Reproducibility of tissue Doppler parameters of asynchrony in patients with advanced LV dysfunction

Eva Mandysova*, Tomáš Mráz, Miloš Taborsky, and Petr Niederle

Department of Cardiology, Hospital Na Homolce, Roentgenova 2, 150 30 Prague 5, Czech Republic

Received 27 December 2006; accepted after revision 15 August 2007; online publish-ahead-of-print 2 October 2007

Aims To assess the reproducibility of tissue Doppler myocardial velocities in patients with dilated ventricles and markedly reduced systolic function (ejection fraction < 35%).

Methods and results Forty-one patients referred for cardiac resynchronization therapy (CRT) were evaluated using tissue Doppler echocardiography. The inter and intra-individual reproducibility of peak systolic myocardial velocities and the intra-ventricular delay in three apical projections was assessed by repeated evaluation of each registered data set. Variability (measured by the coefficient of variation) ranged between 18 and 56% for the peak systolic velocities and between 32 and 117% for the time intervals.

Conclusion The reproducibility of the tissue Doppler echocardiography parameters (peak systolic myocardial velocity and intra-ventricular delay) was poor in our set of patients with dilated left ventricles and low ejection fraction. The most probable causes of our poor results are discussed including the missing standardization of the TDI measurements.

KEYWORDS Tissue Doppler echocardiography; Myocardial velocity; Reproducibility of measurement; Cardiac resynchronization therapy; Heart failure

Introduction

The increasing incidence of patients with heart failure (HF) has become an enormous public health problem.1 Besides coronary artery disease, idiopathic dilated cardiomyopathy is frequently the underlying cause of chronic HF. Despite advances in medical therapy, many patients remain severely symptomatic. Cardiac resynchronization therapy (CRT) is a recently introduced and promising method of treatment. CRT has beneficial effects on left ventricular function, symptoms and exercise capacity in most of these patients but approximately in 20–30% of patients no improvement or even worsening was reported.2,3 For the better identification of these non-responders to CRT new methods for evaluating the presence of intra-ventricular asynchrony have been suggested.

Two-dimensional and Doppler echocardiography provides us with several methods for direct or indirect evaluation of asynchrony (septal-to-posterior wall mechanical delay in M-mode, inter-ventricular delay and others). Tissue Doppler imaging (TDI) can provide quantitative information about myocardial velocities throughout the cardiac cycle.4

Velocity and tissue displacement measurements are easier to reproduce than strain rate and strain.5

Recently, TDI was suggested as a method for assessing absolute or relative myocardial wall velocities and for determining time delays between opposing segments of the left ventricle. Longitudinal myocardial motion can be quantified when TDI data are registered from apical projections. Delayed contractions of the lateral wall identified before CRT correlate with chronic improvement in ejection fraction as well as with reduced cardiac volumes after resynchronization.6

Reproducibility of longitudinal myocardial velocities has been studied in a relatively large pool of experimental animals7,8 and healthy volunteers9 with good inter-observer and intra-observer variability and in small numbers of patients with non-dilated ventricles and mildly reduced ejection fractions.10,11 Reproducibility of data in patients with dilated ventricles and significantly reduced ejection fraction has only been reported using small groups of patients.12,13

Colour-coded TDI13 may reduce patient scanning time and eliminate errors introduced by beat-to-beat variations in loading conditions or heart rate. The use of colour-coded measurements may improve accuracy of assessment of cardiac asynchrony compared with the use of pulsed-wave TDI analysis only.14

Statistical calculations were performed by Jakub Hrkal from the Institute of Health Information and Statistics of the Czech Republic using Stata v. 8.

* Corresponding author. Tel: +420257272204; fax: +4202572 73297.
E-mail address: eva.mandysova@homolka.cz (E. Mandysova).

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2007.
For permissions please email: journals.permissions@oxfordjournals.org.
The aim of our study was to evaluate the variability of the peak systolic myocardial velocity measurements in a larger series of patients referred for resynchronization therapy.

