Importance of dynamic dyssynchrony in the occurrence of hypertensive heart failure with normal ejection fraction

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Aims
The impact of haemodynamic stress on left ventricular (LV) dyssynchrony in heart failure with normal ejection fraction (HFNEF) remains unknown. We sought to evaluate the relationship and predictive value of dynamic changes of LV dyssynchrony on hypertensive HFNEF.

Methods and results
A total of 131 subjects including 47 hypertensive HFNEF patients, 34 hypertensive patients with left ventricular hypertrophy (LVH) without HFNEF, and 50 normal controls were studied by dobutamine stress echocardiography with tissue Doppler imaging. Systolic and diastolic dyssynchrony were assessed using the LV six-basal–six-mid-segment model and cut-off values were derived from normal controls. The mean basal segments longitudinal systolic (mean Sm) and early diastolic (mean Em) velocities were measured. In normal controls, systolic and diastolic dyssynchrony did not develop during stress. The prevalence of resting systolic (36.2% vs. 38.2%, \( P = 0.85 \)) and diastolic (34.0% vs. 29.4%, \( P = 0.66 \)) dyssynchrony was similar in HFNEF and LVH groups. During stress, the prevalence of systolic and diastolic dyssynchrony increased dramatically to 85.1% and 87.2%, respectively, in HFNEF group, but only 52.9% and 58.8% in LVH group (\( P < 0.005 \)). In HFNEF group, stress-induced increase in mean Sm was significantly blunted (2.8 ± 2.0 vs. 4.2 ± 2.4 cm/s, \( P = 0.004 \), and the increase was abolished for mean Em (\( -0.3 \pm 2.5 \) vs. \( 2.4 \pm 3.4 \) cm/s, \( P < 0.001 \)). On multivariate analysis, stress-induced changes in mean Em (OR = 0.69, \( P = 0.004 \)) and mean Sm (OR = 0.66, \( P = 0.001 \)) and diastolic (OR = 4.6, \( P = 0.005 \)) and systolic dyssynchrony during stress (OR = 4.3, \( P = 0.038 \)) were independent determinants for occurrence of HFNEF.

Conclusion
Dynamic dyssynchrony during stress and impaired myocardial longitudinal function reserve are characteristics of HFNEF.

Keywords
Heart failure • Echocardiography • Hypertension • Stress test

Introduction
At least one-half of patients with heart failure have a preserved left ventricular ejection fraction (LVEF) and are referred to as heart failure with normal ejection fraction (HFNEF), where hypertension is an important risk factor.\(^1\) Despite the high prevalence, morbidity and mortality of HFNEF, its fundamental pathophysiology remains controversial. In systolic heart failure, left ventricular (LV) dyssynchrony has been recognized as an important factor associated with poor prognosis.\(^2\) Recent data suggested that a high prevalence of LV dyssynchrony also exists in patients with HFNEF.\(^3\,4\) However, it is unsure if LV dyssynchrony plays a role in its pathophysiology process. Furthermore, while previous studies only measured LV dyssynchrony at rest, patients with HFNEF often develop symptoms during exertion or stress. It is largely unknown whether the status of LV dyssynchrony would change with haemodynamic stress in HFNEF, and whether this plays a contributory role in the pathophysiology. Therefore, the objective of
the present study was to examine whether LV systolic and diastolic
dysynchrony would change during haemodynamic stress in
patients with hypertensive HFNEF using dobutamine as a stressor,
and decide whether dynamic dysynchrony is an important deter-
minant for the development of HFNEF in hypertensive patients. In
order to achieve these objectives, patients with hypertensive
HFNEF were compared with age- and gender-matched hyperten-
sive patients with left ventricular hypertrophy (LVH) but without
history of HFNEF, and with normal healthy controls.

