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ORIGINAL ARTICLE

Prognostic Value of Pulmonary Transit Time by Cardiac Magnetic Resonance on Mortality and Heart Failure Hospitalization in Patients With Advanced Heart Failure and Reduced Ejection Fraction

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BACKGROUND: Pulmonary transit time (PTT) from first-pass perfusion imaging is a novel parameter to evaluate hemodynamic congestion by cardiac magnetic resonance (cMR). We sought to evaluate the additional prognostic value of PTT in heart failure with reduced ejection fraction over other well-validated predictors of risk including the Meta-Analysis Global Group in Chronic Heart Failure risk score and ischemic cause.

METHODS: We prospectively followed 410 patients with chronic heart failure with reduced ejection fraction (61±13 years, left ventricular (LV) ejection fraction 24±7%) who underwent a clinical cMR to assess the prognostic value of PTT for a primary endpoint of overall mortality and secondary composite endpoint of cardiovascular death and heart failure hospitalization. Normal reference values of PTT were evaluated in a population of 40 asymptomatic volunteers free of cardiovascular disease.

RESULTS: PTT was significantly increased in patients with heart failure with reduced ejection fraction as compared to controls (9±6 beats and 7±2 beats, respectively, $P<0.001$), and correlated not only with New York Heart Association class, cMR–LV and cMR–right ventricular (RV) volumes, cMR-RV and cMR-LV ejection fraction, and feature tracking global longitudinal strain, but also with cardiac output. Over 6-year median follow-up, 182 patients died and 200 reached the secondary endpoint. By multivariate Cox analysis, PTT was an independent and significant predictor of both endpoints after adjustment for Meta-Analysis Global Group in Chronic Heart Failure risk score and ischemic cause. Importantly in multivariable analysis, PTT in beats had significantly higher additional prognostic value to predict not only overall mortality (χ^2 to improve, 12.3; hazard ratio, 1.35 [95% CI, 1.16–1.58]; $P<0.001$) but also the secondary composite endpoints (χ^2 to improve=20.1; hazard ratio, 1.23 [95% CI, 1.21–1.60]; $P<0.001$) than cMR-LV ejection fraction, cMR-RV ejection fraction, LV–feature tracking global longitudinal strain, or RV–feature tracking global longitudinal strain. Importantly, PTT was independent and complementary to both pulmonary artery pressure and reduced RV ejection fraction<42% to predict overall mortality and secondary combined endpoints.

CONCLUSIONS: Despite limitations in temporal resolution, PTT derived from first-pass perfusion imaging provides higher and independent prognostic information in heart failure with reduced ejection fraction than clinical and other cMR parameters, including LV and RV ejection fraction or feature tracking global longitudinal strain.

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Key Words: cardiovascular disease ■ heart failure ■ magnetic resonance imaging ■ mortality ■ prognosis

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CLINICAL PERSPECTIVE

In this retrospective study, evaluating 410 patients with heart failure and reduced ejection fraction undergoing cardiac magnetic resonance, pulmonary transit time from first-pass perfusion imaging was found to be a strong independent predictor of overall and cardiovascular mortality over median follow-up of 6 years. Pulmonary transit time, an integrative marker of hemodynamic congestion, was found to have high intra and interobserver reproducibility. More importantly, it had not only an independent predictive value above clinical parameters such as Meta-Analysis Global Group in Chronic Heart Failure score and ischemic cause, but also it was the most powerful imaging parameter with higher prognostic value than cardiac magnetic resonance–derived left and right ventricular ejection fraction and strain. This suggests that systematic evaluation of pulmonary transit time by cardiac magnetic resonance should be integrated into the risk stratification process of patients with heart failure with reduced ejection fraction. Nevertheless, the retrospective design in a single center of our study remains a limitation. Additional clinical studies should confirm the value of pulmonary transit time in prospective, multicenter design, to allow more general recognition of this method for risk stratification of patients with heart failure with reduced ejection fraction.

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Pulmonary transit time (PTT) is a well-known parameter to evaluate global cardiopulmonary function containing information not only from right and left ventricle (LV) pump function but also pulmonary blood volume and hemodynamic congestion. It can be measured either invasively using indicator dilution methods with direct heart catheterization or using different noninvasive imaging methods, such as radionuclide imaging,[1] computed tomography,[2] and contrast-enhanced transthoracic echocardiography.[3,4] Recently, it was proposed that PTT measurements could be derived from first-pass perfusion by measuring the time for a bolus of contrast to pass from the right ventricle (RV) to the LV.[5–9] Furthermore, cardiac magnetic resonance (cMR)–derived PTT was shown to be increased both in heart failure (HF) with reduced and preserved ejection fraction (EF).[9] However, the prognostic value of this parameter has not yet been compared with other known clinical and imaging parameters.

Therefore, we sought to evaluate the prognostic significance of PTT by first-pass perfusion cMR in patients with HF with reduced EF (HFrEF). We thus compared the ability of PTT to predict both overall mortality and a combined endpoint of cardiovascular survival and HF hospitalization over and above other well-validated parameters in the prognosis of HF and in direct comparison with LV and RV feature tracking (FT) global longitudinal strain (GLS).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We retrospectively identified consecutive patients in optimal medical therapy with stable chronic HF and LV ejection fraction (LVEF) <35% who underwent cMR between 2002 and 2018 in our institution. All patients included in the study were either outpatients or stable inpatients hospitalized for pretransplant evaluation. Inclusion criteria were patients in sinus rhythm who had transthoracic echocardiography within 30 days of cMR. Exclusion criteria were nonsinus rhythm, right to left shunts, cardiac devices, moderate and severe primary valve disease, severe chronic kidney disease defined as a glomerular filtration rate <30 mL/ (min·1.73 m^2), severe chronic obstructive pulmonary disease (stage III–IV), pulmonary fibrosis, or life expectancy <1 year due to other comorbidities.

The study protocol was approved by the Institutional Review Board (2011/11AVR/144, 2017/02MAR/117, and 2014/19NOV/599), and subjects gave informed consent. Patients' history and treatment were retrieved from medical files and from review of visit or hospital records. The HF cause was considered ischemic when patients had previous history of myocardial infarction or >70% narrowing in at least one major epicardial artery on angiography by visual inspection.

Normal reference values of PTT and other cMR parameters were evaluated in a previously published population of 40 asymptomatic volunteers free of cardiovascular disease.[10]

Transthoracic Echocardiography

Standardized comprehensive transthoracic echocardiography exams acquired according to established guidelines using commercial ultrasound systems were analyzed off-line retrospectively by a single experienced observer (Dr Houard) blinded to follow-up clinical and cMR data. Estimated pulmonary systolic artery pressure (eSPAP) was calculated from tricuspid regurgitation maximum jet velocity and pulmonary hypertension was considered when eSPAP was calculated above 40 mm Hg. LV filling pressure markers and RV systolic function parameters, such as tricuspid annular plane systolic excursion and fractional area change, were measured as stated by the established guidelines on a focus 4-chamber view.

