Systolic time intervals as simple echocardiographic parameters of left ventricular systolic performance: correlation with ejection fraction and longitudinal two-dimensional strain

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Aims
Conventionally, the evaluation of left ventricular (LV) systolic function is based on ejection fraction assessment, which may be supplemented by other echocardiographic techniques, such as tissue Doppler imaging, 3D evaluation, and speckle tracking strains. However, these imaging modalities have a high technicity and are time-consuming, while being associated with reproducibility limitations. In this context, the usefulness of simpler measurements such as systolic time intervals (STI) by pulsed Doppler echocardiography must be emphasized.

Methods and results
In this multicentre study, left ventricular ejection fraction (LVEF), dP/dtmax, LV stroke volume, myocardial longitudinal deformation, aortic pre-ejectional period (PEP, ms), and left ventricular ejection time (LVET, ms) were prospectively investigated and compared in 134 consecutive heart failure (HF) patients and 43 control subjects. Feasibility of STI measurements was 100%. Intra-observer reproducibility was 98% for PEP, 96% for LVET, 87% for LVEF, and 93% for global longitudinal strain (GLS). By subgroup analyses, with increasingly altered LVEF or GLS, PEP significantly increased, whereas significantly LVET decreased, resulting in a significantly increased PEP/LVET ratio (P < 0.001). In the HF patients group, a correlation between LVEF and PEP/LVET was found, with r = 0.55 (y = −0.003x + 0.75, P < 0.001). Based on receiver operating curve analyses, the area under the curve was 0.91 for PEP/LVET > 0.43, which allowed us to detect LVEF < 35% with a sensitivity of 87%, and a specificity of 84%.

Conclusion
STI can be easily and accurately measured in clinical practice, and may be used for detecting alterations in LV systolic function. Moreover, this method is likely to have potential applications in the management of HF patients.

Keywords
Left ventricular function • Echocardiography • Systolic time intervals • 2D strain

Introduction
Echocardiography is commonly used in the evaluation of left ventricular (LV) systolic function. However, the reproducibility of LV ejection fraction has been a matter of controversy. More recently, new techniques such as tissue Doppler imaging (TDI), 3D evaluation, and speckle tracking echocardiography have been proposed to more precisely quantify LV systolic function.1–4 Yet, these methods are technically complex, time-consuming, and user-dependent.

Timing of mechanical cardiac events, particularly LV ejection, described 40 years ago using a phonocardiogram, an
electrocardiogram, and an external carotid pulse.\textsuperscript{5–12} can be measured by echocardiography.\textsuperscript{13} This approach is likely to be of benefit for several practical and clinical applications, such as LV function evaluation under difficult conditions. Moreover, this method could help to optimize different therapies such as cardiac resynchronization in heart failure (HF) patients. To this purpose, usefulness, accuracy, and reproducibility of systolic time intervals (STI) (aortic pre-ejectional period [PEP] and left ventricular ejection time [LVET]) in detecting LV systolic dysfunction were tested and compared with conventional and newer techniques. Clinical applications for STI have been previously reported in mitral valve stenosis, coronary artery disease, arterial hypertension, or atrial fibrillation.\textsuperscript{14–17} Moreover, some therapies improved only patients with abnormal PEP/LVET.\textsuperscript{18–20} Since PEP is a time interval based on a fine balance between intrinsic myocardial contractility, LV preload and afterload as well as electrical activation, LVET is dependent on intrinsic contractility and influenced by LV preload and afterload.\textsuperscript{5,21} However, both parameters will be dependent to some degree on heart rate or QRS width and it is crucial to consider the validity of STI measurements in regard to loading conditions, heart rate, and electrical activation.

This study aimed to prospectively compare STI echocardiographic measurements with conventional LV function parameters, including myocardial strain by speckle tracking in consecutive unselected HF patients and control subjects from three cardiologic centres.

