

Automated Analysis of Strain Rate and Strain: Feasibility and Clinical Implications

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Background: This study evaluated 3 new automated methods, based on a combination of speckle tracking and tissue Doppler, for the analysis of strain rate (SR) and strain. Feasibility and values for peak systolic strain rate (SR_s) and end-systolic strain (S_{es}) were assessed.

Methods: Thirty patients with myocardial infarction and 30 normal subjects were examined. Customized software with automatic definition of segments was used for automated measurements. SR_s and SR_{es} were measured over each segment simultaneously and identified automatically. The study compared tissue Doppler-based SR and strain measurements without (method 1) and with segment tracking (method 2) to speckle tracking-based measurements (method 3). For tracking, speckle tracking and tissue Doppler were used in combination. Standard manual analysis was used as a reference.

Results: The automated analysis (16 segments, 3 apical views) required 2 minutes; manual analysis took 11 minutes. Accuracy was compared in 56 segments (28 mid-infarcted and 28 normal) from 28 patients and was 93.9% for method 1, 93.8% for method 2, 95.8% for method 3, and 96.2% for the manual method. In the normal group, mean SR_s (0.27 s⁻¹) was less with method 3 than with the other methods ($P < .001$).

Conclusions: Our findings indicate that automated analysis of SR and strain, with some manual adjustment, is feasible and quicker than manual analysis. Diagnostic accuracy was similar with all methods. SR_s was lower in the speckle tracking-based method than in the Doppler-based methods. (J Am Soc Echocardiogr 2005;18:411-8.)

Strain rate (SR) and strain are new methods for quantifying regional deformation rate and deformation by either tissue Doppler¹ or speckle tracking.² Manual analysis is time-consuming, and the postprocessing required for acceptable results requires experience. Further, strain rate imaging (SRI) has a high variability and thus is currently of limited clinical use. The new scanner technology simultaneously acquires not only high-quality 2-dimensional images with adequate frame rates for gray-scale imaging, but also high-frame-rate tissue Doppler data, enabling applications that use both modalities.^{3,4}

Both tissue Doppler-based and speckle tracking-based SR have strengths and weaknesses. Doppler-

based ultrasound techniques quantify only the axial component of motion (ie, motion along the direction of the transmitted ultrasound wave) and thus are angle-dependent.⁵⁻⁸ They are also prone to errors induced by random noise. Other errors can occur because although conventional SRI measures the SR at a fixed point in space, deformation occurs in myocardial segments displaced during the cardiac cycle. The importance of tracking the region of interest (ROD) through the cardiac cycle has been emphasized,⁹ although not yet documented.

In gray-scale images, interference by backscattered ultrasound from neighboring structures results in a random speckled pattern. This gives each small area a unique pattern that remains relatively constant from 1 frame to the next. Hence a suitable pattern-matching algorithm can identify the displacement from 1 frame to the next, allowing the motion of the myocardium to be followed in 2 dimensions.^{2,10} Time-domain speckle tracking techniques are effective for quantifying tissue velocities.^{11,12} However, the low frame rate of gray-scale images may lead to undersampling, reducing peak values. If the frame rate is too low, then the speckle pattern will change too much from one frame to the next, preventing the myocardial region from being followed precisely. In contrast, increasing the frame rate will reduce line density, reducing lateral resolution and yielding poor transverse tracking.¹³

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We developed methods for automatic segmental analysis by combining speckle tracking and tissue Doppler in various combinations. The purposes of the study were (1) to assess the feasibility of automated analysis compared with manual analysis, and (2) to evaluate diagnostic accuracy and compare measurement values of 3 different automated methods of measuring SR and strain (using speckle tracking and tissue Doppler in 3 different ways) in comparison with standard manual analysis.

