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*Heart* 2010 96: 948-955
doi: 10.1136/hrt.2009.185181

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Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography

Yu Ting Tan,¹ Frauke Wenzelburger,¹,² Eveline Lee,² Grant Heatlie,² Michael Frenneaux,¹ John E Sanderson¹,²

ABSTRACT

Objectives This study tests the hypothesis that patients with treated hypertension with well-controlled blood pressure, without ventricular hypertrophy and normal resting echocardiography, may have abnormalities of ventricular function that are apparent only on exercise and contribute to symptoms of exertional dyspnoea.

Methods Patients with hypertension with well-controlled blood pressure on medication and normal baseline echocardiography underwent cardiopulmonary exercise testing to determine their peak oxygen consumption (VO2max), followed by rest and submaximal supine exercise echocardiography (standard, tissue Doppler and speckle tracking).

Results 30 patients with treated hypertension with a history of exertional dyspnoea (mean age 71±8 years; 18 women) and 22 age-matched healthy controls (70±6 years; 16 women) had rest and exercise images of sufficient quality for analysis. Both groups had comparable standard echocardiographic findings at rest. On exercise, the patients had reduced systolic longitudinal function (reserve index 0.97±1.34 vs 2.32±1.24, p=0.001), delayed early untwisting (20.4±7.6 vs 30.6±7.8%, p=0.001) and reduced ventricular suction (velocity propagation 10.6±10.9 vs 24.5±12.2 m/s, p<0.001) compared with healthy controls, which correlated with significantly reduced VO2max.

Conclusion Patients with treated hypertension with normal resting echocardiography can have exercise limitation associated with widespread systolic and diastolic left ventricular dysfunction on exercise. Normal resting echocardiography does not preclude the presence of significant functional abnormalities on exercise that can contribute to symptoms.

High arterial blood pressure is a major cause of cardiac disease, in particular left ventricular hypertrophy (LVH), coronary artery disease and heart failure. LVH is a maladaptive response to increased ventricular loading and is due not only to cardiac myocyte hypertrophy but also to major changes in the extracellular matrix and collagen. LVH is often associated with breathlessness on exertion. However, LVH probably reflects a late stage of ventricular damage by the time it is apparent on the electrocardiogram or echocardiography. In addition, many patients with treated hypertension may have dyspnoea on exertion, and if standard echocardiography is normal it is frequently concluded that the breathlessness is not cardiac. New developments in echocardiography now enable a much fuller assessment of left ventricular systolic and diastolic function, including measurements of myocardial deformation or strain in three planes, ventricular twist and untwist, annular motion (longitudinal function) and left ventricular suction, which is a vital mechanism in early diastolic ventricular filling. These can also be assessed during exercise. We sought to determine if there were abnormalities of ventricular function particularly involving longitudinal ventricular function and twist mechanics in a group of patients with treated hypertension without LVH and apparently normal systolic function on routine echocardiography.

METHODS

We assessed left ventricular systolic and diastolic function non-invasively at rest and on submaximal exercise in patients with an established diagnosis of hypertension and healthy controls. All subjects underwent a pulmonary function test and cardiopulmonary exercise test to determine their peak oxygen consumption (VO2max) and to rule out other causes of their breathlessness before rest and exercise echocardiography studies.

Study subjects

Patients referred by general practitioners to a heart failure clinic, with well-controlled blood pressure on medication and complaining of exertional dyspnoea without an alternative explanation for their symptoms and with normal echocardiographic findings during their initial assessment were recruited. Healthy controls of comparable age, without past medical history and on no medication were recruited from another echocardiographic study. Exclusion criteria were uncontrolled blood pressure, the presence of LVH or evidence of pulmonary hypertension on echocardiography, obstructive or restrictive pulmonary disease, congenital or valvular heart disease, the presence of arrhythmia (including atrial fibrillation), electrical pacemaker or implantable cardiac defibrillators and an established history of ischaemic heart disease. All subjects gave written informed consent before their participation and the study was approved by the local research ethics committee.