Cardiac Magnetic Resonance

Details are given in expanded Data Supplement. All patients and volunteers underwent a standardized cMR myocardial viability study on a 1.5T or 3T scanner as described previously.[11] After short- and long-axis cine single shot fast precession images for assessment of myocardial function, a first Gadolinium contrast bolus was injected at a speed of 3 mL/s followed by a saline chaser of 20 cc. During contrast injection, a dynamic first-pass

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perfusion scan of 40 phases was acquired using an ECG-gated saturation recovery interleaved spoiled gradient echo pulse sequence with parallel imaging, allowing 8 short-axes images to be acquired every other heartbeat (temporal resolution 2 heartbeats). Additional Gadolinium contrast (total dose of 0.2 mmol/kg) was injected, and 10 to 15 minutes thereafter, late gadolinium enhancement (LGE) images were acquired using a 2-dimensional–inversion recovery sequence allowing for the assessment of myocardial viability in identical prescriptions of short- and long-axis slices as cine images.

cMR studies were analyzed using the freely available software Segment version 2.2 (http://segment.heiberg.se)[12] by one experienced observer level III European Association of Cardiovascular Imaging certified observer (Dr Gerber), and PTT data was evaluated by Dr Houard. End-diastolic and end-systolic RV and LV volumes and EF were computed from the short-axis cine images and indexed to the body surface area. Presence and extent of LGE were evaluated visually and quantified with a semi-automated algorithm using 4.7 SD of remote region to define LGE, as previously reported.[11] RV-FT-GLS was computed in apical 4-chamber view and LV-FT-GLS cMR was calculated from the average of 3 long-axis-cine-views. For PTT computation, circular regions of interests were placed in the center of the RV and the LV on a basal slice of the first-pass perfusion study ascertaining that the regions of interests remained in the respective cavity, and time attenuation curves were generated. PTT was calculated automatically as the lag time between the RV and LV bolus peaks, relying on a peak-detection algorithm implemented in Python (appendix 1). The PTT was expressed both in seconds and number of heartbeats. Indexed pulmonary blood volume was computed by the product of PTT beats and the anterograde phase-contrast stroke volume indexed to body surface area.[13] Example of PTT measurements in a healthy volunteer and an HFrEF patient is shown in Figure 1.

Follow-Up

Two independent researchers (Dr Rousseau and S.A. Ahn blinded for clinical data) prospectively followed the study population until November 2018 by phone contact with the patients, their relatives, or their physician. All deaths were recorded and categorized as cardiac or noncardiac. Cause of death was adjudicated by the 2 researchers, as previously mentioned. Cardiac death was defined as death attributable to congestive HF (ie, death preceded by acute worsening or exacerbation of HF), myocardial infarction, sudden death (ie, unexpected, unwitnessed, or witnessed death in absence of other apparent causes), or occurring after cardiac revascularization. The primary endpoint was overall mortality and the secondary endpoints were cardiovascular death and HF hospitalization. Heart transplantations were censored at the date of the procedure since the waiting time for that kind of surgery is more determined by the organ availability rather by the patient status.

Statistical Analysis

Statistical analyses were performed using R software (version 3.3.2). All tests were 2 sided, and $P<0.05$ was considered statistically significant. Continuous variables were summarized as mean±1 SD and median and interquartile range, categorical variables as counts and percentages, and compared using paired t test, Wilcoxon U, and χ^2 test, respectively. Hazard ratios (HR) were expressed with 95% CI. The correlation between PTT versus cMR and echocardiographic measures was assessed using Pearson or Spearman correlation

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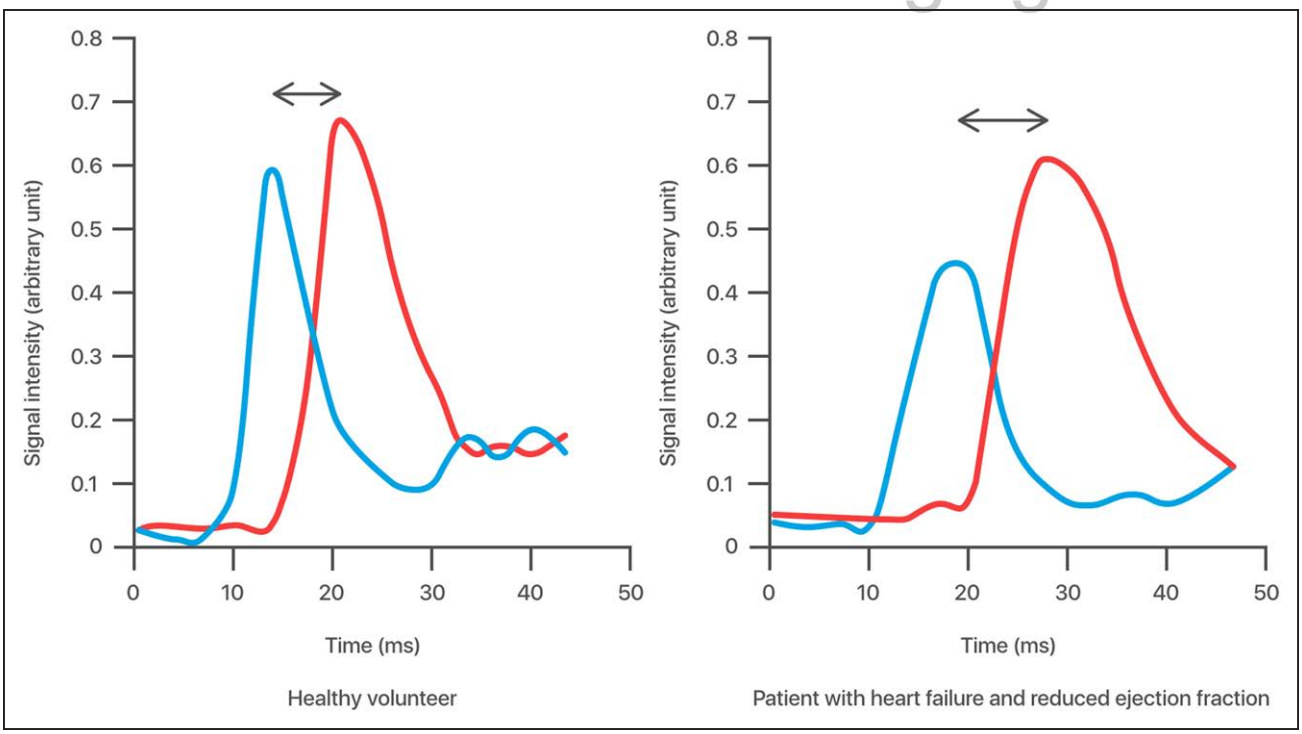

Figure 1. Example of pulmonary transit time measurements.
The blue line represents the bolus peak from the right ventricle and the red line the bolus peak from the left ventricle.

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coefficient. Univariable and multivariable Cox proportional hazard models were used to assess predictors of primary and secondary endpoints. Secondary endpoint was evaluated using competing risk analysis. Weibull distribution was used in case of violation of proportional hazard (RVEF). Multivariable analysis included all MR parameters except those with evident collinearity together with the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Risk score[14] and ischemic cause. Detailed statistical methods are given in the Data Supplement.

For the full assessment of the incremental benefit of PTT, we compared the potential additive prognostic value of PTT and other cMR parameters to improve the prediction of death over the baseline model including MAGGIC score and ischemic cause using multiple discrimination measures including likelihood ratio and the additional increase of χ^2 of the combined model over the baseline model, net reclassification improvement, and the integrated discrimination improvement index.

