Peak systolic velocity indices are more sensitive than end-systolic indices in detecting contraction changes assessed by echocardiography in young healthy humans

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Aims

It remains to be proven whether left ventricular (LV) peak systolic velocity indices (peak systolic annulus tissue velocities, ejection velocity, and strain rate) are more closely related to contraction than LV end-systolic echocardiographic indices (ejection fraction, fractional shortening, systolic annulus displacement, global strain, and ejection velocity time integral). The study aimed to compare the ability of different echocardiographic methods in detecting contraction changes of the LV.

Methods and results

Thirty-three healthy volunteers (20–32 years) were examined by echocardiography at rest, during 10 μg/kg/min dobutamine (n = 20), and after injection of 15 mg metoprolol (n = 20). The effects of dobutamine and metoprolol on peak systolic velocity indices and end-systolic indices were compared. The relative increase from rest to dobutamine stress and the relative decrease after injection of metoprolol were 62 and −15% for peak systolic annulus tissue velocity, 60 and −11% for LV outflow tract (LVOT) peak velocity, 56 and −11% for peak systolic strain rate, 25 and 1% for ejection fraction, 30 and −5% for systolic mitral annulus displacement, 30 and −5% for LVOT velocity time integral, and 21 and −3% for global strain, respectively. The changes of the peak systolic indices were significantly higher (all P < 0.05) than the changes of the end-systolic indices.

Conclusion

Peak systolic velocity indices (mitral annulus tissue velocities, ejection velocities, and strain rate) exhibited greater variation than end-systolic indices during inotropic alterations from which it is assumed that they better reflected LV contraction.

Keywords

β-Blocker • contractility • dobutamine • myocardial deformation • speckle tracking • strain

Introduction

Myocardial systolic function depends upon the interaction of myocardial contractility, preload, and afterload. Force development (contractility of the myocytes) which generates sufficient pressure to open the cardiac valves should be distinguished from deformation (shortening of the myocytes) which gives rise to the actual volume ejection. True contractility of the myocardium is currently not measurable non-invasively in clinical practice. However, myocyte contraction occurs in the first part of systole, which corresponds well to the timing of the echocardiographic peak systolic velocity indices such as peak systolic annulus tissue velocities, ejection velocity, and peak systolic strain rate, but it is still questionable whether these indices are closely related to contraction. In contrast to force development, deformation and volume ejection continue until the end of systole, and end-systolic
contractions in young healthy humans

Methods

Study population

A complete echo/Doppler study at rest was performed in all the subjects. Low-dose dobutamine stress echocardiography was performed in 13 subjects. Both low-dose dobutamine stress echocardiography and echocardiography after intravenous administration of metoprolol were performed in seven subjects. Echocardiography after intravenous administration of metoprolol was performed on 13 subjects. In total, 20 paired rest-dobutamine recordings and 20 paired rest-metoprolol recordings were obtained and the subsequent measurements were categorized into three contractile states: β-blocker, rest, or dobutamine.

The low-dose dobutamine protocol started with a dose of 5 μg/kg/min for 3 min, followed by 10 μg/kg/min until the recordings were completed. The recordings during 10 μg/kg/min dobutamine infusion started after 3 min of steady state. For the β-blocker study, 15 mg of metoprolol was injected over 10 min, and a new complete echo/Doppler study started 10 min after the last injection. For those who received both dobutamine and metoprolol, the recordings after infusion of metoprolol started 20 min after the infusion of dobutamine was ended.

Echocardiographic image acquisition

Real-time 3D echocardiography recordings were performed immediately after the 2D examination. From the apical approach, four to six consecutive ECG-gated subvolumes were acquired during end-expiratory apnoea to generate full-volume data sets (mean frame rate 26 s⁻¹). Care was taken to encompass the entire LV cavity and, if unsatisfactory, the data set was re-acquired.

Analysis of B-mode and Doppler echocardiography

LV volumes and LV ejection fraction (LVEF) were measured by biplane Simpson’s rule from the apical four- and two-chamber views. End-diastolic volume was measured at the time of mitral valve closure, and end-systolic volume was measured on the image with the smallest LV cavity. LV internal end-diastolic and end-systolic dimensions were measured perpendicular to the long axis of the ventricle at the mitral valve leaflet tips in the parasternal long-axis view, using anatomical M-mode echocardiography. The FS was calculated as the difference between LV internal end-diastolic and end-systolic dimensions divided by the LV internal end-diastolic dimension.

