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Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction

Y T Tan,1 F Wenzelburger,1,2 E Lee,2 P Nightingale,3 G Heatlie,2 F Leyva,1 J E Sanderson1,2

ABSTRACT

Aims The cardinal symptom of heart failure with a normal ejection fraction (HFNEF) is exertional dyspnoea. The authors hypothesised that failure of left atrial (LA) compensatory mechanism particularly on exercise contributes to the genesis of symptoms in HFNEF patients.

Methods and Results Fifty HFNEF patients, 15 asymptomatic hypertensive subjects and 30 healthy controls underwent rest and submaximal exercise echocardiography. Rest and exercise systolic, early diastolic and late diastolic (Am) mitral annular velocities were assessed using colour tissue Doppler echocardiography. Left atrial functional reserve index was calculated.

Am at rest was comparable between all three groups, but exercise Am was significantly lower in HFNEF compared with hypertensive subjects and healthy controls resulting in a lower LA functional reserve index (0.84 (1.34) vs 2.39 (1.27) and 1.81 (1.39), p<0.001). LA volume index was significantly higher in HFNEF patients (30.4 (9.2) vs 27.9 (6.3) and 23.2 (7.1) ml/m², p=0.002). There was a significant correlation between Am on exercise with peak VO₂ max (r=0.514, p<0.001) and E/Em on exercise (r = −0.547, p<0.001). Area under the receiver operating characteristic for Am on exercise was 0.768 (95% CI=0.660 to 0.877).

Conclusion HFNEF patients have reduced LA function on exercise in addition to left ventricular systolic and diastolic dysfunctions. Reduced LA function probably contributes significantly to exercise intolerance and breathlessness in HFNEF patients.

Methods

Left ventricular and LA functions were assessed non-invasively at rest and on submaximal exercise in patients with clinical diagnosis of HFNEF, asymptomatic hypertensive subjects and healthy controls. All subjects underwent pulmonary function test and cardiopulmonary exercise test to determine their peak oxygen consumption and to rule out pulmonary causes of their breathlessness before rest and exercise echocardiography studies.

Study subjects

Patients with signs and symptoms of heart failure who had ejection fraction of >50% seen in heart failure clinics at the university hospitals were recruited. Asymptomatic controls with comparable age were chosen randomly from local primary care surgeries. Exclusion criteria were uncontrolled blood pressure on medication, moderate to severe pulmonary disease, significant valvular or congenital heart disease, presence of arrhythmia (including atrial fibrillation (AF)), electrical pacemaker or

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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 test**
Subjects had standard spirometry before they underwent incremental treadmill exercise testing with metabolic gas exchange and simultaneous heart rate (HR), blood pressure and oxygen saturation monitoring using a modified Bruce protocol.11 12 A respiratory exchange ratio of >1 was taken to indicate maximal effort.15 Breathing reserve of <15 L/min was taken as a respiratory limitation.

**Two-dimensional and tissue Doppler echocardiography**
All subjects underwent full echocardiography examination using a GE Vingmed Vivid Seven scanner (Horten, Norway) at rest and on exercise. Symptom-limited (fatigue or dyspnoea) exercise testing was done on a semirecumbent and tilting bicycle ergometer (Lode BV, Groningen, The Netherlands) at a 25 watt increment to a HR of 100 bpm (submaximal exercise to maximise frame rates). Imaging was commenced at the onset of symptoms and continued simultaneously during exercise maintaining the same work load throughout the entire process. 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). LV volume and ejection fraction were measured using the modified biplane Simpson method from the apical 4 and 2 chamber views.14 Left ventricular mass was calculated according to Devereux formula.15 LA volume was calculated using the biplane area-length method from the apical 4 and 2 chamber views and indexed to body surface area to derive LA volume index (LAVI).16 The early (E) and atrial filling (A) peak velocities, E/A ratio, deceleration time of early filling and isovolumic relaxation time were measured from transmitral flow. Fusion of the E and A waves on exercise were excluded from analysis.