**Methods**

**Patients**

Throughout the period from December 2003 to April 2004 we studied 41 consecutive patients (35 men and 6 women) with an average age of 67 ± 17 years (ranged from 48 to 83) having ischemic heart disease (IHD) – 13 patients – or dilated cardiomyopathy (DCMP) – 28 patients. All the patients had clinical symptoms of heart failure (NYHA classification grade III–IV) and fulfilled ACC/AHA/NASPE criteria for resynchronization therapy. Patients with atrial fibrillation were not included in this study.

**Echocardiography**

An echocardiographic examination of each patient was performed using a broadband transducer with a transmitting frequency from 1.7 to 4.0 MHz on commercially available equipment (Vivid 7, GE, USA). The left ventricular end-diastolic diameter was assessed from a two-dimensional projection in a parasternal long axis view, and the left ventricular ejection fraction (from parasternal long axis) was calculated according to the Teichholz formula. The image quality was assessed by a three-step scale (1 – excellent, 2 – good, 3 – poor), but for the following statistical evaluation only a two-step scale was used (1 + 2 = good, 3 = poor).

The sets of two-dimensional Doppler colour tissue data were registered by an experienced operator from three apical views (apical four-chamber, apical long axis and apical two-chamber), together with the ECG tracings. All the data sets were recorded during passive end-expiration to minimize cardiac motion during respiration. The same depth and Nyquist’s limit were constantly used while examining each patient.

Registered images were analyzed off-line by two independent operators: the first had originally registered the data sets, and the second was well experienced in tissue Doppler evaluations. Analysis was done using the Echopac PC, version 3.1. The time–velocity curves were extracted from the basal segments of each of the opposite walls approximately 1.5 cm from the mitral annulus. (In the case when wall curvature was evident in the proximal part of the wall, the time–velocity curve was taken from the point just above this curvature to avoid distortion of the velocity values by the nonlinear position of the wall to the ultrasound beam.)

Each operator selected two representative time–velocity curves from each projection, so the total of 492 time–velocity curves were available immediately after data set acquisitions. On each time–velocity curve the maximum systolic myocardial velocity ($S_m$) was measured together with the time-to-peak velocity interval ($Q–S_m$), defined as the time between the onset of the Q wave on ECG and peak systolic velocity $S_m$. In each of the three projections intra-ventricular delay was calculated as an absolute time difference between $Q–S_m$ values of each of the opposite walls in a given projection (Figure 1).

After a period of 10–20 days, the first operator repeated all the measurements made in his own recordings in order to assess the intra-observer reproducibility of the evaluations.

From all 41 patients a final total of 738 curves were generated, and 738 maximum velocities of systolic motion (i.e. 123 velocities for each wall) together with 369 values of intra-ventricular delay (i.e. 123 for each projection) were obtained. Nine variables were used for statistical analysis: six peak systolic velocities of septum ($S_{msept}$), lateral wall ($S_{mlat}$), anteroseptal ($S_{mas}$), posterolateral ($S_{mpl}$), anterior ($S_{mant}$) and posterior ($S_{mpost}$) wall and three intra-ventricular delays of septum-to-lateral wall ($q_{sept–lat}$), anteroseptal-to-posterolateral wall ($q_{as–pl}$) and anterior-to-posterior wall ($q_{ant–post}$).

**Comparison of measurements**

All the measurements performed independently by both observers were compared in two independent sub-studies:

---

![Figure 1](https://academic.oup.com/ehjcimaging/article-abstract/9/4/509/2402923)  
**Figure 1** Chart of measurements. In the bottom left-hand picture, two small rings mark the points in the basal septum and lateral wall from where the two tissue velocity curves (see right-hand picture) are derived. At each of the curves peak systolic velocities are measured, $Q–S_m$ intervals are stated and inter-ventricular ($V–V$) delay is calculated as an absolute difference between $Q–S_{msept}$ and $Q–S_{mlat}$, lateral, $Q$, Q wave on ECG curve, sept., septal, and $S_m$, peak systolic myocardial velocity.
Intra-individual variability of velocity tracing evaluation
Inter-individual variability of velocity tracing evaluation.