Survival graphs were used to compare patients with normal and abnormal PTT and RVEF. Interobserver and intraobserver reproducibility of measurement of PTT was evaluated in 30 randomly selected patient population using intraclass correlation coefficient and Bland-Altman analysis with computation within-subject coefficient of variation. Test-retest reproducibility of PTT was assessed using coefficient of variation and intraclass correlation coefficient in 12 subjects from prior studies: that is, 8 healthy volunteers (3 male, mean age 30±1 years)[10] and 4 patients (3 male, mean age 66±7 years) with myocardial infarcts[15] in whom we had performed contrast-enhanced cMR using the same protocol on 2 consecutive days.

RESULTS

Patient's Population

Four hundred ten patients satisfied the inclusion criteria and constituted the final study population (Figure 2). Table 1 shows the characteristics of the patients with HFrEF. The mean age was 61±13 years, and 75% were male. Cause of HF was ischemic in 59% of patients, and 48% were in New York Heart Association (NYHA) class III or IV. Average LVEF was 24±7%, and average LV-FT-GLS was –6.6%. Average RVEF was 42%, and RV-FT-GLS was –11.7%. After cMR, 79 patients underwent implantable cardioverter-defibrillator implantation (of which 10 for secondary prevention after arrhythmic event), 33 patients had a cardiac resynchronization therapy–defibrillator and 29 a cardiac resynchronization therapy–pacemaker implantation.

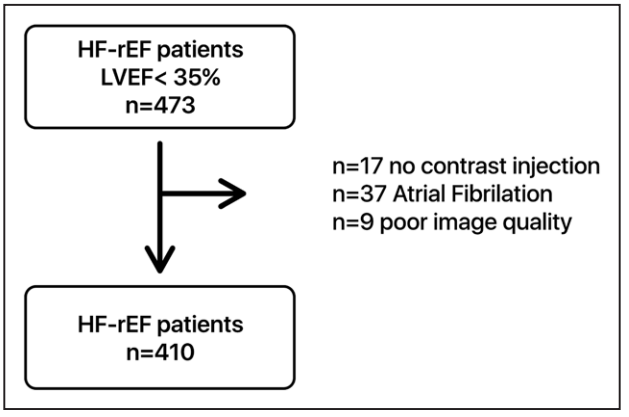

Figure 2. Flowchart of patient inclusion.
HFrEF indicates, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

Pulmonary Transit Times

Normal values of cMR-PTT in 40 asymptomatic controls (mean age, 51±18 years, 51% female, average heart rate 68±11 bpm, systolic blood pressure 127±18 mm Hg) were, respectively, 7±2 beats (95% CI, 2.2–11.1 beats) and 6.2±2.2 seconds (95% CI, 2.5–11.1 seconds).

Average PTT in patients with HFrEF was significantly higher (9±6 beats or 11.0±6.3 seconds, both $P<0.001$) relative to volunteers. Based on normal 95% CI of asymptomatic volunteers, patients were stratified into normal (<11 beats) and abnormal (ie, ≥11 beats) PTT. As shown in Table 1, patients with high PTT were significantly older, had higher NYHA class, worse renal function and higher diuretic use, higher echocardiographic filling pressures as indicated by higher mitral E to A wave ratio and E/e′ mitral E to e′ wave ratio, more pulmonary hypertension, and worse RV function (lower tricuspid annular plane systolic excursion and fractional area change) by echocardiography. By cMR, they presented larger LV and RV volumes, lower LVEF and RVEF, lower cardiac output, and lower LV and RV-FT-GLS. Interestingly there was no difference in PTT between patients with ischemic and nonischemic cause; however, there was higher prevalence of LGE and septal stripe in patients with high PTT. There was also no significant difference in the number of patients with high PTT who underwent implantable cardioverter-defibrillator or cardiac resynchronization therapy implantation during follow-up (20% versus 19%, $P=0.89$).

To better emphasize these differences, patients were also grouped based on PTT quartiles (Table I in the Data Supplement).

As expected, PTT in beats and seconds were highly correlated among each other ($r=0.91$, $P<0.001$). Table II in the Data Supplement shows correlation with other hemodynamic parameters, PTT correlated significantly, however moderately, with mitral E to A wave ratio, cMR-LV–end-diastolic volume index, LV–end-systolic volume index, RV–end-diastolic volume index, RV–end-systolic volume index, LV-FT-GLS, and RV-FT-GLS. It also correlated inversely but moderately with RVEF and LVEF and the cardiac output. All correlations were higher for PTT in seconds than in beats.

Survival

Follow-up was 100% complete for a median duration of 6 years. During follow-up, 28 patients underwent

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Table 1. Clinical Characteristics of Patients With HFrEF According to Normal and Abnormal PTT

	All (N=410)	PTT<11 beats (n=322)	PTT≥11 beats (n=88)	*P* value
Clinical parameters				
Age, y	61±13	60±13	64±13	0.21
Female sex, n (%)	103 (25%)	88 (27%)	15 (17%)	0.053
Ischemic cause, n (%)	243 (59%)	193 (60%)	50 (56%)	0.63
BMI, kg/m^2	25.9±4.8	25.9±4.8	25.9±5.0	0.83
BSA, m^2	1.89±0.23	1.88±0.23	1.89±0.22	0.88
MAP, mm Hg	87±13	87±13	84±12	0.06
Heart rate, bpm	76±15	78±14	72±15	<0.001
COPD, n (%)	58 (14%)	47 (15%)	11 (13%)	0.73
Diabetes, n (%)	105 (26%)	82 (25%)	23 (26%)	0.89
NYHA III–IV, n (%)	198 (48%)	141 (44%)	57 (65%)	<0.001
GFR, mL/(min·1.73 m^2)	71±22	73±23	63±17	<0.001
Hemoglobin, g/dL	13.5±1.8	13.4±1.8	13.8±1.8	0.06
Beta-blockers, n (%)	361 (88%)	281 (87%)	80 (91%)	0.46
Diuretics, n (%)	267 (65%)	201 (62%)	66 (75%)	0.032
ACE inhibitor/ARBs/SA-VAL, n (%)	401 (98%)	314 (97%)	87 (99%)	0.69
Spironolactone, n (%)	286(70%)	217 (67%)	69 (78%)	0.05
MAGGIC-HF score	25±6	25±6	28±7	<0.001
Echocardiographic parameters				
E/A ratio	1.50±0.86	1.41±0.83	1.83±0.92	<0.001
e/e′ ratio	17.5±8.5	17.1±8.7	19.2±7.8	0.06
TR 2–3, n (%)	35 (9%)	15 (5%)	20 (24%)	<0.001
eSPAP >40 mm Hg, n (%)	152 (37%)	104 (32%)	48 (55%)	<0.001
TAPSE, mm	18.0±4.8	18.3±4.6	16.8±5.3	0.02
FAC, %	36.5±12.0	37.8±11.6	31.7±12.5	<0.001
cMR parameters				
cMR-LV-EDVi, mL/m^2	151±47	146±44	172±54	<0.001
cMR-LV-ESVi, mL/m^2	117±44	112±41	138±52	<0.001
cMR-LV-SVi, mL/m^2	34±10	34±10	34±12	0.80
cMR-LVEF, %	24±7	24±7	20±7	<0.001
cMR-LV-FT-GLS, %	−6.6±2.7	−6.9±2.6	−5.5±2.5	<0.001
CO, L/(min·m^2)	2.56±0.76	2.63±0.76	2.33±0.68	0.001
cMR-RV-EDVi, mL/m^2	85±31	78±27	106±39	<0.001
cMR-RV-ESVi mL/m^2	52±31	47±26	72±39	<0.001
cMR-RV-SVi, mL/m^2	33±10	33±10	34±11	0.54
cMR-RVEF, %	42±15	44±14	36±16	<0.001
cMR-RV-FT-GLS, %	−11.7±4.4	−12.4±4.3	−9.4±4.2	<0.001
Septal stripe, n (%)	80 (20%)	50 (16%)	30 (34%)	<0.001
LV LGE, n (%)	258 (63%)	192 (60%)	66 (75%)	0.009
LGE size (%)	3.9 [0.4–12.0]	3.0 [0.4–11]	6.0 [1.0–14]	0.052
cMR-PBVi, mL/m^2*	306±254	229±103	596±404	<0.001
cMR-PTT, s	11.0±6.3	8.6±2.9	19.9±7.6	<0.001
cMR-PTT (heartbeats)	8.9±5.5	6.7±2.2	16.9±6.8	by design

