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RESEARCH

Pulmonary transit time measurement by contrast-enhanced ultrasound in left ventricular dyssynchrony

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Abstract

Background: Pulmonary transit time (PTT) is an indirect measure of preload and left ventricular function, which can be estimated using the indicator dilution theory by contrast-enhanced ultrasound (CEUS). In this study, we first assessed the accuracy of PTT-CEUS by comparing it with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Secondly, we tested the hypothesis that PTT-CEUS correlates with the severity of heart failure, assessed by MRI and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Methods and results: Twenty patients referred to our hospital for cardiac resynchronization therapy (CRT) were enrolled. DCE-MRI, CEUS, and NT-proBNP measurements were performed within an hour. Mean transit time (MTT) was obtained by estimating the time evolution of indicator concentration within regions of interest drawn in the right and left ventricles in video loops of DCE-MRI and CEUS. PTT was estimated as the difference of the left and right ventricular MTT. Normalized PTT (nPTT) was obtained by multiplication of PTT with the heart rate. Mean PTT-CEUS was 10.5 ± 2.4 s and PTT-DCE-MRI was 10.4 ± 2.0 s ($P = 0.88$). The correlations of PTT and nPTT by CEUS and DCE-MRI were strong; $r = 0.75$ ($P = 0.0001$) and $r = 0.76$ ($P = 0.0001$), respectively. Bland–Altman analysis revealed a bias of 0.1 s for PTT. nPTT-CEUS correlated moderately with left ventricle volumes. The correlations for PTT-CEUS and nPTT-CEUS were moderate to strong with NT-proBNP; $r = 0.54$ ($P = 0.022$) and $r = 0.68$ ($P = 0.002$), respectively.

Conclusions: (n)PTT-CEUS showed strong agreement with that by DCE-MRI. Given the good correlation with NT-proBNP level, (n)PTT-CEUS may provide a novel, clinically feasible measure to quantify the severity of heart failure.

Clinical Trial Registry: NCT01735838

Key Words

- pulmonary transit time
- contrast echocardiography
- cardiac magnetic resonance imaging
- B-type natriuretic peptide
- heart failure

Introduction

Intrathoracic transit time of blood flow can be used to estimate preload, blood volumes, and global ventricular function (1). More than five decades ago, it was demonstrated that the invasively measured pulmonary blood volume was related to the severity of heart failure as expressed by the New York Heart Association (NYHA) classification (2). Also, the relationship between the intrathoracic circulation time derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and different heart failure parameters has been confirmed (3, 4).

Pulmonary transit time (PTT), which is a component of intrathoracic transit time, might be suitable to quantify the severity of congestive heart failure, a disease characterized by increased circulation times and elevated filling pressures (3, 4, 5). Nowadays, there is an increasing interest to assess PTT less invasively by applying the indicator dilution theory to contrast-enhanced ultrasound (CEUS) (5, 6, 7). Experimental research has validated the relationship between PTT measurement by CEUS and the extent of heart failure (8). The reliability of transit time measurements and volume estimations with CEUS is accurate and reproducible, whereas the traditional thermodilution measurements tended to overestimation, probably because of extravascular indicator loss (7, 9). The promising results of PTT measurements by CEUS make it a potential clinical tool, easy to apply at the bedside (5, 10).

In this study, we investigated the agreement between the PTT measured by CEUS and DCE-MRI in a cohort of heart failure patients referred for cardiac resynchronization therapy (CRT). We hypothesized that PTT is a parameter related to the severity of congestive heart failure and therefore correlates with MRI parameters of left ventricular dysfunction, echocardiographic estimates, and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Methods

Study population

The patient population consisted of 20 patients referred to the Catharina Hospital in Eindhoven (the Netherlands) for implantation of a CRT device. According to the hospital protocol, all patients underwent extensive evaluation before resynchronization that included echocardiography, electrocardiography, and measurement of NT-proBNP level. The majority of patients were in heart failure (New York Heart Association (NYHA) functional classes II–IV) with left ventricular systolic failure (ejection fraction ≤35%) and electrical dyssynchrony (QRS duration >120 ms). Patients were eligible for inclusion if they were in sinus rhythm and had no contraindications for ultrasound contrast agents (UCAs) or gadolinium (i.e., acute coronary syndrome or acute heart failure within the past 3 months, any mechanical or biological valve prosthesis, atrial septal defect, right to left shunt, severe pulmonary hypertension, uncontrolled arterial hypertension, known allergy to sulfur hexafluoride, end-stage renal or hepatic disease, pregnancy) as well as general contraindications to DCE-MRI. The Institutional Review Board of the Catharina Hospital, Eindhoven, approved the study (NCT01735838), and written informed consent was obtained from all subjects.