Peak mitral annular myocardial velocity of the left ventricle septal and lateral walls were recorded from the apical 4-chamber view with real-time pulsed-wave tissue Doppler method, and results were averaged as previously described.17 The sample volume and gain were optimised, and the Nyquist limit set to 15–20 cm/s. The early diastolic (E’) mitral annular velocities were measured and E/E’, an index of LV filling pressure, was calculated.18 Colour-coded tissue Doppler images were also acquired over three consecutive cardiac cycles for each myocardial walls and analysed offline as previously described.19 20 Systolic (Sm), early diastolic (Ed) and late diastolic (Ad) velocities were measured by placing a 4×4 mm region of interest in the mid-myocardial area of LV each wall and results averaged. Fusion of Ed and Ad were excluded from analysis. The LA functional reserve index was calculated as follows: ΔAm×[1–(1/Am REST)] as described in the study by Ha et al.21

**Statistics**
Statistical analysis was performed using SPSS v.15.0 for Windows. Continuous variables were expressed as mean (SD). Fisher exact test was conducted for nominal variables. One-way analysis of variance (ANOVA) was used for normally distributed data to compare all groups followed by Tukey post hoc analysis to determine significant pairwise differences. Non-normally distributed data were analysed using Mann–Whitney U test. Interclass comparisons of the changes of parameters from rest to exercise were made using the general linear model for repeated measurements at two levels. Receiver operator curves were plotted to examine the ability of Am at rest and on exercise to differentiate HFNEF patients and healthy controls. A Pearson correlation coefficient was used to examine associations between variables. Linear regressions were performed using VO2 max and E/E’ as dependent variables against Am on exercise.

**RESULTS**
A total of 148 subjects were recruited in this study (90 patients with symptoms and 58 asymptomatic subjects). Forty patients were excluded (4 had evidence of respiratory restriction, 5 had AF, 1 had significant coronary artery disease, 11 were unable to exercise and 19 did not have adequate exercise images for analysis). Thirteen asymptomatic subjects were excluded (1 was tachycardic at rest due to anxiety and 12 did not have adequate exercise images for analysis). The remaining 50 patients with symptoms fulfilled the recent American Society of Echocardiography recommendations for diastolic dysfunction (38 grade 1 diastolic dysfunction and 12 grade 2 diastolic dysfunction)22 and were classified as HFNEF patients. The remaining 45 asymptomatic subjects were divided into those with a history of hypertension and blood pressure well controlled on medication (n=15) and those completely healthy individuals on no regular medications (n=30). The mean age of all study subjects were comparable between the three groups (table 1). HFNEF patients were all with symptoms and were classified according to the New York Heart Association classification classes II and III and had a significantly higher body mass index compared with hypertensive subjects and controls. The VO2 max and the achieved percentage of predicted oxygen consumption were significantly lower in HFNEF patients but were comparable between hypertensive patients and healthy controls (table 1). The medical and drug histories of all subjects are summarised in table 1. All HFNEF patients had a history of hypertension, and the duration of diagnosis of hypertension is significantly longer than that of the hypertensive subjects. During image acquisition on submaximal supine exercise, the HR and blood pressure were comparable at similar workload between all three groups (table 2).

**TWO-DIMENSIONAL ECHOCARDIOGRAPHY**
The left ventricular ejection fraction, fractional shortening, end-systolic and end-diastolic dimensions and the left ventricular end-systolic and end-diastolic volume indices were all comparable between the three groups (table 1). The left ventricular mass index was not significantly different between all three groups. The diastolic interventricular septal thickness of HFNEF patients was significantly thicker than that of healthy controls, whereas the posterior wall thickness was significantly thicker than that of both hypertensive subjects and healthy controls (table 1).

