Comparison of Valsalva manoeuvre and exercise in echocardiographic evaluation of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

Morten K. Jensen*, Ole Havndrup, Redi Pecini, Morten Dalsgaard, Christian Hassager, Steffen Helqvist, Henning Kelbæk, Erik Jørgensen, Lars Køber, and Henning Bundgaard

Department of Cardiology, 2142 The Heart Centre, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

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Aims
Several methods are used to induce latent left ventricular outflow tract (LVOT) gradients in patients with hypertrophic cardiomyopathy (HCM). We compared LVOT gradients induced by Valsalva manoeuvre (VM) and exercise echocardiography (EE) in patients with HCM treated with percutaneous transluminal septal myocardial ablation (PTSMA).

Methods and results
Left ventricular outflow tract gradients were measured at rest, during VM, and during EE in 57 patients 3.8 ± 2.8 years after PTSMA. Measurement succeeded in all patients during VM and in 96% during EE. There were no differences in LVOT gradients between VM [17 (9–33) mmHg] and EE [18 (10–30) mmHg, P = 0.31] [median (interquartile range)], but the differences ranged from −45 to 84 mmHg in individual patients. In 93% of patients, EE had no influence on the categorization into manifest-, latent- or non-obstructive phenotypes. The 7%, who revealed LVOT gradients ≥ 30 mmHg only during EE, did not reach LVOT gradients of 50 mmHg. Patients improving two New York Heart Association (NYHA) classes after PTSMA had higher baseline LVOT gradients during VM [115 (72–160) vs. 88 (54–114) mmHg, P = 0.04] and a larger reduction in VM-induced LVOT gradients [80 (48–139) vs. 61 (28–83) mmHg, P = 0.02] than patients improving one NYHA class.

Conclusion
Valsalva manoeuvre and EE induce similar degrees of LVOT gradient, but categorization into obstructive phenotypes was not influenced by EE in more than 90% of patients. Valsalva manoeuvre should be the primary choice of stress modality in HCM patients treated with PTSMA, but EE is essential for the clinical management of the entire cohort.

Keywords
Hypertrophic cardiomyopathy • Exercise echocardiography • Valsalva manoeuvre • Left ventricular outflow tract obstruction • Stress test • Percutaneous transluminal septal myocardial ablation • Septal reduction therapy

Introduction
Left ventricular outflow tract obstruction (LVOTO) (gradient ≥ 30 mmHg) is present in 25–30% of hypertrophic cardiomyopathy (HCM) patients at rest and during exercise echocardiography (EE) in 70–75% of patients with HCM.1,2 The LVOTO is caused by narrowing of the LVOT due to septal hypertrophy and systolic anterior movement (SAM) of the mitral leaflets.3,4 Obliteration of the left ventricular lumen during systole and papillary muscle abnormalities may also contribute to the LVOTO.5–7 In the individual patient, the LVOTO is highly variable over time and is dependent on factors such as level of hydration, physical activity, intra-thoracic pressure, posture, and drugs.8–10 Consequently, measurements of LVOTO are highly dependent on a standardized...
environment. Current consensus suggests the use of Valsalva manoeuvre (VM) and/or EE to reveal stress-induced LVOTO in HCM patients.\textsuperscript{2,11} Indications for invasive procedures such as septal myectomy or percutaneous transluminal septal myocardial ablation (PTSMA) are based on these measurements. Therefore, it is of major importance that the stress modalities used are validated against each other and correlated with the symptomatic improvement after invasive procedures.

In this study, we compared the results of echocardiographic measurements of LVOT gradients at rest and during both VM and EE in patients treated with PTSMA and analysed the correlation to the symptomatic improvement.

Methods

We evaluated the measurements of LVOT gradients obtained by two stress modalities in relation to long-term results after PTSMA in a consecutive cohort of 77 HCM patients treated with PTSMA (from 1999 to 2008) at the Department of Cardiology, The Heart Centre, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark (tertiary referral centre). Percutaneous transluminal septal myocardial ablation was performed in HCM patients with an LVOT gradient $\geq 50$ mmHg at rest or $\geq 100$ mmHg during stress testing with drug refractory New York Heart Association (NYHA) class III or IV symptoms and a suitable coronary anatomy. All patients had absolute hypertrophy (maximal wall thickness $\geq 13$ mm) or relative hypertrophy according to the American Society Echocardiography (ASE) recommendations.\textsuperscript{12} The PTSMA procedures were guided by transthoracic or transoesophageal echocardiography using intra-coronary echocardiography contrast (Levovist\textsuperscript{5}).