PTT estimation

Mean transit times (MTTs) of the indicator, UCA in echocardiography (Fig. 1) and gadolinium in DCE-MRI were obtained using the indicator dilution theory (6, 11). Briefly, the transcardiac passage after an injection of a bolus indicator was registered by the ultrasound or MRI scanner. From the acquired video clips, indicator dilution curves (IDCs) were generated by measuring the time evolution of, respectively, acoustic intensity (echocardiography) or MR signal from regions of interest (ROIs) drawn within the right and left ventricle (Fig. 1). As for both indicators, the applied dose ensured linearity between concentration and reflected intensity, IDCs reliably represent contrast concentration changes (6, 11). For the echo loops, ROI tracing was performed using commercially available software (Qlab 8.1 Advanced Quantification Software, Philips Healthcare). For the MRI signal within the ROIs, custom-made software was used in MATLAB 2014b (The Mathworks, Natick, MA, USA) (11). The IDCs were then fitted according to the local density random walk (LDRW) model using MATLAB 2014b. This model gives a physical description of the indicator transport through the circulation as a convective dispersion process (12, 13, 14). MTTs of both right and left ventricles were subsequently derived from the fitted IDCs. The difference between the MTT in the left and right ventricles represented the PTT. As the PTT can be influenced by the heart rate, it was normalized to heart rate (nPTT) by multiplication with the number of heart beats per second. The heart rate was estimated by the R-R interval of the pulsed Doppler aortic flow and phase-contrast angiography for echocardiography and MRI, respectively. The nPTT

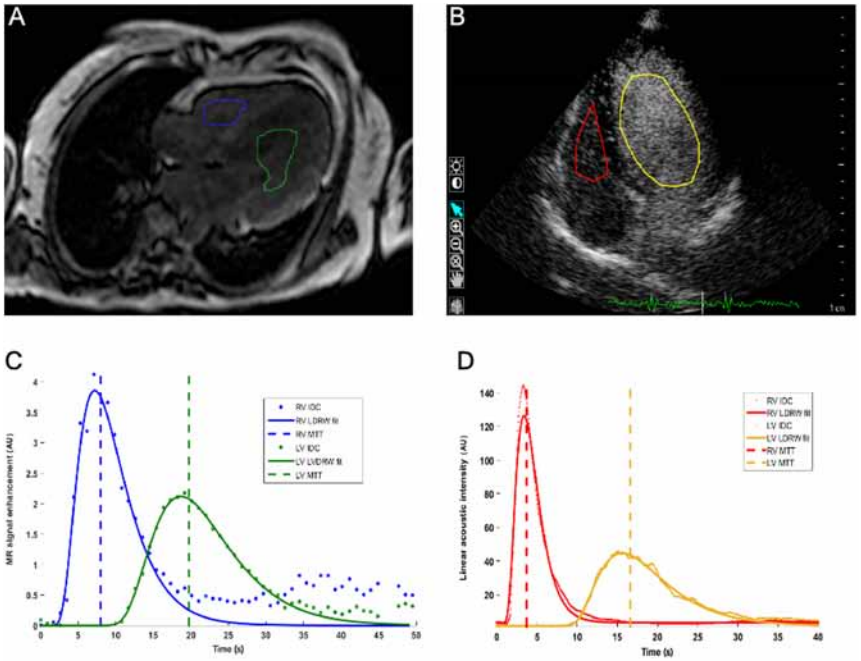

Figure 1
Overview of a DCE-MRI (A) and CEUS (B) in one patient. A bolus of gadolinium (A) and UCA, SonoVue 10 μL mL^{-1} (B), passed through the right and left ventricles (RV and LV). ROIs are drawn in the right (blue ROI (A) and red ROI (B)) and left ventricle (green ROI (A) and yellow ROI (B)), and signal or acoustic IDCs are estimated within the ROIs, expressed in panels C and D. The raw IDC (dotted lines) are fitted to the LDRW model (straight lines), and MTT (dashed vertical lines) of the contrast bolus in both ventricles is estimated. The difference in MTT is referred to as the pulmonary transit time. AU, arbitrary units.

expresses the number of stroke volumes needed to pass the pulmonary vascular bed (15).

