Left ventricular strain and strain rate: characterization of the effect of load in human subjects

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Received 22 July 2009; accepted after revision 19 November 2009; online publish-ahead-of-print 20 December 2009

Aims

Left ventricular (LV) strain and strain rate have been proposed as novel indices of systolic function; however, there are limited data about the effect of acute changes on these parameters.

Methods and results

Simultaneous Millar micromanometer LV pressure and echocardiographic assessment were performed on 18 patients. Loading was altered sequentially by the administration of glyceryl trinitrate (GTN) and saline fluid loading. Echocardiographic speckle tracking imaging was used to quantify the peak systolic strain (S) and peak systolic strain rate (SR S) and dp/dt max was recorded from the micromanometer data. GTN administration decreased preload (LV end diastolic pressure [LVEDP]: 15.7 vs. 8.4 mmHg, P < 0.001) and afterload (end systolic wall stress: 74 vs. 43 × 10³ dyn/cm², P < 0.001). Administration of fluid increased preload (LVEDP: 11.3 vs. 18.1 mmHg, P < 0.001) and increased wall stress (53 vs. 62 × 10³ dyn/cm², P < 0.003). Administration of GTN resulted in increased circumferential SR S (−1.2 vs. −1.7s⁻¹, P < 0.01) and longitudinal SR S (−0.9 vs. −1.0s⁻¹, P < 0.001). The administration of fluid resulted in decreased circumferential SR S (−1.5 vs. −1.3s⁻¹, P < 0.01) and longitudinal SR S (−1.0 vs. −0.9s⁻¹, P < 0.01). As preload and afterload increased, decrease in circumferential SR S (r = 0.63, P < 0.001; r = 0.56, P < 0.001) and longitudinal SR S were observed (r = 0.42, P < 0.003; r = 0.49 P < 0.001).

Conclusion

Circumferential and longitudinal peak strain and systolic strain rate are sensitive to acute changes in load, an important factor that needs to be considered in their application as indices of systolic function.

Keywords

Strain • Strain rate • Echocardiography • Speckle tracking imaging • Micromanometer

Introduction

The echocardiographic measures of left ventricular (LV) myocardial deformation, strain and strain rate, have been proposed as important novel indices of cardiac function. In recent years a number of studies have shown potential clinical utility for the measurement of strain and strain rate in detecting myocardial ischaemia,1 facilitating accurate stress echocardiographic analysis,2 predicting response to cardiac resynchronization therapy,3,4 and the detection of subclinical myocardial disease.5,6

However, ventricular loading conditions can vary in patients over time and there are limited data about the effect of acute changes in loading conditions on strain and strain rate parameters and their relation to invasive measures of cardiac function. The available literature has largely focused on systolic function using tissue Doppler imaging (TDI) methods that have the advantage of high frame rates, but are angle dependent, whereas a more recently developed non-Doppler technique, speckle tracking imaging (STI)7,8 is angle independent, but dependent on image quality.9,10

Load dependence of peak strain was demonstrated in early work on isolated muscle strip preparations.11 Weidemann et al.12 measured radial strain and strain rate using a TDI-based technique in a porcine model where loading conditions were altered by atrial...
pacing, esmolol and dobutamine infusions and found that radial strain was related to stroke volume, whereas strain rate was related to the contractility index. Greenberg et al. conducted a similar experiment in a canine model, measuring longitudinal strain rate in the basal septum and found a close relation with $\frac{dp}{dt}$ max. In a recent closed-chest porcine study using TDI, Rosner et al. confirmed that longitudinal strain and strain rate were indeed load dependent.

In human subjects, the relationship between load and systolic deformation measures has not been tested using invasive measures of function as a reference standard. Thus, we undertook a simultaneous micromanometer–echocardiography study using STI to quantify strain and strain rate with preload and afterload manipulation.

**Methods**

**Patient selection**

Patients referred for routine coronary angiography to investigate chest pain were invited to participate. Patients with ejection fraction <45%, acute coronary syndrome, chest pain or ECG changes at the time of angiography, regional wall motion abnormality, significant valvular heart disease, atrial fibrillation, permanent pacemaker, history of CABG, renal impairment (eGFR < 60 mL/min/1.73 m$^3$) and abnormal QRS complex morphology on ECG were excluded. This study complies with the Declaration of Helsinki and was undertaken with the approval of the Human Research Ethics Committee of St Vincent’s Health and written informed consent was obtained from all subjects.