LVEF was also obtained from the 3D recordings (4D auto LV quantification, version BT11, GE Vingmed Ultrasound). End-diastolic and end-systolic volumes were measured after manual alignment followed by automatic detection of endocardial surface which were manually adjusted by placing as many additional points as needed in 3D at both end-diastole and end-systole. Finally, the automatically detected epicardial borders were manually adjusted in 3D at end-diastole in order to calculate LV mass.

From the spectral TD recordings, peak systolic mitral annular velocities (S spectral TD) were measured at the peak of the Doppler spectrum with a low gain setting (Figure 1A). Peak systolic mitral annular velocities were also measured by colour TD (S colour TD) (Figure 1B). Systolic mitral annular excursion (MAE) was measured using anatomical M-mode echocardiography from the apical position (MAE M-mode) (Figure 1C) and from TD by integration of the velocity curves (MAE colour TD) (Figure 1C). The annular plane motion and velocity indices of the septal, lateral, inferior, and anterior walls were averaged to give global measurements of LV performance.

The LVOT peak velocity was measured from the LVOT spectrum using a low gain setting. The LVOT velocity time integral (VTI) was measured by tracing the modal velocity throughout systole (Figure 1D). All indices reflected the average of three cardiac cycles during quiet respiration.

Analysis of deformation indices

Segmental longitudinal strain and strain rate were measured in the three standard apical views.

Longitudinal end-systolic strain was obtained by speckle tracking in grey-scale recordings by 2D speckle-tracking echocardiography (2D-ST) (Automated Function Imaging; EchoPAC PC version BT 09, GE Vingmed, Horten, Norway). The regions of interest (ROIs) were manually adjusted to include the entire LV myocardium and simultaneously avoid the pericardium (Figure 1E). Segments with poor tracking were excluded manually. End-systolic strain was measured at the automatically detected aortic valve closure (manually corrected if necessary).

Longitudinal strain rate was calculated from colour TD recordings, using the TD velocity gradient along the ultrasound beam (Q-Analysis; EchoPAC PC version BT 09, GE Vingmed). For each segment, a
stationary ROI with offset length 12 mm was manually positioned in the middle of the myocardium. The ROI was adjusted up to 10 mm longitudinally and 5 mm laterally in order to avoid noise. Peak systolic strain rate (SRS) was measured as the maximal negative value during ejection time and reflected the average of three cardiac cycles.

Segmental longitudinal strain and SRS (TD) were analysed in an 18-segment model of the LV, and global averages were calculated from the standard ASE 16-segment model. 5

Statistics
Values are reported as mean and SD. Calculation of the relative change (the measured difference between rest and the different contractile states, divided by the measurement at rest) was done for all echocardiographic indices. For multiple comparisons, one-way ANOVA with post hoc Tukey’s correction were used. The area under the receiver-operating characteristic (ROC) curve (AUC) for detection of different contractile states was also used for comparison of the methods. We also calculated the intervals given by mean ± 2SD for indices at rest and during the different contractile states and compared the percentage overlap relative to the mean at rest of these intervals.

Data reproducibility
Reproducibility was tested on a different population in relation to the HUNT study, and the results are published elsewhere. 6,7 The inter-observer mean error (the percentage difference between two experienced physician echocardiographers’ measurements on separate recordings) was 7–10% for the peak systolic velocity indices and 4–14% for the end-systolic indices.

Table 1  Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (2.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179 (6.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>BSA (m^2)</td>
<td>1.9 (0.2)</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>180 (27)</td>
</tr>
<tr>
<td>LV volume (mL)</td>
<td>134 (27)</td>
</tr>
</tbody>
</table>

The parameters are displayed as mean (standard deviation). BMI, body mass index; BSA, body surface area; LV, left ventricular. LV mass and volume were obtained from real-time 3D echocardiography.

Results

Study population and feasibility
Table 1 shows the basic characteristics of the study population, and Table 2 summarizes the haemodynamic response to low-dose dobutamine and metoprolol. All participants completed their prespecified protocol. No participants had ST-segment changes, symptomatic blood pressure changes, or arrhythmias during any of the drug infusions. All subjects had synchronous LV activation assessed by visual assessment. Estimation of biplane 2D and 3D
**Table 2** The haemodynamic response to dobutamine and metoprolol

<table>
<thead>
<tr>
<th></th>
<th>Rest (n = 33)</th>
<th>Dobutamine (n = 20)</th>
<th>Metoprolol (n = 20)</th>
<th>Metoprolol after dobutamine (n = 7)</th>
<th>Only metoprolol (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean change (%)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>61 (9)</td>
<td>67 (12)</td>
<td>51 (6)</td>
<td>−12</td>
<td>54 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49 (6)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118 (10)</td>
<td>135 (15)</td>
<td>98 (9)</td>
<td>−14</td>
<td>99 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>98 (10)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70 (9)</td>
<td>62 (9)</td>
<td>55 (8)</td>
<td>−22</td>
<td>56 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55 (9)</td>
</tr>
</tbody>
</table>

BP, blood pressure; SD, standard deviation.