Methods

Study population

This multicentre prospective study consists of three groups of subjects:
(1) hypertensive patients with HFNEF; (2) hypertensive patients with
LVH but without clinical features or past history of HFNEF; and (3)
age- and gender-matched healthy controls. The HFNEF patients
were prospectively identified from consecutive patients admitted to
the hospitals with the admission diagnosis code of heart failure
(ICD-10 code: I50). Heart failure was rigorously defined by Framing-
ham criteria and independently adjudicated by two cardiologists. All
HFNEF patients, who have been hospitalized for pulmonary congestion
diagnosed by chest radiogram and clinical examination, had a prior
history of hypertension and EF > 50% on echocardiography within
24–72 h of index admission.5 The LVH group was identified from
our outpatient echocardiography database of hypertensive patients
and the lack of clinical HFNEF was confirmed by formal history and
physical examination. Left ventricular hypertrophy was defined as left
ventricular mass index (LVMI) > 95 g/m² for women and > 115 g/m²
for men as calculated from LV linear dimensions according to rec-
ommendations from the American Society of Echocardiography.6
A total of 105 patients (60 patients with HFNEF and 45 patients
with asymptomatic LVH) were screened. Coronary angiogram was
performed in 31 patients (19 patients in the HFNEF group and 12
patients in the LVH group) as a result of positive stress tests or at
the discretion of physicians. Eight of them (five with HFNEF and
three with LVH) had >50% epicardial coronary artery stenosis and
were excluded from the study. The remaining 23 patients had no or
mild (<50%) coronary stenosis and were included in this study for
analysis. Other exclusion criteria include recent acute coronary syn-
drome or revascularization (<6 months), prior myocardial infarction,
prior history of a positive stress test, primary cardiomyopathy, signifi-
cant valvular disease, chronic pulmonary disease, chronic renal failure,
permanent atrial fibrillation, and those who had received pacemaker
implantation. After excluding these subjects, 47 patients with HFNEF
(HFNEF group) and 34 with asymptomatic LVH (LVH group) were
recruited for this study. Fifty sex- and gender-matched healthy subjects
referred for evaluation of atypical chest pain but had otherwise normal
history, physical examination, electrocardiography, echocardiography
and stress test were recruited as normal controls. The study protocol
was approved by ethics committee of the institution and informed
consent was signed by all subject.

Echocardiography

All subjects underwent dobutamine stress echocardiography (DSE)
(Vivid 7, Vingmed-General Electric, Horten, Norway) with tissue
Doppler imaging (TDI). The HFNEF group underwent DSE 3
months after acute hospitalization when they were in compensated
clinical state without active HF symptoms. Dobutamine infusion was
started at 5 μg/kg/min and increased every 3 min to 10, 20, 30, and
40 μg/kg/min. The test was terminated if any of the following end-
points was reached: achieved the target heart rate [85% × (220 –
age in years)], new regional wall-motion abnormality, significant
arrhythmia, persistent haemodynamic compromise, angina or intoler-
able symptoms. In the absence of contraindications, atropine (0.3–
1.0 mg intravenously) was given if the target heart rate was not
reached. Image acquisition with 2D and colour-coded TDI was per-
formed at rest and at peak stress using the apical four-chamber, two-
chamber, and long-axis views.

Assessment of systolic and diastolic functions

All the echocardiographic measurements were performed offline by
the core echocardiographic laboratory in a blinded manner by an oper-
ator who was unaware of the diagnostic groups. The LV end-diastolic
volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were
measured from the apical four-chamber and two-chamber views
using the modified Simpson method.6 The LV longitudinal systolic myo-
cardial function was assessed by averaging the peak systolic myocardial
velocities at the six basal segments (mean Sm) by offline TDI analysis
with the sample volumes placed just above the mitral annulus. Similarly,
the LV longitudinal early diastolic myocardial function was assessed by
averaging the early diastolic myocardial velocities of the six basal seg-
ments (mean Em).7 Doppler-derived mitral inflow velocities were
determined at rest and diastolic function classification grade I–IV
was assigned as previously described.8 In eight patients, diastolic func-
tion was classified as undetermined.

Assessment of arterial elastance

Effective arterial elastance was estimated as end-systolic pressure
divided by stroke volume. The stroke volume was calculated from
the difference between LVEDV and LVESV. End-systolic pressure was
estimated as systolic pressure times 0.9, as previously validated.9