All HCM patients previously treated with PTSMA were invited to an extended echocardiographic follow-up programme including clinical examination, interview, standard exercise (SE) test, resting echocardiography, and stress echocardiography during VM and EE. The study was approved by the local Ethics Committee, and all patients gave their informed consent.

Resting echocardiography

Resting 2D echocardiography was performed and analysed according to ASE guidelines.\textsuperscript{12,13} All echocardiographic assessments were performed on a General Electric, Vivid 7-dimension ultrasound system. The anatomical and haemodynamic relations during systole were investigated by the combined use of colour Doppler, pulse-wave Doppler and continuous-wave (CW) Doppler echocardiography. Once the location of the maximal outflow velocity was found, the maximal outflow velocity was measured by CW. Outflow gradients were automatically calculated from the flow velocities by the modified Bernoulli equation $[\text{gradient} = 4 \times (\text{flow velocity})^2]$. The heart rate was calculated at the time of gradient measurement from the average of three R–R intervals.

Valsalva manoeuvre

Patients were asked to increase their intra-thoracic pressure to a maximum at a mid-range lung volume to maintain an apical window for echocardiographic imaging.\textsuperscript{14} During the entire sequence of increase, steady state and the subsequent decrease in the intra-thoracic pressure\textsuperscript{15} outflow gradients were measured by CW at the same location and angle that was identified at rest. The VM was repeated at least three times, and the highest outflow gradient was registered.

Exercise echocardiography

Exercise echocardiography was performed according to the European Association of Echocardiography (EAE) guidelines\textsuperscript{16} at least 10 min after the previous VM to ensure a haemodynamic steady state at the start of EE. Exercise echocardiography was performed as a treadmill test in a semi-supine position and with a left lateral tilt to enable simultaneous transthoracic echocardiography. Starting at 25 W, the work load was increased by 25 W every 2 min following the Bruce protocol to a maximum of 100 W or less if the patient was limited by symptoms. Outflow velocities were measured by CW Doppler at each step at the same location and angle that were identified at rest, and the highest outflow gradient measured during the entire test was registered. The heart rate was calculated from the average of three R–R intervals at the time of maximal outflow velocity measurement.

Standard exercise test

A standard upright computerized treadmill test with continuous ECG and blood pressure monitoring was performed for comparison to the exercise level during the EE. According to the Bruce protocol, the work load was increased from initially 25 W and by 25 W every 2 min to the maximal symptom-limited work load. The maximal work load was calculated as exercise time $\times 12.5$ W/min. The maximal heart rate during SE was recorded.

Assuming that heart rate was linearly correlated to work load and oxygen consumption,\textsuperscript{17} the relative level of exercise was calculated as the heart rate increase during EE divided by the heart rate increase during SE.

We considered the exercise performance during EE maximal, if patients stopped due to symptoms at a work load $\leq 100$ W or if they performed 100 W during EE and $\leq 125$ W during SE. In patients performing $>125$ W during SE, the exercise stress was considered submaximal, if their performance during EE was not limited by symptoms. In patients not performing SE, the exercise performance was considered maximal if they stopped at a workload $\leq 100$ W during EE due to symptoms.

Categorization of phenotypes

A non-obstructive phenotype was defined as an LVOT gradient $< 30$ mmHg at rest as well as during VM and EE.\textsuperscript{1,2} A latent LVOTO was defined as a LVOT gradient $< 30$ mmHg at rest together with an LVOT gradient $\geq 30$ mmHg during VM or EE. A manifest LVOTO was defined as an LVOT gradient $\geq 30$ mmHg at rest.\textsuperscript{1,2}