**Methods**

**Study population**

Consecutive HF patients with chronic dilated or ischaemic cardiomyopathy and left ventricular ejection fraction (LVEF) of <50%, who prospectively underwent echocardiography between January and November 2007 in three cardiologic centres: Rennes, Bordeaux, and Marseille (France), were included. The exclusion criteria were haemodynamic instability, HF event < 3 months, atrial fibrillation, valvular regurgitation >grade 2/4 or more than mild valvular stenosis, valvular prosthesis, and cardiac stimulator. A control group was selected on a population of subjects without heart disease, diabetes, or hypertension and presenting normal echocardiography and EKG. All subjects gave their consent to participating in the study.

**Echocardiographic analysis**

All patients underwent echocardiographic evaluation using a Vivid 7 machine (GE Medical Systems-Vingmed, Horten, Norway) with a 4-MHz transducer. Doppler gains were adjusted at a 100 mm s\textsuperscript{-1} sweep speed. Standard echocardiogram included assessment of LV diameters as well as volumes, left atrial end-systolic area, LVEF by biplane Simpson method, LV peak tissue Doppler systolic velocity (S\textsuperscript{\prime}, cm s\textsuperscript{-1}) at the lateral part of the mitral annulus and at the right ventricular free wall, dP/dt max (mmHg s\textsuperscript{-1}) by Barggiga method, aortic time velocity integral (cm), LV cardiac output, and systolic pulmonary artery pressure (mmHg), according to American Society of Echocardiography guidelines.\textsuperscript{22} LV diastolic function was evaluated using mitral inflow (early diastolic peak E wave velocity, cm s\textsuperscript{-1}), early diastolic tissue Doppler velocity (E\textsuperscript{\prime}, cm s\textsuperscript{-1}) at the lateral part of the mitral annulus, and mitral propagation flow velocity in colour M-mode (Vp, cm s\textsuperscript{-1}). Mitral regurgitation severity was quantified using the PISA method (effective regurgitant orifice area (EROA), mm\textsuperscript{2}). All measurements were performed off-line, blindly of clinical data, and averaged from three cardiac cycles on digital stored images with dedicated software (EchoPac, version BT08, GE-Vingmed, Horten, Norway) by the same operator.

**Systolic time intervals**

Based on pulsed Doppler aortic acquisitions, STI were obtained: aortic pre-ejectional period (PEP: delay from Q wave of QRS to aortic valve opening, ms) and LV ejection time (LVET, ms) (Figure 1). In simple terms, PEP is the interval from the onset of ventricular depolarization to the beginning of aortic ejection. LVET represents the interval from beginning to termination of aortic flow. PEP/LVET ratio was also calculated. Figure 1 depicts PEP and LVET measurements in both a control subject (Figure 1A) and an HF patient (Figure 1B).

**Speckle tracking strain analysis**

For speckle tracking longitudinal strain analysis, 2D greyscale cardiac cycle acquisitions were recorded in apical 4-, 2-, and 3-chamber views, with a frame rate adjusted between 70 and 80 Hz. Using EchoPac software, strain was measured as previously described.\textsuperscript{23} Two-dimensional strain is a non-Doppler-based method to evaluate systolic myocardial deformations based on standard 2D acquisitions. Global longitudinal strain (GLS) was averaged on three consecutive cardiac cycles.

**Reproducibility**

A first observer performed all echocardiograms, all measurements being repeated under blinded conditions. Intra-observer reproducibilities of STI, LVEF, and GLS were calculated by averaging the differences between 10 measures. Intra-observer reliability of PEP and LVET was equally performed on two different acquisitions for 20 subjects. The studies were analysed off-line by a second observer blinded to the values obtained for 10 patients. Inter-observer reproducibilities were also computed.