Cardiopulmonary exercise testing

All subjects had full pulmonary function with standard spirometry (forced expiratory volume in 1 s and forced vital capacity) before the start of incremental treadmill exercise testing, using the
modified Bruce protocol, with metabolic gas exchange recording and simultaneous heart rate and rhythm, systolic and diastolic blood pressure (manually assessed every minute with cuff sphygmomanometer) and oxygen saturation (finger probe pulse oximetry) monitoring. A respiratory exchange ratio greater than 1 indicates anaerobic work and was taken to indicate maximal effort and adequate cardiovascular stress. Breathing reserve of less than 15 L/min was taken as a marker of respiratory limitation. Blood samples were taken pre and post-exercise for N-terminal pro-brain natriuretic peptide (NT-proBNP) analysis.

Two-dimensional and tissue Doppler echocardiography
All subjects underwent full echocardiography examination using a GE Vingmed Vivid Seven scanner (Horton, Norway) at rest and on exercise. Exercise testing was done on a semifl exible bicycle ergometer (Lode BV, The Netherlands) with a workload increment of 25 W. Image acquisition commenced at the onset of symptoms while patients continued to exercise at a sustained workload. Healthy controls were scanned when exercise heart rate was over 90 bpm and workload was maintained to keep a heart rate of 100 bpm (ie, submaximal exercise to maximise frame rates). The heart rate, symptom status, brachial blood pressure and heart rhythm were monitored continuously during exercise. Two-dimensional images and colour-coded tissue Doppler images (TDI) from the parasternal (long axis and short axis at basal, mid-ventricular and apical levels) and apex (two, three and four-chamber views) were obtained and stored digitally. At least three sets of images with loops consisting of at least three consecutive cardiac cycles each were stored for offline analysis using a customised software package (EchoPac, GE). Left ventricular dimensions and wall thickness were measured according to the recommendation of the American Society of Echocardiography. Left ventricular volume and ejection fraction were measured using the modified Simpson’s method from the apical four and two-chamber views. Left ventricular mass was calculated according to the Devereux formula. A left ventricular mass index (LVMI) of greater than 115 g/m² (male) and greater than 95 g/m² (female) were defined as LVH. Left atrial volume was calculated using the biplane area-length method from the apical four and two-chamber views and indexed to body surface area to derive the left atrial volume index (LAVI). The early filling (E) and atrial filling (A) peak velocities, E/A ratio, deceleration time of early filling and isovolumic relaxation time were measured from transmitral Doppler flow. The fusion of E and A waves were excluded from analysis.

Colour M-mode Doppler was obtained by positioning the scan line through the mitral valve with the Nyquist limit and the colour baseline was adjusted to obtain the best spatial resolution. The mitral flow propagation velocity (Vp) was measured by the slope along the aliasing isovelocit line as previously described. Vp approximates the intraventricular pressure gradient during early diastole and is a recognised indicator of left ventricular suction.

The mitral annular myocardial velocity of the left ventricular septal and lateral walls was recorded using the real time pulsed wave tissue Doppler method and results averaged as previously described. The peak systolic (S’), early diastolic (E’) and late diastolic (A’) mitral annular velocities were measured and E/E′, an index of left ventricular filling pressure, was calculated. Colour-coded tissue Doppler images were also acquired for each of the four myocardial walls (septal, lateral, anterior and inferior) as previously described. Peak systolic (Sm) and diastolic (Em and Am) mitral annular myocardial velocities were measured by placing a 4×4 mm region of interest in the myocardium of each wall at the mitral annular level. Fusion of Em and Am were excluded from analysis. Systolic and diastolic longitudinal function reserve indexes were calculated by: ΔSm (or Em) × (1−1/Sm(or Em)rest).14

Speckle tracking echocardiography
Left ventricular longitudinal strain, radial strain and rotation were assessed using the speckle tracking method. Offline analysis of apical four and two-chamber images, and short axis images at three levels (basal, mid-ventricular and apical) were completed by tracing the endocardium at end-diastole and the thickness of the region of interest adjusted to include the entire myocardium. The software automatically tracks the myocardial motion on the subsequent frame and results were displayed graphically. Rotation and strain in the radial and longitudinal planes were measured as previously described. The average longitudinal strain of all four walls (12 segments) was taken as the global longitudinal strain. Radial strain was taken as the average of six segments of the mid-ventricular short axis plane. The percentage untwist was assessed by marking the averaged rotation curve as 25% increment points from peak rotation (0%) to peak untwist (100%). All echocardiographic measurements were done in duplicate by two independent observers (YTT and FW) blinded to each other’s results.

Stroke volume was calculated by using the aortic valve pulse wave Doppler method whereby the velocity time integral of aortic annular flow was obtained by tracing the pulsed Doppler profile and multiplied by the area of the aortic annulus. Cardiac output was calculated as the product of stroke volume and heart rate.

