Pacing tachycardia exaggerates left ventricular diastolic dysfunction but not systolic function and regional asynergy or asynchrony in patients with hypertrophic cardiomyopathy

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Aims
Myocardial ischaemia and angina have been demonstrated in patients with hypertrophic cardiomyopathy (HCM). We hypothesized that left ventricular (LV) systolic or diastolic dysfunction would be provoked by pacing tachycardia in patients with HCM.

Methods and results
We investigated LV global and regional systolic and diastolic function in 17 patients with HCM without LV outflow obstruction and 7 normal subjects by analysing LV angiograms and simultaneously obtained high-fidelity LV pressures before and after rapid cardiac pacing (150 b.p.m.). Biplane LV silhouettes were digitized frame by frame (50 frames/s). To quantify regional dynamics, the ventricular area of the right anterior oblique projection was divided into six sections originating from the midpoint of the long axis at end-diastole. There were no significant changes in LV function after pacing in normal subjects. In HCM, the ejection fractions remained unchanged. However, LV end-diastolic pressures rose (+12 mmHg, \(P<0.01\)), and the time constants of isovolumic pressure decay were significantly increased (\(T_{1/2}: +5.2 \text{ms}, P<0.01\); \(T_{1/e}: +6.8 \text{ms}, P<0.01\)). The LV global diastolic pressure–volume relationships and regional diastolic pressure–area relationships of regional myocardium shifted upward (indicating decreased diastolic distensibility) in all patients. These diastolic abnormalities were not accompanied by regional asynchrony or asynergy.

Conclusion
Most patients with HCM have a reduced reactive capacity to chronotropic stress, which is haemodynamically characterized by evenly distributed diastolic dysfunction. In contrast with coronary artery disease, these diastolic abnormalities were not accompanied by systolic dysfunction, regional asynchrony, asynergy, or inhomogenous diastolic distensibility.

Keywords
Cardiomyopathy • Diastole • Hypertrophy • Ischaemia

Introduction
Coronary flow reserve, despite normal epicardial coronary arteries, is severely blunted, and anginal symptoms are common in hypertrophic cardiomyopathy (HCM). The mechanisms for myocardial ischaemia may be related to functional and structural derangement of intramural coronary arterioles, extravascular compressive forces such as ventricular haemodynamic load, and diastolic perfusion time. Recent studies have demonstrated that myocardial ischaemia and its sequelae fibrosis could play an important role in clinical outcome in HCM, including left ventricular (LV) dysfunction and sudden death. In contrast, although some metabolic and haemodynamic data of myocardial ischaemia have been reported during pacing-induced tachycardia, there have been no attempts to precisely investigate global and regional ventricular systolic and diastolic function in patients with HCM.

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We hypothesized that LV systolic or diastolic dysfunction would be provoked by pacing tachycardia in patients with HCM and aimed to precisely investigate LV global and regional systolic and diastolic function with similar heart rates before and immediately after a rapid cardiac pacing.

**Methods**

**Study patients**

The study group comprised 17 patients with HCM and a control group of 7 subjects investigated mainly for chest pain who proved to have angiographically normal coronary arteries, LV wall motion, and normal function. We defined HCM as apparently unexplained LV hypertrophy. The patients with HCM were 15 men and 2 women with an average age of 51 years (range, 20–71 years). In this study, all patients with HCM had asymmetrical septal hypertrophy with a septal-to-LV posterior wall ratio of 1.3:1 or more. The thickness of the interventricular septum and LV posterior free wall was 20.5 ± 4.5 and 12.2 ± 2.6 mm, respectively. All patients had normal sinus rhythm. Patients with LV outflow tract pressure gradient or apical form of HCM were not included. All medications were terminated at least 5 days before cardiac catheterization. In the normal control subjects, there were seven men with an average age of 49 years (range, 35–66 years). They underwent cardiac catheterization because of chest pain or positive stress test. The study protocol was approved by the Ethics Committee of Mie University of Medicine. Informed consent was obtained from each patient.

