Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters

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Aims Different layers of myocardium may contribute differently to myocardial deformation. Speckle tracking based on high resolution two-dimensional (2D) echocardiography has been used to define myocardial deformation parameters of whole left ventricular (LV) segments. This study evaluated with a Novell analysis modality allowing layer-specific analysis of deformation if there are differences in myocardial deformation between different layers of myocardium.

Methods and results In 30 normal subjects and 20 patients with impaired myocardial function 2D parasternal short-axis echocardiographic views of the LV were acquired at the basal, mid-papillary, and apical levels. Using a Novell automatic frame-to-frame tracking system of natural acoustic echocardiographic markers (EchoPAC, GE Ultrasound, Haifa, Israel), circumferential strain (CS) and strain rate of the endocardial, mid-myocardial and epicardial layer was calculated for each LV segment in an 18-segment model. Wall motion for each segment was defined as normokinetic, hypokinetic, and akinetic based on 2D echocardiographic images. Peak systolic CS could be analysed in 837 segments (93%). In the normal subjects peak systolic CS was greatest in the endocardial layer, lower in the mid-myocardial layer, and lowest in the epicardial layer (38.1 ± 9.0%, 28.9 ± 9.3%, and 24.0 ± 9.4%, respectively, P < 0.001). In the patients with impaired LV function 151 segments were hypokinetic and 92 segments akinetic by visual analysis. In all myocardial layers peak systolic CS and strain rate decreased with decreasing segmental function.

Conclusion Decreasing myocardial deformation from endocardial to epicardial layers can be demonstrated with the use of an advanced analysis system allowing definition of deformation parameters for three myocardial layers. Myocardial deformation is reduced in all layers of segments with impaired wall motion.

Introduction

Characterization of global and regional left ventricular (LV) function is the focus of numerous imaging techniques. Most imaging techniques consider the complete myocardial wall thickness in the analysis of myocardial function without further distinction between different layers of the myocardium ranging from endocardium to epicardium. However, differences of myocardial performance and deformation across the ventricular wall can be suspected from previous observations already in normal myocardium.1–3 Furthermore, different diseases are known from histologic analysis to affect the myocardial layers to a different extent, resulting in either homogenous morphologic alterations or alterations being predominant in specific layers.4,5 The morphologic pattern of myocardial disease is likely reflected by similar patterns of functional impairment. Thus, any technique allowing a more detailed quantitative analysis of function including myocardial layers analysis is likely to increase the morphologic and pathophysiological understanding of myocardial disease and may enable an improved characterization of different diseases or disease stages. Tissue Doppler imaging and magnetic resonance imaging (MRI) have been used to obtain insight into layer-specific differences in myocardial function.6,7 However, these techniques are not widely available and their application is time consuming.

Recent improvements in two-dimensional (2D) echocardiographic image resolution have enabled detection of tissue pixels and tracking of acoustic markers from frame-to-frame.8,9 Assessment of radial, circumferential...
and longitudinal strain and strain rate from tissue pixel tracking systems based on 2D echocardiographic images has been described. Previous analysis systems have considered total wall thickness with averaging of deformation parameters for whole LV segments. This study used an advanced technique which allows analysis of myocardial deformation based on speckle tracking separately within each of three myocardial layers, an endocardial, mid-myocardial, and epicardial layer. The aim of this study was: (i) to determine myocardial deformation for the three myocardial layers in normal subjects; (ii) to define the effect of regional ischaemic LV dysfunction on deformation of each of the three layers.

Methods

Study population

The study population consisted of two groups. Group 1 included 30 normal subjects (mean age 60.5 ± 16.5 years, 20 men) in whom normal LV function (ejection fraction >55% and no segmental wall motion abnormality) was documented by cineventriculography and coronary artery disease was excluded by coronary angiography. The normal subjects were evaluated to define normal values for speckle tracking based strain in the endocardial, mid-myocardial, and epicardial layers.

Group 2 consisted of 20 patients (61.5 ± 16.0 years, 16 men) with ischaemic LV dysfunction. Nine patients had anterior infarcts, eight patients had posterior/inferior infarcts, and three patients had anterior and posterior infarcts. Coronary artery disease was documented by coronary angiography within 24 h prior to the echocardiographic study. This study was approved by the local ethical committee and all subjects gave written informed consent.