Statistical analysis
Statistical analysis was performed using SPSS version 15.0. Continuous variables were expressed as mean±SD. Comparisons between patients and controls were performed using the unpaired t test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Fisher’s exact test was conducted for nominal variables. Comparisons within patients and controls were performed using the paired t test only as all data were normally distributed. Linear regression (Pearson’s coefficient) was performed to test correlations.

Interobserver and intra-observer agreements were performed using readings of 10 randomly selected subjects and calculated using alpha model reliability analysis and reported as interclass correlation coefficient (ICC) with 95% CI. A value of p<0.05 was considered significant.

RESULTS
A total 70 subjects was recruited in this study (48 patients and 22 controls). Eighteen patients were excluded—one had evidence of LVH on repeat echocardiography, three had evidence of ischaemia on exercise, six had poor picture quality not suitable for analysis, four were unable to exercise and four had left atrial enlargement on subsequent analysis of left atrial volume. The remaining 30 symptomatic patients with hypertension and 22 healthy subjects had adequate images at rest and on exercise for analysis. The mean age of patients was 71±8 years and 60% were women. Control subjects were of comparable age (70±6 years, p=ns) and 72% were women. The past medical history and drug history of patients are summarised in table 1. Previous coronary angiography of the six patients with a past medical history of diabetes and coronary artery disease showed
Hypertension

Table 1  Clinical and echocardiographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 30)</th>
<th>Controls (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 ± 8</td>
<td>70 ± 6</td>
<td>0.524†</td>
</tr>
<tr>
<td>Gender</td>
<td>189 (63)</td>
<td>167 (64)</td>
<td>0.380*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 5</td>
<td>25 ± 4</td>
<td>0.001‡</td>
</tr>
<tr>
<td>NYHA</td>
<td>Class II–III</td>
<td>Class II–III</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{O_{2max}} (ml/min per kilogram) (%)</td>
<td>18.0 ± 4.0</td>
<td>29.0 ± 5.5</td>
<td>0.001‡</td>
</tr>
<tr>
<td>(% of predicted)</td>
<td>(77 ± 18%)</td>
<td>(133 ± 22%)</td>
<td></td>
</tr>
<tr>
<td>Years of hypertension</td>
<td>6.5 ± 5.2</td>
<td>0</td>
<td>0.001†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6/30 (20%)</td>
<td>0/22 (0%)</td>
<td>0.033‡</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6/30 (20%)</td>
<td>0/22 (0%)</td>
<td>0.033‡</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>10 (33%)</td>
<td>0</td>
<td>0.003*</td>
</tr>
<tr>
<td>Angiotensin 1 receptor blocker</td>
<td>7 (23%)</td>
<td>0</td>
<td>0.015*</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>11 (37%)</td>
<td>0</td>
<td>0.001*</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>9 (30%)</td>
<td>0</td>
<td>0.007†</td>
</tr>
<tr>
<td>Diuretic</td>
<td>15 (50%)</td>
<td>0</td>
<td>0.001*</td>
</tr>
<tr>
<td>Alpha blocker</td>
<td>4 (13%)</td>
<td>0</td>
<td>0.124*</td>
</tr>
<tr>
<td>Statin</td>
<td>11 (37%)</td>
<td>0</td>
<td>0.001*</td>
</tr>
<tr>
<td>IVSD (mm)</td>
<td>9.7 ± 2.4</td>
<td>9.8 ± 2.0</td>
<td>0.841‡</td>
</tr>
<tr>
<td>PW thickness (mm)</td>
<td>9.8 ± 1.7</td>
<td>9.0 ± 1.1</td>
<td>0.158‡</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>46.7 ± 5.7</td>
<td>46.1 ± 5.8</td>
<td>0.892‡</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>29.0 ± 4.8</td>
<td>28.7 ± 4.6</td>
<td>0.793‡</td>
</tr>
<tr>
<td>FS (%)</td>
<td>38 ± 7</td>
<td>38.7</td>
<td>0.595‡</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>78.6 ± 22.4</td>
<td>81.0 ± 18.8</td>
<td>0.693‡</td>
</tr>
<tr>
<td>LVEDVI (ml)</td>
<td>42.7 ± 12.2</td>
<td>40.9 ± 9.6</td>
<td>0.014‡</td>
</tr>
<tr>
<td>LVESVI (ml)</td>
<td>16.4 ± 6.5</td>
<td>15.8 ± 5.8</td>
<td>0.775‡</td>
</tr>
<tr>
<td>LVF (Simpson) (%)</td>
<td>62 ± 6</td>
<td>62 ± 8</td>
<td>0.944‡</td>
</tr>
<tr>
<td>LAVI (ml/m²)</td>
<td>26.9 ± 6.0</td>
<td>25.4 ± 6.4</td>
<td>0.457‡</td>
</tr>
</tbody>
</table>