DCE-MRI Cardiac magnetic resonance (CMR) imaging was performed on a clinical whole-body 1.5-T Achieva Intera scanner (Philips Healthcare) with acquisition of two-chamber, four-chamber, and short-axis steady-state free precession cine loops. Patients were positioned in the supine position. Phase-contrast angiography for estimation of the cardiac output and the R-R intervals, a retrospective gated fast field echo sequence with a 20° flip angle, and a repetition time (TR) of 5 ms across the aorta was used. Cardiac output and forward stroke volume were estimated off-line using quantitative software (CAAS, Pie Medical Imaging, Maastricht, the Netherlands). DCE-MRI was used to estimate the MTTs in the left and right ventricles. The DCE-MRI scan used a T_1-weighted scan, after intravenous administration of a single bolus of 0.1 mmol gadolinium diluted in 5 mL saline (Prohance, gadoteridol, Bracco Imaging S.p.A., Milan, Italy) by a Spectris MR injector (Medrad, Indianola, PA, USA) programmed at the rate of 5 mL s^{-1} and followed by a saline flush of 15 mL. A dynamic single-shot single-slice spoiled turbo field echo was used; sequence parameters were flip angle of 7°, TR of 5.7 ms, and echo time (TE) of 2.7 ms. A saturation prepulse with a delay of 200 ms was used to obtain T_1 weighting. Under these circumstances, a linear relationship between gadolinium and MR signal was obtained (11). The sequence was prospectively triggered by the R-peak on the vectorcardiogram to acquire one image per cardiac cycle in mid-diastole and to minimize motion artifacts. These measurements were performed during end-expiratory breath hold. Parallel imaging using sensitivity encoding (SENSE) with a factor of 2 was used in combination with a half-scan technique to reduce the shot duration to approximately 170 ms. The typical voxel size was $1.7 \times 1.7 \times 10\,mm^3$. Commercially available postprocessing software (ViewForum, Philips Healthcare) was used to measure left ventricular volumes and ejection fraction by combining all short-axis tracings at end-systole and end-diastole according to the Simpson's rule algorithm.

CEUS and Doppler echocardiography Two-dimensional and Doppler transthoracic echocardiography (TTE) were performed within 1 h after the MRI using an iE33 ultrasound scanner equipped with a S5-1 transducer (Philips Healthcare) with the patient in the left lateral recumbent position. Two-dimensional echocardiography included Doppler outflow signals of the mitral valve, right and left ventricles, and aortic valve as well as contrast-enhanced apical four-chamber and two-chamber views. Tissue Doppler recordings were made of the ventricular septal wall. Interventricular mechanical delay (IVMD) as a measure of interventricular dyssynchrony (threshold 40 ms) was defined as the time difference between the onset of QRS and the onset of right ventricular and left ventricular ejection, respectively (16). Intraventricular dyssynchrony was evaluated by determining the time difference between peak septal and peak posterior

wall excursion on midventricular short-axis M-mode recordings (septal-to-posterior wall motion delay (SPWMD); threshold 130 ms) (17).

PTT was estimated after intravenous administration of UCA, SonoVue (Bracco Imaging S.p.A., Milan, Italy) consisting of microbubbles with a SF_6 gas enclosed in a phospholipid monolayer shell. All dynamic contrast-enhanced TTE imaging was performed by an experienced imaging-cardiologist (PH) recording four-chamber apical views using harmonic imaging selecting a four-chamber apical view without breath-hold (18). Three different bolus injections of 10 mL saline with gradual increasing SonoVue concentrations (2.5 µL mL^{-1} (*low dose*), 5 µL mL^{-1} (*half dose*), and 10 µL mL^{-1} (*full dose*)) were used by diluting 1 mL SonoVue in saline (1:400, 1:200, and 1:100). This historical hospital protocol was adopted in a dose-finding study; however, the interdose difference is minimal and highly repeatable (18). The protocol has not been changed as it enables us to use the minimal total amount of SonoVue. These low doses provided an approximately linear relationship between the UCA concentration and the measured acoustic intensity, which is a prerequisite for application of the indicator dilution theory (6, 9).

N-terminal pro-B-type natriuretic peptide sampling

NT-proBNP sampling was performed in all patients to exclude other pathologies for exertional dyspnea and to evaluate the severity of heart failure in relationship to CRT (19, 20).