METHODS

Study Population

The main study examined 30 patients (mean age 65 ± 9 years; 11 women) with a first myocardial infarction (17 inferior/13 anterior, 23 Q-wave, mean creatine kinase MB $266 \mu\text{g/L}$, mean troponin T $7.4 \mu\text{g/L}$) and 30 subjects (mean age 57 ± 12 years; 15 women) with normal ventricles, coronary angiography, and dobutamine stress echocardiography. Finally, to evaluate the influence of B-mode frame rate on undersampling and precision in speckle tracking (method 3), further analysis was done in 10 healthy individuals (mean age 28 ± 6 years; 5 women). No patient was excluded due to poor acoustic window. The approval of the regional ethics committee was obtained, and all subjects gave written informed consent.

Echocardiography Image Acquisition

The main study examinations were performed with either a Vivid 5 scanner (12 examinations) or a Vivid 7 scanner (58 examinations) (GE Vingmed Ultrasound, Horten, Norway), using a phased-array transducer. The frame rate study was performed on a Vivid 7. Three cine loops from the 3 standard apical planes (4-chamber, 2-chamber, and long-axis) were recorded simultaneously in both tissue second harmonic mode and tissue Doppler mode. The mean frame rate on the Vivid 7 was 155 frames per second (FPS) (range, 109-209 FPS) for tissue Doppler and 49 FPS (range, 36-70 FPS) for B-mode. The mean frame rate on the Vivid 5 was 133 FPS (range, 130-147 FPS) for both tissue Doppler and B-mode. The pulse repetition frequency was 1000 Hz.

In the additional B-mode frame rate study, recordings were made at 70 FPS and reduced to 35 FPS in gray-scale data in apical 4-chamber, 2-chamber, and long-axis views. The sector angle was set to 60 degrees, with equal frame rates for B-mode and tissue Doppler images.

Echocardiography Data Analysis

Automated identification of myocardial segments. For the automated measurements, we used customized software (GcMat; GE Vingmed Ultrasound), a postprocessing system that runs under Matlab (MathWorks, Natick, Mass). For each apical view, the apex, mitral ring, and the endocardial border were identified automatically⁴ and the

myocardium was divided into 6 equal segments (Figure 1), subject to manual adjustment.

A speckle tracking method, using minimum SAD (sum of absolute differences) of the B-mode pixel data¹⁴ combined with tissue Doppler velocities, was used to track the position of a kernel region (a chosen region of the myocardium with a unique speckle pattern) of the segment borders throughout the cardiac cycle. Tracking was done axially by tissue Doppler data and laterally by speckle tracking. Tracking by tissue Doppler along the ultrasound beam limited the search area to a sector extending in the lateral direction and thus reduced the time for the speckle search. To avoid drift, the tracking algorithm was applied both forward and backward, and the results were averaged. The position of the kernel regions could be adjusted manually if tracking was poor. This search procedure enabled tracking of segment position, segment orientation, and segment length throughout the cycle. The following parameters were used for GcMat analysis: axial averaging, 1 mm; temporal averaging, 10 ms. The distance for SR calculation was 15 mm (for methods 1 and 2).

Aortic valve closure. The timing of aortic valve closure (AVC) was defined from the Doppler spectrum of aortic flow, pulsed wave, in the apical 4-chamber view. The value was stored and displayed automatically in all curves, adjusted to the heart rate in the actual image being analyzed.

Methods. In method 1, a stationary ROI was placed automatically in the center of the defined segment at end-diastole. SR was calculated from the velocity gradient along the ultrasound beam¹ at a fixed position in space, as illustrated in Figure 1 between p1 and p2. Tracking was not used in this method; only automated segmentation and ROI placement are used.

In method 2, a dynamic ROI was placed automatically in the center of the segment at end-diastole, and the midpoint of the segment was tracked throughout the cardiac cycle. Axial movement was measured by tissue Doppler; lateral movement, by speckle tracking. SR and strain measurements were calculated as in method 1 by tissue Doppler.