Statistics

Data were analysed using the SAS\textsuperscript{\textregistered} statistical software version 9.1. Data were presented as mean $\pm$ standard deviation when normally distributed or as median (inter-quartile range) in non-normally distributed variables. Standard error of the mean (SEM) was reported for mean differences between VM and EE. Proportions were presented as per cent (%). Paired comparisons of continuous variables were done with Student’s $t$-test when differences were normally distributed and Wilcoxon’s signed rank test when non-normally distributed. Unpaired comparisons were performed using Student’s $t$-test or Wilcoxon’s rank sum test (Mann–Whitney $U$ test) as appropriate according to the distribution. Proportions were compared with the $\chi^2$ test or Fisher’s exact test when unpaired and McNemar test when paired. One-way ANOVA was used to compare continuous variables between classes and the Cochran–Armitage trend test was used to compare proportions between classes (2 $\times$ 3 tables). ‘Baseline’ refers to pre-PTSMA values. A two-sided probability of $< 0.05$ was considered significant.
Results

A consecutive cohort of 77 HCM patients was treated with 84 PTSMA procedures from 1999 to 2008 at the Department of Cardiology, The Heart Centre, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark. Twelve patients died prior to this study and 8 patients declined participation for combined reasons of age, comorbidity, and travel distances. Fifty-seven patients were examined clinically and by echocardiography at rest, during VM, and EE 3.8 ± 2.8 years after their first PTSMA procedure.

Valsalva manoeuvre

Measurement of LVOT gradients during VM was possible in all patients. Left ventricular outflow tract gradients during VM were reduced from 95 (60–130) mmHg at baseline to 17 (9–33) mmHg (P < 0.001) at follow-up (this study). Apart from slight transient dizziness, no adverse effects were registered during VM.

Exercise echocardiography

Measurement of LVOT gradients was possible in 96% of patients during EE. Left ventricular outflow tract gradients increased from 12 (7–20) mmHg at rest to 18 (10–30) mmHg during EE (P < 0.001). The relative level of exercise during EE was 67 ± 21% of the maximal exercise during SE. In 84% of patients, the exercise stress during EE was considered maximal.

One patient experienced a self-limiting episode of sustained VT at the end of the EE that he performed to 100 W without limiting symptoms. Two patients experienced severe but transient dizziness during EE, and one patient stopped due to chest pain at a work load of 75 W. The remaining patients, who performed symptom-limited EE, stopped due to dyspnoea or leg muscle fatigue.

Comparison of Valsalva manoeuvre and exercise echocardiography

There were no differences in LVOT gradients between VM 17 (9–33) mmHg and EE 18 (10–30) mmHg at follow-up (P = 0.31). The mean difference in LVOT gradients (EE−VM) was 1.5 ± 18 mmHg (SEM = 2.4 mmHg), but in individual patients the differences ranged from −45 to 84 mmHg (Figure 1A and B).

Fifty-six per cent of patients had a non-obstructive phenotype at follow-up, and 12% had manifest LVOTO (Figure 2). Twenty-one per cent had latent LVOTO only during EE. This included 5% who had latent LVOTO during both VM and EE (Figure 2). In 93% of patients, EE did not influence the categorization into obstructive phenotypes (Table 1, Figure 2). No patients were classified as latent LVOTO during VM and EE (Figure 2). In 93% of patients, EE did not influence the categorization into obstructive phenotypes (Table 1, Figure 2). No patients with latent LVOTO during VM and EE were classified as latent LVOTO during both VM and EE (Figure 2). In 93% of patients, EE did not influence the categorization into obstructive phenotypes (Table 1, Figure 2). No patients with latent LVOTO during VM and EE were classified as latent LVOTO during both VM and EE (Figure 2).

Relations between left ventricular obstructive flow gradients and symptoms

Patients, who experienced a symptomatic improvement of two NYHA classes after PTSMA, had higher baseline LVOT gradients during VM [115 (72–160) mmHg, P = 0.04] and a larger reduction from baseline to follow-up of their VM-induced LVOT gradients [80 (48–139) vs. 61 (28–83) mmHg, P = 0.02] compared with patients, who improved one NYHA class (Figure 4A and B). The relationship between improvement of NYHA classification and baseline LVOT gradients at rest as well as reductions of resting LVOT gradients after PTSMA showed a similar tendency. One patient had unchanged symptoms and

Figure 1 (A) Scatter plot of left ventricular outflow tract gradient during Valsalva manoeuvre vs. left ventricular outflow tract gradient during exercise echocardiography at follow-up. (B) Bland–Altman plot of differences between left ventricular outflow tract gradients measured by Valsalva manoeuvre and exercise echocardiography at follow-up.
Echocardiographic categorization of 57 hypertrophic cardiomyopathy patients treated with percutaneous transluminal septal myocardial ablation. Left ventricular outflow tract gradients were measured at rest as well as during Valsalva manoeuvre and exercise echocardiography.