Data are means ± SD.
†Fisher’s exact test.
‡Mann–Whitney U test.
*Unpaired t test.

BMI, body mass index; FS, fractional shortening; IVSD, diastolic interventricular septal thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVI, left ventricular end-systolic volume index; LVMl, left ventricular mass index; NYHA, New York Heart Association classification for heart failure; PW, posterior wall; V_{O_{2max}}, peak oxygen uptake.

significant increase in stroke volume on exercise. This suggests that patients increase their cardiac output by solely increasing their heart rate, whereas controls were able to increase both heart rate and stroke volume (table 2).

Longitudinal ventricular function

Sm and Em at rest were comparable between patients and controls but became significantly different on exercise. We were able to analyse the exercise TDI data of 83% of patients and 91% of controls. An example of recordings is given in figure 1. Patients failed to increase Sm and Em to the same extent as controls on exercise (figure 2A). As a result, the systolic and diastolic longitudinal function reserve indexes were significantly lower in patients (table 2). Am was significantly higher in controls at rest and on exercise. When longitudinal function was assessed using speckle tracking, the global longitudinal strain was found to be significantly lower in patients not only on exercise but also at rest. The global longitudinal strain result was based on the 63% of patients and 82% of controls who had exercise images of sufficient quality for speckle tracking. Even though patients had a significant increase in longitudinal strain on exercise, the magnitude of longitudinal strain on exercise was only comparable with the magnitude of longitudinal strain in controls at rest. Only Am and global longitudinal strain were found to be significantly lower in patients compared with controls at rest while other parameters were comparable at rest and only became abnormal on exercise.

Radial function, rotation and untwist

There were no differences in radial strain at rest and on exercise between patients and controls (figure 2B). This was reflected in the comparable ejection fraction and fractional shortening between the two groups of subjects at rest indicating that radial function is largely preserved. Again, only 65% of patients and 82% of controls had mid-left ventricular short axis images of adequate quality on exercise for analysis. However, ventricular rotation in systole, which was comparable at rest in both groups, was found to be significantly reduced in patients on exercise (figure 2C). Similar to the findings for longitudinal strain, the magnitude of apical rotation on exercise in patients increased only to a level comparable with controls at rest. In diastole, the percentage left ventricular untwist in early diastole and mid-diastole were comparable at rest but became significantly different on exercise, indicating delayed untwisting in early diastole on exercise (figure 3).

Left ventricular suction

Vp was found to be comparable between patients and controls at rest but became significantly different only on exercise due to a significant increase in Vp on exercise in control subjects (10.6 ± 10.9 m/s vs 24.5 ± 12.2 m/s, p < 0.001) (table 2, figure 2D). Ninety-seven per cent of patients and 100% of controls had good quality colour M-mode profile on exercise for analysis.

Abnormal left ventricular function on exercise

Using the mean ± SD of healthy controls as a cut-off we found 73% of patients had at least one abnormality of ventricular function on exercise compared with 9% of healthy controls. Using mean ± 1 SD apical rotation was abnormal in 77% of patients compared with none of the controls.

Correlations between V_{O_{2max}} and echocardiographic parameters

V_{O_{2max}} correlated with the following echocardiographic parameters on exercise: Sm (r = 0.66, p < 0.001); Em (r = 0.645,
Table 2  Haemodynamic, Doppler and speckle tracking data