In method 3, strain was calculated directly from the variation of the segment length using the tracked end points: $\text{strain} = (L - L_0)/L_0$, as illustrated in Figure 1 between p3 and p4. SR was calculated as the temporal derivative of strain, with correction to Eulerian SR. This enabled angle-independent measurements of SR and strain. Segment tracking was done as in method 2. In the automated analysis, measurements from a segment were only accepted or discarded. Thus if the kernel region failed to properly track laterally and/or axially after adjustment, then the segment was discarded. The segment also was discarded if the B-mode image showed regions with missing ultrasound data (dropouts) or larger reverberations. For methods 1 and 2, segments were discarded if the angular deviation exceeded 25 degrees.

For standard manual measurements of tissue Doppler, we used commercial software, EchoPAC PC (GE Vingmed Ultra-

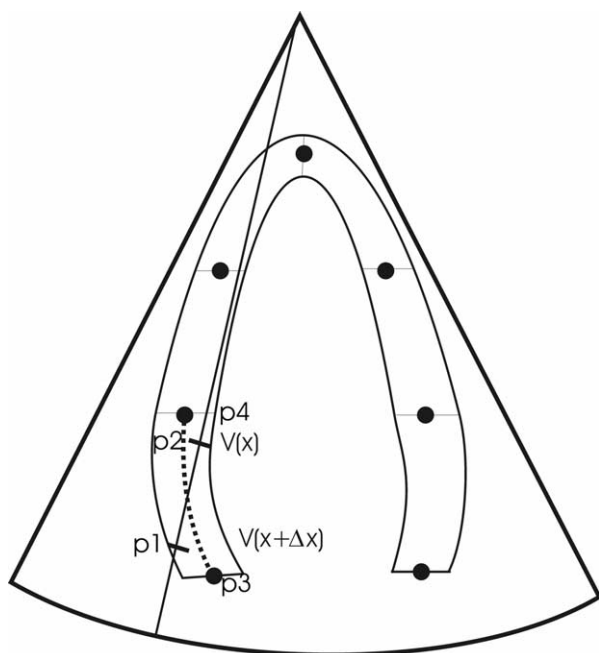


Figure 1 Ultrasound sector with 1 beam and an apical view of the left ventricle. Seven material points (1 apical, 2 in the atrioventricular plane, and 2 in each wall between the apex and the basis) are set automatically by an edge detector algorithm. These points divide the ventricle into 6 segments. The differences between the strain rate calculations are illustrated in the basal segment on the left side. For the speckle-based method, strain is calculated between p3 and p4 defining the segment (as shown by dotted line), independent of the angle to the beam. For tissue Doppler-based methods, SR is calculated along the ultrasound beam between the marked lines for offset, p1 to p2. In the stationary method (method 1), the ROI is set in space rather than in the myocardium. SR, strain rate; ROI, region of interest.

sound). A stationary ROI was placed manually in the center of a segment at mid-systole with an offset of 12 mm for SR calculation. The size of the ROI was adjusted to cover the segment length. If artifacts were seen on the B-mode image, then the size and position of the ROI was adjusted to avoid them. For the apical segments, only the lower third was used. In manual analysis, the segmental ROI could be adjusted, which reduced the number of discarded segments. Segments were also discarded if the SR curve was very noisy, if the peak of the SR curve came close to aortic valve opening or closing, or if the curve was flat and lacked E- and A-waves. Segments were also discarded if the angular deviation exceeded 25 degrees. Strain curves were discarded if they did not return to baseline at the end of the cycle.