Table 1  Clinical characteristics of 55 percutaneous transluminal septal myocardial ablation-treated patients categorized by phenotype

<table>
<thead>
<tr>
<th></th>
<th>Non-obstructive</th>
<th>Latent obstructive</th>
<th>Manifest obstructive</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>n</td>
<td>32</td>
<td>16</td>
<td>7</td>
<td></td>
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<tr>
<td>Follow-up (years)</td>
<td>4.6 ± 2.6</td>
<td>2.7 ± 2.9</td>
<td>3.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 11</td>
<td>63 ± 14</td>
<td>60 ± 14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47%</td>
<td>37%</td>
<td>71%</td>
<td></td>
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<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>NYHA (III/IV)</td>
<td>13%</td>
<td>6%</td>
<td>27%</td>
<td>ns</td>
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<tr>
<td><strong>Standard exercise test</strong></td>
<td></td>
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<tr>
<td>Maximal work load (W)</td>
<td>95 (75–125)</td>
<td>104 (83–115)</td>
<td>81 (50–100)</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal heart rate (min⁻¹)</td>
<td>120 ± 23</td>
<td>125 ± 25</td>
<td>125 ± 15</td>
<td>ns</td>
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<tr>
<td>METs</td>
<td>4.8 ± 2.6</td>
<td>5.3 ± 2.3</td>
<td>3.4 ± 2.4</td>
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<td><strong>Echocardiography</strong></td>
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<tr>
<td>IVSd (mm)</td>
<td>15 ± 4</td>
<td>18 ± 4</td>
<td>15 ± 2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>44 ± 9</td>
<td>45 ± 7</td>
<td>40 ± 4</td>
<td>ns</td>
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<tr>
<td>LVPWd (mm)</td>
<td>12 ± 3</td>
<td>13 ± 3</td>
<td>14 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>La dimension (mm)</td>
<td>41 ± 9</td>
<td>47 ± 6</td>
<td>43 ± 5</td>
<td>0.09</td>
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<td>Mitral regurgitation</td>
<td>90%</td>
<td>94%</td>
<td>100%</td>
<td>ns</td>
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<tr>
<td>SAM</td>
<td>45%</td>
<td>75%</td>
<td>86%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVOTG rest (mmHg)</td>
<td>8 (5–11)</td>
<td>20 (15–24)</td>
<td>39 (35–45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOTG VM (mmHg)</td>
<td>10 (5–12)</td>
<td>35 (28–47)</td>
<td>49 (35–90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exercise echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVOTG EE (mmHg)</td>
<td>13 (8–19)</td>
<td>29 (19–38)</td>
<td>66 (30–86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal performance</td>
<td>78%</td>
<td>88%</td>
<td>100%</td>
<td>ns</td>
</tr>
<tr>
<td>Relative exercise level (%)</td>
<td>68 ± 21</td>
<td>69 ± 24</td>
<td>58 ± 9</td>
<td>ns</td>
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</table>

NYHA, New York Heart Association classification; METs, metabolic equivalent tasks; IVSd, septal diastolic dimension; LVEDd, left ventricular end-diastolic dimension; LVPWd, left ventricular posterior wall diastolic dimension; La, left atrium; SAM, systolic anterior movement of anterior mitral leaflet; LVOTG, left ventricular outflow tract gradient; VM, Valsalva manoeuvre. Comparisons were performed by one-way ANOVA, χ² test, Fisher’s exact test or the Cochran–Armitage trend test.

*Two patients excluded because of failed exercise echocardiography.
persistent high LVOT gradient during VM after PTSMA and was referred for a successful second PTSMA. Seven other patients had unchanged symptoms after PTSMA, despite significant reductions \([90 (29–125) \text{ mmHg} (n = 6)]\) of LVOT gradients during VM.