Across-group *P* value is for the difference across the PTT cutoff value by paired *t* test (normal distribution), X^2 Wilkoxon *U* (non-normal data), or χ^2 test (discrete data). ACE inhibitor/ARBs indicates angiotensin-converting-enzyme inhibitor/angiotensin II receptor blockers; BMI indicates body mass index; BSA, body surface area; cMR, cardiac magnetic resonance; CO, cardiac output; COPD, chronic obstructive pulmonary disease; EDVi, end-diastolic volume index; EF, ejection fraction; eSPAP, estimated systolic pulmonary artery pressure; ESVi, end-systolic volume index; FAC, fractional area change; FT-GLS, feature tracking global longitudinal strain; GFR, glomerular filtration rate; HFrEF, [add expansion]; LGE, late gadolinium enhancement; LV, left ventricular; MAGGIC-HF, Meta-Analysis Global Group in Chronic Heart Failure Risk; MAP, mean arterial pressure; NYHA, New York Heart Association; PBVi, pulmonary blood volume index; PTT, pulmonary transit time; RV, right ventricular; SA-VAL, sacubitril-valsartan; SVi, stroke volume index; TASPE, tricuspid annular plane systolic excursion; and TR 2–3, tricuspid regurgitation moderate.

*n=261 patients.

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heart transplantation and were censored at the time of transplant. One hundred eighty-two patients died, 152 patients of cardiovascular causes: 72 suddenly, 60 of HF, 11 of cardiogenic shock, 5 of stroke and 4 postoperatively, and 30 patients of noncardiac causes. One hundred one patients underwent hospitalization for HF. Accordingly, 182 patients reached the primary endpoint of overall mortality, and 200 the secondary endpoint of cardiac death or HF hospitalization.

Predictors of Outcomes

As shown in Figure 3, overall unadjusted survival in patients with prolonged PTT was significantly reduced. Table 2 lists univariate cox regression analysis predictors of survival. In univariate analysis, age, ischemic cause, arterial hypertension, diabetes, NYHA functional class III to IV, MAGGIC-HF risk score, cMR-LV and cMR-RV volumes, EF and FT-GLS, LV LGE, PTT, mitral E to A wave ratio and e/e′ mitral E to e' ratio, eSPAP>40 mm Hg, tricuspid annular plane systolic excursion, RV–fractional area change, and glomerular filtration rate were associated with overall mortality. Regarding the secondary composite end point, not only the same parameters listed above were associated with cardiovascular mortality and HF hospitalization but also LVEF by cMR and female sex (Table III in the Data Supplement).

MAGGIC-HF risk score and ischemic cause were independent predictors of primary and secondary endpoints, and because these are well-known predictors of mortality in HFrEF, they were used as baseline multivariable predictors. Figures 4 and 5 and Tables IV and V in the Data Supplement show the incremental prognostic value of different cMR parameters over MAGGIC-HF risk score and ischemic cause. Importantly, LVEF was not included since statistically nonsignificant in univariate analysis. The incremental prognostic value of PTT beats was significantly higher than PTT in seconds, cMR-LGE, RV-FT-GLS, LV-FT-GLS, and RVEF for the primary endpoints. For the secondary endpoint, both PTT in beats and in seconds had better predictive value than cMR-LGE, RV, and LV-FT-GLS. PTT in beats but not in seconds had also significantly higher predictive value than RVEF. Table 3 shows the multivariable model including all cMR parameters for our primary endpoint and Table 4 for the secondary endpoint accounting for competing risk. In multivariable analysis, PTT either in seconds or beats had additional prognostic value over MAGGIC-HF risk score and ischemic cause. Interestingly, LV-FT-GLS showed only a significant incremental value in predicting the secondary composite endpoints but not the primary endpoint. This is well illustrated in Figures 4 and 5 and Tables IV and V in the Data Supplement. Additionally, the incremental prognostic value of PTT >11 beats was also demonstrated by other discrimination measures. Indeed, the continuous net reclassification improvement for adding PTT >11 beats in the baseline model was 0.45 (0.19–0.65) for overall mortality and 0.49 (0.26–0.56) for the secondary endpoint at 1 year (P<0.001). The integrated discrimination improvement index was significantly increased (P=0.02) for the secondary endpoint but not for the primary endpoint (P=0.16).

PTT in beats retained its high prognostic value in predicting both endpoints even if eSPAP by echocardiography was considered in the model (X^2 to enter 12, P<0.001 and X^2=8, P<0.001, respectively).

A subanalysis was performed in 261 patients who had aortic flow phase data allowing to compute indexed pulmonary blood volume and the cardiac output. In this

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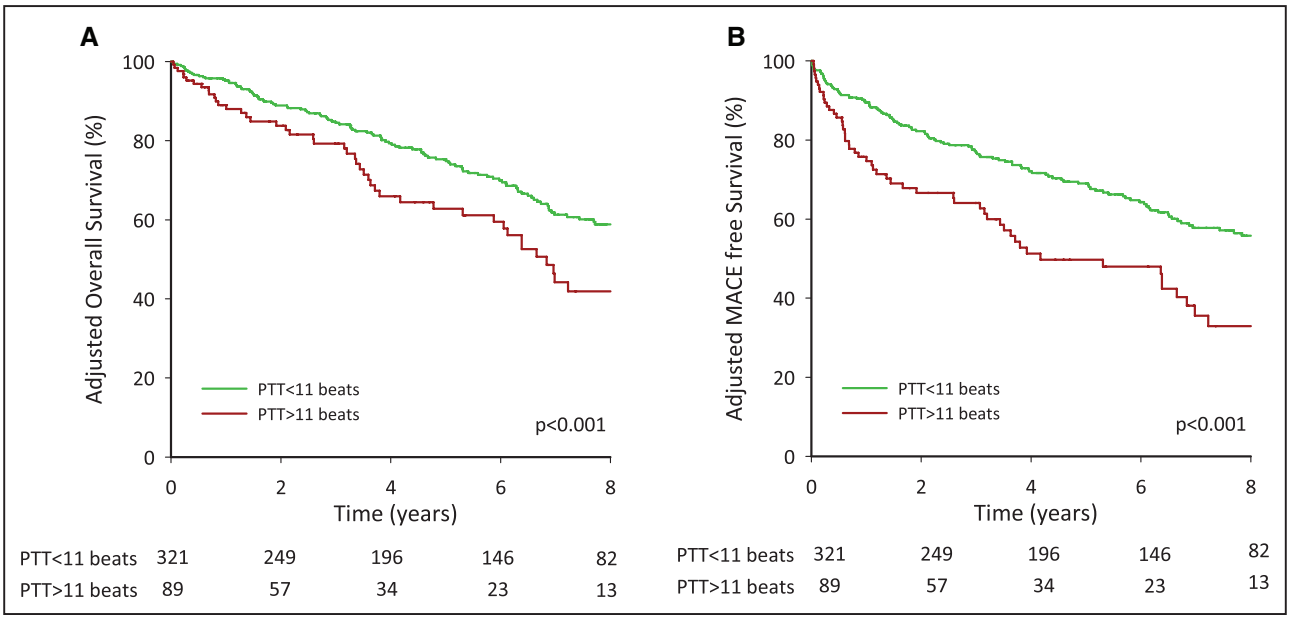