**Statistical analysis**

Statistical Package for Social Sciences, version 11.5 (Chicago, IL), was used for statistical evaluation. All values were expressed as mean ± SD. The Student t-test, ANOVA, and Friedman tests were used to compare the patient data to those of control subjects. A P-value of <0.05 was considered statistically significant. Pearson test and linear regression analysis were used to seek correlations. Using the area under the receiver operating characteristic (ROC) curve analysis, the optimal cut-off value, sensitivity, and specificity of STI in detecting LVEF < 35% and LVEF < 45% were determined.

**Results**

**Population characteristics**

The study population included 134 patients (63 ± 17 years; 73% men) with dilated (59%) or ischaemic cardiomyopathy (41%). Sixteen per cent of them were in NYHA functional class I, 44.7% in NYHA II, 16.4% in NYHA III, and 5.2% in NYHA IV; 83.1% of them were treated with beta-blockers, while 89.4% were given angiotensin-converting enzyme inhibitors or angiotensin receptors blockers. Forty-three control subjects were recruited (43 ± 14 years; 39% men) (Table 1).
Echocardiography

Table 1 displays echocardiographic characteristics of HF and control subjects. LVEF was 30.3 ± 9.0%, and GLS was -9.3 ± 3.4% in HF patients vs. 65.5 ± 4.4% (P < 0.001), and -22.0 ± 1.8% (P < 0.001), respectively, for controls. STI measurement was feasible in 100% of cases. PEP was longer, whereas LVET was shorter in HF patients than controls (P < 0.001). Consequently, PEP/LVET was significantly increased in HF patients (0.50 ± 0.14 vs. 0.24 ± 0.03 in controls, P < 0.001).

Subgroup analysis

A subgroup analysis was performed. STI was evaluated by LV systolic function levels. Figure 2A provides values of the timing measurements in group 1 (patients with LVEF ≤ 20%, n = 21), group 2 (21% ≤ LVEF ≤ 40%, n = 95), group 3 (41% ≤ LVEF ≤ 59%, n = 25), and group 4 (LVEF ≥ 60%, n = 36). Figure 2B shows values of the timing time measurements in group 1 (GLS ≥ -6.25%, n = 23), group 2 (-12.5% ≤ GLS ≤ -6.26%, n = 85), group 3 (-18.74% ≤ GLS ≤ -12.6%, n = 25), and group 4 (GLS ≤ -18.75%, n = 33). In both cases, PEP increased from group 4 to group 1, while LVET decreased from group 4 to group 1, and consequently, PEP/LVET significantly increased from group 4 to group 1.

Correlation analysis

Pearson correlations were performed to compare STI measurements with LVEF, dP/dtmax, stroke volume, LV output, LV S’ TDI, and GLS (Table 2). All STI correlated with LV systolic performance parameters. High correlation levels were observed between STI and LVEF (r = -0.71 for PEP [P < 0.001], r = 0.64 for LVET.

Figure 1 Measurements of pre-ejectional period and left ventricular ejection time. (A) In a control subject: LVEF = 63%, GLS = -22%, PEP = 67 ms, LVET = 273 ms, PEP/LVET = 0.24. (B) In a heart failure patient: LVEF = 10%, GLS = -3.4%, PEP = 171 ms, LVET = 245 ms, PEP/LVET = 0.70.
[P < 0.001], and r = −0.78 for PEP/LVET [P < 0.001]), and between STI and GLS (r = 0.68 for PEP [P < 0.001], r = −0.61 for LVET [P < 0.001], and r = 0.75 for PEP/LVET [P < 0.001]). Figure 3 depicts linear regression analysis between PEP/LVET and LVET in the entire population (Figure 3A) (y = −0.0074x + 0.72, r = 0.78, P < 0.001) and the HF group (Figure 3B) (y = −0.0063x + 0.75, r = 0.55, P < 0.01).

