Noninvasive pulmonary transit time: A new parameter for general cardiac performance

Anouk G.W. de Lepper MD1 | Ingeborg H.F. Herold MD, PhD2 | Salvatore Saporito PhD3 | R. Arthur Bouwman MD, PhD2 | Massimo Mischi PhD3 | Hendrikus H.M. Korsten MD, PhD2,3 | Koen D. Reesink PhD4 | Patrick Houthuizen MD, PhD1

1Department of Cardiology, Catharina Hospital Eindhoven, Eindhoven, The Netherlands
2Department of Anesthesiology and Intensive-Care, Catharina Hospital Eindhoven, Eindhoven, The Netherlands
3Department of Electrical Engineering, Signal Processing Systems, Eindhoven University of Technology, Eindhoven, The Netherlands
4Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands

Correspondence
Email: anouk.d.lepper@catharinaziekenhuis.nl

Funding information
Dutch Heart Foundation, Dekker student grant, Grant/Award Number: 2015SB007.

Introduction: Pulmonary transit time (PTT) assessed with contrast-enhanced ultrasound (CEUS) is a novel tool to evaluate cardiac function. PTT represents the time for a bolus of contrast to pass from the right to the left ventricle, measured according to the indicator dilution principles using CEUS. We investigated the hypothesis that PTT is a measure of general cardiac performance in patient populations eligible for cardiac resynchronization therapy (CRT).

Methods: The study population consisted of heart failure patients referred for CRT with NYHA class II–IV, left ventricular ejection fraction (LVEF) ≤35% and QRS ≥120 ms. CEUS, ECG, and blood were analyzed, and participants completed a quality of life questionnaire at baseline and 3 months after CRT implantation. Normalized PTT (nPTT) was calculated to compensate for the heart rate. Correlations were assessed with Pearson’s or Spearman’s coefficients and stratified for rhythm and NYHA class.

Results: The study population consisted of 94 patients (67 men) with a mean age of 70±8.9 years. (n)PTT was significantly correlated with left ventricular parameters ($r_s=-.487, P<.001$), right ventricular parameters ($r_s=-.282, P=.004$), N-terminal pro-B-type natriuretic peptide (NT-proBNP) ($r_s=.475, P<.001$), and quality of life ($r_s=.364, P<.001$). Stronger significant correlations were found in patients in sinus rhythm.

Conclusion: CEUS-derived PTT and nPTT correlate to a fair degree with measures of systolic and diastolic function, NT-pro-BNP, and quality of life. As CEUS-derived PTT can be obtained easily, noninvasively and at the bedside, it is a promising future measure of general cardiac performance.

Keywords
contrast echocardiography, diastolic dysfunction, heart failure, left ventricular function, right ventricular function, systolic function, pulmonary transit time

1 INTRODUCTION

Pulmonary transit time (PTT) measured by contrast-enhanced ultrasound (CEUS) is a possible new physiological parameter to evaluate cardiac function. Cardiac function is currently assessed by means of multiple parameters, and most of them measure either systolic or diastolic ventricular function. One important indicator of cardiac function is left ventricular ejection fraction (LVEF), which is derived from the ratio of left ventricular end-diastolic volumes (LVEDV) and left ventricular end-systolic volumes (LVESV). However, the ultrasound measures are not always accurate, as calculation is based on geometrical assumptions of a 3D structure or suboptimal image quality.

From this perspective, PTT measured by contrast-enhanced ultrasound is a promising alternative as it is reproducible and less
dependent on image quality. PTT represents the time for a bolus of contrast to pass from the right ventricle to the left ventricle, measured according to the indicator dilution principles. An increase in PTT reflects a reduction in cardiac output and an increase in pulmonary blood volume in congestive heart failure. Normalizing the PTT values per heart rate can compensate the influence of heart rate. This normalized PTT (nPTT) indicates the number of stroke volumes needed for the contrast bolus to pass the pulmonary circulation.

Previous research has shown that variations in pulmonary blood volume and PTT can be accurately evaluated using MRI. Moreover, normalized left atrial transit times are correlated with invasive left ventricular pressure measurements. CEUS-derived PTT correlates well with true volumes in an in-vitro setup, with PTT measured via MRI and with levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Choi et al. showed that cardiac output measured by right heart catheterization correlates with transit times measured with contrast echocardiography. This was shown earlier already by Sherman et al., assessing intracardiac hemodynamics using CEUS validated against right heart catheterization and survival. Importantly, both Brittain and Herold et al. showed that CEUS-derived PTTs are reproducible and can be obtained with low intra- and inter-individual variability. The study by Brittain et al. also showed, albeit in a small study population, that PTT correlated with several ultrasound parameters of left ventricular systolic and diastolic function, right ventricular function, and pulmonary vascular status.