Figure 3. Adjusted survival curves showing overall and MACE free survival according to abnormal/normal pulmonary transit time (PTT) in beats. Left panel (**A**) overall survival; right panel (**B**) combined end point of cardiovascular survival and survival free of heart failure hospitalization.

Table 2. Univariate Analysis Primary End Point

	Alive N=228	Dead; N=182	HR (95% CI)	*P* value
Clinical characteristics				
Age, y	57±14	66±11	1.68 [1.41–2.00]	<0.001
Female sex, n (%)	64 (28%)	39 (21%)	0.82 [0.58–1.17]	0.27
Ischemic cause, n (%)	99 (43%)	144 (79%)	2.23 [1.55–3.19]	<0.001
AHT, n (%)	90 (40%)	109 (60%)	1.53 [1.14–2.07]	0.004
Diabetes, n (%)	46 (20%)	59 (32%)	1.52 [1.12–2.07]	0.008
NYHA III–IV, n (%)	93 (41%)	105 (60%)	1.72 [1.27–2.31]	<0.001
Beta-blockers, n (%)	207 (91%)	154 (85%)	0.62 [0.41–0.92]	0.026
Diuretics, n (%)	135 (59%)	132 (73%)	1.74 [1.25–2.42]	<0.001
GFR, mL/(kg·1.73 m^2)	74±23	67±21	0.75 [0.64–0.88]	<0.001
MAGGIC-HF score	24±6	27±6	1.65 [1.44–1.88]	<0.001
ICD implantation as time-dependent covariate	58 (25%)	21 (11%)	0.88 [0.56–1.39]	0.59
CRT as time-dependent covariate	45 (20%)	17 (9%)	0.67 [0.41–1.11]	0.13
Echocardiographic parameters				
TAPSE, mm	18.3±4.7	17.8±4.9	0.83 [0.0.72–096	0.01
RV-FAC, %	37±12	36±12	0.84 [072–0.97]	0.018
eSPAP >40 mm Hg	68 (38%)	84 (46%)	1.74 [1.29–2.33	<0.001
E/a ratio	1.47±0.85	1.52±0.88	1.19 [1.02–1.39]	0.026
E/e´	16.5 ±7.9	19.2 ± 9.3	1.32 [1.12–1.56]	0.001
cMR parameters				
RV-EDVi, mL/m^2	82±32	89±31	1.25 [1.09–1.44]	0.001
RV-ESVi, mL/m^2	50±31	55±31	1.2441 [1.09–1.42]	0.001
RVEF, %	43±14	42±15	0.82 [0.71–0.95]	0.01
RV-GLS, %	−12±5	−12±4	1.24 [1.041–1.39]	0.01
LV-EDVi, mL/m^2	152±49	150±44	1.11 [0.96–1.29]	0.14
LV-ESVi, mL/m^2	118±47	116±41	1.12 [0.97–1.30]	0.11
LV-SVi, mL/m^2	35±11	33±9	0.99 [0.85–1.15]	0.89
Cardiac output, L/min	4.8±1.4	4.8±1.5	0.90 [0.77–1.05]	0.16
LVEF, %	23.5±7.6	23.5±6.5	0.866 [0.74–1.00]	0.06
LV-GLS, %	−7±3	−6±3	1.32 [1.13–1.54]	<0.001
Presence of LV scar, n (%)	117 (51%)	141 (78%)	1.87 [1.32–2.66]	<0.001
Septal stripe, n (%)	48 (21%)	32 (18%)	1.11 [0.76–1.64]	0.58
PBVi, mL/m^2*	283±256	335±250	1.31 [1.17–1.47]	<0.001
PTT in beats	8.2±5.5	10.4±6.6	1.31 [1.16–1.49]	<0.001
PTT in seconds	9.6±5.5	11.7±5.8	1.47 [1.29–1.67]	<0.001

HR: for standardized value. AHT indicates arterial hypertension; cMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; EDVi, end-diastolic volume index; EF, ejection fraction; eSPAP, estimated systolic pulmonary artery pressure; ESVi, end-systolic volume index; FAC, fractional area change; GFR, glomerular filtration rate; GLS, global longitudinal strain; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LV, left ventricular; MAGGIC-HF, Meta-Analysis Global Group in Chronic Heart Failure Risk; NYHA, New York Heart Association; PBVi, pulmonary blood volume index; PTT, pulmonary transit time; RV, right ventricular; SVi, stroke volume index; and TAPSE, tricuspid annular plane systolic excursion.

*n=261 patients.

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subpopulation, 100 patients died, 87 from cardiovascular death. By univariate analysis, the same parameters than with the entire population were associated with both of the end points, with in addition indexed pulmonary blood volume.

In multivariable analysis using the same baseline model, PTT in beats still had significantly (*P*=0.02) higher additional value than indexed pulmonary blood volume (X^2 to enter 17.6 *P*<0.001 versus 11.2, *P*=0.001, respectively).