Measurements. Peak systolic strain rate (SR_s) and end systolic strain (S_{es}) were chosen as the primary parameters and were measured in 18 segments from 3 apical views. Two apical segments were excluded according to the standard 16-segment model of the American Society of Echocardiography.¹⁵ Figure 2 illustrates the automatically generated SR curves. Mean values and standard deviation (SD) were ana-

lyzed in all segments for all 60 subjects. For comparison of diagnostic accuracy between the 4 methods, we analyzed 28 patients with a first myocardial infarction; 2 patients with negligible infarct size were excluded. SR_s was measured in 1 infarct segment from the central part of the infarction area (from ECG and coronary angiography) and in 1 remote (normal) segment from each patient, for a total of 28 infarcted and 28 normal segments. The normal value for SR_s was defined as a value $\leq -1 \text{ s}^{-1}$, based on earlier studies in which we found that SR_s was -1.2 s^{-1} in normal segments and -0.75 s^{-1} in segments with wall motion score 2.¹⁶ The cutoff for the normal segments was in between these numbers, because SR has a high variability and normal values must be defined with a wide confidence interval.

Intraobserver and interobserver variability was tested in 16 patients, 8 with normal dobutamine stress echocardiography and coronary angiography and 8 with acute myocardial infarction. We reanalyzed 18 segments from each, for a total of 288 segments. For the manual method, 251 infarcted and normal segments were randomly selected from the infarct population for intraobserver and interobserver variability.

Statistical Analysis

Measurements are presented as mean \pm SD. One-way analysis of variance was used to compare mean values between the 4 methods, with post hoc analysis done using Scheffe's test. Area under the receiver operating characteristic (ROC) curve was used to compare sensitivity and specificity between methods. A P value $< .05$ was considered statistically significant. For intraobserver and interobserver variability, the Bland and Altman 95% limits of agreement and coefficient of variation (COV) were used.

RESULTS

Feasibility Data

In all, 799 segments (665 normal and 134 infarcted) were analyzed by all 4 methods. Between 20% and 25% of all segments analyzed using automated methods had to be discarded, compared with only 8% of segments analyzed manually (Table 1). Method 3 yielded the greatest number of analyzable segments for both SR_s and S_{es} (81.5% and 80.3%, respectively) of the automated methods, but still fewer than manual analysis (92.3% and 90.3%, respectively) (Table 1). Feasibility was lowest in the lateral and anterior wall, especially in the mid-lateral and apical anterior segments (Table 2).

Reverberation was the major cause for discarding segments, accounting for 50% of the discards in methods 1 and 2 and 54% of the discards in method 3. Dropouts (no data) were the second-leading cause, accounting for 21% of the discards in all methods. Misalignment of the imaging plane caused 10% of the discards in methods 1 and 2, and 9% of