The aim of our study was to investigate whether PTT and nPTT measured by CEUS correlate with traditional echocardiographic parameters for left and right ventricular function, as well as with NT-proBNP levels and with the subjective burden of disease in a heart failure population.

### METHODS

#### 2.1 Selection and description of participants

The study population consisted of patients with systolic heart failure who were referred for cardiac resynchronization therapy (CRT) to the Catharina Hospital (Eindhoven, The Netherlands) between January 2012 and December 2013. Patients were, therefore, in NYHA class II–IV with a LVEF ≤35% and QRS duration over 120 msec. Exclusion criteria were mainly dependent on contra-indications for the ultrasound contrast agent, namely: acute coronary syndrome or acute heart failure 3 months before CRT implantation, atrial septal defects, right to left shunts, severe pulmonary hypertension, uncontrolled arterial hypertension, allergy to sulfur-hexafluoride, end-stage renal or hepatic disease, and pregnancy. The local ethical committee approved the study and all patients provided written informed consent regarding the use of their data for scientific purposes.

#### 2.2 Quality of life questionnaire, laboratory analysis, and ECG

Before CRT implantation, patients were asked to complete a quality of life questionnaire (Minnesota Living With Heart Failure Questionnaire, MLHFQ). Besides, the patient’s physician assessed the NYHA-score and performed a standard 12-lead ECG. Moreover, a laboratory investigation was performed to measure plasma hemoglobin, renal function (creatinine and Modification of Diet in Renal Disease [MDRD]), and NT-proBNP. Three months after CRT implantation, all these investigations were repeated together with the ultrasound examination.
Routine transthoracic echocardiography (TTE) was performed according to the hospital’s protocol and the EACVI/ASE guidelines. For the recordings, we used an iE33 ultrasound scanner equipped with a S5-1 transducer (Philips Healthcare, Andover, MA, USA). All recordings were made in left recumbent position, and patients were instructed to breathe slowly without holding breath or coughing during image acquisition. Two-dimensional B-mode recordings were made from standard parasternal and apical views, and pulsed and/or continuous-wave Doppler signals were obtained from the pulmonary veins, the mitral valve, the left ventricular outflow tract, and the aortic valve. All measurements were executed offline by an experienced imaging cardiologist (PH). Contrast-enhanced images were used to calculate left ventricular volumes and ejection fraction using Simpson’s biplane method. Basic dyssynchrony measures were also calculated, including interventricular mechanical delay (threshold limit 40 msec) and intraventricular septal-to-posterior-wall motion delay for the left ventricle (threshold limit 130 msec). All these measurements were repeated 3 months after CRT implantation.

### 2.3 | Echocardiography

#### 2.4 | PTT measurements

At baseline and 3 months after CRT implantation, PTTs were obtained by CEUS as described by Herold et al. A peripheral vein was used to administer a bolus injection of 10 mL saline with 10 μL/mL SonoVue (Bracco SpA, Milan, Italy) concentration. SonoVue consists of microbubbles of SF6 gas encapsulated by a single phospholipid layer. Briefly, the transcardiac course of the bolus indicator was registered by ultrasound. The obtained echo loops were used to create indicator dilution curves by measuring the time evolution of acoustic intensity from regions of interest (ROIs) drawn within the right and left ventricles.
TABLE 2 Correlations with echocardiographic parameters. NT-proBNP and subjective burden of disease (N=94)

<table>
<thead>
<tr>
<th>Measure</th>
<th>PTT</th>
<th>nPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$ or $r_s$</td>
<td>BCa 95% CI</td>
</tr>
<tr>
<td>LVEDV</td>
<td>0.331&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.197; 0.464]</td>
</tr>
<tr>
<td>LVESV</td>
<td>0.357&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.232; 0.488]</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.389&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[-0.523; -0.230]</td>
</tr>
<tr>
<td>CO</td>
<td>-0.257&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[-0.423; -0.058]</td>
</tr>
<tr>
<td>LA-volume</td>
<td>0.361&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.210; 0.528]</td>
</tr>
<tr>
<td>E/A-ratio</td>
<td>0.266&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.076; 0.444]</td>
</tr>
<tr>
<td>E/E’</td>
<td>0.217&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.025; 0.409]</td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.248&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[-0.416; -0.063]</td>
</tr>
<tr>
<td>TV regurgitation</td>
<td>0.368&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.225; 0.493]</td>
</tr>
<tr>
<td>Visual dysynchrony</td>
<td>-0.279&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[-0.419; -0.112]</td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.174&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.003; 0.34]</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.475&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.329; 0.601]</td>
</tr>
<tr>
<td>MLHFQ</td>
<td>0.178&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[0.013; 0.326]</td>
</tr>
<tr>
<td>NYHA-score</td>
<td>0.287&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[0.106; 0.467]</td>
</tr>
</tbody>
</table>