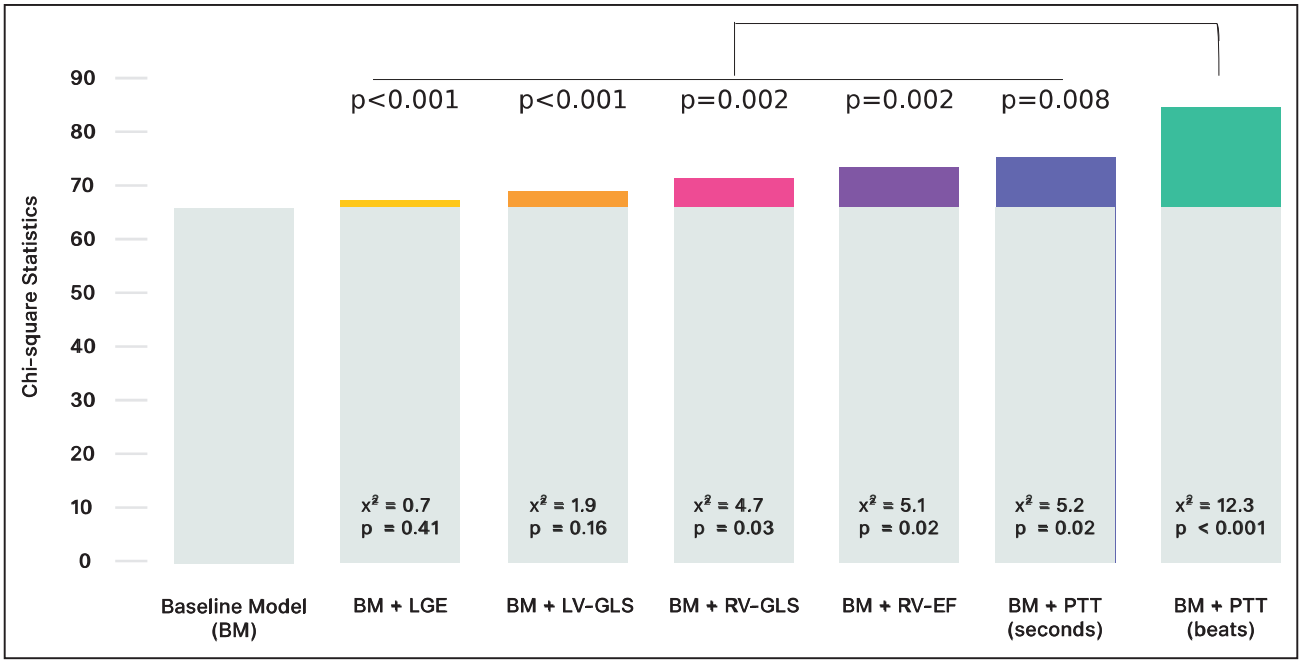

Figure 4. χ^2 statistics bar chart: additional prognostic value of the parameters over a baseline model (BM) to predict overall mortality.
GLS indicates global longitudinal strain; LGE, late gadolinium enhancement; LV, left ventricular; PTT, pulmonary transit time; RV, right ventricular; and RVEF, RV ejection fraction. *P<0.05.

To better illustrate this increased risk in patient with high PTT, we evaluated hazard ratios relative to PTT (Figure 6). This graph shows that the risk of mortality starts to exponentially increase when PTT is >11 beats. This is also demonstrated in the adjusted survival curves stratified by quartiles of PTT (Figure I in the Data Supplement).

Finally, we examined the interaction between RV function and PTT in the prognostic stratification. Therefore, patients were separated according to normal (≤11 beats) and abnormal (>11 beats) PTT and low (<42%) and high median (≥42%) RVEF. Both RVEF<42% (HR, 1.68 [1.23–2.31], P<0.001 for overall mortality and HR, 1.76 [1.32–2.35], P<0.001 for the combined end point) and PTT>11 beats (HR, 1.48 [1.04–2.1] with a P= 0.03 and HR, 1.65 [1.27–2.32] with a P<0.001 for overall mortality and the combined endpoint, respectively) independently predicted

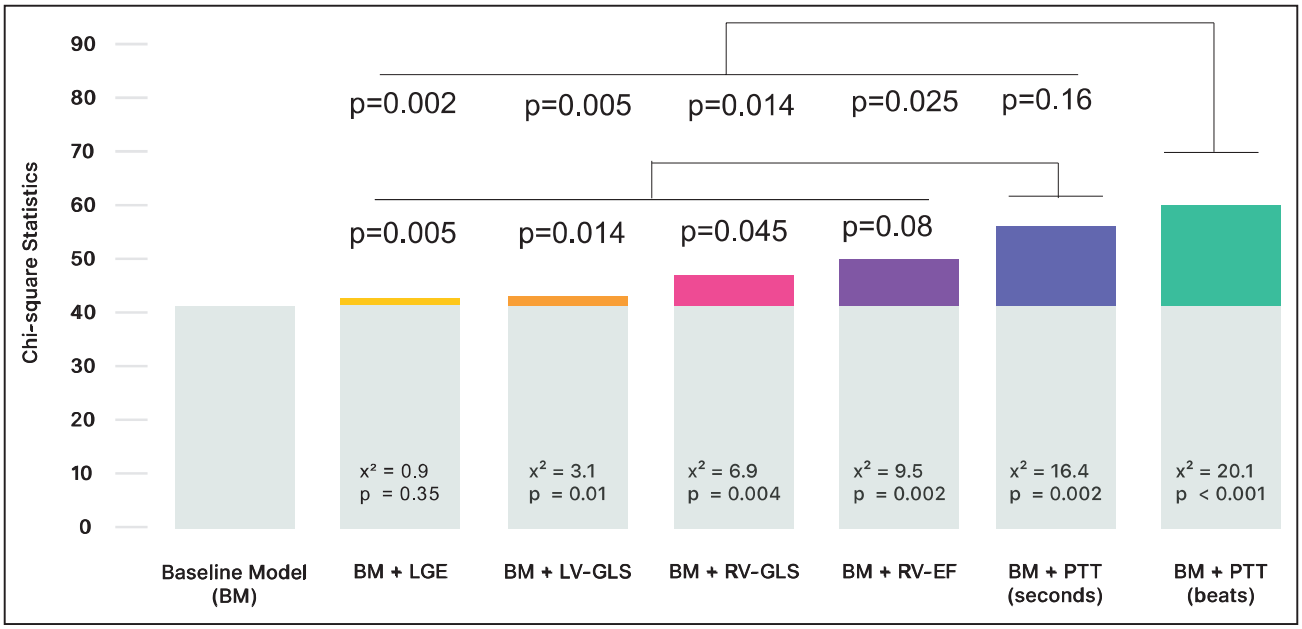

Figure 5. χ^2 statistics bar chart: additional prognostic value of the parameters over a baseline model (BM) to predict the secondary end point of cardiovascular mortality and heart failure hospitalization.
GLS indicates global longitudinal strain; LGE, late gadolinium enhancement; LV, left ventricular; PTT, pulmonary transit time; RV, right ventricular; and RVEF, RV ejection fraction. *P<0.05.

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Table 3. Multivariable Analysis for Primary End Point

Parameter	Partial HR	X^2	*P* value
MAGGIC-HF score	1.46 [1.24–1.71]	23.3	<0.001
Ischemic cause	2.46 [1.59–3.73]	17.3	<0.001
PTT (beats)	1.33 [1.12–1.57]	10.55	<0.001
cMR-RVEF	0.88 [0.75–1.03]	2.25	0.12
cMR-LV-FT-GLS	1.04 [0.87–1.29]	3.87	0.72
cMR-RV-FT-GLS	1.04 [0.86–1.27]	0.33	0.66
cMR-LV-LGE	1.06 [0.72–1.57]	0.10	0.74

HR of continuous values were standardized. PTT (s) and PBV were not entered together, as highly correlated with PTT (beats). cMR indicates cardiac magnetic resonance; FT-GLS, feature tracking global longitudinal strain; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; MAGGIC-HF, Meta-Analysis Global Group in Chronic Heart Failure Risk; PBV, [add expansion]; PTT, pulmonary transit time; RV, right ventricular; and RVEF, RV ejection fraction.