Statistical analysis
All the data from each sub-study were subjected to statistical analysis.
We also tested whether the two selected factors — diagnosis (IHD vs. DCMP) and image quality (grade 1 vs. grade 2) had any influence on the variability assessment.

Results are presented as mean ± standard deviation (SD). SD was expressed in the original units or in % (the coefficient of variation). Confidence limits (95%) of differences were calculated as t(n−1,0.025)/SD/20.5 and expressed as absolute values and percentages of the average values (Table 1). To test the variability of errors of measurement according to selected factors (diagnosis and quality of image), the Mann-Whitney two-sample test was applied to test the differences. The average relative error of measurement for each sub-study and the statistical significance of this error were calculated for each factor. A value was considered statistically significant at P < 0.05.

Results
Variability measured by the coefficient of variation (CV) ranged between 18 and 56% for the peak systolic velocities and between 32 and 117% for the time interval (Table 2).

The highest intra-observer variability of the peak systolic myocardial velocities was observed in posterolateral wall (CV = 35%), the lowest one in septum and anteroseptal wall (both, CV = 18%), the highest inter-observer variability (CV = 56%) of the same parameter was found in anterior wall (CV = 56%) and the lowest in anteroseptal wall (CV = 19%).

Differences of measurements in relation to selected conditions
There was only one significant difference in the variability of errors of measurement found in relation to quality of image (Table 2).

Relation to diagnosis
Significant inter-individual and intra-individual variability value differences of peak systolic myocardial velocities in patients with IHD vs. DCMP (P < 0.05) were not found. The same was true for the intra-ventricular delay.

Relation to image quality
There was a trend to a lower variability of peak systolic myocardial velocities in patients with good image quality but it reached a statistically significant difference only in intra-individual variability of the peak systolic velocities of posterior wall (P = 0.04). Borderline statistical significance (P = 0.06) was also reached for inter-individual variability.

Table 1 Variability of measurements

<table>
<thead>
<tr>
<th>Sub-study Variable</th>
<th>Sm septum (cm/s)</th>
<th>Sm lateral wall (cm/s)</th>
<th>q septum-lateral wall (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
<td>a</td>
</tr>
<tr>
<td>Mean of values</td>
<td>284</td>
<td>280</td>
<td>222</td>
</tr>
<tr>
<td>1 SD (units)</td>
<td>52</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>CI 95% (units)</td>
<td>75</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>CI 95% (%)</td>
<td>26</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Sm anteroseptal wall (cm/s)</td>
<td>281</td>
<td>279</td>
<td>215</td>
</tr>
<tr>
<td>1 SD (units)</td>
<td>50</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>CI 95% (units)</td>
<td>72</td>
<td>77</td>
<td>108</td>
</tr>
<tr>
<td>CI 95% (%)</td>
<td>26</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Sm posterior wall (cm/s)</td>
<td>251</td>
<td>258</td>
<td>36</td>
</tr>
<tr>
<td>1 SD (units)</td>
<td>55</td>
<td>143</td>
<td>49</td>
</tr>
<tr>
<td>CV (%)</td>
<td>22</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>CI 95% (units)</td>
<td>79</td>
<td>204</td>
<td>70</td>
</tr>
<tr>
<td>CI 95% (%)</td>
<td>32</td>
<td>80</td>
<td>28</td>
</tr>
</tbody>
</table>

a: Intra-individual variability of measurement; b: inter-individual variability of measurement; Sm: peak systolic myocardial velocity; q: intra-ventricular delay; SD: standard deviation (in the original units); CV: coefficient of variability (in %); and CI: 95% confidence interval (in the original units or in %) calculated as t(n−1,0.025)/SD/20.5.
of the same parameter and similar borderline values (\(P = 0.08\) and \(P = 0.07\)) were found in intra as well as inter-individual variability of peak systolic velocities of anteroseptal wall (Table 2).