Correlation coefficients are indicated as Pearson’s $r$ or Spearman’s $r_s$.

<sup>a</sup>Correlation is significant at the 0.05 level (2-tailed).

<sup>b</sup>Correlation is significant at the 0.01 level (2-tailed). The significance levels are provided with their bias-corrected and accelerated bootstrap 95% confidence intervals (BCa 95% CI).

2.5 Statistical data analysis

All analyzes were carried out using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0; IBM Corp., Armonk, NY, USA). Frequency tables were generated, with the applicable percentages, for the description of ordinal and nominal variables at baseline. For all cardiac function parameters, normality was assessed by means of probability–probability plots, histograms, skewness, and kurtosis, even if the central limit theorem was applicable. Normally distributed continuous variables at baseline were described in terms of mean and standard deviation. Median and interquartile range described the nonparametric variables.

Pearson’s correlation coefficient ($r$) was used for all normally distributed continuous variables. Spearman’s correlation coefficient ($r_s$) was used if the assumptions for Pearson’s correlation were not met. Both correlation coefficients were accompanied by their 95% bias-corrected and accelerated confidence intervals (BCa 95% CI). Baseline and 3-month follow-up measurements were pooled to calculate the correlation coefficients. Stratification was performed for sinus rhythm (SR) and atrial fibrillation (AF), as well as a per NYHA class. A $P$-value lower than .05 was considered significant.

3 RESULTS

3.1 Study population

In total, 96 patients received a CRT device during the inclusion period, and all were asked to participate in our study. Two patients did not provide informed consent forms and were, therefore, excluded from the study. Hence, 94 patients were included and underwent baseline examinations. At follow-up, no ultrasounds were available for 34 patients, due to various reasons. Therefore, only their baseline ultrasounds were used to calculate correlations.

Table 1 provides an overview of baseline patient characteristics. The population included predominantly males with an average age of 70±8.9 years old. Common comorbidities were diabetes, decreased kidney function, and hypertension. The intraventricular conduction delay was most commonly based on a left bundle branch block, generally in combination with underlying SR. In the cohort, there was a
extensive appearance of both systolic and diastolic left ventricular dysfunction. More than half of the patients were reported as NYHA class III at baseline.

### 3.2 Correlations of PTT and nPTT

Table 2 presents an overview of the correlations of PTT and nPTT with echocardiographic parameters. Systolic parameters (LVESV, LVEDV, and LVEF) frequently were statistically significantly correlated to either PTT or nPTT ($P<.05$), with LVEF showing the strongest correlation ($r_s = -0.487$), as shown in Figure 2. No significant correlations were observed for interventricular mechanical delay, stroke volume and forward stroke volume. Interestingly, diastolic measures were also significantly correlated to both PTT and nPTT and were strongest for LA-volume ($r_s = .361$, $P<.001$). The tricuspid valve regurgitation was also assessed and revealed a significant correlation ($r_s = .368$, $P<.001$). The same holds for visual dyssynchrony and QRS duration as shown in Table 2. Moreover, NT-proBNP was correlated to both PTT and nPTT, with coefficients of $r_s = .475$ and $r_s = .437$, respectively ($P<.001$). LVEF and NT-proBNP demonstrated a significant correlation with (n)PTT in all subgroups of SR, AF, and NYHA class II and III. Finally, subjective burden of disease was also significantly correlated to both PTT and nPTT. The strongest correlations were found between nPTT and the MLHFQ score ($r_s = .252$, $P = .002$) and between nPTT and the NYHA-score ($r_s = .364$, $P<.001$).