**Study protocol**

Cardiac catheterization was performed via the percutaneous femoral approach. After routine right and left heart catheterization, a pacing catheter was placed in the right atrium and LV pressure measurements and biplane cineventriculography were performed before and immediately after rapid cardiac pacing. Left ventricular pressure was measured with an 8 F pigtail angiographic micromanometer catheter (Millar Instruments). After a pause of at least 20 min for dissipation of the contrast material, we confirmed that LV pressure had returned to the control state value.

Atrial pacing was accomplished by increasing the heart rate by 20 b.p.m. until chest pain developed. The target heart rate was 150 b.p.m. As two patients developed atrioventricular block before the target heart rate, right ventricular pacing was substituted. Right atrial or ventricular pacing was increased stepwise every 3 min by 20 b.p.m. Pacing was continued for 3 min at the target heart rate and then abruptly discontinued. We repeated a second ventriculogram in the post-pacing period during the first 8–15 beats in the same manner as in the control state.

Simultaneous biplane cineventriculograms were obtained in the 30° right anterior oblique (RAO) and 60° left anterior oblique projections. The film speed was 50 frames/s. Left ventricular pressures were recorded simultaneously during ventriculograms at a paper speed of 150 mm/s (Electronics for Medicine VR-12). In 6 patients with HCM, right atrial pressure (fluid-filled system) was measured before and after pacing.

**Analysis of global left ventricular function**

To assess LV relaxation, we calculated the time constant of isovolumic pressure decay. Left ventricular pressure was measured every 5 ms from the point of minimal dP/dt to a level 5 mmHg above the end-diastolic pressure (EDP) of the next beat. Left ventricular pressure and time during this interval were fit by an exponential method with a variable asymptote to the following equation:

\[
P(t) = ae^{-t/T} + c\]

where \(P\) is the LV pressure (mmHg), \(t\) the time (ms), \(c\) the asymptote of pressure fall (mmHg), and \(a\) and \(b\) the constants. From this equation, two time constants were calculated and were defined as the times required for the LV pressure to decay to 1/e (\(T_{1/e}\)) and half (\(T_{1/2}\)) of its value at LV peak-negative dP/dt. To avoid erroneous changes in time constant induced by a shift of the starting point or of the endpoint of the time constant analysis, we also calculated individual time constants (\(T_{1/e}\) and \(T_{1/2}\)) from curve fits with identical starting point (the lower pressure at which LV peak-negative dP/dt occurred) and endpoint (the pressure that equaled the higher LVEDP plus 5 mmHg) as proposed by Paulus et al. The correlation coefficients of the exponential fits were all above 0.995.

We analysed biaxial LV silhouettes by digitizing frame by frame and calculated volumes by the biaxial area–length method (Figure 1). Biplane cineangiograms of 10 out of 17 patients with HCM and all 7 normal subjects could be satisfactorily digitized frame by frame for an entire cardiac cycle both before and after pacing. We could not analyse cineangiograms of seven patients with HCM because of multiple ventricular extrasystoles either before or after pacing. In these seven patients with HCM, we analysed only the LV pressures of the normal sinus beats. To describe LV early diastolic filling, we measured the peak filling rate (PFR) and the time from the end-systolic frame to the PFR (TPFR) after smoothing technique (Figure 1).

The atrioventricular pressure gradient (AVPG) between the left atrium and ventricle plays an important role in LV early diastolic filling. Because we could not measure left atrial pressure, we noted the pressure just before the frame in which unopacified blood appeared within the LV on the left ventriculogram. That was defined as the left atrial opening pressure. The difference between the left atrial opening pressure and LV minimal pressure was defined as an index of the AVPG.

To assess the alterations in global LV diastolic distensibility, we plotted diastolic pressure–volume relationships before and after pacing from the point of minimal LV pressure to end-diastole.

**Analysis of regional left ventricular function**

To quantify systolic and diastolic regional dynamics, we divided the ventricular area of the RAO projection into six sections originating from the midpoint of the long axis at end-diastole. We defined the long axis in the RAO view as the line from the apex to the midpoint of the aortic valve plane. Starting at the middle of the aortic valve plane, we divided the areas at 60° increments from the midpoint of the diastolic long axis to their intersection with the contour border, and numbered these areas from A1 to A6 in clockwise order. From each section, time–area curves were also obtained after using similar smoothing technique for global time–volume curves.