Linear regression analyses were undertaken to search for a potential correlation between STI and heart rate or QRS width. Figure 4 illustrates that no correlation was observed between PEP and heart rate (Figure 4A), whereas a correlation was found between LVET and heart rate (r = 0.51, P < 0.001) (Figure 4B). Moreover, no significant correlation between PEP/LVET and heart rate was found (Figure 4C). Figure 5 illustrates that no correlation was observed between LVET and QRS width (Figure 5A), whereas a correlation was found between PEP or PEP/LVET and QRS width (r = 0.56, P < 0.001 and r = 0.43, P < 0.001, respectively) (Figure 5A and 5C). PEP and PEP/LVET are both significantly related to QRS width whereas LVET is significantly related to heart rate. Similar to Weisssler et al.,11 we derived data from regression equation and we can propose these corrections to heart rate and to QRS width: LVETc = 1.5 HR + LVET; PEPc = 0.46 QRS width + PEP; PEP/LVETc = 0.017 QRS width + PEP/LVET. Correlations between corrected STI and other parameters of LV systolic function are presented on Table 3. Finally, no significant correlation was found between mitral regurgitation EROA and STI measurements.

Receiver operating characteristic curves analysis
Areas under ROC curves were analysed for both PEP and PEP/LVET in order to identify predictors of LVEF < 35% and LVEF < 45%. Figure 6A depicts ROC curves for detecting LVEF < 35%. The best area under the ROC curves was observed for PEP/LVET (AUC = 0.91, optimal cut-off > 0.43, sensitivity 87%, and specificity 84%). PEP and PEP/LVET had similar and strong capabilities for detecting LVEF < 45%, with areas under ROC curves of 0.96 and 0.98, respectively (Figure 6B).

Reproducibility
Mean intra-observer variability was 13% for LVEF, 7% for GLS, 2% for PEP, and 4% for LVET. Based on two different acquisitions, mean intra-observer variability was 7.6% for PEP, and 4.3% for LVET. Inter-observer variability was 15% for LVEF, 8% for GLS, 3% for PEP, and 4.5% for LVET.

Discussion
Despite recent developments in echocardiography for estimating LV systolic function, this prospective study demonstrates that STI measurements are precise, reproducible, and probably the simplest method to perform. Numerous studies demonstrated that external measurements of STI directly reflected the intra-cardiac events measured simultaneously from high-fidelity catheters in the LV.
and the aorta but STI can be also evaluated by conventional echocardiographic techniques such as M-mode or pulsed Doppler. Our study evaluated STI using Doppler measurements in subjects with different LVEF levels, and compared them with conventional parameters of LV systolic function, as well as to newer technologies such as longitudinal deformations assessed by speckle tracking methods.

Factors influencing systolic time intervals

STI provide a temporal description of sequential phases of the cardiac cycle physiologically influenced by the same variables as those affecting other global performance. LV performance indices are based on capacity to pump blood (stroke volume cardiac output), ability to generate force (pressure, $dP/dt_{\text{max}}$) and to shorten with each contraction (ejection fraction, longitudinal deformation), the temporal relationships of contraction (STI), as well as on a combination of these variables.

In subgroup analyses by systolic performance levels, with decreasing LVEF or GLS values, PEP significantly increased, whereas LVET significantly decreased, resulting in a significantly increased PEP/LVET. Several studies using external measurements of STI have shown that interventions altering LV performance produce directionally similar changes in STI as well as in other LV performance indices. The diminished rate of $dP/dt_{\text{max}}$
results in a prolongation of isovolumic contraction time and PEP. This is accounted for by that PEP is equal to electromechanical delay plus isovolumic contraction time. Therefore, changes in PEP are largely dependent on isovolumic contraction time. In our study, a better correlation existed between dP/dt_max and PEP than with LVET. The shortening of LVET with LV dysfunction is more complex. In case of LV failure, there is a delay in the onset of ejection, while the velocity of myocardial fibre shortening is reduced. As the extent of fibre shortening is also reduced, LVET tends to be shortened. LVET was shown to be related to stroke volume.\textsuperscript{11,12,25,29,30} Because GLS is influenced by both the isovolumic contraction period and the degree of myocardial shortening, this parameter correlated with both PEP and LVET, and even more with PEP/LVET ratio. As PEP is lengthened, and LVET is shortened in the case of LV dysfunction, PEP/LVET is a more useful index of overall LV performance.\textsuperscript{11,12} In our study, we observed that PEP/LVET was more strongly correlated to LVEF and GLS than either PEP or LVET.