Statistical analysis

Statistical analysis was performed in IBM SPSS Statistics for Windows version 22.0 (IBM). Continuous variables were assessed for normality with the Shapiro–Wilk test and presented as mean with S.D. or median with range. Dichotomous data are presented as numbers and percentages. Differences between normal distributed parameters were calculated using Student's *t*-test or one-way analysis of variance. Differences between nonparametric parameters were assessed with Mann–Whitney *U*-tests or Kruskal–Wallis tests. The level of agreement between PTT and nPTT by CEUS and DCE-MRI was assessed by correlation and Bland–Altman analysis using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) (21). The relationship between PTT and nPTT by CEUS and DCE-MRI and several echocardiographic and laboratory heart failure parameters was evaluated by Pearson's *r* or Spearman's rho correlation depending on the distribution of the data. Interpretation of the strength of the correlation is performed by the differentiation by Evans (22). For all analyses, a *P* value less than 0.02 was considered statistically significant, due to the small sample size, to prevent a type I error.

Results

Patient characteristics and demographic data are given in Table 1. Twenty-three patients were enrolled in the study. In two patients, MRI analysis was not possible because of a violation of the acquisition protocol, and in one patient, the CEUS images were accidentally lost from the digital archive. The mean PTT-MRI was 10.4±2.0 s. Of all 60 SonoVue injections (three injections per patient), in two (3.3%), it was not possible to fit the LDRW model to the acoustic IDC. In the remaining 58 PTT-CEUS measurements, the mean PTT-CEUS was 10.2±2.1 s, 10.4±2.7 s, and 10.6±2.3 s ($P=0.86$) for full, half, and low dose, respectively. The mean PTT-CEUS of all doses was 10.5±2.4 s and was not different compared with PTT-MRI ($P=0.88$). The correlation between both techniques was $r=0.75$ (95% confidence interval (CI) 0.46–0.90; $P=0.0001$). For the normalized values, nPTTs were comparable (11.3±2.5 vs 11.2±3.0 for nPTT-CEUS and nPTT-MRI, respectively; $P=0.93$), and correlation between nPTT from CEUS and MRI was $r=0.76$ (95% CI: 0.49–0.90; $P=0.0001$) (Fig. 2). Bland–Altman analysis showed a bias of 0.1 s with limits of agreement of −3 to 3.2 s and a bias of 0.1 with limits of agreement of −3.9 to 3.7 for PTT and nPTT, respectively (Fig. 3).

PTT as a measure for cardiac function

Correlations between PTT measurements and other heart failure parameters are given in Table 2. Spearman's rank correlation coefficient between NT-proBNP was strong for nPTT by CEUS and MRI, whereas was moderate for the PTT by CEUS (Fig. 4 and Table 2).

The left ventricular end-diastolic volume index measured by MRI moderately correlated with nPTT by CEUS and MRI. The left ventricular end-systolic volume index by MRI correlated significantly with the nPTT by both techniques. Stroke volume measurement by MRI showed no correlation with the PTT or nPTT measurement. However, the forward stroke volume using phase-contrast MR angiography showed a trend correlation in 19 patients with nPTT by both techniques. Ejection fraction measured by MRI correlated strongly with nPTT-CEUS and (n)PTT-MRI.

Table 1 Demographics of the subjects ($n = 20$).

Age (year)	67 ± 10
Male/female (*n*)	10/10
BMI (kg m^{-2})	28.9 ± 6.2
BSA	1.9 ± 0.2
QRS (ms)	160 ± 18
LBBB (*n*)	18/20
Non-LBBB (*n*)	2/20
NYHA functional classes (*n*)	
I	4/20
II	6/20
III	10/20
IV	0
Mitral valve insufficiency (*n*)	19/20
Mild	14
Moderate	3
Severe	2
Cardiovascular medication	
ACEi (*n*)	15/20
AR blockers (*n*)	4/20
Beta blocker (*n*)	19/20
Aldosteron inhibitor(*n*)	6/20
Diuretic (*n*)	11/20
Echocardiographic parameters	
LVEDV index (mL m^{-2})	120 ± 41
LVESV index (mL m^{-2})	82 ± 38
EF (%)	35 ± 11
IVWD (ms)	48 ± 31
SPWMD (ms)	294 ± 117
MRI parameters	
LVEDV index (mL m^{-2})	137 ± 42
LVESV index (mL m^{-2})	97 ± 42
EF (%)	32 ± 13
fSV (mL)	68 ± 13
Laboratory parameter	
NT-proBNP (pmol L^{-1})*	188 ± 216

Results are presented as mean ± S.D. or as absolute numbers. ACE, angiotensin-converting enzyme inhibitor; AR, angiotensin-II receptor antagonist; BMI, body mass index; BSA, body surface area according to the Dubois & Dubois equation; EF, ejection fraction; fSV, forward stroke volume; IVMD, interventricular mechanical delay; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume ; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Classification; SPWMD, septal-to-posterior wall motion delay; asterisk indicates 18 patients.

