Increased left ventricular torsion in uncomplicated type 1 diabetes: the role of coronary microvascular function

Short title: LV torsion in uncomplicated type 1 diabetes

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Objective: We used speckle tracking echocardiography to study the early changes in left ventricular (LV) torsion in young patients with uncomplicated type 1 diabetes (T1DM) and used stress magnetic resonance imaging (MRI) to assess its interrelationships with coronary microangiopathy.

Research design and methods: 33 asymptomatic subjects with T1DM and 32 age-matched healthy controls (HC) were recruited. All subjects underwent echocardiogram and stress MRI was performed in 30 subjects (8 HC) to compute myocardial perfusion reserve index (MPRI).

Results: A significant increase in LV torsion (2±0.7 °/cm vs 1.4±0.7 °/cm, P<0.05) was identified in longer term and retinopathy (+) T1DM subjects (1.9±0.7 °/cm vs 1.4±0.7 °/cm, P<0.05) as compared to HC. The MPRI was independently associated with increased LV torsion.

Conclusions: We demonstrate that LV torsion is increased in young patients with uncomplicated T1DM and coronary microvascular disease may play a key pathophysiological role in the development of increased LV torsion.
There is increasing evidence for the presence of diabetic cardiomyopathy as a separate entity. However, detection of early changes in the myocardium is challenging in patients with diabetes. Speckle tracking echocardiography is a novel method of measuring LV strain and rotation(1,2). Previous studies with tagged MRI have shown increased torsion in patients with both T1DM and T2DM (3,4). The main aim of the study was to confirm and extend these findings by exploring the potential pathophysiological mechanisms involved. We utilized speckle tracking to measure LV torsion and stress MRI to compute MPRI which is a measure of coronary microvascular function.

**RESEARCH DESIGN AND METHODS**

65 subjects who provided informed consent were recruited. The project was approved by Multicenter Regional Ethics Committee in Birmingham. We recruited 33 subjects with T1DM [subgroups- recently diagnosed (<5 yr diabetes duration) and longer term T1DM (diagnosed >10 years previously)] and 32 age and sex matched controls with no cardiac history or diabetes mellitus. All subjects were without evidence of coronary artery disease (CAD) or heart failure based on history, 12 lead electrocardiogram, a normal ejection fraction on echocardiography and exercise testing.

Echocardiography was performed with a Vivid 7 (GE Vingmed) echocardiographic machine using a 2.5-MHz transducer and standard echocardiographic views were obtained. Cardiac MRI was performed on a 3 T Phillips Achieva MRI scanner with a dedicated Cardiac Sense Coil. First pass images at rest were obtained after Gadolinium contrast injection (0.1ml/kg body weight, 4ml/sec). For perfusion images a single shot Turbo Field Echo SENSE pulse sequence was used with three slices per heart beat. After a gap of twenty minutes stress first pass images were obtained at three minutes of adenosine infusion at a rate of 140mcg/kg/min.

**Analysis:** LV torsion was measured using a speckle tracking system in an ECHOPAC (version 4.2.0) workstation as previously described(5). Our reproducibility data demonstrated intra-observer and inter-observer variability of 0.24 ± 0.58 (bias ± 1.96 SD) and 0.15 ± 0.69 respectively, which are acceptable. The MPRI was obtained from the ratio of LV relative peak upslope at stress compared to rest as described earlier(6).

**Statistics:** SPSS (v15.0) was used to perform the statistical operations. Continuous variables are expressed as means ± standard deviation. Comparison between means was performed using ANOVA or Chi-Square test. Pearson correlation coefficient (r) was used to describe the relationship between variables. Bland Altman plot was used to assess data reproducibility using MedCalc (v9.2.1.0).

**RESULTS**

The baseline characteristics are summarized in table 1. The E/A ratio was not different between T1DM and HC (1.5±0.4 vs 1.6±0.4, P=ns) and E/E’ was significantly higher in T1DM (7.7±1 vs 6.4±1, P<0.001). Overall, the mean MPRI in T1DM was 1.9±0.5 and significantly lower than in HC (2.3±0.4, P<0.05).

Overall, peak LV torsion was significantly increased in the T1DM subjects compared to HC (1.9±0.6 °/cm vs 1.4±0.7 °/cm, P<0.01). LV torsion was significantly increased (2±0.7 °/cm vs 1.4±0.7 °/cm, P<0.05) in longer term T1DM compared to HC and was midway between that of longer term T1DM and HC subjects in recently diagnosed T1DM (1.7±0.4 °/cm). The LV torsion in retinopathy (+) T1DM subjects was significantly increased as compared to HC (1.9±0.7 °/cm vs 1.4±0.7 °/cm, P<0.05). Retinopathy (-) T1DM subjects had a non-
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LV torsion was significantly lower in patients with retinopathy (1.7±0.4°/cm vs 1.9±0.7°/cm, P=ns). On univariate analysis, LV torsion negatively correlated with MPRI (r=-0.40, P<0.05), VO2 max (r=-0.26, P=0.05) and anterior-lateral E'/A’ (r=-0.37, P<0.01). On multivariate regression analysis only MPRI (r=-0.41, P<0.05) was an independent predictor of LV torsion.