**Table 3** Systolic echocardiographic indices at rest and during dobutamine

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) at rest</th>
<th>Mean (SD) during stress</th>
<th>Mean change (95% CI)</th>
<th>Mean ± 2SD overlap rest vs. dobutamine (% overlap)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S’(spectral TD)</td>
<td>9.4 (1.0) cm/s</td>
<td>15.1 (1.8) cm/s</td>
<td>62% (53–71)%</td>
<td>−0.10 cm/s (no overlap)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>S’(colour TD)</td>
<td>7.6 (0.9) cm/s</td>
<td>11.5 (1.0) cm/s</td>
<td>52% (43–62)%</td>
<td>−0.06 cm/s (no overlap)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>LVOT peak</td>
<td>1.0 (0.1) m/s</td>
<td>1.7 (0.2) m/s</td>
<td>60% (48–73)%</td>
<td>0.11 m/s (11%)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Global SRs (TD)</td>
<td>−1.2 (0.1) s⁻¹</td>
<td>−1.8 (0.1) s⁻¹</td>
<td>56% (50–61)%</td>
<td>0.2 s⁻¹ (no overlap)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>End-systolic indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global strain (2D-ST)</td>
<td>−0.19 (0.02)</td>
<td>−0.23 (0.02)</td>
<td>21% (17–25)%</td>
<td>0.03 (18%)</td>
<td>0.95 (0.86–1.00)</td>
</tr>
<tr>
<td>LVOT vti</td>
<td>21 (4) cm</td>
<td>27 (4) cm</td>
<td>30% (20–40)%</td>
<td>8.6 cm (41%)</td>
<td>0.89 (0.79–1.00)</td>
</tr>
<tr>
<td>MAE (M-mode)</td>
<td>15 (2) mm</td>
<td>20 (2) mm</td>
<td>30% (25–36)%</td>
<td>2.8 (18%)</td>
<td>0.96 (0.91–1.00)</td>
</tr>
<tr>
<td>MAE (colour TD)</td>
<td>15 (2) mm</td>
<td>18 (2) mm</td>
<td>23% (17–29)%</td>
<td>3.4 mm (23%)</td>
<td>0.93 (0.85–1.00)</td>
</tr>
<tr>
<td>2D LVEF</td>
<td>0.57 (0.06)</td>
<td>0.70 (0.06)</td>
<td>25% (20–30)%</td>
<td>0.11 (21%)</td>
<td>0.95 (0.89–1.00)</td>
</tr>
<tr>
<td>3D LVEF</td>
<td>0.56 (0.04)</td>
<td>0.69 (0.04)</td>
<td>24% (21–27)%</td>
<td>0.03 (5%)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>FS</td>
<td>0.32 (0.04)</td>
<td>0.42 (0.06)</td>
<td>31% (24–37)%</td>
<td>0.10 (32%)</td>
<td>0.89 (0.60–1.00)</td>
</tr>
</tbody>
</table>

AUC, area under the receiver-operating characteristic curve for detection of increased contraction; CI, confidence interval; FS, fractional shortening; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAE, mitral annulus excursion; S, mean peak systolic mitral annulus velocity; SD, standard deviation; SRs, peak systolic strain rate; ST, speckle tracking echocardiography; vti, velocity time integral; TD, tissue Doppler; 2D, two-dimensional; 3D, three-dimensional.

LVEF, mitral annulus velocity and -motion indices, and systolic flow indices were feasible in all recordings. Estimation of diastolic flow and TD indices and flow Doppler time intervals, presented in Supplementary data online, Table S1, were also feasible in all recordings. One thousand and eighty-four (83%) segments post-processed by 2D-ST and 1120 (85%) segments post-processed by the TD velocity gradient method were accepted for analysis. The rest of the segments were excluded because of reverberations, valvular interference, or tracking difficulties. The percentages of rejected segments were 14% at rest, 20% during dobutamine stress, and 15% after injection of metoprolol.