(n)PTT-CEUS in relation to echocardiographic parameters

Our patient population consisted mainly of left ventricular systolic heart failure patients. The left atrial size was mean 38 ± 12 mL m^{-2}. The left atrial size correlated significantly with PTT and nPTT by CEUS (Table 3). Parameters of left ventricular filling pressures showed a median mitral valve *E*/*A* ratio of 0.89 (IQR 0.66–1.30) in 19 patients and a median tissue Doppler *E*/*e′* ratio at the septal mitral valve annulus of 13.5 (IQR 11.0–17.7) in 18 patients. Both markers correlated significantly with nPTT-CEUS (Table 3). Right ventricular function according to tricuspid annular plane systolic elevation was measured in 19 patients as 17.9 ± 5.1 mm; this value did not correlate with (n)PTT-CEUS. In only eight patients, tricuspid regurgitation was obtainable with a maximum tricuspid regurgitation velocity of 246 ± 32 cm s^{-1} (Table 3).

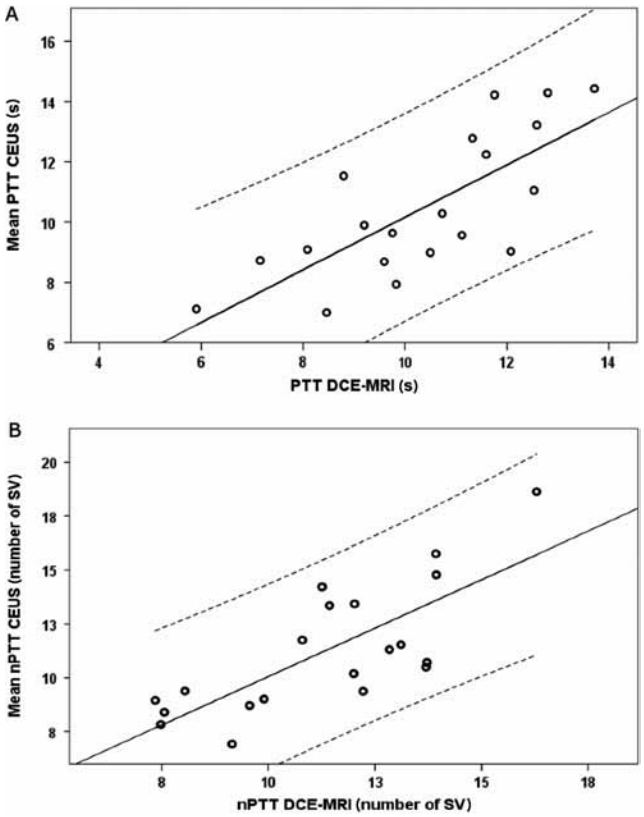

Figure 2
The correlation between PTT-MRI and mean PTT-CEUS of three measurements by CEUS (A). Correlation between both techniques for nPTT (B). The dotted lines indicate the 95% CIs.

Discussion

This study demonstrates that assessment of PTTs with CEUS is feasible in heart failure patients. Our measurements proved independent of the dose of UCA, and the observed dropout rate was minimal. In combination with the good agreement with MRI, these results indicate that CEUS may serve as a reliable method for bedside measurement of PTTs. Moreover, the observed relation between PTTs, left ventricular ejection fraction, and NT-proBNP suggests that PTTs may be used as an independent parameter for heart failure. In our patient group with systolic heart failure, we found accompanying elevated filling pressures by Doppler measurement and increased left atrial volumes,