Regional systolic function was assessed by per cent fractional contraction of their areas estimated as (end-diastolic area – end-systolic area) × 100/ (end-diastolic area).

Regional asynchrony and asynergy was assessed according to the method of Betocchi et al. Systolic asynchrony was evaluated by adding the individual values of time measured from end-diastole to the minimum area in the six sections of the RAO projection and by computing their coefficient of variation. Regional PFR was calculated in a fashion similar to that for global time–volume curves, and then diastolic asynchrony was determined by the coefficient of variation of the regional time intervals from end-diastole to PFR.
Asynergy was evaluated from the coefficient of variation of the areas, which were expressed as a percentage of end-diastolic area, for different time points of the cardiac cycle namely end-systole, mitral valve opening (MVO), the time of PFR, the end of rapid filling period, and the beginning of atrial contraction on the global volume curve.

To assess the alterations in regional diastolic distensibility, we plotted diastolic pressure–area relationships before and after cardiac pacing, similar to that for the global pressure–volume relationships.

Statistical analysis

Data before and after cardiac pacing were compared using the two-tailed paired *t*-test for paired data. A comparison of the haemodynamic data between HCM patients and normal subjects or between HCM patients with and without developing chest pain was performed with use of the unpaired *t*-test. A significant difference was indicated by a *P*-value of <0.05. Values are expressed as mean ± SD unless stated.

Results

The effects of cardiac pacing on haemodynamics and left ventricular global systolic function

Seven out of the 17 patients with HCM developed chest pain with a pacing rate of 150 b.p.m. No chest pain occurred in the normal subjects.

In patients with HCM, there was a slight but significant increase in LV peak systolic pressure (+8 mmHg, *P* < 0.05) and LV end-systolic pressure (ESP) (+12 mmHg, *P* < 0.05) after rapid cardiac pacing. Heart rate also increased slightly after pacing (+5 b.p.m., *P* < 0.05). Left ventricular ESP rose in all patients from a mean control value of 16–28 mmHg (*P* < 0.01). Left ventricular peak-positive dP/dt increased significantly (+92 mmHg/s, *P* < 0.01), whereas LV peak-negative dP/dt remained unchanged after pacing.

There were no significant changes in LV end-diastolic volumes (EDV) after pacing, despite significant increases in LVEDP. Mean values for end-systolic volume (ESV) increased significantly (+5 mL, *P* < 0.05), but ejection fractions (EFs) were unchanged (−0.02%, NS). To assess the possibility that pacing-induced increases in ESV might have been induced by the increases in ESP, ESP–V relationships were assessed in each patient. All seven patients in whom the ESPs increased after pacing showed an increase in ESV, whereas three patients in whom ESPs decreased after pacing had a decrement in ESV. Thus, an increase in LVESV might be attributable to increased afterload rather than to decreased contractility.

There were no differences in LV haemodynamics between patients with and without chest pain before and after pacing in this or subsequent analyses, and therefore, their data were combined.

Among normal subjects, heart rate also increased significantly after pacing (+7 b.p.m., *P* < 0.05). However, there were no significant change in LVEDP, LVEDVs, ESVs, and EFs (Table 1).

Left ventricular relaxation and diastolic filling

The time constants of LV pressure decay, which were calculated from the point of minimal dP/dt to a level 5 mmHg above the EDP, showed a significant prolongation after pacing (*T*1/e: +6.8 ms, *P* < 0.01; *T*1/2: +5.2 ms, *P* < 0.01) (Figure 2 and Table 1). The time constants of LV pressure decay calculated over the same range of isovolumic LV relaxation also showed a similar prolongation after pacing (*T*1/e: +3.7 ms, *P* < 0.05; *T*1/2: +2.7 ms, *P* < 0.05).

The PFR and the TPFR during the rapid filling period remained unchanged after pacing. The left atrial opening pressure and LV
minimal pressure were both significantly increased after pacing, but
the extent of increase in pressure was less in LV minimal than in
the left atrial opening pressure (+7 vs. +16 mmHg, \( P < 0.01 \)).
As a result, the AVPG was increased significantly (+10 mmHg, \( P < 0.05 \)). An increase in AVPG might counterbalance a reduction
of early diastolic filling, resulting in no significant change in the PFR
after pacing in patients with HCM.