**Systolic indices during low-dose dobutamine stress**

Table 3 shows the mean (SD) at rest and during stress, and the effect of stress, for all the systolic indices of LV performance. All indices increased significantly (all P < 0.001) from rest to stress. The relative increase in the peak velocity indices ranged from 51 to 62%, and these changes were significantly higher (all P < 0.05) than the relative changes of all end-systolic indices which ranged from 21 to 31%. In the ROC analysis, the AUC was between 0.93 and 1.00 for all methods, and differences between peak velocity- and end-systolic indices were not significant. The range and the mean ± 2SD at rest and during stress overlapped for all indices except S’(spectral TD), S’(colour TD), and SRs (TD) (Table 3 and Figure 2).

**Systolic indices after metoprolol**

Table 4 shows the mean (SD) at rest and after injection of metoprolol for all systolic indices of LV performance. The absolute changes were significantly less pronounced (all P < 0.001) after injection of metoprolol compared with the change induced by
low-dose dobutamine. All indices decreased significantly after injection of metoprolol (all \( P < 0.05 \)), except global strain, MAE (M-mode), and 2D LVEF. The relative changes of the peak velocity indices ranged from \(-15\%\) to \(-11\%\) and the relative changes of all end-systolic indices ranged from \(-5\%\) to \(+1\%\). There was a trend for all peak systolic indices to have higher AUC for detection of decreased contraction compared with the end-systolic indices, and this was significant for SRS (TD) compared with all end-systolic indices and for \(S'\) (spectral TD) compared with global strain, MAE (M-mode), and 2D LVEF. The range and the mean ± 2SD at rest and after injection of metoprolol overlapped for all indices.

**Discussion**

To our knowledge, this is the first study that directly compares the influence of contractility changes on LVEF, traditional Doppler indices, TD indices, and newer speckle-tracking-based indices in the same human data set. In this study, peak systolic velocity indices exhibited greater variation than end-systolic indices during inotropic alterations. We suggest from this that the peak systolic velocity indices better reflected LV contraction.

**Study population and study design**

We randomly selected a study population from a relatively homogenous sample of young and healthy subjects. The population was chosen in order to induce uniform alterations in contraction and avoid any pathological response to dobutamine or metoprolol. The main effect of dobutamine at low dose is increased inotropy without a profound effect on heart rate, and it is thus well suited for studying changes in contraction. In line with previous studies, low-dose dobutamine increased the heart rate by \(+13\%\) \(^8\) and metoprolol reduced the heart rate by \(-12\%\). No invasive reference method was used, but dobutamine and metoprolol have well-documented positive and negative inotropic effects, and has previously been used to define inotropic states in several studies. \(^3,8,10,11\) Low-dose dobutamine has previously induced \(\geq 50\%\) increase in the maximal first derivative of LV pressure (LV dP/dt\(_{max}\)) obtained by cardiac catheterization in different populations, \(^12-14\) which is in the same range as the measured increase in peak systolic velocity indices during low-dose dobutamine in this study.

**Peak systolic vs. end-systolic indices**

The study shows a significantly different response to positive and negative inotropic stimulation between peak systolic velocity indices and end-systolic indices. This is supported by findings in several previous studies: inotropic alterations affected the peak velocity considerably more than the velocity time integral of LVOT and aortic blood velocity waveform in two studies. \(^8,15\) In studies of patients with heart disease, \(S'\) had a better correlation to LV pressure development than LVEF, MAE, and LVOT vti. \(^16,17\) \(S'\)
increased considerably more than LVEF, FS, and e′ during low-dose dobutamine in a study on healthy humans.9

S′, LVOT peak, and peak SRs are almost simultaneous events in the heart cycle,18 and their timing corresponds well to the timing of peak force development on a myocyte level, which occurs in the first part of systole.19 End-systolic indices are much less dependent of peak force development on a myocyte level, which occurs in the temporal component of deformation compared with peak systolic indices, and end-systolic indices are more related to stroke volume, i.e. the total amount of work performed by the ventricle during systole. This is influenced not only by contractility (force), but also by afterload, as well as the total time span of the work. Thus, end-systolic indices are more heart rate-sensitive than peak systolic indices, and the modest changes in heart rate induced by inotropic alterations in this study could partly explain the less pronounced changes of the end-systolic indices. However, according to other studies, such modest changes in heart rate have negligible influence on Doppler myocardial imaging parameters.20,21 Furthermore, SRs showed larger variation and better correlation to LV pressure development compared with end-systolic strain during inotropic alterations independent of heart rate in the study of atrial paced pigs.5

**Clinical implications of our study**

LVEF is a key functional and prognostic marker of LV function. However, LVEF overestimates the myocardial function in small hypertrophic hearts, has limited reproducibility, and is a poor indicator of the contractile properties of the myocardium.1 The present and other studies22–24 indicate that peak systolic velocity indices give important supplementary information to LVEF and global strain. In this study, peak systolic velocity indices were more sensitive in detecting contraction changes, and therefore, it may be suggested that peak systolic velocity indices are more sensitive to detect changes of cardiac function also in clinical practice.