All STI components have been known for long to vary inversely with heart rate, and corrections must thus be made.\textsuperscript{21} PEP/LVET correlated better with other LV performance measurements than either PEP or LVET and was considered to be independent of heart rate. However, this is still a matter of debate.\textsuperscript{31,32} In our study, we observed a correlation between QRS width and both PEP and PEP/LVET and between heart rate and LVET. Other factors known to influence PEP are positive and negative inotropes as well as preload changes, while those influencing LVET include positive and negative inotropes, LV failure, reduced afterload, and increased preload.\textsuperscript{5,21}

| Table 2 Pearson correlations between systolic intervals and other left ventricular systolic performance indices |
|-----------------|------|------|-----------------|
|                | PEP  | LVET | PEP/LVET         |
| LVEF           | −0.71* | 0.64* | −0.78*          |
| GLS            | 0.68* | −0.61* | 0.75*          |
| dP/dt_max      | −0.41* | 0.32† | −0.49*          |
| LV S’ TDI      | −0.58* | 0.39* | −0.59*          |
| LV stroke volume | −0.34* | 0.65* | −0.53*          |
| LV output      | −0.47* | 0.36* | −0.53*          |

*P < 0.001, †P < 0.01.

**Figure 3** Linear regression analysis between pre-ejectional period/left ventricular ejection time and left ventricular ejection fraction.
**Interest of systolic time intervals compared with more time-consuming techniques**

Although STI is less attractive than new techniques such as 2D strain or 3D evaluation of LV systolic function, it presents some advantages. First, it can be obtained with each ultrasound machines whereas new technologies require the last generation of echographs. Second, it is characterized by its simplicity, reliability, and rapidity to obtain whereas other tools need experience, learning curve, and require much time for analysis. Third, it is particularly helpful in case of poor quality window because pulsed Doppler does not require a 2D image.

Recently, the Hunt study, conducted on healthy volunteers, reported intra- and inter-observer variability of LVEF of 5% and 6% and for GLS of 3% and 6%. However, in clinical practice,

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**Figure 4** Linear regression analysis between systolic time intervals and heart rate. (A) Linear regression analysis between pre-ejectional period and heart rate. (B) Linear regression analysis between left ventricular ejection time and heart rate. (C) Linear regression analysis between pre-ejectional period/left ventricular ejection time and heart rate.
more important variations on the reproducibility of LVEF or GLS are reported in HF patients: mean 18% for LVEF in the VALLIANT study.\textsuperscript{34} 

In Figure 7, we propose a diagnostic algorithm allowing a multiparametrical approach of LV systolic function in clinical practice accordingly quality of acoustic window and available techniques. STI measurements appear particularly helpful when LVEF evaluation is suboptimal. Use of STI to qualitatively appreciate LV systolic function should be particularly helpful for initial evaluation and follow-up of patients with poor quality window in circumstances which need this evaluation for therapeutic reasons such as before implantation of cardiac defibrillator or resynchronization therapy or to optimize parameters of stimulation.

**Figure 5** Linear regression analysis between systolic time intervals and QRS width. (A) Linear regression analysis between pre-ejectional period and QRS width. (B) Linear regression analysis between left ventricular ejection time and QRS width. (C) Linear regression analysis between pre-ejectional period/left ventricular ejection time and QRS width.
Figure 6 Receiver operating characteristic curve analyses. (A) Prediction of LVEF < 35%. Dark grey: pre-ejectional period (AUC = 0.86, optimal cut-off > 117 ms, sensitivity 67%, specificity 89%). Light grey: pre-ejectional period/left ventricular ejection time (AUC = 0.91, optimal cut-off > 0.43, sensitivity 87%, specificity 84%). (B) Prediction of LVEF < 45%. Dark grey: pre-ejectional period (AUC = 0.96, optimal cut-off > 99 ms, sensitivity 98%, specificity 85%). Light grey: pre-ejectional period/left ventricular ejection time (AUC = 0.98, optimal cut-off > 0.33, sensitivity 95%, specificity 82%).