**Left ventricular systolic and diastolic functions**
Peak E at rest was significantly higher in HFNEF patients but became comparable between all three groups of exercise. There was no significant difference in the isovolumic relaxation time between the three groups. The deceleration time was significantly longer in the hypertensive group compared with that
Table 1 Clinical and echocardiographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>HFNEF (n = 50)</th>
<th>Hypertension (n = 15)</th>
<th>Healthy controls (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>72 (8)</td>
<td>70 (7)</td>
<td>71 (6)</td>
<td>0.541*</td>
</tr>
<tr>
<td>Female sex</td>
<td>35 (70%)</td>
<td>9 (60%)</td>
<td>22 (73%)</td>
<td>0.655†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31 (5)</td>
<td>25 (4)</td>
<td>24 (4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>46.1 (5.6)</td>
<td>47.7 (3.9)</td>
<td>45.3 (5.1)</td>
<td></td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>28.3 (5.2)</td>
<td>30.0 (4.0)</td>
<td>28.7 (4.5)</td>
<td></td>
</tr>
<tr>
<td>LVEF (Simpson), %</td>
<td>62 (6)</td>
<td>62 (9)</td>
<td>62 (7)</td>
<td></td>
</tr>
<tr>
<td>LAVI, ml/m²</td>
<td>30.4 (9.2)</td>
<td>27.9 (6.3)</td>
<td>23.2 (7.1)</td>
<td>0.002*</td>
</tr>
<tr>
<td>VO₂ max, ml min⁻¹ (per cent of predicted)</td>
<td>18.2 (4.4)</td>
<td>28.4 (9.4)</td>
<td>29.6 (5.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Submaximal work load, watts</td>
<td>27 (8)</td>
<td>32 (12)</td>
<td>31 (10)</td>
<td>0.197*</td>
</tr>
<tr>
<td>Years of hypertension</td>
<td>8.7 (6.9)</td>
<td>3.7 (2.4)</td>
<td>0</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (30%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.014$^\circ$</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (18%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.103$^\circ$</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>18 (36%)</td>
<td>4 (27%)</td>
<td>0 (0%)</td>
<td>0.757$^\circ$</td>
</tr>
<tr>
<td>ARB</td>
<td>14 (28%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.029$^\circ$</td>
</tr>
<tr>
<td>ß-Blocker</td>
<td>19 (38%)</td>
<td>4 (27%)</td>
<td>0 (0%)</td>
<td>0.544$^\circ$</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>17 (34%)</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
<td>0.196$^\circ$</td>
</tr>
<tr>
<td>Diuretic</td>
<td>26 (52%)</td>
<td>6 (40%)</td>
<td>0 (0%)</td>
<td>0.558$^\circ$</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>15 (30%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.014$^\circ$</td>
</tr>
<tr>
<td>Statin</td>
<td>22 (44%)</td>
<td>5 (33%)</td>
<td>0 (0%)</td>
<td>0.559$^\circ$</td>
</tr>
<tr>
<td>VSOD, mm</td>
<td>10.9 (3.1)</td>
<td>9.7 (2.3)</td>
<td>9.3 (1.7)</td>
<td>0.040*</td>
</tr>
<tr>
<td>VWD, mm</td>
<td>10.9 (2.4)</td>
<td>8.6 (1.2)</td>
<td>9.2 (1.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>46.1 (5.5)</td>
<td>47.7 (3.9)</td>
<td>45.3 (5.1)</td>
<td>0.392$^\circ$</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>28.3 (5.2)</td>
<td>30.4 (4.0)</td>
<td>28.7 (4.5)</td>
<td>0.463$^\circ$</td>
</tr>
<tr>
<td>FS, %</td>
<td>39 (7)</td>
<td>38 (6)</td>
<td>37 (7)</td>
<td>0.505$^\circ$</td>
</tr>
<tr>
<td>LVML, g/m²</td>
<td>93.1 (36.3)</td>
<td>82.9 (22.1)</td>
<td>76.0 (18.3)</td>
<td>0.100$^\circ$</td>
</tr>
<tr>
<td>LVEDVI, ml/m²</td>
<td>40.4 (9.4)</td>
<td>41.4 (9.4)</td>
<td>39.1 (9.2)</td>
<td>0.108$^\circ$</td>
</tr>
<tr>
<td>LVEVI, ml/m²</td>
<td>15.5 (4.8)</td>
<td>15.7 (5.2)</td>
<td>15.3 (5.4)</td>
<td>0.784$^\circ$</td>
</tr>
<tr>
<td>LVEF (Simpson), %</td>
<td>62 (6)</td>
<td>62 (9)</td>
<td>62 (7)</td>
<td>0.989$^\circ$</td>
</tr>
<tr>
<td>LA, cm</td>
<td>3.8 (0.6)</td>
<td>3.5 (0.5)</td>
<td>3.2 (0.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LAVI, ml/m²</td>
<td>30.4 (9.2)</td>
<td>27.9 (6.3)</td>
<td>23.2 (7.1)</td>
<td>0.002$^\circ$</td>
</tr>
</tbody>
</table>

**One-way ANOVA for normally distributed data.**

†Fisher exact test for nominal data comparing patients to hypertensive group.