Table 4. Multivariable Analysis for Prediction of Secondary End Points

Parameter	Partial HR	*P* value
MAGGIC-HF score	1.28 [1.11–1.49]	<0.001
Ischemic cause	1.59 [1.05–2.41]	0.03
PTT (beats)	1.34 [1.15–1.57]	<0.001
cMR-RVEF	0.88 [0.76–1.02]	0.08
cMR-LV-GLS	1.10 [0.92–1.30]	0.30
cMR-RV-GLS	1.03 [0.87–1.22]	0.71
cMR-LGE	1.07 [0.72–1.59]	0.73

HR of continuous values were standardized. PTT (s) and PBVi were not entered, as highly correlated with PTT (beats). cMR indicates cardiac magnetic resonance; GLS, global longitudinal strain; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; MAGGIC-HF, Meta-Analysis Global Group in Chronic Heart Failure Risk; PBVi, [add expansion]; PTT, pulmonary transit time; RV, right ventricular; and RVEF, RV ejection fraction.

primary and secondary outcome over MAGGIC Score and ischemic cause. Figure 7 shows adjusted survival curves of overall survival and secondary endpoint stratified by normal/abnormal RVEF and PTT. This figure illustrates clearly that the prognosis of patients is independently influenced by both RVEF and PTT. Indeed, survival was highest when both RVEF and PTT were normal and worst when RVEF was low and PTT was increased. Patients with poor RVEF but preserved PTT or patients with normal RVEF but increased PTT had intermediate prognosis.

Reproducibility

Intraobserver and interobserver reproducibility of PTT measurements was high (intraclass correlation coefficient, 0.99/0.98 and coefficient of variation 3.7%/5.7%, respectively). Test-retest reproducibility of PTT resulted in absolute difference measurement on 2 consecutive days of 0±1.2 seconds (95% CI, −2.3 to 2.4 seconds), with a coefficient of variation of 6.4% and an intraclass correlation coefficient of 0.84. Interstudy reproducibility of other conventional cMR and FT measurements were recently published.[16]

DISCUSSION

The salient findings of our study were

1. PTT measurements can be easily obtained automatically from analysis of contrast kinetics during routine clinical cMR first-pass perfusion scans with high intra, inter, and test-retest reproducibility.
2. PTT was significantly increased in patients with HFrEF as compared to controls and correlated with NYHA class, cMR-LV and cMR-RV volumes, RV and LV systolic function (EF and FT-GLS), cardiac output, and with echocardiographic parameters of diastolic function.
3. PTT both in beats and seconds were independent predictors of overall long-term mortality and combined end point of cardiovascular mortality and HF hospitalization with significant additional value over a strong baseline model including well-validated parameters in patient with HF.
4. Importantly, the additional prognostic value of both PTT in beats and seconds was greater than RV and LV-FT-GLS and EF and independent of eSPAP and RVEF in predicting both end points.

PTT, defined as the time for a bolus of contrast to pass from the RV to the LV, is a well-known measurement for evaluation of cardiopulmonary status. Indeed circulation time measurements are used since the mid-twentieth century for diagnosis of HF. PTT was first determined using radionuclide tracers[17] then also using other techniques such as contrast-enhanced echocardiography and injected CT. Recently, it was proposed that PTT measurements could be derived from first-pass perfusion cMR imaging[5–9] such as in our present work.

Several investigators demonstrated that PTT is prolonged both in HFrEF[9] and in isolated pulmonary hypertension.[7] According to the indicator dilution theory,[18] PTT is directly proportional to pulmonary blood volume and indirectly related to the RV cardiac output.[19] Hemodynamic studies[3,7,9,20] confirmed that PTT correlates not only with RV stroke volume, RV cardiac output,[4,9] LVEF, and RVEF [21,22] but also importantly with parameters of increased pulmonary congestion.[7,9] Indeed, in our previous work,[2] we demonstrated a strong correlation between PTT assessed by CT scanner, mean pulmonary artery pressure (r=0.68), and pulmonary artery wedge pressure (r=0.74). PTT was also shown to correlate with N-terminal pro-B-type natriuretic peptide[2,4] which is indicative of volume and pressure overload in congestive HF. This is in accordance with our findings. Overall, this suggests that prolonged PTT is not only a measurement of low cardiac output but also mainly related to increased blood volume and thus, a parameter estimating pulmonary congestion in different types of HF.

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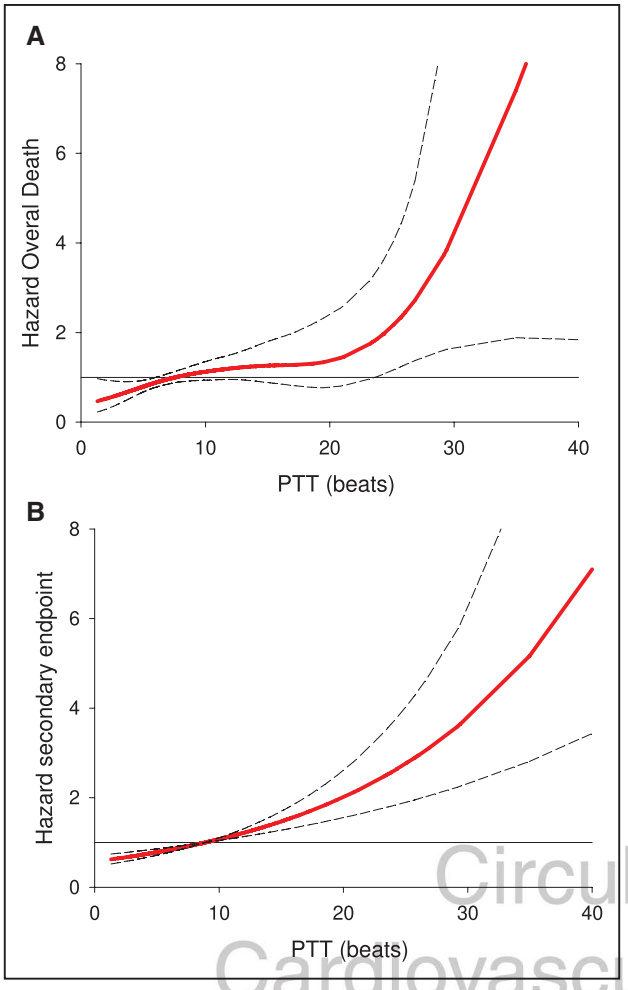

Figure 6. Hazard ratio for pulmonary transit time (PTT) in beats to predict outcome.
A, Overall death and (**B**) combined end point of cardiovascular survival and survival free of heart failure hospitalization.

In our study, normal values of PTT in healthy volunteers were in line with other reports.[7–9,13,22] Patients with HFrEF had significantly prolonged PTT, however, with considerable overlap of normal PTT values when compared with volunteers. Indeed, only about 20% of patients with HFrEF presented significantly prolonged PTT. However, this was clearly associated with more severe left (LVEF and LV-GLS) and RV (RVEF, RV-GLS, tricuspid annular plane systolic excursion and fractional area change) dysfunction, more severe symptomatic state (NYHA class), and more severe congestion (higher E/e′).

Increased PTT predicted independently long-term overall survival and survival free of HF hospitalization and cardiovascular death. Indeed, normalized PTT in beats was the only variable statistically significant in the multivariable models when we allow to simultaneously enter all cMR parameters together with ischemic cause and MAGICC score parameters. All the cMR parameters that had evident collinearity were not added in the multivariable models to avoid issue related to selecting parameters.