<table>
<thead>
<tr>
<th></th>
<th>Patients rest</th>
<th>Patients exercise</th>
<th>p Value*</th>
<th>Controls rest</th>
<th>Controls exercise</th>
<th>p Value†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>69±12</td>
<td>89±9</td>
<td>p&lt;0.001</td>
<td>70±10</td>
<td>91±5</td>
<td>p&lt;0.001</td>
<td>p=0.877†</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>141±18/74</td>
<td>163±19/85</td>
<td>p&lt;0.001</td>
<td>139±14/79</td>
<td>163±12/87</td>
<td>p&lt;0.001</td>
<td>p=0.617§</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.68±0.16</td>
<td>0.93±0.15</td>
<td>p&lt;0.001</td>
<td>0.56±0.12</td>
<td>0.96±0.11</td>
<td>p&lt;0.001</td>
<td>p=0.006‡</td>
</tr>
<tr>
<td>ΔE (m/s)</td>
<td>0.26±0.15</td>
<td>0.40±0.12</td>
<td>p=0.001</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>0.84±0.19</td>
<td>0.68±0.15</td>
<td>p&lt;0.001</td>
<td>0.90±0.18</td>
<td>0.91±0.02</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>SV (ml/min)</td>
<td>71±17</td>
<td>74±23</td>
<td>p=0.006</td>
<td>62±14</td>
<td>75±15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.9±1.6</td>
<td>6.4±2.1</td>
<td>p=0.007</td>
<td>4.2±1.1</td>
<td>6.8±1.8</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>A (m/s)</td>
<td>37.3</td>
<td>37.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Am (cm/s)</td>
<td>7.12±1.23</td>
<td>6.12±1.07</td>
<td>p=0.001</td>
<td>5.75±0.91</td>
<td>7.77±0.95</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sm (cm/s)</td>
<td>4.82±1.02</td>
<td>4.82±0.59</td>
<td>p&lt;0.001</td>
<td>1.85±0.95</td>
<td>1.65±0.95</td>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>SLRI</td>
<td>1.23</td>
<td>1.34</td>
<td>p&lt;0.001</td>
<td>2.32±1.24</td>
<td>4.80±1.19</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>Em (cm/s)</td>
<td>1.92±1.19</td>
<td>1.92±1.19</td>
<td></td>
<td>3.05±1.63</td>
<td>3.40±3.02</td>
<td>p=0.020</td>
<td></td>
</tr>
<tr>
<td>ΔEm (cm/s)</td>
<td>1.83±1.65</td>
<td>1.83±1.65</td>
<td></td>
<td>3.05±1.63</td>
<td>3.40±3.02</td>
<td>p=0.020</td>
<td></td>
</tr>
<tr>
<td>Am (cm/s)</td>
<td>7.12±1.23</td>
<td>8.37±1.20</td>
<td>p=0.008</td>
<td>8.12±1.24</td>
<td>9.79±1.79</td>
<td>p=0.002</td>
<td></td>
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<tr>
<td>ΔAm (cm/s)</td>
<td>1.33±1.50</td>
<td>1.33±1.50</td>
<td></td>
<td>1.54±1.45</td>
<td>1.73±1.45</td>
<td>p=0.721</td>
<td></td>
</tr>
<tr>
<td>Global long strain (%)</td>
<td>−19.0±2.4</td>
<td>−21.2±3.8</td>
<td>p=0.007</td>
<td>−20.9±3.1</td>
<td>−23.8±2.6</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Rad strain (%)</td>
<td>41.6±9.9</td>
<td>53.3±14.4</td>
<td>p=0.014</td>
<td>45.3±8.5</td>
<td>59.6±14.5</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Apical rot (°)</td>
<td>10.9±4.3</td>
<td>13.1±4.6</td>
<td>p=0.056</td>
<td>12.8±2.7</td>
<td>17.0±3.4</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Early UT (%)</td>
<td>27.6±10.5</td>
<td>20.4±7.6</td>
<td>p=0.056</td>
<td>29.9±9.5</td>
<td>30.6±7.8</td>
<td>p=0.907</td>
<td></td>
</tr>
<tr>
<td>Mid UT (%)</td>
<td>55.0±13.3</td>
<td>51.9±14.1</td>
<td>p=0.029</td>
<td>57.4±8.3</td>
<td>63.3±7.5</td>
<td>p=0.040</td>
<td></td>
</tr>
<tr>
<td>Late UT (%)</td>
<td>77.2±4.5</td>
<td>78.7±12.4</td>
<td>p=0.086</td>
<td>81.3±7.9</td>
<td>84.7±5.0</td>
<td>p=0.011</td>
<td></td>
</tr>
<tr>
<td>Vp (m/s)</td>
<td>37.3±7.6</td>
<td>47.2±9.7</td>
<td>p=0.001</td>
<td>38.4±7.3</td>
<td>63.3±12.3</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ΔVp (m/s)</td>
<td>10.6±10.9</td>
<td>24.5±12.2</td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD.
*Paired t test between rest and exercise for patients.
†Paired t test between rest and exercise for controls.
‡Unpaired t test between patients and controls at rest.
§Unpaired t test between patients and controls on exercise.
A, late mitral diastolic inflow velocity; Am, late diastolic annular velocity; Apical rot, peak apical rotation; BP, blood pressure; CO, cardiac output; d, diastole; DLRI, diastolic longitudinal reserve index; DT, deceleration time of peak early Doppler mitral filling velocity; E, early mitral diastolic inflow velocity; E/A, ratio of early to late mitral inflow velocities; E/A, ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; Em, early diastolic annular velocity; Global long strain, global longitudinal strain; HR, heart rate; IVRT, isovolumic relaxation time; LVEF, left ventricular ejection fraction (Simpson); Rad strain, radial strain; s, systole; SLRI, systolic longitudinal reserve index; SV, stroke volume; Sm, systolic mitral annular velocity; UT, untwist; Vp, mitral flow propagation velocity.