No statistically significant differences in the variability values were found for intra-ventricular delay values in either group.

### Discussion

Tissue Doppler echocardiography has been suggested as a modern method for evaluating left ventricular asynchrony. This method has the temporal resolution for quantifying regional longitudinal myocardial velocities.\(^{15}\)

In spite of the fact that myocardial motion is very complex, including translational, rotational and deformational movements, TDI measurements have a low variability in healthy subjects. Our results, however, support the assumption that this may not be true for peak systolic myocardial velocities in patients with advanced myocardial disease.

In our series of patients the variability of peak systolic myocardial velocities was lower than the variability of the intra-ventricular delay. This is probably entirely due to the fact that the same numbers in the lower values of intra-ventricular delay would cause proportionally bigger differences than in the higher values of peak systolic velocities.

The unexpected generally high intra- and inter-individual variability of the intra-ventricular delay was further apparently overcome in one parameter: the inter-individual variability of the septum to-lateral wall delay (CV = 117%).

With the aim of finding an explanation for this finding, a more detailed analysis of this parameter was carried out. We found that in several cases the slightest differences in sample volume placement could give rise to markedly different shapes of systolic time–velocity curves with significantly different timing of peak systolic myocardial velocities resulting in different values of intra-ventricular delay (Figures 2A, B).

One would presume a lower variability of TDI values in DCMP in comparison with IHD patients as the contractions are less regional in DCMP. On the other hand, walls replaced by large scars could have very homogeneous time–velocity curves. We could only speculate why our results did not reveal significant differences.

Sub-optimal image quality could represent another factor contributing to a higher variability of measurement. Actually, in almost all cases, we saw a slight relationship between lower variability and better image quality. This factor, however, did not reach statistical significance (with one exception – peak systolic myocardial velocities of the posterior wall). It may be because the two-dimensional image rather than TDI was chosen for image quality grading.

Our explanation for the high variability of measurements in patients with advanced heart failure based on systolic dysfunction may be complex. Slight differences in the data set acquisition could not have been the main reason for the variability as a non-significantly higher inter-individual in comparison with intra-individual variability was found.

### Table 2: Variability of errors of measurements according to selected factors

<table>
<thead>
<tr>
<th>Sub-study</th>
<th>Sm septum (cm/s)</th>
<th>Sm lateral wall (cm/s)</th>
<th>q septum–lateral wall (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>15 30</td>
<td>23 25</td>
<td>38 20</td>
</tr>
<tr>
<td>DCMP</td>
<td>17 16</td>
<td>28 28</td>
<td>31 67</td>
</tr>
<tr>
<td>Sign. (P)</td>
<td>0.93 0.88</td>
<td>0.83 0.87</td>
<td>0.46 0.51</td>
</tr>
<tr>
<td>Quality of image</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>24 25</td>
<td>31 25</td>
<td>36 26</td>
</tr>
<tr>
<td>Poor</td>
<td>13 19</td>
<td>25 28</td>
<td>32 64</td>
</tr>
<tr>
<td>Sign. (P)</td>
<td>0.19 0.13</td>
<td>0.13 0.93</td>
<td>0.23 0.95</td>
</tr>
</tbody>
</table>

The average relative error of measurement for each category and the statistical significance of this error are stated for each factor. The Mann–Whitney two-sample test was applied to test the differences.

\(a\): Intra-individual variability of measurement; \(b\): inter-individual variability of measurement; \(Sm\): peak systolic myocardial velocity; \(q\): intra-ventricular delay; \(IHD\): ischemic heart disease; \(DCMP\): dilated cardiomyopathy; sign. (\(P\)): statistic significance at \(P\)-value; and anterosep–posterolat: anteroseptal-to-posterolateral.
Both investigators were experienced with the evaluation of TDI images. They interrogated the region of interest first and then tried to choose the most robust curve that would, according to their individual judgment, represent the region. But the impossibility of stating a fixed point for measurement may have resulted in the generation of significantly different tissue Doppler tracings (Figure 3).