However, this has to be tested in a clinical setting. Compared with deformation imaging, indices of annular tissue velocities appear superior with respect to feasibility and time efficiency. Thus, the average peak systolic mitral annulus tissue velocity currently seems to be the preferred marker of contraction among frequently used echocardiographic methods in everyday clinical practice. As real-time 3D echocardiography with low frame rate is now available in clinical practice, it is important to keep in mind that peak systolic indices require higher frame rate than end-systolic indices.

### Limitations

The subjects were fairly young and without heart disease, which probably gave a more homogenous response to inotropic alterations than would have been expected in a general population. It remains to be tested whether our results could be extrapolated to a more general population of patients with heart disease or whether our results are useful for predicting outcomes during longer-term follow-up in patients with heart disease. In addition, the present study addresses only global indices, and regional indices may perform better in conditions with regional dysfunction. Furthermore, the present study addresses only global indices, and regional indices may perform better in conditions with regional dysfunction. It remains to be tested whether our results could be extrapolated to a more general population of patients with heart disease or whether our results are useful for predicting outcomes during longer-term follow-up in patients with heart disease. In addition, the present study addresses only global indices, and regional indices may perform better in conditions with regional dysfunction.

### Table 4  Systolic echocardiographic indices at rest and after metoprolol

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) at rest</th>
<th>Mean (SD) after metoprolol</th>
<th>Mean change (95% CI)</th>
<th>Mean ± 2SD overlap rest vs. metoprolol (% overlap)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic velocity indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S′ (spectral TD)</td>
<td>8.9 (1.0) cm/s</td>
<td>7.5 (1.1) cm/s</td>
<td>−15% (−19 to −11)%</td>
<td>2.9 cm/s (33%)</td>
<td>0.85 (0.72–0.98)</td>
</tr>
<tr>
<td>S′ (colour TD)</td>
<td>7.5 (1.0) cm/s</td>
<td>6.5 (0.7) cm/s</td>
<td>−13% (−16 to −10)%</td>
<td>2.3 cm/s (30%)</td>
<td>0.78 (0.63–0.92)</td>
</tr>
<tr>
<td>LVOT peak</td>
<td>1.0 (0.1) m/s</td>
<td>0.9 (0.1) m/s</td>
<td>−11% (−15 to −6)%</td>
<td>0.6 m/s (56%)</td>
<td>0.77 (0.62–0.92)</td>
</tr>
<tr>
<td>Global SRs (TD)</td>
<td>1.2 (0.1) s⁻¹</td>
<td>1.1 (0.1) s⁻¹</td>
<td>−11% (−14 to −8)%</td>
<td>0.2 s⁻¹ (14%)</td>
<td>0.91 (0.83–1.0)</td>
</tr>
</tbody>
</table>

**AUC**, area under the receiver-operating characteristic curve for detection of decreased contraction; **CI**, confidence interval; **FS**, fractional shortening; **LVEF**, left ventricular ejection fraction; **LVOT**, left ventricular outflow tract; **MAE**, mitral annulus excursion; S′, mean peak systolic mitral annulus velocity; SD, standard deviation; SRs, peak systolic strain rate; ST, speckle tracking echocardiography; vti, velocity time integral; TD, tissue Doppler; 2D, two-dimensional; 3D, three-dimensional.
nuclear imaging. The subjects were not examined during changes in loading conditions.

**Conclusion**

Peak systolic velocity indices (peak systolic mitral annulus tissue velocities, ejection velocities, and peak systolic strain rate) exhibited greater variation than end-systolic indices during inotropic alterations from which it is assumed that they better reflected LV contraction. Considering feasibility and time efficiency, peak systolic annulus tissue velocity seems to be the preferred marker of contraction among frequently used echocardiographic methods.

**Supplementary data**

Supplementary data are available at European Journal of Echocardiography online.

**Conflict of interest:** none declared.

**Funding**

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**References**

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