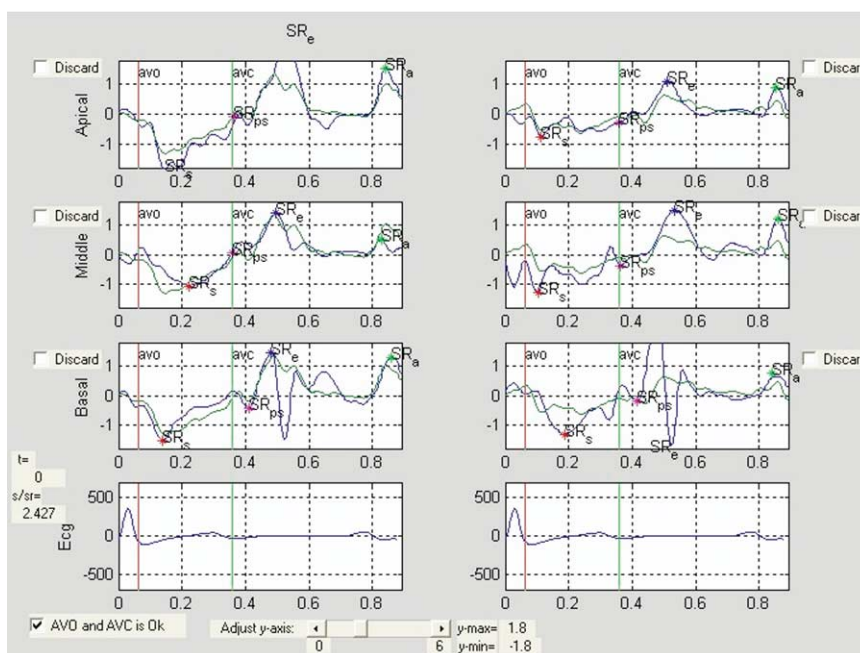


Figure 2 User interface for display and correction of the automated analysis results. The application shows SR or strain curves from all 6 segments simultaneously, in this case from a 4-chamber view, with septal segments to the left; lateral segments to the right; apical, mid-wall, and basal segments from the top downward; and the ECG waveform at the bottom. The darker curve is from the segment; the lighter curve is the average of the 3 segments in the wall for comparison. Timing of aortic valve opening (AVO) and closure (AVC) is imported from the Doppler recordings. Points representing SR_s , postsystolic strain rate (SR_{ps}), and peak strain rate during E and A waves (SR_e and SR_a , respectively) are suggested by the software, subject to manual correction. Finally, the segment can simply be discarded by ticking the appropriate boxes.

Table 1 Mean values for SR_s and S_{es} in normal and infarcted segments, for the 4 methods

| | Method 1 | Method 2 | Method 3 | Manual method |
|--|--------------|--------------|-----------------|----------------|
| Normal segments SR_s (s^{-1}) | -1.45 (0.53) | -1.48 (0.52) | -1.15 (0.32)*** | -1.32 (0.44) |
| Normal segments S_{es} (%) | -18.3 (7.4) | -18.9 (7.6) | -16.9 (4.9)* | -17.3 (6.8) |
| Infarcted segments SR_s (s^{-1}) | -0.60 (0.42) | -0.61 (0.45) | -0.61 (0.37) | -0.46 (0.27)** |
| Infarcted segments S_{es} (%) | -2.9 (8.3) | -3.3 (8.7) | -4.5 (6.1) | -4.0 (5.8) |

A 16-segment model was used, and 988 normal segments and 169 infarcted segments were analyzed. In the normal group, mean SR_s for method 3 was significantly lower than in the other methods ($P < .001$). For S_{es} , there was a significant difference between methods 1 and 3 ($P < .05$). In the infarcted group, mean SR_s was significantly lower than in the other methods ($P < .01$). There were no differences for S_{es} .

S_{es} , End systolic strain rate; SR_p , peak systolic strain rate.

* $P < .05$; ** $P < .01$; *** $P < .001$.

the discards in method 3. Segmental angle deviation of > 25 degrees between the wall and the ultrasound beam caused 9% of the discards in methods 1 and 2. Finally, tracking of the kernels was evaluated visually, and segments were discarded if the tracking did not follow the myocardium, even when any of the aforementioned problems were not visibly present. This was the case in 12% of the discarded segments in method 3.

Time Difference Manual/Automated Method

Full patient analysis, AVC, SR_s , postsystolic SR, peak early diastolic SR, peak late diastolic SR, S_{es} , and

postsystolic strain of 16 segments from 3 apical views took about 2 minutes by automated analysis and 11 minutes by manual analysis.

Mean Values for the Different Methods

In the normal group, the mean SR_s was less in method 3 than in the other methods ($P < .001$) (Table 1). The difference for S_{es} was much smaller and not significant between method 3 and manual (Table 1). In the infarcted segments, SR_s was greater ($P < .01$) for the automated methods than manually, with no significant differences between the auto-

Table 2 Number of segments in which SR_s could be analyzed by the 4 methods

| Segment level/wall | Number segments/ method | Method 1 | Method 2 | Method 3 | Manual method |
|--------------------|----------------------------|----------|----------|----------|---------------|
| Basal | 288 | 194 | 210 | 219 | 270 |
| Mid | 288 | 194 | 186 | 179 | 263 |
| Apical | 192 | 129 | 96 | 169 | 168 |
| Septal | 144 | 112 | 101 | 130 | 139 |
| Lateral | 144 | 77 | 81 | 100 | 134 |
| Inferior | 144 | 114 | 109 | 131 | 142 |
| Anterior | 144 | 83 | 80 | 86 | 116 |
| Inferior lateral | 96 | 66 | 58 | 64 | 89 |
| Anterior septal | 96 | 65 | 63 | 60 | 81 |

SR_s , Peak systolic strain rate.

mated methods. There was no difference between the methods for S_{es} in the infarcted segments (Table 1).