Table 3 Pearson correlations between systolic intervals (corrected to heart rate or QRS width) and other left ventricular systolic performance indices

<table>
<thead>
<tr>
<th></th>
<th>PEPc to QRS width</th>
<th>LVETc to heart rate</th>
<th>PEP/LVETc to QRS width</th>
<th>PEPc/LVETc</th>
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</thead>
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<tr>
<td>LVEF</td>
<td>−0.38 *</td>
<td>0.74 *</td>
<td>−0.57 *</td>
<td>−0.48 *</td>
</tr>
<tr>
<td>GLS</td>
<td>0.36 *</td>
<td>−0.70 *</td>
<td>0.47 *</td>
<td>0.43 *</td>
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<tr>
<td>dP/dt max</td>
<td>−0.61 *</td>
<td>0.25</td>
<td>−0.59 *</td>
<td>−0.64 *</td>
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<tr>
<td>LV S’ TDI</td>
<td>−0.17</td>
<td>0.57 *</td>
<td>−0.20</td>
<td>−0.23</td>
</tr>
<tr>
<td>LV stroke volume</td>
<td>−0.12</td>
<td>0.46 *</td>
<td>−0.43 *</td>
<td>−0.24</td>
</tr>
<tr>
<td>LV output</td>
<td>−0.15</td>
<td>0.52 *</td>
<td>−0.23</td>
<td>−0.24</td>
</tr>
</tbody>
</table>

*P < 0.001, †P < 0.01.

Figure 7 Algorithm for evaluation of left ventricular systolic function.
Potential clinical applications
Clinical applications for STI have been reported in patients with mitral valve stenosis, coronary artery disease, arterial hypertension, or atrial fibrillation. STI may be used to define the severity of LV muscle dysfunction for initial assessment and for long-term follow-up and therapy evaluation. Patients with coronary disease and abnormal PEP/LVET are reported to exhibit a significantly poorer 5-year prognosis. Moreover, STI measurements have allowed physicians to demonstrate that medical therapy such as beta-blockers or coronary bypass surgery improved only in patients with abnormal PEP/LVET. STI may also be used to investigate changes in LV performance occurring during haemodialysis. In our study, ROC curve analysis illustrates the usefulness of STI, particularly PEP/LVET, in detecting LVEF < 35% (AUC 0.91, optimal cut-off value >0.43), with an 87% sensitivity and an 84% specificity. This could prove relevant in the selection of patients requiring cardiac resynchronization or cardiac implantable defibrillator, especially when precise LVEF evaluation by echocardiography proves difficult or if the evaluation is done by novice sonographers. STI measurements could be another echocardiographic parameter in guiding management in dilated cardiomyopathy.

Limitations
Since PEP and PEP/LVET are linked to QRS width and LVET is linked to heart rate, corrections as described in the present study or this one of Weissler et al. should be applied. Moreover, all STI measurements are dependent on loading conditions. Consequently, important precautions must be taken into account for interpretation of the data.

Conclusion
This study demonstrates the easiness of obtaining an accurate LV systolic performance evaluation using a simple tool such as STI measurement by Doppler echocardiography. STI correlated well with conventional LV systolic performance indices, yet showing less measurement variability. This method may be particularly useful in the case of poor quality windows, for detecting LVEF < 35%, especially when the question of resynchronization therapy or cardiac implantable defibrillators is raised for refractory HF patients.

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Conflict of interest: none declared.

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