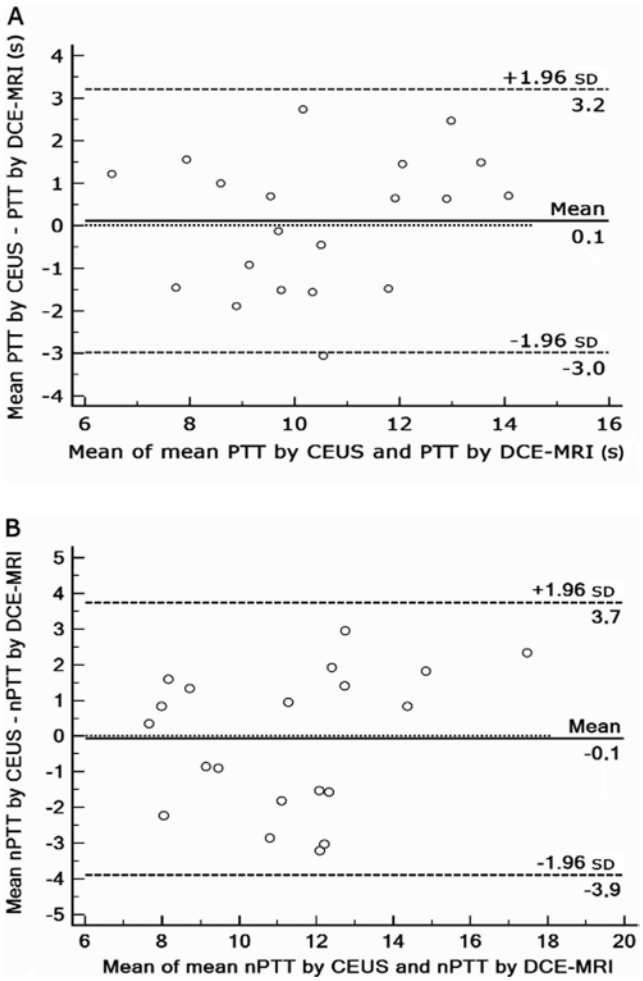

Figure 3
Bland–Altman analysis of PTT-CEUS and PTT-MRI (A). Solid line is the mean difference (bias); dashed lines are the limits of agreement (1.96 s.d.). Bland–Altman analysis of nPTT-CEUS and nPTT-MRI (B).

both correlating with (n)PTT-CEUS. However, a relationship with right ventricular function was not found in this small patient group.

Previous work indicated the feasibility of transit time assessment using CEUS *in vitro* and also in patients (7, 9). Several authors suggested a relationship between PTT and different systolic and diastolic heart failure parameters obtained with MRI (3, 4). They found a significant prolongation in cardiopulmonary transit time in heart failure patients (3, 4). Moreover, Brittain and coworkers have recently demonstrated in a pilot study the relation of CEUS-derived transit times with heart failure parameters (5). Our present results are in line with these previous observations and add to this current knowledge that obtaining PTTs using CEUS is also feasible and valid in patients with severe heart failure requiring resynchronization therapy.

Based on our experience with thermodilution-obtained transit times, we expected to find a bias between (n)PTT by CEUS and MRI. Thermodilution in comparison with CEUS is known to overestimate transit times most likely due to extravasation (7, 9). UCAs are true intravascular indicators, producing more accurate estimates of blood pool volumes. As gadolinium is not bound to proteins and is known to extravasate, a difference between PTT-CEUS and PTT-MRI was expected. However, Bland–Altman analysis showed minimal difference and extravasation in the first pass was not substantiated (Fig. 3). This suggests that PTT measurement by MRI or CEUS in patients with larger PTTs is feasible. The relatively wide limits of agreement, possibly due to the differences in timing or positioning during PTT measurement, may pose a limitation for the use of PTT in clinical practice and warrants further exploration in future studies.

We compared the (n)PTT-CEUS with the MRI ventricular volumes as echocardiographic volumes are known for inaccuracies due to image plane positioning errors and foreshortening of the left ventricle (LV) (23, 24).

The transit times derived from CEUS correlating with the ventricular volumes and NT-proBNP seemed to

Table 2 Correlation of (n)PTT with volumes measured by MRI and NT-proBNP.

	PTT_{CEUS}	$nPTT_{CEUS}$	$PTT_{DCE-MRI}$	$nPTT_{DCE-MRI}$
$LVEDV_{MRI}$ (mL m^{-2})	0.46 $P=0.043$	0.58 $P=0.008$	0.45 $P=0.047$	0.65 $P=0.002$
$LVESV_{MRI}$ (mL m^{-2})	0.45 $P=0.048$	0.58 $P=0.007$	0.50 $P=0.026$	0.70 $P=0.001$
SV_{MRI} (mL)	0.12 $P=0.625$	0.07 $P=0.766$	-0.16 $P=0.504$	–0.15 $P=0.531$
fSV_{MRI} (mL)	–0.06 $P=0.797$	–0.34 $P=0.157$	–0.07 $P=0.779$	–0.44 $P=0.058$
EF_{MRI} (%)	–0.44 $P=0.053$	–0.52 $P=0.019$	–0.61 $P=0.004$	–0.71 $P<0.001$
NT-proBNP (pmol L^{-1})	0.54* $P=0.022$	0.68* $P=0.002$	0.64* $P=0.004$	0.79* $P<0.001$