Assessment of left ventricular dyssynchrony

To evaluate LV systolic and diastolic dysynchrony, myocardial velocity
curves obtained from colour-coded TDI were reconstituted offline
using the six-basal–six-mid-segment model consisting of the anterior,
antero-septal, infero-septal, inferior, posterior, and lateral segments at
basal- and mid-ventricular levels.10 Pulse repetition frequency, colour
saturation, sector size and depth were optimized to maximize the
frame rate to 100 Hz or higher. At least three consecutive beats in
sinus rhythm were stored, and the images were analysed offline by
an investigator blinded from clinical information using a customized
software (EchoPac-PC, version 7.0.0, Vingmed-General Electric). All
measurements were averaged over at least three consecutive cardiac
cycles. The time to peak myocardial systolic velocity during the ejec-
tion period (Ts) and the time to peak myocardial early diastolic vel-
ocity (Te) were measured for each segment with reference to the
onset of QRS complex. The standard deviation (SD) of Ts (Ts-SD)
and Te (Te-SD) of the 12 LV segments were calculated. The intra-
and inter-observer variability of the dysynchrony parameters was
determined in 40 consecutive measurements. The intra-observer varia-
bility for Ts-SD at rest was 3.6%, Te-SD at rest 3.3%, Ts-SD during
stress 5.4%, and Te-SD during stress 5.2%. The corresponding
figures for inter-observer variability were 4.3%, 4.4%, 6.5%, and 6.9%.

Statistical analysis

Data were analysed using a statistical software (SPSS for Windows,
version 13.0, SPSS Inc., Chicago, IL). Results were expressed as
mean ± SD or number of patients (%) as appropriate. Paired t-test
was used for within-group comparisons of continuous variables.
Results

Clinical characteristics and haemodynamic responses to stress

There were no differences in age (HFNEF: 57 ± 14 years vs. LVH: 61 ± 14 years vs. controls: 58 ± 13 years; P = 0.377) and gender [HFNEF: 21 men (45%) vs. LVH: 15 men (44%) vs. controls: 27 men (54%); P = 0.956] distribution among the three groups. The prevalence of cardiovascular risk factors and co-morbidities, including smoking, diabetes, hyperlipidaemia, and prior stroke, and the medications were similar between the two hypertensive patient groups. The majority of patients had normal QRS duration (<120 ms) with no significant stress-induced changes (Table 1). The haemodynamic and echocardiographic characteristics were shown in Table 2. Systolic blood pressure during stress was significantly higher in the HFNEF group compared with the LVH group (P < 0.001), despite being similar between the two groups at rest. Effective arterial elastance was significantly higher in the hypertensive patients. It increased significantly during stress with the greatest exaggeration in the HFNEF group (P < 0.001). The HFNEF group had significantly greater LV wall thickness and LVMI than the LVH group (P < 0.001). The resting LVESV, LVEDV, LVEF, and diastolic function classification grade were similar. During stress, LV volumes decreased and LVEF increased (P < 0.01) in both hypertensive patient groups (Table 2).

Comparisons of left ventricular dyssynchrony at rest and stress

The standard deviation of Ts and Te did not significantly differ between rest and stress in normal subjects (Table 3). At rest, Ts-SD was significantly greater both in hypertensive patient groups (both P < 0.05 vs. normal controls), but similar between the two groups. Interestingly, Ts-SD increased significantly after stress in both hypertensive groups (P < 0.05), but the magnitude of change (ΔTs-SD) was significantly greater in the HFNEF group compared with the LVH group (P < 0.001) (Table 3). We defined systolic dyssynchrony as two SD above the mean Ts-SD of normal controls. As the mean and distribution of Ts-SD did not change with stress in normal subjects, the cut-off for systolic dyssynchrony was >33 ms both at rest and stress. At rest, 36.2% of patients in the HFNEF group and 38.2% in the LVH group had systolic dyssynchrony (χ² = 0.036, P = 0.85). Upon stress, the prevalence of systolic dyssynchrony increased dramatically to 85.1% in the HFNEF group, but to only 52.9% in the LVH group (χ² = 10.04, P = 0.002) (Figure 1).

For diastolic dyssynchrony, Te-SD was also significantly prolonged in both hypertensive patient groups compared with normal controls (both P < 0.001 vs. controls) (Table 3). However, there was no significant difference between the two groups at rest. Upon stress, Te-SD increased in both hypertensive patient groups, but the change (ΔTe-SD) was significantly greater in the HFNEF group (P < 0.001) (Table 3). We defined diastolic dyssynchrony as the upper two SD of normal controls, i.e. >34 ms (similar to systolic dyssynchrony, the cut-off remained the same at rest and stress). Resting diastolic dyssynchrony was evident in 34.0% of the HFNEF group and 29.4% of the LVH group (χ² = 0.194, P = 0.66). During stress, the prevalence of diastolic dyssynchrony increased significantly in the HFNEF group to 87.2%, which became significantly higher than the 58.8% in the LVH group (χ² = 8.564, P = 0.003) (Figure 1).