Frame Rate for B-Mode Images

In the B-mode frame rate study (frame rates of 70 FPS and 35 FPS), we analyzed 160 segments. SR_s was analyzable in 134 (84%) and 132 segments (83%), respectively. Slightly fewer segments were analyzable for S_{es} (128 and 129, respectively). Mean SR_s was $-1.12 (0.31) s^{-1}$ at 70 FPS and $-1.13 (0.42) s^{-1}$ at 35. Mean S_{es} was -18.7% (5.1%) and -19.1% (5.3%), respectively.

Sensitivity/Specificity/Accuracy/Receiver Operating Characteristic

In all, 56 segments (28 mid-infarcted and 28 normal) were analyzed by all methods (Figure 3). The normal value for SR_s was defined as $\leq -1 s^{-1}$. Sensitivity was greatest for method 3 (100%), and specificity was greatest for method 3 and the manual method (96%) (Table 3). Accuracy was 96.2% for the manual method and 95.8% for method 3 (Table 3). The area under the ROC curve was 0.989 for method 1, 0.987 for method 2, 1.0 for method 3, and 0.994 for the manual method (Figure 4).

Reproducibility Data

The COV between the 3 automated methods was 15%-20%, with method 3 the lowest. The COV was almost the same for intraobserver and interobserver measurements. Reproducibility was the lowest in manual analysis, with the highest COV for interobserver analysis (Table 3).

DISCUSSION

The present study has demonstrated that automated analysis methods are feasible and faster than standard manual analysis, but they enable analysis of fewer segments. The automated methods still require some manual adjustments.

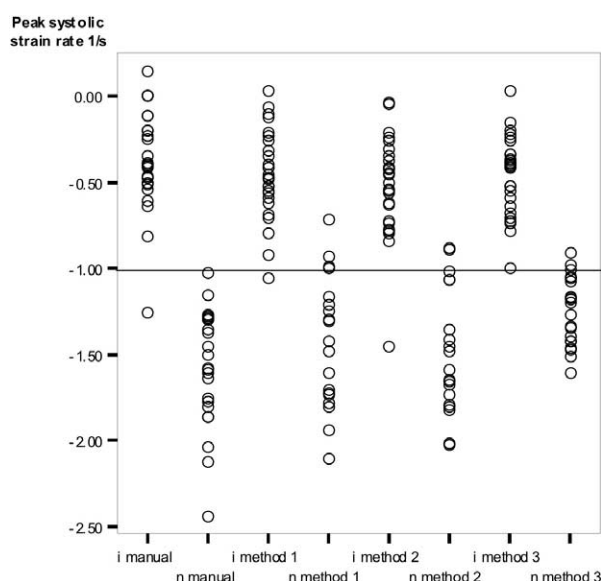


Figure 3 Scatterplot with SR_s values of 28 mid-infarcted segments (i) and 28 normal remote segments (n) of the same patient. All 4 methods used in the study are represented; the normal value for SR_s was defined as a value of $\leq -1 s^{-1}$.

Feasibility of the Different Methods and Reasons for Exclusion

Method 3 had the greatest feasibility of the automated methods. Because of its angle independence, it was as feasible as manual analysis at the apex. Tracking the ROI (method 2) did not increase feasibility compared with stationary ROI (method 1). The major reason for exclusion of normal segments was reverberations, a difficult factor to improve in image quality. Angular deviation exceeding 25 degrees was of less importance. Manual analysis was the most feasible, probably because it was possible to adjust the ROI to avoid reverberations and unsuitable angular deviation.