**Simultaneous micromanometer left ventricular pressure and echocardiography**

Studies were undertaken in the catheterization laboratory with the subjects in the supine position. Echocardiography was performed using a VIVID 7 echocardiograph (GE Medical Systems, Princeton, NJ, USA). A single-use 5 French Millar micromanometer catheter (SPC-454D, Millar Instruments Inc, Houston) was placed within the LV using a right femoral approach. LV pressures were recorded using Powerlab/4sp recording unit (ADI Instruments, CA, USA) connected to an iMac desktop computer (Apple, CA, USA).

Simultaneous echocardiograph and pressure recordings were obtained under four conditions prior to coronary angiography: PreGTN; in the fasting state; GTN; at the nadir of LV pressure after sublingual glyceryl trinitrate (GTN) administration (if the subject’s resting LV pressure was <110 mmHg [five subjects]), 300 μg of sublingual GTN was administered; for the remainder of patients 600 μg was administered; prefluid: stable haemodynamic state at least 15 min after GTN administration; and fluid: after rapid infusion of 750 ml normal saline (warmed to 37°C).

LV pressure data were acquired using Chart 3.6.3 for MacOS (ADI Instruments, California). LV end diastolic pressure (LVEDP) was recorded from the pressure vs. time trace. Data from five cycles at each condition were analysed and averaged.

**Echocardiographic and combined echo-invasive measures**

Echocardiographic data were acquired at end expiratory apnoea. Ejection fraction was calculated using biplane Simpson’s method and LV mass index (LVMI) was calculated using the area-length method and LV hypertrophy (LVH) was defined according to the standard criteria. LVMI > 115 g/m$^2$ for males and >95 g/m$^2$ for females.

Afterload was quantified by LV end systolic wall stress (ESWS) using the formula validated by Reichek et al.17, wall stress ($\sigma$) ($\times 10^5$ dyn/cm$^2$) = \[\frac{(0.334 \times P \times LVID)}{(1 + PWT/LVID)}\]; where LVID is the end systolic LV internal dimension (cm), PWT is end systolic posterior wall thickness (cm) and P is end systolic pressure (mmHg).

**Speckle tracking analysis**

STI and strain analysis were undertaken as previously described. Briefly, off-line speckle tracking analysis of raw ultrasound data was performed using EchoPac PC software (Version 4.1, GE Medical Systems, Horton, Norway) on single focus, parasternal short axis images (50–90Hz) at the level of the papillary muscles for circumferential strain and apical four chamber images for longitudinal strain. Peak strain (S) and peak systolic strain rate (SR S) were recorded for each of the six segments defined by the 2D strain algorithm and averaged. Segments that could not be accurately tracked (as assessed by the tracking score within the algorithm) were excluded from the analysis.

**Statistics**

The effect of load manipulation was analysed using paired t-tests with the effect of GTN and the effect of fluid loading regarded as separate experiments because there were significant differences between the PreGTN and prefluid haemodynamics. Normality of data was assessed using the Kolmogorov–Smirnov statistic. Where data were not normally distributed, log transformation was applied. For the normally distributed variables, paired t-tests were used to compare the changes with load manipulation. To correct for the fact that multiple observations were performed on the same subjects, repeated-measures linear regression was performed using the subjects as random variables to quantify the relationship between strain and invasive indices of cardiac function as previously described. The commercially available statistics software SPSS (SPSS Inc, Chicago) was used. Data are presented as mean ± SD unless otherwise specified and $P < 0.05$ was considered significant.

**Results**

**Feasibility and demographic data**

The demographic data for the 18 subjects are summarized in Table 1. Nine patients had angiographically smooth coronary

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Age (mean ± SD, range)</td>
<td>65.7 ± 7.6 (47–77)</td>
</tr>
<tr>
<td>Body mass index (mean ± SD, range)</td>
<td>28.0 ± 3.9 (22.2–36.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Medications:</td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>5 (28)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Angiotensin receptor antagonist</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>0</td>
</tr>
</tbody>
</table>

Values in parenthesis are represented in percentage.
Table 2  Effect of change in load on invasive and echocardiographic indices

<table>
<thead>
<tr>
<th></th>
<th>PreGTN</th>
<th>GTN</th>
<th>Prefluid</th>
<th>Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>60.4 ± 6.6</td>
<td>65.0 ± 11.7*</td>
<td>63.1 ± 10.4</td>
<td>62.1 ± 10.2</td>
</tr>
<tr>
<td>LV peak systolic (mmHg)</td>
<td>145.4 ± 28.9</td>
<td>111.3 ± 19.7†</td>
<td>120.4 ± 21.8</td>
<td>131.6 ± 24.6‡</td>
</tr>
<tr>
<td>Dp/dt max (mmHg/s)</td>
<td>1157 ± 210</td>
<td>1223 ± 276*</td>
<td>1123 ± 208</td>
<td>1024 ± 188‡</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>55.3 ± 4.7</td>
<td>59.0 ± 6.3†</td>
<td>59.4 ± 5.4</td>
<td>61.5 ± 4.9</td>
</tr>
</tbody>
</table>

(mean ± SD, *P < 0.05, †P < 0.01, ‡P < 0.001).