Table 1  Left ventricular haemodynamics before and after rapid cardiac pacing in 17 patients with HCM and 7 normal
subjects (N)

<table>
<thead>
<tr>
<th></th>
<th>HR (b.p.m.)</th>
<th>LVPSP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>LVESP (mmHg)</th>
<th>Max(+)/dp/dt (mmHg/s)</th>
<th>Min(−)/dp/dt (mmHg/s)</th>
<th>LVEDV (mL)</th>
<th>LVESV (mL)</th>
<th>EF</th>
</tr>
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<tbody>
<tr>
<td>HCM</td>
<td>C</td>
<td>67 ± 13</td>
<td>136 ± 32</td>
<td>16 ± 4</td>
<td>119 ± 31</td>
<td>1519 ± 161</td>
<td>1261 ± 352</td>
<td>147 ± 20</td>
<td>46 ± 25</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>72 ± 13*</td>
<td>144 ± 33*</td>
<td>28 ± 7†</td>
<td>131 ± 34*</td>
<td>1611 ± 275*</td>
<td>1264 ± 338</td>
<td>151 ± 23</td>
<td>51 ± 29*</td>
</tr>
<tr>
<td>N</td>
<td>C</td>
<td>62 ± 13</td>
<td>117 ± 14</td>
<td>13 ± 4</td>
<td>107 ± 12</td>
<td>1451 ± 342</td>
<td>1616 ± 240</td>
<td>135 ± 14</td>
<td>46 ± 8</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>69 ± 13*</td>
<td>122 ± 22</td>
<td>15 ± 5</td>
<td>111 ± 19</td>
<td>1526 ± 368</td>
<td>1558 ± 357</td>
<td>137 ± 12</td>
<td>49 ± 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>T_{1/2} (ms)</th>
<th>T_{1/e} (ms)</th>
<th>PFR (mL/s)</th>
<th>TPFR (ms)</th>
<th>MVOP (mmHg)</th>
<th>Min LVP (mmHg)</th>
<th>AVPG (mmHg)</th>
<th>Mean RAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>C</td>
<td>41.4 ± 6.9</td>
<td>55.7 ± 8.8</td>
<td>562 ± 208</td>
<td>221 ± 77</td>
<td>18 ± 7</td>
<td>5 ± 3</td>
<td>12 ± 6</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>46.6 ± 7.5†</td>
<td>62.5 ± 10.5†</td>
<td>579 ± 190</td>
<td>209 ± 65</td>
<td>34 ± 9†</td>
<td>12 ± 4†</td>
<td>22 ± 8*</td>
</tr>
<tr>
<td>N</td>
<td>C</td>
<td>32.4 ± 4.0</td>
<td>45.3 ± 5.7</td>
<td>550 ± 174</td>
<td>174 ± 16</td>
<td>19 ± 3</td>
<td>4 ± 2</td>
<td>15 ± 3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>33.7 ± 4.5</td>
<td>46.6 ± 6.1</td>
<td>497 ± 157</td>
<td>170 ± 26</td>
<td>19 ± 4</td>
<td>4 ± 2</td>
<td>16 ± 4</td>
</tr>
</tbody>
</table>

AVPG, atrioventricular pressure gradient; C, control; EF, ejection fraction; HR, heart rate; LVPSP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVESP, left ventricular end-systolic pressure; LVEDV, left ventricular end-systolic volume; LVSP, left ventricular peak systolic pressure; min LVP, minimal left ventricular pressure; MVOP, mitral valve opening pressure; P, post-pacing; PFR, peak filling rate; RAP, right atrial pressure; T, time constant of isovolumic pressure decay; TPFR, time from end-systole to peak filling rate.

\(* P < 0.05\).

\([P < 0.01 \text{ vs. control.}]

In normal subjects, there were no significant changes in indexes of relaxation and filling after pacing.

