MK Kalra, PA Gevenois, eds. *Radiation Dose from Multidetector CT*. 2nd ed. Heidelberg: Springer; 2012. p209–229.
21. Meneely GR, Chesnut JL. A relation between the size of the heart and the velocity of the blood. *Am Heart J* 1947;**33**:175–81.
22. Kopelman H. The circulation time as a clinical test. *Br Heart J* 1951;**13**:301–8.
23. Morris LE, Blumgart HL. Velocity of blood flow in health and disease. *Circulation* 1957;**15**:448–60.
24. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol* 2017;**69**: 1718–34.
25. Cao JJ, Wang Y, McLaughlin J, Rhee P, Passick M, Ngai N *et al*. Effects of hemodynamics on global and regional lung perfusion: a quantitative lung perfusion study by magnetic resonance imaging. *Circ Cardiovasc Imaging* 2012;**5**:693–9.
26. Dock D, Kraus W, Mcguire I, Hyland J, Haynes F, Dexter L. The pulmonary blood volume in man. *J Clin Invest* 1961;**40**:317–28.
27. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. *J Am Coll Cardiol* 2015;**65**:1231–48.
28. Ricci F, Barison A, Todiere G, Mantini C, Cotroneo AR, Emdin M *et al*. Prognostic value of pulmonary blood volume by first-pass contrast-enhanced CMR in heart failure outpatients: the PROVE-HF study. *Eur Heart J Cardiovasc Imaging* 2018;**19**:896–904.