We also demonstrated that PTT had higher incremental prognostic value than FT-GLS in predicting not only overall mortality but also the combined end point of cardiovascular death and HF hospitalization. Additionally, the incremental benefit of PTT over a strong baseline model to predict both the end points was illustrated using three measures of discrimination such as the likelihood ratio test which is the uniformly most powerful test for nested models and also by the net reclassification improvement and the integrated discrimination improvement index. Although the net reclassification improvement increase was modest, it demonstrated clearly a clinical reclassification of patients over a strong baseline model incorporating predictive parameters already well-validated in patients with HF.

In this respect, we think that the specific clinical value of our data is the fact that it demonstrates that patients with HFrEF with normal PTT (beats) should be reclassified to a lower risk. Also, PTT was independent and complementary to eSPAP to predict outcomes. This is in agreement with the fact that both clinical and hemodynamic congestion are important predictors of mortality in HF.[23–26] Although clinical congestion, which is always associated with signs and symptoms of HF, may rapidly resolve with diuretics, hemodynamic congestion may be incomplete despite aggressive treatment. Our study is, to our knowledge, the first to demonstrate the strongly independent and additional value of PTT to predict outcome over other cMR derived parameters which are well-known prognostic factors in patients with HFrEF, such as RVEF[27] and LV-FT-GLS[28] and RV-FT-GLS.[27] Interestingly, the prognostic value of PTT was prolonged and persistent over a median follow-up of 6 years. This is remarkable because one could conceive that the degree of pulmonary congestion might change over time in patients with HFrEF with progression of disease, or with treatment changes. A potential explanation could be that patients in our study underwent cMR during stable conditions, thus not during acute congestion, and thus that an increased PTT would reflect an incomplete hemodynamic decongestion which seems to be the main cause of early readmission.[29]

Clinical Implication

HFrEF has variable prognosis, and assessment of pulmonary congestion is known to be relevant in HFrEF. Our study shows that cMR-PTT assessment is a simple, robust, and highly reproducible parameter, which might allow detection of pulmonary congestion noninvasively and which had significant and prognostic value over other clinical and cMR parameters, such as RVEF, in HFrEF both to predict mortality and HF hospitalization. Since PTT can be easily made from routine clinical cMR scans without any additional cost, we think that PTT should be systematically analyzed during viability studies for risk stratification and identification of patients with HFrEF at

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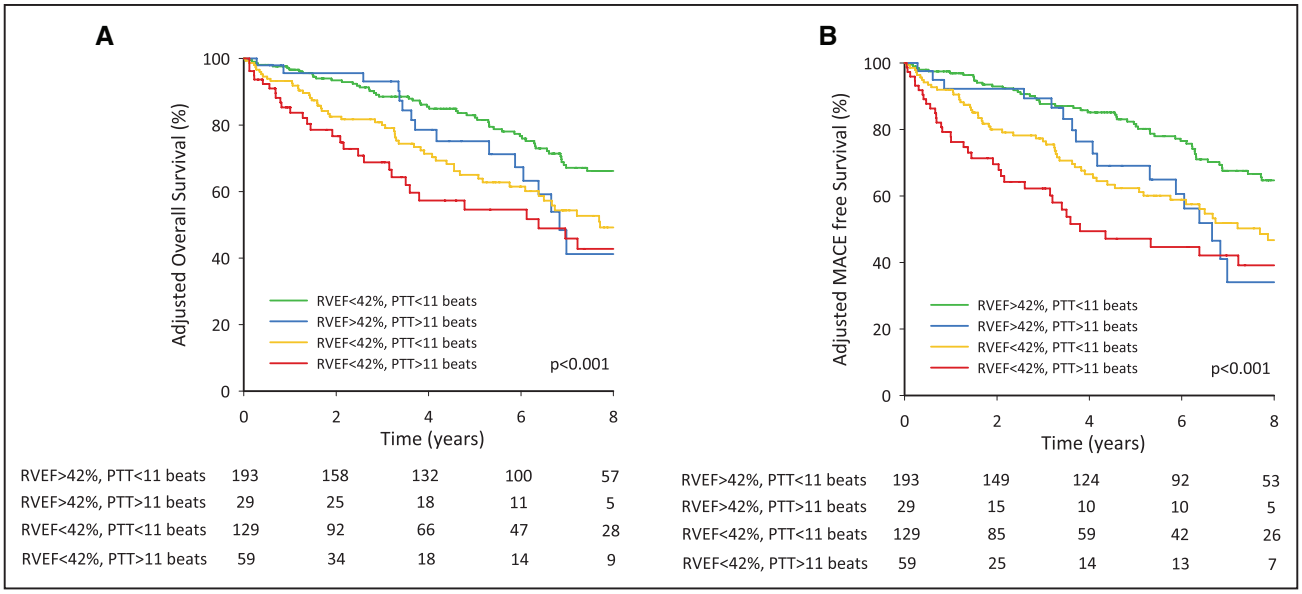

Figure 7. Adjusted survival curves demonstrating interaction between right ventricular ejection fraction (RVEF) and pulmonary transit time (PTT) for predicting outcome.
Left panel (**A**) overall survival and right panel (**B**) combined end point of cardiovascular survival and survival free of heart failure hospitalization.

high risk of death and acute HF which potentially could benefit from more intensive monitoring and therapy. Indeed, PTT measurements could potentially be derived automatically from analysis of first-pass image intensity, and the parameter could be computed within seconds.

Limitations

Our study was a single-center retrospective observational study, with a potential referral reference bias to undergo cMR. Limitations related to this retrospective design include no quality control of acquired imaging and potential referral bias as we excluded patients with atrial fibrillation, devices, severe lung disease, and renal failure. Therefore, our findings may not apply to these populations. Additionally, only one single observer performed the measurement of PTT. However, PTT measurement was performed automatically. Furthermore, image acquisitions were performed with a sequence with full cardiac coverage and temporal resolution limited to 2 heartbeats and contrast was injected at 3 cc/s. This might have limited the ability to detect the sharpness of the contrast peak and might have limited precision of measurement. Higher temporal resolution and injection speed might allow for more pronounced contrast peaks with more accurate estimates of PTT.[30] Absolute difference between the normal and abnormal PTT groups was small representing only 2 beats, which is explained by the fact that majority of patients had normal PTT and only 20% to 25% of patients had increased PTT. Importantly, we think that the clinical relevance of a biomarker can only be accurately demonstrated by its effect on patient management and outcomes which need to be confirmed in further prospective studies. Our baseline model was created based on well-validated variables in the outcome in HF to add flexibility and robustness to our model. We used software validated for LGE quantification only in ischemic pattern of fibrosis. We also used the same approach for nonischemic scar because there is no universally recognized quantification strategy to detect focal fibrosis for this population. As our work may have predated the widespread use of extracellular volume fraction, this technique was not evaluated. Because we did not perform phase-contrast measurements of systemic or pulmonary stroke volume in all patients, we were able to compute pulmonary blood volume[13] only in a subgroup of our population. Finally, brain natriuretic peptide and invasive right heart catheterization measurements were not available for all the population, and therefore, these parameters could not be included in our analysis.

Conclusions

In HFrEF, PTT is an integrative marker of hemodynamic congestion, which has significantly additional prognostic value to predict overall mortality, cardiovascular death, and HF hospitalization over and above other well-known risk factors. Importantly, PTT measurements are highly reproducible because it can be automated and easily made from routine clinical cMR. We, therefore, suggest that PTT should be integrated into the risk stratification process of patients with HFrEF.

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Disclosures

None.

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