As measurements might have been influenced by AF, we repeated our analysis in the subsets of patients in SR (66.7%) and AF (19.4%). The correlations found in these analyzes are shown in Table 3. In the subgroup of SR patients, correlations were comparable to those described above in the whole group. In the AF subgroup, LVEDV and NT-proBNP were strongly significantly correlated to PTT. The corresponding correlation coefficients were $r_s = .551$ ($P<.005$) and $r_s = .666$ ($P<.001$), respectively. The number of observations was too little for tricuspid valve insufficiency, QRS duration, and visual dyssynchrony to calculate the correlations in the subgroups. These parameters for the whole population are shown in Tables S1 to S3.

Subgroup analysis stratified per NYHA class, shown in Table S4, indicated that correlations between NT-proBNP and PTT were generally

**FIGURE 2** Spearman’s ($r$) or Pearson’s ($r_s$) correlation of pulmonary transit time (PTT) and normalized PTT (nPTT) with (upper panel) left ventricular ejection fraction (%), (middle panel) left atrial volume (mL), (lower panel) TAPSE (tricuspid annular plane systolic excursion in cm). The middle line indicates the best fit, and the two outside lines indicate 95% confidence intervals.
TABLE 3 Correlations of pulmonary transit time (PTT) and normalized (n) PTT with echocardiographic parameters, NT-proBNP and subjective burden of disease, stratified by rhythm

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sinus rhythm (n=62)</th>
<th>Atrial fibrillation (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r or rs BCa 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>r or rs BCa 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>LVEDV</td>
<td>0.271b [0.104; 0.431]</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>0.296b [0.139; 0.462]</td>
<td>.003</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.349b [-0.518; -0.139]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>-0.173 [-0.443; 0.110]</td>
<td>.140</td>
</tr>
<tr>
<td>LA-volume</td>
<td>0.421b [0.238; 0.599]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>0.270a [0.057; 0.468]</td>
<td>.019</td>
</tr>
<tr>
<td>E/A- ratio</td>
<td>0.192 [-0.062; 0.441]</td>
<td>.126</td>
</tr>
<tr>
<td></td>
<td>-0.300b [-0.500; -0.096]</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>-0.300b [-0.500; -0.096]</td>
<td>.004</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.456b [0.242; 0.636]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>0.456b [0.242; 0.636]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MLHFQ</td>
<td>0.115 [-0.090; 0.322]</td>
<td>.258</td>
</tr>
<tr>
<td></td>
<td>0.260b [0.042; 0.448]</td>
<td>.009</td>
</tr>
<tr>
<td>NYHA-score</td>
<td>0.260b [0.042; 0.448]</td>
<td>.009</td>
</tr>
</tbody>
</table>

Correlations coefficients are indicated as Pearson’s r or Spearman’s rs.

aCorrelation is significant at the 0.05 level (2-tailed).
bCorrelation is significant at the 0.01 level (2-tailed). The significance levels are provided with their bias-corrected and accelerated bootstrap 95% confidence intervals (BCa 95% CI).

stronger in higher NYHA class II and III, r=.482 (P<.001) and r=.403 (P=.003), respectively. NYHA class IV consisted of only two patients and therefore was not performed. A strong correlation was found within NYHA class I between nPTT and LVEDV (r=.641, P=.001) and LVESV (r=.629, P=.001).

4 | DISCUSSION

The aim of our study was to establish whether and how PTT and nPTT relate to traditional ultrasound parameters, laboratory tests, and quality of life scores that are clinically used to define the various modes of cardiac dysfunction. As: pulmonary blood volume (L)=cardiac output (L/min)×PTT (sec), PTT is proportional to pulmonary blood volume. PTT could therefore be used to measure pulmonary congestion. Consequently, PTT reflects general cardiopulmonary function.

Our results demonstrate that, in heart failure patients referred for resynchronization therapy, CEUS-derived PTT and nPTT correlate to parameters of both systolic (eg, LVEF) and diastolic (eg LA-volume) ventricular function, NT-proBNP, and subjective burden of disease as measured by quality of life scores. This relation with NT-proBNP appears to hold in patients with AF and is generally stronger within higher NYHA classes. It was not shown that PTT is superior to conventionally used parameters, nor that it correlates to one specific cardiac function (eg right ventricular function). Which is to be expected considering PTT is an indicator of general cardiopulmonary function.

Our results are in line with previous observations, but our study included a larger study population than previous studies and used echocardiography. Brittain et al.19 also found a negative correlation between PTT and LVEF. Contrary to our results, however, they found a stronger correlation with the velocity time integral of the left ventricular outflow tract and tricuspid annular plane systolic excursion (TAPSE). This could be attributed to the smaller study population,
which comprised more obese patients with better systolic left ventricular function. In another study by Shors et al., correlations between PTT and LVEF, LVEDV, and LVESV were comparable to ours, but measured with MRI. In contrast to our study, they also found a correlation for cardiac output. These differences can probably be attributed to the method of measuring PTT. Brittain et al.\(^1\) defined PTT as the time passed between the first RV peak and the first LA peak on the time-intensity curves. Shors et al.\(^2\) calculated the transit times by subtracting the time of peak signal intensity on the pulmonary artery from the peak on the ascending aorta curve.