p<0.001); apical rotation (r=0.611, p<0.001); Vp (r=0.594, p<0.001) and early untwist (r=0.525, p=0.007) (figure 4).

Inter and intra-observer variability
The interobserver variability at rest by ICC was between 0.88 and 0.95. On exercise ICC varied from 0.70 to 0.98, Vp had the highest interobserver variability. The intra-observer variability by ICC at rest varied from 0.88 to 0.98 and on exercise from 0.69 to 0.98. Again Vp had the highest variability compared with other measurements.

DISCUSSION
We have shown that in patients with well-treated hypertension there are significant abnormalities of ventricular function affecting longitudinal function, rotation, untwisting rates and left ventricular suction on exercise despite a normal standard

Hypertension

Heart 2010;96:948–955. doi:10.1136/hrt.2009.185181
Echocardiography examination and the absence of LVH. These abnormalities, which are apparent on exercise, correlate significantly with VO2max and probably account for the symptom of breathlessness on exertion.

In the normal heart the rotational motion during systole pulls the mitral annulus down towards the apex during systole (which also helps suck blood into the atrium) and stores energy, which is released with the corresponding untwisting process with recoil in early diastole of the annulus and generation of the negative intraventricular pressure gradient or suction in early diastole. This is a tightly coordinated process both temporally and functionally. The rapid motion of the mitral annulus back towards the base of the heart aids ventricular filling by moving the mitral annulus around the column of the incoming blood.

All these aspects of ventricular function increase on exercise, not only to accelerate ventricular ejection, increase stroke volume and cardiac output, but more importantly to enable rapid filling of the ventricle during a shortened diastole while maintaining a low filling pressure. These relationships have been shown to be disrupted in hypertrophic cardiomyopathy and recently we have found similar abnormalities in patients with heart failure and a normal or preserved ejection fraction and now even in patients with hypertension with seemingly normal left ventricular function and no LVH. Our results showed that even when blood pressure is controlled and routine echocardiography appeared to be normal, patients with hypertension with a history of exertional dyspnoea have abnormal left ventricular function, which may progress to the development of clinical heart failure. Therefore, our findings have significant implications for the treatment of hypertension and emphasise the importance of using agents that may prevent or reverse these early significant abnormalities of ventricular architecture and function.

**Figure 1** Examples of longitudinal function measured by colour tissue Doppler images (TDI), longitudinal strain, rotation and untwist, and mitral valve propagation velocity measured by colour M-mode. Em, early diastolic annular velocity; Sm, systolic mitral annular velocity; Vp, mitral flow propagation velocity.
Our results are especially relevant to the clinical problem of deciding whether the symptom of breathlessness is cardiac in origin or not. Often in practice a normal echocardiogram is used to exclude a cardiac cause and the breathlessness is then considered to be respiratory or due to obesity. Previous studies have questioned the true frequency of heart failure with a normal ejection fraction because of normal echocardiography and other presumed aetiologies such as obesity or lung disease. Our patients did have higher BMI. However, the cardiopulmonary exercise testing results were corrected to age, gender and BMI. Our results demonstrate clearly that these patients may have major abnormalities of ventricular function, which become apparent only on exercise associated with their symptoms, and are only detected with more sophisticated measurements and analysis. Ventricular function is clearly not normal despite a normal LVEF at rest.