Echocardiography

All studies were performed using a Vivid Seven digital ultrasound scanner (GE Ultrasound, Horten, Norway) equipped with a 1.7/3.4 MHz transducer within 24 h of coronary angiography. Left ventricular ejection fraction was determined by manual tracing of end-systolic and end-diastolic endocardial borders using apical four-chamber and two-chamber views, employing biplane Simpson’s Method. End-systole was marked as aortic valve closure in apical long-axis views. The time difference from the QRS complex was transferred to the other views. Parasternal short-axis views at basal, mid-ventricular, and apical levels of the LV were acquired using 2D tissue harmonic imaging. To obtain circular parasternal views of the LV wall at each of the three levels, the transducer position was altered using different intercostal spaces. The focus was adjusted to the centre of the LV cavity to optimize myocardial speckle characteristics of all segments of the short-axis views. The frame rate for these studies was between 56 and 92 frames/s. Wall motion for each LV segment was assessed by visual analysis of the parasternal short-axis views as normokinetic = 1, hypokinetic = 2, or akinetic/dyskinetic = 3.

Speckle tracking analysis

Analysis of the parasternal short-axis 2D echocardiographic images was performed offline on a personal computer with the aid of a software package (EchoPAC, GE Ultrasound, Haifa, Israel). Loops of three consecutive cardiac cycles were acquired. Deformation parameters were determined as average of the three loops. All three acquired parasternal short-axis views were analysed using the system to obtain quantitative function parameters for each segment in an 18 segment LV model (six segments at each LV level). Part of the analysis package has been described previously. It involves automatic grading by the system of each segment regarding the tracking quality on a scale ranging from 1.0 for optimal to 3.0 for unacceptable. Segments with suboptimal tracking quality (grading >2.0 by the system) were systematically dismissed from the analysis. Spatial and temporal smoothing was set to the medium level in the analysis algorithm of deformation parameters. Analysis of myocardial deformation parameters for whole LV segments was performed as described previously. In addition to analysis of peak systolic circumferential strain (CS) and CS rate (CSR) of complete LV segments, deformation parameters were obtained for three separate myocardial layers. For this purpose, the total myocardial thickness from the endocardium to epicardium was automatically divided into three layers of similar thickness, an endocardial, mid-myocardial, and epicardial layer.

Strain rate is equivalent to the spatial gradient of pixel movements as described before.

In 10 subjects the analysis of peak systolic CS and strain rate data was repeated 4 weeks apart being the same observer on the same 2D echocardiographic loop and the same cardiac cycle to define the interobserver variability in the analysis, and performed in addition by a second independent observer on the same cardiac cycle to define the interobserver variability in the analysis of tissue tracking-derived deformation parameters. For each segment the difference of strain data was calculated and given as relative deviation between these two measurements. The indicated variability is a sum of all 18 segments and in 10 normal subjects.

Coronary angiography

Significant coronary artery disease was considered present when >50% reduction of vessel diameter by quantitative coronary angiography was observed in at least one major coronary artery.

Statistical analysis

Statistical analysis was performed with SPSS (version 14.0). Data are expressed as means ± standard deviation. Comparison of continuous variables was performed with Student’s t-test or ANOVA (analysis of variance) as appropriate. Overall significance level is 0.05.

Results

Baseline clinical characteristics of the normal subjects of Group 1 and the patients with ischaemic LV dysfunction of Group 2 are given in Table 1. Ejection fraction defined by biplane echocardiography was 59.1 ± 3.2% in normal subjects and 37.3 ± 11.1% in patients with impaired LV contractility.

<table>
<thead>
<tr>
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<th>Normal subjects (N = 30)</th>
<th>Ischaemic dysfunction (N = 20)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>60.5 ± 16.5</td>
<td>61.5 ± 16.0</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>20 (67)</td>
<td>16 (80)</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>59.1 ± 3.2</td>
<td>37.3 ± 11.1</td>
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<tr>
<td>Location of prior myocardial infarction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior (%)</td>
<td>9 (45)</td>
<td></td>
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<tr>
<td>Posterior/inferior (%)</td>
<td>8 (40)</td>
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<tr>
<td>Anterior and posterior/inferior (%)</td>
<td>3 (15)</td>
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<tr>
<td>Severity of coronary artery disease (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel disease (%)</td>
<td>6 (30)</td>
<td></td>
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<tr>
<td>Two-vessel disease (%)</td>
<td>4 (20)</td>
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<tr>
<td>Three-vessel disease (%)</td>
<td>10 (50)</td>
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</table>

Table 1 Baseline clinical characteristics of normal subjects and patients with ischaemic left ventricular dysfunction
function. Visual analysis of regional LV function was possible in 828 (92%) of segments. Image quality was sufficient to allow strain and strain rate analysis from parasternal short-axis views in 837 segments (93%; tracking quality > 2.0 as defined by the analysis software). There was no difference between the segments in the rate of adequate tracking quality.

For the 837 segments with adequate tracking of acoustic markers segmental analysis of LV function by 2D echocardiography indicated normal function in 594 segments, hypokinesia in 151 segments, and akinesia in 92 segments.