Table 1 Clinical and demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>LVH group (n = 34)</th>
<th>HFNEF group (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 14</td>
<td>58 ± 13</td>
<td>0.377</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>15 (44%)</td>
<td>21 (45%)</td>
<td>0.956</td>
</tr>
<tr>
<td>Risk factors/co-morbidities [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (21%)</td>
<td>9 (19%)</td>
<td>0.872</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (15%)</td>
<td>7 (15%)</td>
<td>0.975</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>11 (34%)</td>
<td>14 (30%)</td>
<td>0.805</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (9%)</td>
<td>5 (11%)</td>
<td>0.787</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>89 ± 13</td>
<td>83 ± 9</td>
<td>0.564</td>
</tr>
<tr>
<td>Stress</td>
<td>90 ± 10</td>
<td>87 ± 9</td>
<td>0.162</td>
</tr>
<tr>
<td>QRS ≥ 120 ms [n(%)]</td>
<td>3 (9%)</td>
<td>7 (15%)</td>
<td>0.412</td>
</tr>
<tr>
<td>NYHA class [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>–</td>
<td>42 (89%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>5 (11%)</td>
<td></td>
</tr>
<tr>
<td>Diastolic function classification grade [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12 (35%)</td>
<td>16 (34%)</td>
<td>0.535</td>
</tr>
<tr>
<td>II</td>
<td>18 (53%)</td>
<td>24 (51%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>–</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Medications [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>26 (76%)</td>
<td>36 (77%)</td>
<td>0.800</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>23 (68%)</td>
<td>32 (68%)</td>
<td>0.964</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>23 (68%)</td>
<td>33 (70%)</td>
<td>0.805</td>
</tr>
<tr>
<td>Diuretics</td>
<td>32 (94%)</td>
<td>44 (94%)</td>
<td>0.924</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; HFNEF, heart failure with normal ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.
The pattern of change in dynamic dyssynchrony was illustrated in Figure 2. Stress-induced systolic dyssynchrony was observed in 51.1% of patients in the HFNEF group, but only 23.5% in the LVH group ($\chi^2 = 11.165, P = 0.011$). Also, persisting systolic dyssynchrony occurred in 34.0% in the HFNEF group, but only 29.4% in the LVH group. Conversely, persistent synchronous contraction both at rest and stress was more frequently observed in the LVH group (57.4 vs. 12.8%). Likewise, stress-induced diastolic dyssynchrony was more commonly observed in the HFNEF group (57.4% vs. 35.3%; $\chi^2 = 9.566, P = 0.023$), while more patients in the LVH group had persistently synchronous relaxation at rest and stress (35.3% vs. 8.5%).

### Comparisons of mean Sm and mean Em at rest and stress

Both hypertensive patient groups had lower resting mean Sm than normal controls (both $P < 0.001$), although it was further reduced in the HFNEF group ($P < 0.001$ vs. LVH group) (Table 3). During stress, the mean Sm increased in all three groups ($P < 0.001$ vs. rest for all groups) but the increment ($\Delta$Sm) was the smallest in HFNEF ($P < 0.05$ vs. LVH; $P < 0.001$ vs. controls) (Table 3, Figure 3). For diastolic function, both hypertensive patient groups had lower resting mean Em than normal controls (both $P < 0.001$), but it was lower in the HFNEF group ($P < 0.001$ vs. LVH group) (Table 3). The mean Em increased significantly during stress in both the LVH group and normal controls ($P < 0.001$ vs. rest), but it was unchanged in the HFNEF group ($P = 0.468$ (Table 3, Figure 3). Patients with diastolic dyssynchrony ($n = 61$) during stress had significantly more blunted $\Delta$Em ($0.4 \pm 2.9$ vs. $2.1 \pm 3.5$ m/s, $P = 0.037$) than those without ($n = 20$).

### Independent predictors for heart failure with normal ejection fraction on multivariate analysis

Multivariate analysis was performed to identify independent predictors of HFNEF. Of all tested variables, $\Delta$Em [Odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.54–0.89, $P = 0.004$], Sm [OR = 0.56, 95% CI: 0.37–0.83, $P = 0.004$], systolic dyssynchrony during stress (OR = 4.6, 95% CI: 1.9–20.9, $P = 0.005$), and diastolic dyssynchrony during stress (OR = 4.3, 95% CI: 1.1–16.7, $P = 0.038$) emerged as independent predictors of HFNEF.