$^\circ$Fisher exact test for nominal data comparing all three groups.

Tukey post hoc analysis:

* p < 0.05 compared with healthy controls.

** p < 0.05 compared with hypertensive group.

healthy controls (table 2). Sm at rest was comparable between all subjects but was significantly lower in HFNEF patients compared with that in healthy controls on exercise. However, Em values at rest and on exercise were significantly lower in HFNEF patients compared with those in both hypertensive subjects and healthy controls. Although there was no significant difference in Sm on exercise between hypertensive subjects and healthy controls, Em on exercise was significantly lower in HFNEF patients compared with those in both hypertensive subjects and healthy controls. Despite the increase in E/E’ on exercise in hypertensive subjects, the hypertensive subjects on exercise had a magnitude similar to healthy controls. Hence, they had the highest atrial functional reserve index compared with all other subjects. Am at rest was lowest in HFNEF patients. HFNEF patients failed to increase Am on exercise normally, and as a result, they had the lowest atrial compensatory mechanism on exercise (figure 1 and 2). Using the general linear model, there was a significant difference in Sm and Em at rest compared with Sm and Em on exercise.

LA function

HFNEF patients had significantly larger LA dimensions than healthy controls but not significantly different compared with hypertensive subjects (table 1). LAVI was comparable between HFNEF patients and hypertensive subjects but significantly higher than that in healthy controls. Peak A at rest was significantly higher in HFNEF patients compared with that in hypertensive subjects and healthy controls but was only significantly higher compared with that in healthy controls on exercise, as the peak A of hypertensive subjects approached that of HFNEF patients on exercise (table 3). There was no difference in Am at rest between the three groups. Am on exercise was lowest in HFNEF patients. HFNEF patients failed to increase Am on exercise normally, and as a result, they had the lowest atrial functional reserve index compared with all other subjects. Am at rest was lowest in hypertensive subjects (not significant), but there was greatest increase in Am on exercise in this group of subjects to a magnitude similar to healthy controls. Hence, they had the lowest atrial functional reserve index indicating a more efficient atrial compensatory mechanism on exercise (figure 1 and 2). Using the general linear model, there is a significant difference in Am at rest compared with Am on exercise. The hypertensive subjects appear to be able to compensate for their reduced Em and increased E/E’ on exercise by increasing Am that HFNEF patients failed to achieve.

Receiver operating characteristic (ROC) showed that Am on exercise was better at differentiating patients from healthy controls (area under ROC 0.768, 95% CI = 0.690 to 0.877). Area under ROC for Am at rest was 0.657 (95% CI = 0.511 to 0.762, figure 3).
### Table 2  Hemodynamic and Doppler parameters