**Left ventricular global diastolic distensibility**

All patients with HCM had an upward shift in the LV dynamic pressure–volume relationships immediately after pacing. Figure 3 summarizes the diastolic pressure–volume relationships in the averaged co-ordinates at five points during diastole, i.e. the point of MVO, LV minimal pressure, end of rapid filling period, end of slow filling (diastasis), and end-diastole. A significant increase in diastolic pressure at each point was observed. An increase in volume was observed only at the endpoint of slow filling (+7 mL, \( P < 0.05 \)). There were no significant changes in right atrial pressures before and after pacing.

In normal subjects, there were no significant shifts in the LV distolic pressure–volume relationships.

**Left ventricular regional asynchrony, asynergy, and diastolic distensibility in patients with hypertrophic cardiomyopathy**

There were no significant differences in the average per cent fractional contraction of regional areas of the LV before and after pacing (Figure 4).
Left ventricular systolic and diastolic asynchrony was not significantly different from normal subjects in patients with HCM. Left ventricular asynergy was significantly higher at end-systole, MVO, and the time of PFR in patients with HCM than in normal subjects (data not shown). In patients with HCM, systolic and diastolic asynchrony did not significantly differ before and after pacing, as evident from the regional variations in time intervals from end-diastole to minimum area (15 ± 8 vs. 17 ± 6%, NS) or to the PFR (6 ± 1 vs. 6 ± 2%, NS). Asynergy was also significantly unchanged for each moment of the cardiac cycle analysed (Figure 5).

There was an upward shift in the diastolic pressure–area relationships in each region after pacing, suggesting that the areas of decreased distensibility were evenly distributed (Figure 6).

**Discussion**

In this study, we demonstrated that pacing-induced tachycardia further exacerbates LV diastolic dysfunction in HCM, as evidenced by significant increases in LVEDP and time constants of LV isovolumic pressure decay, along with upward shifts in the LV diastolic pressure–volume relationships. These diastolic abnormalities, however, were not accompanied by regional asynchrony, asynery, and inhomogeneous diastolic distensibility and also not by global or regional LV systolic dysfunction.

It is widely accepted that an increase in LV diastolic pressure associated with a prolonged time constant of isovolumic relaxation and upward shift of diastolic pressure–volume relationships are characteristic features of pacing or exercise-induced angina in patients with coronary artery disease (CAD).10,12,13 These haemodynamic abnormalities are usually associated with LV regional asynery, asynchrony, and both.10,13 However, there was neither regional asynery nor asynchrony in our patients with HCM. Moreover, an upward shift in the regional pressure–area relationship was observed in each region of the myocardium. These diastolic abnormalities observed in patients with HCM are clearly contrasted with those in patients with CAD. This finding may provide new insight into haemodynamic aspects of myocardial ischaemia in HCM or differentiation of HCM with and without significant CAD in the clinical setting.

Our patients with HCM showed a significant prolongation of the time constant of LV relaxation after pacing. Left ventricular isovolumic relaxation is controlled by a complex interaction between myocardial inactivation, loading conditions, and non-uniformity of...
Myocardial inactivation relates to the processes underlying calcium extrusion from the cytosol to achieve its diastolic levels and cross-bridge detachment. First, we noted a significant increase in LV peak systolic pressure after pacing, which might prolong the time constant of isovolumic pressure decay. The average increase of 8 mmHg in LV systolic pressure or 6 mmHg in LV pressure at peak-negative dP/dt, however, is too small to explain the prolonged isovolumic pressure decay in HCM patients with normal systolic function. We also observed a prolongation of the time constants of relaxation in six patients who did not show an increase in LV pressure at peak-negative dP/dt. Secondly, spatial and temporal non-uniformity (asynnergy and asynchrony) of the LV could further prolong LV relaxation after pacing in patients with HCM. However, we could not find a significant change in either regional asynnergy or asynchrony after pacing. Thus, impaired LV relaxation after pacing should be mainly attributed to impaired myocardial inactivation associated with myocardial ischaemia rather than alterations in loading conditions or non-uniformity.