Correlation expressed as Pearson's *r* of pulmonary transit time (PTT) measurements by contrast-enhanced ultrasound (CEUS) and dynamic contrast-enhanced MRI (DCE-MRI) with left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), stroke volume (SV), forward stroke volume (fSV) measured by phase-contrast MR angiography in 19 patients, ejection fraction (EF), and NT-proBNP (18 measurements). Asterisk indicates Spearman's ρ.

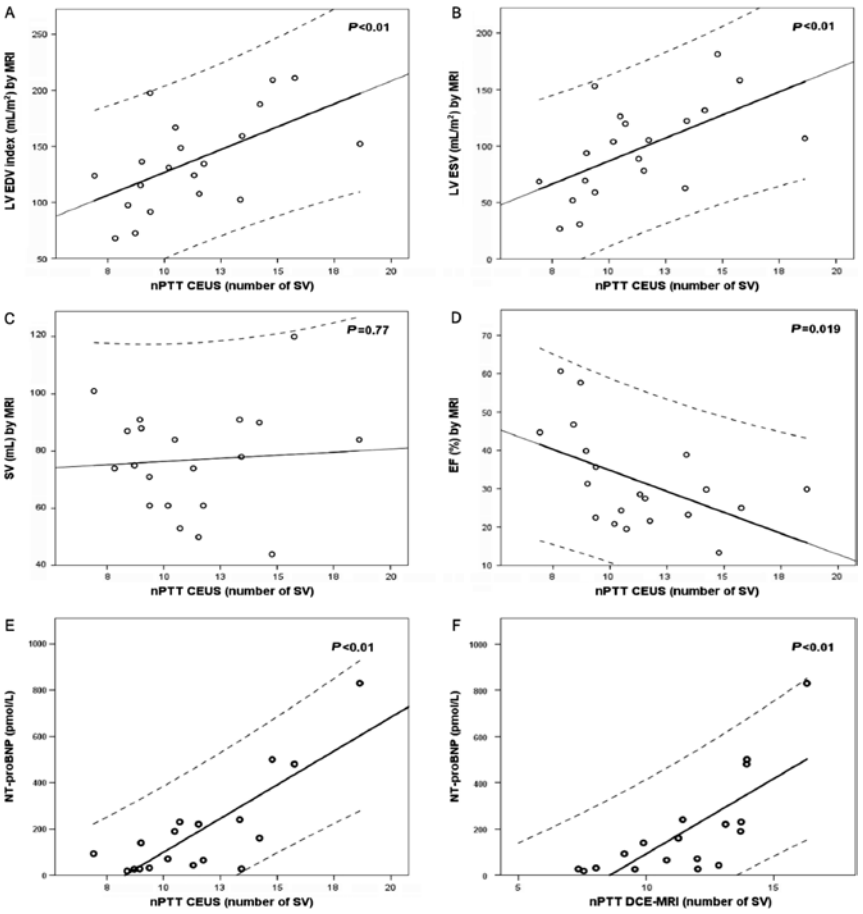

Figure 4
Correlations of nPTT by CEUS and left ventricular end-diastolic volume (*LVEDV*) index (A), left ventricular end-systolic volume (*LVESV*) index (B), stroke volume (*SV*) nonsignificant (C), ejection fraction (*EF*) (D), and *NT-proBNP* (E), and correlation of nPTT by DCE-MRI with NT-proBNP (F). Dotted lines represent 95% CI for the predicted values.

become stronger after normalization of the heart rate. This phenomenon is confirmed by other studies (4, 5, 15, 25). The correction for the heart rate is important, as a larger PTT can be due to a lower heart rate or smaller stroke volume. This has been shown in a study on healthy athletes whose pulmonary blood volumes and PTTs were increased to meet the increased aerobic capacity. However, after correction for the heart rate, nPTTs were in the same range as nontrained healthy subjects (26).

Furthermore, the relationship between (n)PTT by CEUS or MRI and stroke volume was not substantiated. In our patient group, the explanation for the absence of this relationship could be a high number of patients with mitral regurgitation (Table 1). Choi and coworkers found an inverse relationship between interventricular transit time by CEUS and cardiac output (which consists of heart rate and stroke volume) measured by right heart catheterization (10). Probably, our study was underpowered to observe a significant effect in comparison with the study of Choi and coworkers. This observation is supported by a positive trend between the forward stroke volume by phase-contrast MR angiography and nPTT-CEUS (Table 2).