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**Table 2** Haemodynamic and echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>Normal controls ($n = 50$)</th>
<th>LVH group ($n = 34$)</th>
<th>HFNEF group ($n = 47$)</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b.p.m.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>70 ± 14</td>
<td>72 ± 14</td>
<td>69 ± 14</td>
<td>0.761</td>
</tr>
<tr>
<td>Stress</td>
<td>129 ± 22*</td>
<td>124 ± 24*</td>
<td>126 ± 18*</td>
<td>0.469</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>129 ± 8</td>
<td>156 ± 11†</td>
<td>156 ± 11†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stress</td>
<td>164 ± 10†</td>
<td>196 ± 13†</td>
<td>214 ± 17†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>75 ± 7</td>
<td>86 ± 7†</td>
<td>86 ± 7†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stress</td>
<td>92 ± 8†</td>
<td>104 ± 7†</td>
<td>104 ± 5†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>51 ± 13</td>
<td>114 ± 9†</td>
<td>129 ± 9†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>8 ± 1</td>
<td>12 ± 1†</td>
<td>15 ± 1†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>8 ± 1</td>
<td>10 ± 1†</td>
<td>15 ± 1†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>108 ± 18</td>
<td>109 ± 15</td>
<td>111 ± 17</td>
<td>0.783</td>
</tr>
<tr>
<td>Stress</td>
<td>112 ± 17*</td>
<td>105 ± 15*</td>
<td>105 ± 19*</td>
<td>0.490</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>42 ± 9</td>
<td>40 ± 8</td>
<td>42 ± 11</td>
<td>0.432</td>
</tr>
<tr>
<td>Stress</td>
<td>29 ± 7*</td>
<td>27 ± 6*</td>
<td>29 ± 12*</td>
<td>0.403</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61 ± 5</td>
<td>64 ± 5</td>
<td>62 ± 7</td>
<td>0.111</td>
</tr>
<tr>
<td>Stress</td>
<td>74 ± 5*</td>
<td>74 ± 5*</td>
<td>73 ± 8*</td>
<td>0.690</td>
</tr>
<tr>
<td>Effective arterial elastance (mmHg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.81 ± 0.39</td>
<td>2.08 ± 0.39†</td>
<td>2.11 ± 0.51†</td>
<td>0.002</td>
</tr>
<tr>
<td>Stress</td>
<td>2.02 ± 0.39</td>
<td>2.34 ± 0.45†</td>
<td>2.59 ± 0.46†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. resting value; †P < 0.05 vs. normal controls; ‡P < 0.05 vs. LVH group. IVST, interventricular septal thickness; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; PWT, posterior wall thickness.
The present study provides novel data on the dynamic property and impact of LV dyssynchrony in hypertensive patients with LVH and HFNEF. Despite a similar severity of resting LV dyssynchrony in both disease groups, both systolic and diastolic dyssynchrony during stress were more prevalent and profound in patients with hypertensive HFNEF. Furthermore, despite...
apparently normal stress-induced increase in LVEF, the HFNEF group had severely blunted augmentation in long-axis myocardial systolic function and absence of increment in long-axis myocardial diastolic function during stress. These findings are suggestive of impairment in systolic reserve and almost absence of diastolic reserve. Finally, independent determinants for the occurrence of HFNEF included diastolic and systolic dyssynchrony during stress as well as reduced augmentation in diastolic and, to a lesser extent, systolic longitudinal myocardial function.

**Dynamic dyssynchrony in heart failure with normal ejection fraction and asymptomatic hypertensive heart disease**

Several recent studies reported a high prevalence of resting LV dyssynchrony in patients with HFNEF. Importantly, in one study, abnormal LV systolic indices including stroke work and myocardial contractility were found to be associated with increased systolic dyssynchrony in HFNEF. A few previous studies reported abnormal systolic function in patients with LVH and HFNEF. The concept of resting diastolic dyssynchrony and its contribution to diastolic dysfunction has been reported in severe hypertrophic conditions including aortic stenosis and hypertrophic obstructive cardiomyopathy. More recently, diastolic dyssynchrony was examined in a clinical study of HFNEF patients, which found that both time constant of relaxation and mean wedge pressure increased in parallel with the prolongation of the diastolic regional time delay. However, most previous studies investigating LV dyssynchrony in HFNEF were performed at resting condition. Intuitively, as the symptoms of HFNEF are often precipitated by haemodynamic stress, evaluation of dyssynchrony during stress is likely to be clinically and pathophysiologically relevant. Indeed, in systolic heart failure, recent studies showed that magnitude of LV dyssynchrony can be altered by stress and the dynamic response of dyssynchrony is variable among individuals.