Table 3 Sensitivity, specificity, accuracy and variability for normal and infarcted segments for SR_s

| | Method 1 | Method 2 | Method 3 | Manual method |
|--|-------------|-------------|-------------|---------------|
| Sensitivity % | 96.4 | 96.3 | 100 | 96.4 |
| Specificity % | 90.5 | 90.5 | 95.8 | 96 |
| Accuracy % | 93.9 | 93.8 | 95.8 | 96.2 |
| Intraobserver | | | | |
| COV (%) | 20 | 16 | 15 | 21 |
| Total mean SR_s (s^{-1}) | -1.36 | -1.43 | -1.30 | -0.92 |
| 95% limits of agreement (lower, upper) | -0.54, 0.56 | -0.42, 0.48 | -0.38, 0.41 | -0.38, 0.38 |
| Bias | 0.014 | 0.031 | 0.012 | -0.001 |
| Interobserver | | | | |
| COV (%) | 28 | 17 | 15 | 30 |
| Total mean, SR_s (s^{-1}) | -1.36 | -1.38 | -1.32 | -1.1 |
| 95% limits of agreement (lower, upper) | -0.52, 0.55 | -0.45, 0.51 | -0.40, 0.40 | -0.69, 0.67 |
| Bias | 0.016 | 0.034 | 0.001 | -0.02 |

For sensitivity, specificity, and accuracy, 28 mid-infarcted and 28 remote normal segments were chosen with a cutoff value for normal segments of $SR_s \leq -1 s^{-1}$. For intraobserver and interobserver variability for the manual method, only the patients with infarct were reanalyzed, not the normal group. For the other methods, segments were randomly selected from both groups; hence the differences in total mean values. COV, Coefficient of variation; SR_s , peak systolic strain rate.

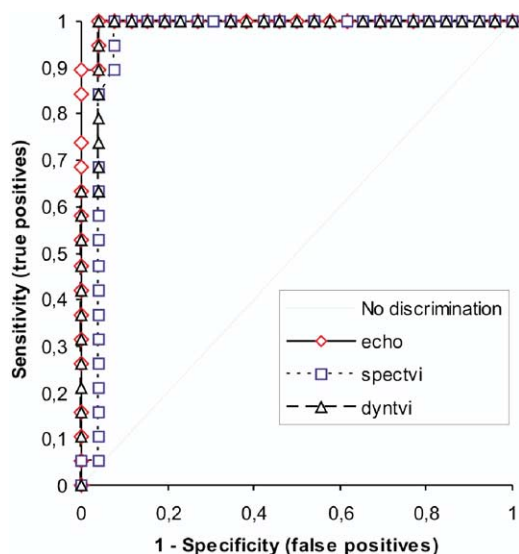


Figure 4 ROC curve of method 2 (dyntvi), method 3 (spectvi), and the manual method (echo). ROC, Receiver operating system.

Differences in Mean Values Among Methods

There were no differences in SR_s and S_{es} between methods 1 and 2, probably because of the poor spatial resolution of SRI based on tissue Doppler. Comparing the stationary ROI with the location of the Doppler beams, it was evident that the values calculated could include information from the other segments inside the ventricle or from the pericardium. However, the possible advantages of a dynamic ROI could not be verified in this study and may be of minor importance.

In normal segments, the mean value of SR_s was lowest in method 3. Because there were few differences between frame rates of 35 and 70 in the

B-mode frame rate study, this finding probably was not due to undersampling. Noise spikes in the tissue Doppler-derived SR could result in excessively high values. The S_{es} measurements are little influenced by random noise, because negative noise and positive noise cancel out during integration. This is also indicated in the results; the mean value in normal segments was similar in method 3 and the manual method.