**Discussion**

This study is to our knowledge the first long-term study to systematically compare the use of two stress modalities, VM and EE, in the evaluation of LVOT gradients in relation to PTSMA results. In previous studies, either VM, exercise, or pharmacological stress was used.\(^{18–21}\) In our study, LVOT gradients \([\text{rest } 12 (7–20), \text{ VM } 17 (9–33), \text{ EE } 18 (10–30) \text{ mmHg} ]\) are comparable to findings in other studies reporting LVOT gradients after PTSMA.\(^{18,20,21}\) We found no differences in the overall ability of VM and EE to reveal latent LVOTO, and neither VM nor EE identified all patients with latent LVOTO (Figures 1 and 2). The different haemodynamic responses to VM and EE\(^ {22–30}\) and the highly variable anatomical substrates for LVOTO in HCM patients may explain why we found large differences in LVOT gradients in individual patients in this study.

We included all available PTSMA-treated patients from our institution in this cross-sectional study regardless of age and co-morbidities, which results in a variable follow-up time. The majority of patients were unable to stress their cardiovascular systems to expected levels during EE. This may explain why the value of adding EE to VM in this study was low, whereas other studies have found a high degree of LVOTO during EE in younger HCM populations.\(^ {1,2}\) However, the finding of LVOTO during vigorous exercise only possibly correlate poorly to symptoms and should probably not indicate invasive treatment of the LVOTO.

Valsalva manoeuvre and EE are in general used side by side and decisions to perform invasive treatments rely partly on these test results.\(^ {2,11}\) It is of major importance that the measurements of LVOT gradients and the reductions measured in relation to myectomy or PTSMA are significantly correlated to the symptomatic improvement, as symptomatic improvement is the primary goal of these therapies. In our study, baseline LVOT gradients during VM and its reduction after PTSMA showed close relationships with the symptomatic improvement. This indicates that the measurement of LVOT gradients during VM is a reliable evaluation

**Figure 3** Left ventricular outflow tract gradients from 16 patients with latent left ventricular outflow tract gradients. VM, Valsalva manoeuvre; EE, exercise echocardiography.

**Figure 4** Relation between left ventricular outflow tract gradients induced by Valsalva manoeuvre and symptomatic improvement after percutaneous transluminal septal myocardial ablation. (A) Baseline left ventricular outflow tract gradient during Valsalva manoeuvre in relation to symptomatic improvement. (B) Percutaneous transluminal septal myocardial ablation induced reduction in left ventricular outflow tract gradients during Valsalva manoeuvre in relation to symptomatic improvement.
of the indication for PTSMA as well as a good assessment of the treatment effect (Figure 4). Other stress modalities have been used to induce LVOTO, but dobutamine-induced LVOTO has been shown to be an unspecific finding.\textsuperscript{31} LVOTO during EE in non-HCM patients is rare.\textsuperscript{32} Thousands of patients, who have received PTSMA treatment worldwide, are in general elderly patients with complex disease and considerable comorbidity. Extrapolation of the results from studies of younger HCM populations with less complex disease to older cohorts of PTSMA-treated patients may be misleading for the clinical management of PTSMA patients. The conclusions of this study are valid for these PTSMA-treated patients only, and the extrapolation of our results to HCM populations with different demographics might be misleading.

**Clinical implications**

In our study, stress by VM was enough to correctly categorize the phenotype of 93% of patients. Exercise echocardiography identified LVOTO in the last 7% of patients, but just as important, excluded LVOTO in the remaining non-obstructive patients. Exclusion of LVOTO in symptomatic patients is of major importance for the clinical management.

Valsalva manoeuvre is cheaper, less time-consuming, feasible in most patients and possibly safer than EE, and relates to the symptomatic improvement. We suggest that VM should be the first choice of stress modality in HCM patients with suspected LVOTO. However, the entire cohort of HCM patients cannot be managed sufficiently without the supplement of EE in a subset of patients. This is in accordance with EAE guidelines on stress echocardiography.\textsuperscript{16}

**Conclusion**

Valsalva manoeuvre and EE induce similar degrees of LVOT gradient, but the phenotype found by echocardiography at rest and during VM was unchanged by EE in more than 90% of patients. Exercise echocardiography solely identifies LVOTO in a few patients, but is especially important for the exclusion of LVOTO in symptomatic patients. Valsalva manoeuvre should be the primary choice of stress modality in HCM patients treated with PTSMA, but EE is essential for the clinical management of the entire cohort.

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**Conflict of interest:** none declared.

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