Figure 1  End diastolic pressure, end diastolic volume and end systolic wall stress under each condition (mean ± SEM, *P < 0.05, **P < 0.01, ***P < 0.001).

Figure 2  Circumferential and longitudinal strain (A and B) and strain rate (C and D) under each condition (mean ± SEM, *P < 0.05, **P < 0.01, ***P < 0.001).
arteries and the remaining nine had at least one coronary stenosis of greater than 50%. No patient described chest pain nor was there any electrocardiographic evidence of ischaemia during the study procedures. Mean LV mass index was 89.2 ± 3.6 g/m² (range 58.3–120.8) and three patients had LVH.

Of the 18 patients, each had six possible strain and strain rate segments predefined by the 2D strain algorithm for circumferential and longitudinal strain. A prefluid data set was not collected in three patients meaning that a total of 414 segments were available for both the circumferential and longitudinal analyses. For the circumferential analysis, 92.3% of segments could be analysed; the segments that could not be analysed comprised of anteroseptal, 1%; anterior, 1.7%; lateral, 2.2%; posterior, 1.9%; inferior, 0.5% and septal, 0.5%. For the longitudinal analysis, 85.3% of segments could be analysed; the segments that could not be analysed comprised of basal septal, 1.9%; mid-septal, 0%; apical septal, 1.7%; apical lateral, 3.4%; mid-lateral, 3.4% and basal lateral, 4.3%.

**Effect of haemodynamic manipulation**

The effect of haemodynamic manipulation on invasive and echocardiographic parameters is summarized in Table 2 and Figure 1. Heart rate increased with GTN administration, but there was no

### Table 3  Effect of change in load on strain indices when patients divided into normal and abnormal coronaries at subsequent angiography (mean ± SD, no significant differences between normal and abnormal)

<table>
<thead>
<tr>
<th></th>
<th>PreGTN Normal</th>
<th>PreGTN Abnormal</th>
<th>GTN Normal</th>
<th>GTN Abnormal</th>
<th>Prefluid Normal</th>
<th>Prefluid Abnormal</th>
<th>Fluid Normal</th>
<th>Fluid Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circ S</td>
<td>−16.4 ± 5.0</td>
<td>−15.5 ± 4.5</td>
<td>−17.8 ± 3.8</td>
<td>−18.7 ± 5.5</td>
<td>−17.9 ± 5.0</td>
<td>−15.6 ± 3.7</td>
<td>−17.5 ± 5.6</td>
<td>−15.3 ± 4.7</td>
</tr>
<tr>
<td>Circ SR S</td>
<td>−1.21 ± 0.45</td>
<td>−1.20 ± 0.38</td>
<td>−1.70 ± 0.47</td>
<td>−1.70 ± 0.47</td>
<td>−1.44 ± 0.28</td>
<td>−1.49 ± 0.36</td>
<td>−1.26 ± 0.28</td>
<td>−1.31 ± 0.34</td>
</tr>
<tr>
<td>Long S</td>
<td>−14.7 ± 2.9</td>
<td>−14.7 ± 1.7</td>
<td>−15.2 ± 3.2</td>
<td>−13.2 ± 1.2</td>
<td>−14.2 ± 1.7</td>
<td>−14.8 ± 2.0</td>
<td>−16.2 ± 4.2</td>
<td>−15.4 ± 1.4</td>
</tr>
<tr>
<td>Long SR S</td>
<td>−0.78 ± 0.15</td>
<td>−0.91 ± 0.14</td>
<td>−1.00 ± 0.17</td>
<td>−1.02 ± 0.12</td>
<td>−0.94 ± 0.21</td>
<td>−1.16 ± 0.31</td>
<td>−0.88 ± 0.27</td>
<td>−0.98 ± 0.14</td>
</tr>
</tbody>
</table>

![Figure 3](https://academic.oup.com/ehjcimaging/article-abstract/11/3/283/2396813)

**Figure 3** Relationship between strain (A and B), systolic strain rate (C and D) and end diastolic pressure.
change in heart rate as a result of fluid administration. Administration of GTN resulted in decreased LV systolic pressure, but increased ejection fraction. \( \frac{dP}{dt} \text{max} \) increased with GTN and decreased with fluid. Administration of GTN resulted in decreased preload (EDP and EDV, Figure 1) and afterload (ESWS, Figure 1), whereas administration of fluid increased preload. Afterload increased with fluid loading, though to a lesser extent than the decrease after GTN administration (Figure 1, \( P < 0.001 \)).