Our findings might have been influenced by the use of curve fitting with the local density random walk model to determine PTT, which constitutes an interpretation of the observed curve. The local density random walk model describes the injection of an indicator into a straight infinitely long tube, where the fluid flows with a constant velocity. It is based on the physics of the dispersion process, and therefore, it is related to the physical interpretation of a dilution process.\(^2\) Model-based quantifications are more robust to noise, such as bubble disruption, artefacts of surrounding tissue and bad mixing and were previously used in validation studies.\(^2\) Another method to calculate PTT, which is more easily applicable in clinical practice but has not yet been validated, is to measure the time differences between times of onset or of peak values. Next to this, the position of ROIs, atrial or ventricular respectively, might also influence PTT.

Transit times describe global cardiac function, while most traditional measurements only look at systolic function (LVEF, stroke volume, cardiac output, TAPSE) or at diastolic function (E/E\(^\prime\), mitral ratio of peak early to late diastolic filling velocity (E/A-ratio), LA-volume) and are, often limited to one chamber. This could explain the moderate correlation for traditional measures and the relatively stronger correlation found for NT-proBNP. As a result, the correlations between LV volumes and PTT are much stronger than those between PTT and the velocity time integral and cardiac output, respectively, which are characterized by a lower signal-to-noise ratio.

### 4.1 Limitations

Our findings may be limited by the fact that not all measurements were performed in all patients. Therefore, the numbers of measurements fluctuate per parameter. This fluctuation is mainly due to poor image quality, which made it impossible to perform all conventional ultrasound measurements. A small additional number of missing data was caused by the fact that not all patients were implanted a CRT device. This inhibits to reveal significant correlations for all cardiopulmonary functions, as the study is underpowered for numerous parameters. This consequence especially holds for the subgroup analysis. All baseline measurements and all the available follow-up measurements were eventually combined to calculate the correlations. This implies that some patient data were used twice, which evidently caused bias. Another limitation is the fact that nPTT was also calculated in AF patients; their ventricular frequency might fluctuate, which could cause uncertainty when interpreting the nPTT in this population. Still, we found a good correlation between nPTT and LVEF in AF patients, which might be explained by a relatively regular frequency in this patient population (treated with \(\beta\)-blockers).

As CEUS is minimally invasive and applicable at bedside, this method can easily be introduced in clinical practice.\(^1\) Analysis can be performed on regular contrast echocardiography images. To improve the implementation, calculation of PTT can be fully automated as previously shown by Saporito et al.\(^2\) Given the feasibility and accuracy\(^6\) of this measuring technique, CEUS-derived transit times might be a promising, additional parameter of general cardiac function. An additional advantage is that this measuring is less dependent on image quality than other techniques for reflecting overall cardiopulmonary function.

In future investigations, the diagnostic potential of PTT to evaluate cardiac function in patients with irregular heart rhythm, such as AF needs to be clarified. Furthermore, it has not been established yet whether PTT has a prognostic value regarding the response to CRT. Finally, the method might also be suitable for quantification of mitral regurgitation and by comparing indicator dilution curves of left atrium and ventricle.

### 5 Conclusion

CEUS-derived PTT and nPTT correlate well with measures of systolic and diastolic function as well as with NT-pro-BNP and heart failure quality of life scores. As CEUS-derived PTT can be obtained easily and noninvasively, it potentially is a promising measure of overall cardiac performance.

### References


SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Population characteristics and demographics (N=94).
Table S2. Correlations with echocardiographic parameters. NT-proBNP and subjective burden of disease (N=94).
Table S3. Correlations of PTT and nPTT with echocardiographic parameters, NT-proBNP and subjective burden of disease, stratified by rhythm.
Table S4. Correlations of PTT and nPTT with echocardiographic parameters, NT-proBNP and subjective burden of disease, stratified by NYHA class.

How to cite this article: de Lepper AGW, Herold IHF, Saporito S, et al. Noninvasive pulmonary transit time: A new parameter for general cardiac performance. Echocardiography. 2017;00:1–8. https://doi.org/10.1111/echo.13590