<table>
<thead>
<tr>
<th></th>
<th>HFNEF (n = 50)</th>
<th>Hypertension (n = 15)</th>
<th>Healthy controls (n = 30)</th>
<th>p Value for one-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR rest, bpm</td>
<td>72 (13)</td>
<td>65 (8)</td>
<td>70 (9)</td>
<td>0.384</td>
</tr>
<tr>
<td>HR Ex, bpm</td>
<td>91 (11)</td>
<td>90 (11)</td>
<td>93 (5)</td>
<td>0.117</td>
</tr>
<tr>
<td>( \Delta ) HR, bpm</td>
<td>21 (7)</td>
<td>24 (7)</td>
<td>23 (8)</td>
<td>0.138</td>
</tr>
<tr>
<td>BP rest, mm Hg</td>
<td>142 (16)/</td>
<td>141 (20)/</td>
<td>137 (15)/</td>
<td>0.466</td>
</tr>
<tr>
<td>BP Ex, mm Hg</td>
<td>77 (11)</td>
<td>77 (7)</td>
<td>79 (8)</td>
<td>0.526</td>
</tr>
<tr>
<td>E/A</td>
<td>0.96 (0.21)†</td>
<td>1.15 (0.29)</td>
<td>1.08 (0.26)</td>
<td>0.020</td>
</tr>
<tr>
<td>DT, ms</td>
<td>241 (53)</td>
<td>268 (56)‡</td>
<td>252 (45)</td>
<td>0.184</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>97 (23)</td>
<td>97 (24)</td>
<td>103 (19)</td>
<td>0.449</td>
</tr>
<tr>
<td>Sm rest, cm/s</td>
<td>5.3 (1.2)</td>
<td>5.8 (1.8)</td>
<td>5.8 (1.2)</td>
<td>0.244</td>
</tr>
<tr>
<td>Sm Ex, cm/s</td>
<td>6.3 (1.6)*</td>
<td>7.4 (1.8)</td>
<td>7.7 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \Delta ) Sm, cm/s</td>
<td>1.0 (1.2)*</td>
<td>1.8 (1.4)</td>
<td>2.0 (1.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Em rest, cm/s</td>
<td>4.3 (1.3)*</td>
<td>6.0 (1.9)</td>
<td>5.4 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Em Ex, cm/s</td>
<td>6.6 (1.5)*</td>
<td>7.9 (1.4)*</td>
<td>8.6 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \Delta ) Em, cm/s</td>
<td>2.2 (1.3)*</td>
<td>1.5 (2.3)*</td>
<td>3.3 (1.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BP, blood pressure; DT, deceleration time of peak early mitral filling velocity; E, early mitral diastolic inflow velocity; E/A, ratio of early to late mitral inflow velocities; Em, early diastolic annular velocity; Ex, on exercise; HR, heart rate; IVRT, isovolumic relaxation time; Sm, systolic mitral annular velocity.

Data are mean (SD).

Tukey post hoc analysis:
*<p>0.05 Compared with healthy controls.
†<p>0.05 Compared with hypertensive group.

### Correlations

Am values at rest and on exercise both correlated significantly with VO₂ max (at rest, r = 0.425, p < 0.01; on exercise, r = 0.514, p < 0.01) and E/E' (at rest, r = -0.315, p < 0.01; on exercise, r = -0.547, p < 0.01). There was a weak correlation between atrial functional reserve index and VO₂ max (r = 0.257, p = 0.039; figure 4).

### Interobserver and intraobserver variability

The interobserver variability of pulsed-wave and colour tissue Doppler imaging assessment of systolic, early and late diastolic myocardial velocities at rest by ICC was between 0.91 and 0.96. On exercise, ICC was between 0.85 and 0.94. The intraobserver variability by ICC was between 0.91 and 0.96.

### DISCUSSION

We have shown for the first time that LA dysfunction on exercise in patients with HFNEF may contribute to the genesis of exertional dyspnoea and reduced exercise capacity in this condition. The major difference between HFNEF and asymptomatic hypertensive patients was atrial reserve on exercise. Because hypertension is a common precursor of HFNEF, one of the factors that may account for the development of symptoms is progressive atrial failure. This study, therefore, suggests that impaired atrial reserve may be another factor that leads to shortness of breath in addition to the abnormalities of early diastolic filling, untwisting and suction that we demonstrated in our previous study. Our results support those of Melenovsky et al. who found evidence of reduced atrial functional reserve to handgrip in HFNEF patients in comparison with hypertensive controls of a comparable age. Although there were increases in HR and blood pressure with sustained isometric exercise, handgrip does not reproduce symptoms experienced by HFNEF subjects that occur on exercise. In addition, there was evidence of more advanced eccentric remodelling in their HFNEF patients compared with the hypertensive subjects, whereas there was no disparate left ventricular mass or volume within our study subjects, and our findings were simultaneous with...
onset and presence of symptoms, and there was a significant correlation with exercise capacity. An inability to increase atrial systolic function on exercise may have a significant negative impact on effective and rapid diastolic filling especially during the very short time available in diastole with higher HRs on exercise.