The effect of load on strain parameters is summarized in Figure 2. Administration of GTN resulted in increased circumferential \( S \) and \( SR \) and longitudinal \( SR \). The administration of fluid resulted in decreased circumferential \( S \) and \( SR \) and longitudinal \( SR \). Longitudinal strain was not affected by load manipulation.

When the subjects were divided into those with normal coronaries and those with at least one coronary stenosis greater than 50%, no statistically significant differences were observed between the groups for any of the indices under any of the conditions (Table 3).

### Relationship between invasive parameters of load, strain and strain rate

As preload and afterload increased (increased EDP and ESWS, respectively) circumferential \( S \), \( SR \) and longitudinal \( SR \) decreased (Figures 3 and 4), but no relationship was observed between longitudinal \( S \) and measures of preload and afterload.

### Discussion

This study demonstrates that peak systolic strain and peak systolic strain rate are sensitive to changes in loading conditions in human subjects. Sensitivity of peak radial systolic strain and longitudinal strain rate to changes in contractile state and loading conditions is well documented in animal models using TDI; however, in human subjects, only peak strain has been studied. Hurlburt et al. acquired radial, circumferential and longitudinal peak systolic strain and wall stress data using a similar method to ours and found inverse correlations between circumferential and longitudinal strain and wall stress which is in keeping with our findings.

Until recently, peak systolic strain rate was thought to be less load dependent. In a porcine model, strain and strain rate decreased with transient descending aortic occlusion (increasing afterload) in keeping with our observations of the effect of decreased afterload. In the same study, colloid infusion led to increased strain and strain rate associated with increased end diastolic pressure which is contrary to our findings. Quantification of afterload was not reported in the study by Rosner et al., however, the systolic pressure did
not rise significantly after fluid infusion suggesting that the effect was largely an increase in preload. In our study, fluid infusion not only increased preload but also significantly increased afterload and systolic pressure, which may explain the small but significant reduction in both invasively measured dp/dt max and peak systolic strain rate. Multivariate analysis of these effects would require a larger cohort than the present study. Vicario et al.22 similarly reported a reduction in strain rate with filling; however, their subjects had abnormal systolic function and without invasive assessment of loading conditions, it is not clear whether this was an effect of increasing afterload or increasing the preload past the inflection point of the Frank–Starling curve.

No statistically significant differences were observed between patients with and without coronary artery disease in baseline strain and strain rate parameters and in the response of these parameters to changes in load. This is in contrast to the findings of Okuda et al.23 who showed, in a closed chest canine model, reductions in peak systolic strain with even mild flow limiting stenosis. To further elucidate the effect of coronary disease, a comparison of segments subtended by stenotic coronary arteries with those subtended by normal coronaries is required; however, this study was not powered for this analysis.

Measurement of strain and strain rate can be performed using both TDI10 and STI.5 STI is a well-validated tool for the quantification of strain and strain rate and correlates well with invasive gold standard measures such as sonomicrometry.24–26 STI is not an angle dependent but is highly sensitive to image quality, particularly image drop and reverberation artefacts.10 This is reflected in the present study by the higher percentage of segments that could not be analysed in the lateral myocardium particularly in the longitudinal plane. Our findings confirm that STI is a feasible method to measure strain and strain rate as parameters of systolic function.

Limitations
The fact that the haemodynamic manoeuvres employed in this study changed both preload and afterload limit, our ability to comment upon the specific impact of each of these loading components, but do allow us to quantify the fact that load does affect strain and strain rate with circumferential strain being more sensitive to load than longitudinal strain. The failure to observe a consistent effect on longitudinal strain may be related to the inclusion of patients with mildly impaired ejection fraction and thus potentially impaired longitudinal function. Manoeuvres to specifically manipulate afterload, such as vasopressor administration, would be of great interest but were felt to be unwarranted in this experiment.

Conclusions
LV peak systolic strain and peak systolic strain rate measured using STI are sensitive to acute changes in load in human subjects, an important factor that needs to be considered in their application as indices of systolic function.

Acknowledgements
We gratefully acknowledge Mr Don Mooney for the acquisition of high-quality echocardiographic images. We thank Drs Andrew McCann, Georg Leitl and Anthony White for their assistance with cardiac catheterization in this study.

Funding
Dr Andrew Burns is supported by a Postgraduate Research Scholarship from the National Heart Foundation of Australia.

References
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2003;16:1195–1216.

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