Previous studies have shown reduced long axis function or mitral annulus motion with LVH and hypertrophic cardiomyopathy. However, in this study we have also demonstrated reduced long axis function at rest in patients with hypertension without LVH. There was also markedly reduced longitudinal functional reserve on exercise. Borges et al.24 found acute treatment with captopril had no significant effect on either Sm or Em in subjects with hypertension with or without LVH. In heart failure subjects Andersson et al.28 found that treatment with metoprolol CR/XL led to an increase in atrioventricular plane displacement after 6 weeks. In patients with heart failure and normal ejection fraction diuretics combined with irbesartan or ramipril led to a small but significant improvement in longitudinal velocities. It is unlikely therefore that the depression in longitudinal velocities seen in our study is due to the drug therapies per se. There does not appear to be any significant previous work on the effect of antihypertensive drug therapy on ventricular twist mechanics.

**Limitations**

Speckle tracking imaging on exercise is technically demanding and we only used apical rotation for analysis as basal rotation on exercise was unreliable due to through-plane motion, which increases during exercise. The left ventricular apex is relatively fixed in position and allows reliable speckle tracking analysis on exercise. In addition, apical rotation has been shown to represent the dominant component of the overall left ventricular torsion. Exercise was submaximal but patients were already symptomatic at this level of exercise, which reflects a realistic level of exercise in

**Figure 2** Boxplots of long axis function, radial function, apical rotation and mitral flow propagation velocity (Vp) at rest and on exercise between patients and controls. (A) Long axis function in systole (Sm) and diastole (Em); (B) radial strain, (C) apical rotation, (D) Vp of patients and controls at rest and on exercise. TDI, tissue Doppler image.
this age group. In addition, this was dictated by the frame-rate limitations of speckle tracking. Twenty per cent of our patients had a history of coronary artery disease and diabetes, which are commonly associated with hypertension and heart failure. This subset of patients did not have occlusive coronary disease on angiography, and the abnormalities found on exercise echocardiography were no worse than the study cohort. Recent work suggests that both Em and Sm may be afterload dependent, but in our study the arterial blood pressure was similar in patients and controls both at rest and on exercise. The ratio E/E\(_9\) did not change significantly on exercise, which may appear to contradict the previous study by Burgess et al, who found that E/E\(_9\) greater than 13 on exercise could accurately identify a raised left ventricular diastolic pressure greater than 15 mm Hg. However, of their 37 subjects 20 neither showed an increase in left ventricular end-diastolic pressure (LVEDP) nor E/E\(_9\) on exercise and these had a normal resting LVEDP. Eight patients had an increased E/E\(_9\) at rest that did not rise significantly with exercise. Only nine patients who had both a normal resting LVEDP and E/E\(_9\) showed an increase in E/E\(_9\). Our patients are similar to their first group of patients with a normal resting LVEDP in whom E/E\(_9\) increased from 9.8 to 10.3, comparable to the change in our patients from 9.4 to 10.1, which was not significant statistically. Furthermore, correlation was good for lower values of LVEDP and E/E\(_9\) but poor for higher values particularly on exercise.

Further doubt has recently been cast on the accuracy of the ratio E/E\(_9\) as a non-invasive measure of LVEDP in all situations. In conclusion, we have shown that in treated subjects with hypertension, without LVH and despite normal standard echocardiography, abnormalities of longitudinal function, twist, strain and ventricular suction are present, which all worsen on exercise. Figure 5 provides an illustrated synopsis of the probable pathophysiology.

**Figure 3** Percentage untwist at rest and on exercise between patients and controls. Percentage untwist 25% (50%, 75%) of total untwist duration.

**Figure 4** Correlation between left ventricular suction on exercise and peak oxygen consumption (VO\(_{2}\)max). Em, early diastolic annular velocity; Sm, systolic mitral annular velocity; Vp, mitral flow propagation velocity.
Figure 5 Schema illustrating the pathophysiology of breathlessness in hypertension without left ventricular hypertrophy.

This study, therefore, has important implications for the diagnosis of breathlessness in the treated patient with hypertension with normal resting echocardiography.

Acknowledgements The authors would like to thank Rebekah Weaver and Stuart Wragg for their assistance.

Funding This research was funded by grants from the British Heart Foundation (PG/06/106/21472) and the North Staffs Heart Committee.

Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by the local research ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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