It was notable that there was no or little LV systolic dysfunction, despite the presence of LV diastolic dysfunction after pacing in patients with HCM. Fifer et al. also suggested that LV systolic contraction was unchanged as assessed by echocardiography during pacing-induced angina in patients with aortic stenosis. In contrast to our clinical findings and those of Fifer et al., Fujii et al. reported that rapid cardiac pacing depressed LV systolic function as suggested by decreased mean velocity of circumferential fibre shortening and decreased LV systolic pressure in experimental LV hypertrophy. Nakano et al. demonstrated selective subendocardial contractile dysfunction associated with selective subendocardial hypoperfusion after a rapid cardiac pacing in dogs with pressure overload LV hypertrophy. Several factors could be responsible for the discrepancy between our data and theirs.
First, there was a difference in the pacing rate. We performed cardiac pacing at a rate of 150 b.p.m. in this study, whereas in the animal studies, pacing rates at 180–240 b.p.m. were employed. Aroesty et al., using serial LV pressure–volume relationships, demonstrated that an ischemic response to pacing-induced tachycardia produces both systolic and diastolic dysfunction in patients with CAD but that diastolic impairment precedes systolic dysfunction. We thus speculate that only diastolic dysfunction was observed after pacing as demonstrated by Aroesty et al., and that with higher pacing rates, LV contractile dysfunction might have developed in our patients. Secondly, because coronary flow reserve is severely limited in the subendocardial layer compared with the subepicardium, there was a possibility that compensated subepicardial systolic hyperfunction might counterbalance subendocardial hypofunction after cardiac pacing in our patients, resulting in no or little change of systolic pump function. Hittinger et al. reported that during exercise in dogs with LV hypertrophy, there were selective subendocardial hypoperfusion and profound selective depression in subendocardial wall thickening. They also demonstrated that the net effect on total wall motion was not changed significantly since decreases in the subendocardial wall motion were offset by increases in subepicardial wall motion. In our study, it was impossible to analyse regional contractile function in different layers by cineventriculography.

We investigated LV systolic and diastolic function with similar heart rates before and in the post-pacing period during the first 8–15 beats but not during pacing because the excessively fast heart rates would greatly modify ventricular systolic and diastolic function. One may wonder whether the effects of myocardial ischaemia were present even after rapid pacing in this study. Fujita et al., using ventriculography in patients with angina pectoris, have reported that the ischaemic myocardial shortening was considerably depressed on the analysed beats from 5 s to 1 min after stopping cardiac pacing. In the preliminary study, we also found that LVEDP remained elevated for ~1 min in patients with HCM after rapid pacing was terminated. The exact mechanisms why the changes were present in the post-pacing period are not clear, but it is speculated that ischaemia-related haemodynamic changes may persist for some time after rapid pacing.

We believe that pacing-induced LV diastolic dysfunction in patients with HCM might result mainly from global myocardial ischaemia limited to the subendocardium. However, other mechanisms such as altered calcium kinetics or autonomic effects might partly modify diastolic abnormalities in HCM during or after pacing tachycardia. Gwathney et al. have reported that resting intracellular calcium and tension were increased after a faster rate of stimulation in papillary muscles in patients HCM. The main reason of the decreased LV diastolic distensibility by pacing-induced ischaemia was speculated that preserved myofilamentary calcium sensibility could allow for diastolic cross‐bridge cycling in the presence of a simultaneous myoplasmic calcium overload during myocardial ischaemia. So, it is possible that calcium overload in HCM might further decrease LV diastolic distensibility by pacing-induced ischaemia. Impaired autonomic cardiac control or cardiopulmonary baroreflex sensitivity might also contribute to abnormal LV haemodynamics in patients with HCM. Further studies will be needed in the future.

**Study limitations**

Seven out of the 17 patients with HCM developed chest pain with cardiac pacing and there were no differences in LV haemodynamics between patients with and without chest pain. These findings strongly suggest that pacing-induced diastolic abnormalities are caused by myocardial ischaemia in most patients with HCM. However, we could not show corroborative or more specific evidence of myocardial ischaemia in our patients. Further study will be needed in this point.

In conclusion, we have shown further impairment of LV isovolumic relaxation and decreased diastolic distensibility after a rapid cardiac pacing in patients with HCM. In contrast to patients with CAD, these diastolic abnormalities were evenly distributed and were not accompanied by systolic dysfunction, regional asynchrony, asynergy, or inhomogenous diastolic distensibility.

**Conflict of interest:** none declared.

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