In the infarcted segments, SR_s was significantly greater for the automated methods than the manual method. This could be an effect of bias in placing the ROI, because the manual analysis was unblinded. S_{es} was the same for method 3 and the manual method in both normal and infarcted segments. This lack of difference may be due to overestimation in tissue Doppler because of noise; speckle tracking-based SR may give more accurate values. On the other hand, the angle dependency of tissue Doppler-based SR is considered to be a problem. Angle deviation often results in underestimation. But method 3, which is angle-independent, results in the lowest values, and thus noise appears to be a more important source of error than angle deviation.

Advantages and Disadvantages of the Automated Methods

Table 4 summarizes the features of the different methods. Method 1 is not dependent on tracking but is based on a stationary ROI set in space, and thus is unable to follow the myocardium through the cardiac cycle. Methods 2 and 3 do not track well in walls with poor B-mode data, in which the unique speckle pattern of each point defining the segments in the myocardium cannot be repeated perfectly from frame to frame. This necessitates manual adjustment in about 25% of the total points. The

Table 4 Features of the different methods

| Method | Feasibility in % for SR _s /S _{es} | Advantages | Disadvantages | Reproducibility (1 = highest; 4 = least) |
|----------|--|--|--|--|
| Method 1 | 75.2% (SR _s) 66.9% (S _{es}) | B-mode independent Time-saving | ROI fixed in space, not in myocardium Angle-dependent | 3 |
| Method 2 | 75.5% (SR _s) 68.0% (S _{es}) | ROI follows myocardium Time-saving | Tracking dependent on B-mode data Angle-dependent | 2 |
| Method 3 | 81.5% (SR _s) | ROI follows myocardium | Tracking dependent on B-mode data and frame rate | 1 |
| Manual | 80.3% (S _{es}) 92.3% (SR _s) 90.3% (S _{es}) | Time-saving, Angle-independent ROI can be adjusted within segment | Time-consuming, Angle-dependent Fixed ROI | 4 |

ROI, Region of interest; S_{es}, end systolic strain; SR_s, peak systolic strain rate.

advantage of methods 2 and 3 is that the ROI stays in the same position relative to the myocardium. Methods 1 and 2 are angle-dependent, because SR is calculated along the ultrasound beam. The effect of the cosine of the insonation angle and/or the use of pericardial or cavity velocity could lead to either underestimation or overestimation.

The advantage of method 3 is that strain and SR can be measured directly by changes in segmental length and by tracking in 2 directions along the direction of the wall, rather than along the ultrasound beam; that is, it is angle-independent and measures longitudinal strain. The disadvantage of method 3 is if the algorithm fails to track one of the segment boundary points, then the measured strain values will be wrong for 2 segments (the 2 segments adjacent to the point). Method 3 is dependent on B-mode frame rate, but this is more important when measuring peak values in diastole and isovolumic phases. There was no difference in SR_s and S_{es} at 70 FPS compared with 35 FPS.

The manual method is extremely time-consuming and less objective compared with the automated methods. The ROI is fixed in space, not in the myocardium, and large lateral movements will influence measurements. However, reverberations can be avoided.

Infarcted Versus Normal Segments

Even though we used preselected segments to establish the accuracy of the methods, our findings demonstrate that the automated methods are as good as the manual method in distinguishing between infarcted and normal segments.

Reproducibility

Intraobserver and interobserver variability were greater than expected for automated analysis, with little difference seen among the methods. The manual method had the least reproducibility, probably because the ROI can be placed differently in the same segment.

Conclusion

Automated analysis methods are faster than and as accurate as manual analysis, but they cannot analyze as many segments as can be done manually. Automated analysis thus may increase the clinical feasibility of SRI. SR based on speckle tracking yielded lower SR_s, which, due to lower noise sensitivity, may be more accurate than tissue Doppler-based measurements. This possibility requires further study.

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