The inability to precisely define the point of interrogation may represent a crucial problem especially in the thinned and diseased myocardial wall. The time course of the systolic myocardial velocities represents another issue. In patients with myocardial disease, the ‘smooth’ shape of the systolic—velocity curve is lost and easily two or more peaks could be distinguished within the systole. Some of the irregularities of the time—velocity curve could be blunted by the use of ‘smoothing function’ but what should we do with ‘two peaks’ on one curve? Maybe the method of identifying responders based on measuring time intervals between peaks cannot be applied in all cases.

Time to onset (or end) of the positive systolic myocardial velocities seems to be more robust (Figure 3), but the aim of our study was not to study this parameter.

Our paper was not primarily designed to test how our measurements would affect our decision-making for CRT.
However, it became an interesting issue after obtaining the results. When testing a six-segment model and the generally accepted cut-off value of 65 ms (calculated as the biggest difference between time and peak intervals of two opposite walls in three apical projections) to assess asynchrony, observer 1 would indicate CRT in 32 cases, and observer 2 in 33 cases. Both observers achieved the same result in 36 (88%) patients (30 patients for CRT, six patients without asynchrony). Both observers came to different conclusions in five cases (12%). Even though the vast majority of patients were classified as having asynchrony, it does not imply a low variability of the intra-ventricular delay, but only the fact that each observer found at least one wall delayed in these patients. These highly concordant decisions were also influenced by the fact that all the patients were primary candidates for CRT according to currently accepted criteria including QRS $130$ ms. Even so, most of them the pronounced mechanical asynchrony of contraction could be expected.

We do not support the statement that the real clinical utility of TDI is doubtful and that it does not give any additional information over conventional methodologies. On the other hand, in our opinion, peak velocities of systolic motion in patients with dilated hearts and significantly depressed systolic function do not represent reliable variables.

We incline to the statement that TDI measurements are ultra-sensitive and that this is especially true for the peak systolic myocardial velocities. This ultra-sensitivity could represent the source of misinterpretations leading to the high variability of measurement.

The introduction of a new technology for routine clinical use should pass through the different phases of scientific assessment from feasibility studies to large multi-centre studies, and from efficacy to effectiveness studies. A more critical approach to this technology would have avoided the inconsistencies in scientific results that have arisen from its application in the clinical arena.

Our results are not surprising when confronting them with clinical practice. Indication criteria of the European Society of Cardiology for CRT, published in June 2005 do not include identification of mechanical asynchrony as an essential condition. This decision was based on the fact that no criteria for reliable echocardiographic quantification of mechanical asynchrony have been so far widely accepted.

On the basis of our results, we do not consider intra-ventricular delay measured from peak systolic myocardial velocities reliable enough to be a single decisive parameter for detecting asynchrony in patients with significantly dilated and dysfunctional hearts.

Study limitations
Our results can only be applied to the conditions under which the study was performed: Vivid 7 GE system, broadband 1.7-4.0 MHz matrix probe, sample volume of 0.5 cm, raw data post-processing/analysis (Echopac PC version 3.1), patients with dilated left ventricle, low ejection fraction and QRS $130$ ms.

Conclusions
Tissue Doppler echocardiography represents a modern highly sensitive method with excellent time resolution enabling time and velocity measurement but the precise standardization of measurements in patients with advanced LV dysfunction is still challenging.

With the use of current techniques and software, the reproducibility of tissue Doppler peak systolic myocardial velocities generated from the same data sets was poor in our set of patients with dilated hearts and low ejection fractions due to coronary heart disease and dilated cardiomyopathy. The sub-optimal parameter chosen together with the lack of standardization of the method used is probably the main reason for our unsatisfactory results.
Acknowledgements

Statistical calculations were performed by Jakub Hrkal from the Institute of Health Information and Statistics of the Czech Republic using Stata v. 8.

References