The peak atrial systolic annular velocity at rest is also a significant predictor of risk. Wang et al. found in a group of 518 subjects that when Am was >4 but <7 cm/s, the HR of cardiac death was increased compared with that when Am >7 cm/s, and when Am was <4 cm/s, the HR was significantly increased compared with that when Am >7 cm/s. The predictive power of Am alone was greater than the ratio of E/E9 that has been claimed to be an index of LV end-diastolic pressure. Am has also been found to be predictive of exercise capacity in chronic heart failure in previous studies. However, in our study, peak Am on exercise correlated better with exercise capacity as measured by peak VO2 max suggesting again that peak atrial performance on exercise is the more critical and relevant measurement. The initial rise in LA contribution to LV filling in mild LV dysfunction probably represents a compensatory response to reduction of early LV filling. As the LV function worsens, the LA contribution diminishes likely secondary to LA morphological and functional changes owing to increased LA workload. This has been shown in earlier studies in dogs.

LAVI was increased in HFNEF, and the HTN subjects had a LAVI in between HFNEF and controls—similar to the results reported by Wakatsuki et al. LA volumes are viewed increasingly as a marker of chronic elevation of LA pressure and hence indirectly of diastolic dysfunction. The fact that LAVI was higher in the HFNEF cohort suggests that over time, LA pressure was higher than in the hypertensive cohort leading to more atrial remodelling. This would lead to reduced contractile function that would also be affected directly by the high incidence of comorbidities in HFNEF such as diabetes (present in approximately 30%), subclinical coronary artery disease (approximately 40–50%), obesity (prevalence of body mass index >30 kg/m2 approximately 40%) and renal failure. AF is common in HFNEF, and the prevalence ranges from 20% to 40% in both epidemiological studies and randomised controlled clinical trials. Fung et al. reported that HFNEF patients with AF had poorer quality of life, lower exercise capacity and, as expected, larger LA dimensions. In addition, patients with HFNEF and AF had more severe diastolic dysfunction when compared with sinus rhythm. It is likely that atrial remodelling combined with progressive atrial failure will lead to the onset of AF. Hypertension per se is also associated with a higher prevalence of AF and structural changes of the extracellular matrix, perhaps related to activation of the renal–angiotensin–aldosterone system, may be involved.

Figure 1 Examples of colour tissue Doppler assessment of left atrial function at rest and on exercise, and LA functional reserve index of HFNEF patient, hypertensive subject and healthy control.
Therefore, asymptomatic hypertensive subjects have latent heart failure and with time might present as HFNEF.

**Limitations**

Although the left ventricular mass index was not significantly different between all three groups, the posterior wall thickness was thicker in HFNEF patients, and this reflects the duration and severity of the disease. Second, the number of asymptomatic hypertensive subjects was smaller than that of the other two groups, but the exercise data illustrated a significant difference in response despite the similarity of the echocardiographic findings at rest. We used the late diastolic annular motion as an index of atrial systolic function. This motion of the mitral annulus towards the base directly reflects atrial mechanical function in the long axis only. Newer techniques measuring strain by tissue Doppler imaging or speckle tracking may provide a better measure of global atrial function. However, it is technically challenging to obtain sufficiently good images on exercise for meaningful speckle tracking analysis. Eight patients were excluded because of fusion of the E and A waves on exercise, but the use of submaximal exercise with maximum HR<100 bpm kept this recognised problem to a minimum. All subjects were studied on medication. The proportion of HFNEF patients and healthy controls.

**Figure 2**  Box plot of late diastolic mitral annular myocardial velocity, Am, at rest and on exercise for HFNEF patients, hypertensive subjects and healthy controls.

**Figure 3**  Receiver operator curves of Am at rest and on exercise for differentiating between HFNEF patients and healthy controls.

**Figure 4**  Scatterplots and regression lines relating peak oxygen consumption, VO₂ max, and left ventricular filling pressure, E/E', to Am on exercise.
hypertensive subjects who were on ACE inhibitor, β-blocker, Ca-
channel blocker and diuretics were comparable, although 28% of
HFNEF patients were on angiotensin 1 receptor blocker
compared with none of the hypertensive subjects, but this is
unlikely to have affected the results, as there is no evidence that
angiotensin 1 receptor blocker therapy impairs LA function, in
fact the contrary.

In summary, we have demonstrated that atrial function is
impaired on exercise with an impaired atrial reserve in patients
with HFNEF. Combined with our earlier findings demonstrating
reduced early diastolic filling, suction and delayed untwisting,13
these observations provide a comprehensive assessment of
ventricular and atrial functions at rest and on exercise in a
typical cohort of HFNEF patients, illustrating the spectrum of
abnormalities in this condition.

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