In the present study, although LV dyssynchrony was evident in hypertensive patients with and without clinical HFNEF, it did not differ between the two groups at rest. However, haemodynamic challenge revealed significant worsening of LV dyssynchrony mainly in the HFNEF group, implicating a higher vulnerability of developing stress-induced dynamic dyssynchrony in hypertensive HFNEF. Interestingly, a shift from resting dyssynchrony to disappearance during stress is very rare, which suggests that the dynamic change is not a random event. Using the same method as ours to assess systolic dyssynchrony, a recent study found that 6 min treadmill exercise test led to deterioration in systolic dyssynchrony only in HFNEF patients but not asymptomatic hypertensive patients with diastolic dysfunction; systolic dyssynchrony during exercise was associated with higher plasma N-terminal pro-BNP levels. Nevertheless, diastolic dyssynchrony was not
Systolic and diastolic myocardial function reserve in heart failure with normal ejection fraction

Another distinguishing feature of patients with HFNEF in this study was the severely blunted response of mean Sm and, in particular, the lack of increment of mean Em during stress. In the LVH group, stress-induced augmentation of mean Sm and mean Em was also blunted, but less severe than that observed in the HFNEF group. Using TDI and speckle strain techniques, recent studies demonstrated the presence of resting long-axis systolic dysfunction in HFNEF patients. Arguably, as patients with HFNEF will predominantly have exertional symptoms, the current study supports the hypothesis that impaired systolic and diastolic function reserves are important in the pathogenesis of HFNEF.

Kass et al. has suggested that systolic and diastolic reserve in HFNEF may be impaired during exercise as a result of systolic ventricular and arterial stiffening. Consistently, a higher arterial elastance was observed in the HFNEF group, even though it may be underestimated in the present study owing to the vasodilatory effect of dobutamine. Dynamic dyssynchrony during DSE has been reported in other afterload mismatch conditions. In one report, dynamic dyssynchrony was implicated as a contributory factor to the lack of contractile reserve in a patient with aortic stenosis. We postulated that stress-induced LV dynamic dyssynchrony, impaired myocardial function reserve, and exaggerated arterial afterload mismatch may all be mutually interacting factors in the complex pathophysiology of HFNEF.

Limitations

Since coronary angiography was not performed in all patients, the possibility of silent ischaemia in the study population cannot be entirely excluded. However, DSE is sensitive in detecting functionally significant ischaemia, and subjects with obstructive coronary artery disease were excluded from the study. Although the reproducibility of the TDI techniques has recently been challenged by the PROSPECT study, it should be recognized that, like any other techniques, a learning curve exists for dyssynchrony analysis. In trained and experienced centres of performing dyssynchrony analysis, a high beat-to-beat reproducibility of myocardial velocity profile has been ascertained and a low inter- and intra-observer variability has been observed.

Increased heart rate during stress may influence the exact definition of dyssynchrony. Nevertheless, the definition of dyssynchrony in this study was derived from age-, gender-matched controls, with similar heart rate both at rest and stress among the three study groups. Interestingly, when using the absolute measure of time delay to assess dyssynchrony, the cut-offs remain unchanged between rest and stress when derived from two SD above mean from normal controls. Consistently, normal controls did not develop dyssynchrony during stress. Therefore, the same cut-offs were applicable during rest and stress in these patients.

Owing to the angle dependency of TDI, radial, rotational, and apical information regarding dyssynchrony was not included in this study. Recently, the use of 2D speckle strain techniques in evaluating myocardial mechanics has been reported. However, the main limitation of speckle tracking is a lower frame rate at the outset, resulting in possible under-sampling of peak values, which may be a problem in tracking in high heart rate during stress.

Conclusions

Our study demonstrated that LV dyssynchrony is highly dynamic in HFNEF patients. Systolic and diastolic dyssynchrony during stress, along with impaired systolic and diastolic reserves, appeared to be independent predictors for the development of clinical HFNEF in hypertensive heart disease. These findings contribute to a better understanding of the pathophysiology of HFNEF and add insights to plan on treatment strategies. As LV dyssynchrony could be absent at rest but provoked by stress, evaluation of dynamic dyssynchrony using stress test may help identifying patients at a higher risk of developing HFNEF. Finally, whether therapies targeting at LVH regression would reverse dynamic dyssynchrony and leads to improvement of symptomatic status and myocardial function reserve warrants further investigations.

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