DISCUSSION

This study demonstrates for the first time that increased LV torsion complicates longer term but not recently diagnosed T1DM. In a previous study of 53 subjects with diabetes without complications, radial contractility was increased and appeared to compensate for reduced longitudinal contractility(7). The longitudinal myocardial fibers are more susceptible to ischaemia and fibrosis(8), which may result in a relative increase in short-axis function due to compensatory ventricular remodeling. Tissue doppler analysis in our study showed mild reductions in longitudinal function in T1DM subjects. Increased torsion may be compensatory for the sub-clinical reduction in long-axis function. However the E/A ratio was not different in the two groups suggesting that increased torsion is one of the earliest stages of diabetic cardiomyopathy detected by echocardiography. Indeed, previous studies have shown increased LV torsion in aortic stenosis(9) and hypertrophic cardiomyopathy(10).

This is the first report which demonstrates that MPRI negatively correlates with and is an independent predictor of LV torsion. MPRI has been shown to be a good indicator of coronary microvascular function(11). Our findings imply that myocardial microvascular disease may play a key pathophysiological role in the development of increased torsion in these patients. We found that the longer term and retinopathy (+) T1DM subjects exhibited the highest LV torsion with abnormalities much less marked in the recently diagnosed and retinopathy (-) subjects. LV torsion in the HC was the lowest of the three subgroups. These data are consistent with previous studies in T1DM and T2DM which have suggested a role for myocardial microvascular disease in the development of diabetic cardiomyopathy. Previous studies by our group have demonstrated that in T1DM, cardiac autonomic neuropathy which begins at the apex is associated with impaired myocardial blood flow regulation (12,13). Thus subclinical dysinnervation of the apex in T1DM may also play a role in increasing apical rotation.

Development of heart failure in diabetes is affected by many secondary factors including hypertension, CAD, renal disease and dyslipidemia. We have shown in our study that in subjects without these complications, increased LV torsion may be one of the earliest features of diabetic cardiomyopathy and it is tempting to speculate that this may ultimately increase susceptibility to heart failure. If confirmed in large scale prospective studies this technique could form the basis of a screening tool for the identification of patients at risk for the development of heart failure facilitating the targeting of preventative approaches.

A limitation of our study was small the sample size and that this was a cross-sectional study and thus the natural history of the development and progression of altered torsion is unknown.

ACKNOWLEDGEMENTS

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REFERENCE LIST


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Table 1: Baseline characteristics and results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Newly diagnosed T1DM</th>
<th>Longer term T1DM</th>
<th>HC</th>
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<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>3 (23)</td>
<td>8(40)</td>
<td>10(31)</td>
</tr>
<tr>
<td>Age, years</td>
<td>31±10</td>
<td>34±6</td>
<td>30±8</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>4.8±3</td>
<td>18.4±7</td>
<td>-</td>
</tr>
<tr>
<td>HBA1C, %</td>
<td>7.4±0.8</td>
<td>8.3±1</td>
<td>-</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>23±2</td>
<td>26±3</td>
<td>25±3</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.3±1.2</td>
<td>4.4±0.7</td>
<td>4.9±0.9</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.5±0.3</td>
<td>1.7±0.5</td>
<td>1.7±0.6</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3±1.2</td>
<td>1.1±0.8</td>
<td>1±0.5</td>
</tr>
<tr>
<td>VO2 max, ml/kg/min</td>
<td>42.6±10.2</td>
<td>35.6±8.4*</td>
<td>44.1±7.2</td>
</tr>
<tr>
<td>Retinopathy, %</td>
<td>5(38)</td>
<td>12(60)</td>
<td>-</td>
</tr>
<tr>
<td>Peak LV torsion, °/cm</td>
<td>1.7±0.4</td>
<td>2±0.7*</td>
<td>1.4±0.7</td>
</tr>
<tr>
<td>MPRI</td>
<td>2.1±0.2</td>
<td>1.7±0.6*</td>
<td>2.3±0.4</td>
</tr>
</tbody>
</table>

BMI-Body mass index; VO2 max-Peak oxygen consumption on exercise; LV-left ventricular; MPRI-myocardial perfusion reserve index
*Significant difference as compared with HC