Observer variability

Intraobserver variability in the analysis of transmural peak systolic CS was found to be 8.8 ± 4.7% of the absolute measured values and interobserver variability was found to be 9.7 ± 5.6% of the absolute measured values. The corresponding intraobserver and interobserver variability data on peak systolic CS for the endocardial, mid-myocardial and epicardial layers were 9.9 ± 5.2%, 9.7 ± 5.1%, 10.2 ± 5.1%, respectively, and 10.8 ± 6.1%, 10.7 ± 5.9%, 10.2 ± 6.2%, respectively.

For transmural peak systolic CSR intraobserver and interobserver variability were 11.4 ± 6.2 and 12.0 ± 5.7%, respectively. The corresponding intraobserver and interobserver variability data on peak systolic CSR for the endocardial, mid-myocardial, and epicardial layers were 11.6 ± 6.9%, 12.1 ± 6.3%, 12.3 ± 6.4%, respectively, and 12.1 ± 7.0%, 12.4 ± 6.4%, 12.6 ± 6.4%, respectively.

Layer-specific strain and strain rate in normal left ventricular function

In the 30 subjects without prior myocardial infarction and without coronary artery disease, CS and CSR parameters were evaluated on a segmental basis. Considering a layer-specific analysis of deformation parameters, peak systolic CS of normal contracting segments was greatest in the endocardial layer, lower in the mid-myocardial layer, and lowest in the epicardial layer (Table 2). Figure 1 demonstrates an example of a layer-specific CS analysis in a normal subject. The difference in peak systolic CS between endocardial and epicardial layer amounted to 36%.

Peak systolic CS for the endocardial, mid-myocardial, and epicardial layers were similar between the basal, mid-ventricular, and apical levels of the LV (Figure 2, Table 2). Similar findings as for peak systolic CS were determined for peak systolic CSR (Table 2).

Layer-specific strain and strain rate in impaired left ventricular function

For 20 patients with impaired LV function peak systolic CS and CSR results related to segmental LV function defined by 2D echocardiography are given in Table 3. Peak systolic CS for segments defined as hypokinetic was reduced by 64% in the endocardial, 65% in the mid-myocardial, and 66% in the epicardial layer compared with normokinetic segments. In akinetic segments layer-specific peak systolic CS was 72% lower in the endocardial, 75% lower in the mid-myocardial, and 73% lower in the epicardial layer compared with normokinetic segments. Similar results were found for layer-specific CSR. Thus, peak systolic CS and CSR were significantly different between normokinetic, hypokinetic, and akinetic/dyskinetic segments. Figure 3 demonstrates an example of regional function impairment in the posterior wall defined by 2D echocardiography and the corresponding CS image as well as the strain curves of one cardiac cycle for all the three layers.

Discussion

The major findings of this study are that: (i) the applied Novell myocardial speckle tracking system demonstrates a prominent difference of the magnitude of myocardial deformation between the endocardial and epicardial layers with a continuous decrease of systolic CS and CSR from subendocardial to mid-myocardial and subepicardial layers; (ii) segmental dysfunction in ischaemic cardiomyopathy is associated with impaired deformation of all the three analysed myocardial layers; (iii) obtained data are affected by only low intra- and interobserver variability.

Analysis of regional myocardial function

Subjective visual graduation of endocardial excursion and wall thickening is still the routinely applied technique in clinical practice to identify regional myocardial dysfunction.
Substantial reader dependence with significant interobserver variability in the interpretation of regional function has been documented in the era before harmonic imaging and to a lesser extent with harmonic imaging. Tissue Doppler-derived myocardial velocities as well as deformation parameters have been described for more objective quantitative analysis of regional function. Speckle tracking of acoustic markers from frame-to-frame within 2D echocardiographic images has recently been evaluated for analysis of regional myocardial function considering total wall thickness deformation.

Layer-specific regional myocardial function

In particular, ischaemic damage to the LV myocardium is known to occur at different stages. According to a ‘wavefront’ model of myocardial necrosis, endocardial layers of the ventricular wall may be affected at an earlier stage in myocardial infarction. Thus, a layer-specific analysis of myocardial function may be of interest in disease conditions resulting in non-homogenous myocardial injury. However, although numerous studies have focused on the characterization of global performance of the LV and on regional changes that may occur with disease or interventions, investigations of relative differences of function between the inner and outer layers of the LV wall are very limited. In experimental models metal markers on the endocardial surface of the LV were shown to be displaced to greater distances during systole than were markers on the epicardial surface. In dog models myocardial segment shortening was shown to be greater along the mid-wall of the LV than in the subepicardium. In another dog model, using ultrasonic crystals, wall thickening and fibre shortening were determined for the subendocardium and the subepicardium. Segments of the subendocardium were shown to shorten by 18% during systole, whereas segments of the subepicardium shortened only by 10%. In addition, the endocardial portion of the wall thickened to a substantially greater extent during systole than the epicardial portion. This was also associated with a lower rate of systolic thickening in the epicardial portion.