NT-proBNP is indicative for volume and pressure overload in congestive heart failure (19). Therefore, the correlation of NT-proBNP with (n)PTT by MRI and CEUS may indicate that (n)PTT could serve as a possible new noninvasive parameter for detecting hemodynamic derangements in these patients. Besides this correlation,

Table 3 Correlation of (n)PTT with different echocardiographic parameters that could influence PTT.

	PTT_{CEUS}	$nPTT_{CEUS}$
Left ventricular parameters		
MR gradient	0.21 $P=0.376$	0.44 $P=0.051$
LA size (mL m^{-2})	0.50 $P=0.025$	0.50 $P=0.025$
MV *E/A* ($n=19$)	0.55* $P=0.014$	0.69* $P=0.001$
TDI *E/e'* ($n=18$)	0.46* $P=0.054$	0.69* $P=0.002$
Right ventricular parameters		
TAPSE (mm) $n=19$	−0.32 $P=0.181$	−0.08 $P=0.743$
TR max velocity (cm s^{-1}) $n=8$	0.69 $P=0.057$	0.47 $P=0.242$

Correlation expressed as Pearson's *r* of mitral regurgitation (MR), left atrium (LA), early and late diastolic Doppler flow ratio across the mitral valve (MV *E/A*), tissue Doppler imaging *E/e'* (TDI *E/e'*), tricuspid annular plane systolic elevation (TAPSE), and tricuspid regurgitation (TR). Asterisk indicates Spearman's ρ.

we found a correlation with the left ventricular end-systolic volumes by MRI. Previous studies showed that not only end-systolic volume but also NT-proBNP changes are significantly higher in CRT responders than in nonresponders (27, 28). Whether (n)PTT-CEUS change agrees to CRT responders and nonresponders remains a topic for future research.

PTT estimate is a supplement to the echocardiographic parameters as this parameter is less dependent on image quality. PTT is a highly reliable, repeatable, and reproducible parameter and obtainable during a standard contrast-enhanced echocardiography at the cost of a longer recording time (18). It is minimally invasive and bedside applicable, even in outpatients. It could be analogous to invasive cardiopulmonary estimates with a discriminative character for cardiopulmonary dysfunction. PTT above a certain threshold could implicate cardiopulmonary pump dysfunction (5, 29). Earlier studies have shown that PTT can have prognostic capabilities even to predict mortality (29).

Limitations

In general, the limits of agreement between (n)PTT-CEUS and (n)PTT-MRI were nearly 30% of the bias. The intertechnique difference in positioning, breathing, and timing could cause some changes in pulmonary blood volume, intrathoracic pressure, and cardiac output. Furthermore, effects due to cardiac displacement by respiration on the IDC within the ROI may influence the accuracy of the measurement. Alternatively, (n)PTT-CEUS is very easy to perform, minimally invasive, and bedside applicable; these advantages may counterweight possible imperfections.

In this study, all patients had sinus rhythm. PTT of patients with atrial fibrillation cannot be normalized for heart rate, which is shown (Table 2) to better reflect cardiopulmonary function. As in our study, the correlation between PTT-CEUS (nonnormalized) and NT-proBNP is still moderate; the relationship between PTT-CEUS and cardiopulmonary function in patients with atrial fibrillation could be of interest and warrants assessment in future studies.

This study covered a small study population limited to patients referred to the hospital with dyspnea due to dyssynchrony and systolic heart failure. Although our patient population consisted of low ejection fractions with a large standard deviation, the discrimination of the PTT is diminished by the lack of normal ejection fractions. However, given the encouraging results of this pilot study, larger studies including patients with different spectra of ejection fractions are desirable.

We used different doses of SonoVue and compared them to one dose of gadolinium. The use of the average PTT could favor the analysis by decreasing variation. However, the variability among the data has been shown to be low (18).

In conclusion, the measurement of (n)PTT-CEUS is an easy-to-perform and feasible procedure; it shows a strong agreement with (n)PTT-MRI. (n)PTT-CEUS also had moderate to strong correlation with Doppler and MRI parameters for heart failure. The strong relationship with NT-proBNP suggests that (n)PTT-CEUS, which is bedside applicable and minimally invasive, may provide a novel and clinically feasible measure of cardiac performance and heart failure.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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