The echocardiographic technique analysed in this study allows description of myocardial function parameters within different myocardial layers. Myocardial deformation demonstrated a significant decrease from endocardial to epicardial layers of the myocardium. This reduction was seen in all LV segments irrespective of their location within the LV. In case of segmental ischaemic dysfunction as defined by visual analysis, deformation parameters were reduced in all myocardial layers. The findings of this study on normal human subjects as well as patients with ischaemic LV dysfunction are in agreement with above-mentioned experimental animal data using invasive analysis techniques. Interestingly, strain and strain rate values in
segments defined to be normokinetic by visual analysis in the group of patients with ischaemic LV dysfunction were lower than in the subjects without coronary artery disease. This finding may indicate that in patients with coronary artery disease even segments remote from obvious visual dyssynergy do not have normal function.

CS and CSR were similar between the basal, mid-ventricular, and apical levels of the ventricle. This finding is in agreement with previous findings derived from MRI studies as well as for total wall thickness strain and strain rate determined by echocardiographic tissue tracking techniques.12,18

The method applied in this study is likely to give important new insights into multiple myocardial disease conditions. Further studies on different pathologies will have to demonstrate whether deformation of the three myocardial layers is impaired to different degrees in case of ischaemic or non-ischaemic LV dysfunction. In particular in ischaemic dysfunction due to partial subendocardial infarction, an inhomogenous reduction of deformation between endocardial and epicardial layers might be possible.

Limitations

This study evaluated layer-specific myocardial deformation in normal subjects and in patients with ischaemic LV dysfunction. The layer-specific analysis of myocardial deformation parameters has not been specifically validated in an experimental model. However, the analysis package is derived from a well validated system for analysis of total wall thickness deformation parameters.10,19–21 The high spatial resolution of the system allowed separation of the total wall thickness into three separate layers. Thus, similar accuracy on the layer-specific analysis level can be assumed as for the previously evaluated total wall thickness accuracy. Furthermore, a validation of layer-specific strain analysis is difficult as even sonomicrometry studies have difficulties to accurately delineate more than two myocardial layers.

There is currently no other good non-invasive imaging modality which can be used in humans to assess obtained layer-specific deformation parameters. Magnetic resonance imaging tagging allows analysis of deformation parameters. However, deformation analysis by MRI tagging is limited by fading signals during late systole and is currently limited to an analysis of two myocardial layers at most. Strain values were not zero in akinetic segments. This may be due to measurement artefacts related to tethering from adjacent segments and has been reported before for analysis of whole myocardial thickness.11 Furthermore, classification of segmental function as akinetic based on visual analysis may have been incorrect. It should be recognized

<table>
<thead>
<tr>
<th></th>
<th>Normokinesia</th>
<th>Hypokinesia</th>
<th>Akinesia</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Circumferential strain</strong></td>
<td></td>
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<tr>
<td>Endocardial layer (%)</td>
<td>33.1 ± 13.7</td>
<td>11.8 ± 8.4</td>
<td>9.3 ± 7.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Mid-myocardial layer (%)</td>
<td>25.3 ± 11.7</td>
<td>8.7 ± 6.7</td>
<td>6.3 ± 5.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Epicardial layer (%)</td>
<td>20.5 ± 12.3</td>
<td>6.9 ± 5.1</td>
<td>5.5 ± 4.6</td>
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<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Circumferential strain rate</strong></td>
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<tr>
<td>Endocardial layer (1/s)</td>
<td>2.18 ± 0.75</td>
<td>0.81 ± 0.66</td>
<td>0.58 ± 0.42</td>
<td>&lt;0.001</td>
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<tr>
<td>Mid-myocardial layer (1/s)</td>
<td>1.67 ± 0.66</td>
<td>0.68 ± 0.57</td>
<td>0.41 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epicardial layer (1/s)</td>
<td>1.27 ± 0.63</td>
<td>0.49 ± 0.37</td>
<td>0.35 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
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that deformation parameters within the three layers are not completely independent. Due to constance of mass and volume, any deformation of the outer layer resulting in circumferential shortening of that segment will result in a deformation of the inner layer even if the inner layer is completely non-functional. Thus, myocardial deformation of each layer is dependent on active function within the layer and passive motion from adjacent layers. This study defined myocardial deformation parameters in an 18-segment model which is different from the 17-segment model recommended by the American Heart Association. This is due to the impossibility to define CS in an apical segment with current techniques.

Conclusions

Layer-specific analysis of myocardial function based on advanced echocardiographic speckle tracking techniques is a promising tool to obtain quantitative insights into layer-specific myocardial function analysis. Decreasing deformation from endocardial to epicardial layers is indicated. Myocardial deformation is reduced in all layers of segments with impaired wall motion.

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References