Sublingual isosorbide dinitrate for the detection of obstruction in hypertrophic cardiomyopathy

David Zemánek¹*, Pavol Tomašov², Stanislava Homolová², Kateřina Linhartová¹, and Josef Veselka¹

¹Department of Cardiology, University Hospital Motol, First and Second Medical School of Charles University, V Uvalu 84, 150 21 Prague, Czech Republic; and ²Department of Cardiology, University Hospital Motol and Second Medical School of Charles University, Prague, Czech Republic

Received 3 March 2011; accepted after revision 29 June 2011; online publish-ahead-of-print 4 August 2011

Aims
Hypertrophic cardiomyopathy (HCM) is predominantly associated with left ventricular outflow tract (LVOT) obstruction. The assessment of the obstruction with a provoking test should be a routine part of HCM evaluation. The aim of the study was to determine the utility of a sublingual spray application of isosorbide dinitrate (ISDN) for detection of an obstruction.

Methods and results
We have prospectively analysed 77 consecutive HCM patients, measuring the LVOT gradient at rest, using the sublingual spray application of ISDN (2.5 mg; after 2, 5, and 10 min), and with exercise echocardiography. An obstruction was defined as a gradient ≥30 mmHg. An obstruction was present in 15 patients (19%) at rest, in 42 patients (55%) after ISDN, and in 55 patients (71%) after exercise. The ISDN test had a sensitivity of 76% and the specificity of 100% relative to exercise echocardiography, while at-rest measurements had a sensitivity of 27% and a specificity of 100%. The chronological difference in the prevalence of obstructions during the ISDN test was statistically significant (P < 0.05); at ISDN plus 2 min, obstructions were seen in only 29 patients (38%, gradient 28.8 ± 25.0 mmHg), however, at ISDN plus 5 and 10 min, obstructions were found in 42 patients (55%, gradient 44.5 ± 39.6 mmHg).

Conclusion
The ISDN test is a reliable screening method for the detection of an HCM obstruction, however, the measurement should be delayed 5–10 min after the application of ISDN. Patients with negative ISDN tests should undergo exercise echocardiography.

Keywords
Hypertrophic cardiomyopathy • obstruction • left ventricular outflow tract • provoking test

Introduction
Hypertrophic cardiomyopathy (HCM) is a heart muscle disorder characterized by a left ventricular myocardial hypertrophy with a left ventricular outflow tract (LVOT) obstruction present in the majority of patients. Obstruction of the LVOT is an important pathophysiological component of HCM, and greatly depends upon the ventricular load and the contractile state; hence its severity can be highly variable. Consequently, while LVOT obstruction at rest is present in ∼25% of patients, the usage of a provoking test can increase the number up to 70%. Evaluation of LVOT obstructions are clinically relevant, because it may be associated with symptoms and can be managed by specific surgical and non-surgical interventions; additionally it is informative regarding prognosis. Many obstruction-provoking tests are able to increase the sensitivity of evaluations. The ‘gold standard’ is exercise echocardiography, however, this test takes time and equipment. In this study we sought to determine the utility of a sublingual spray application (2.5 mg) of isosorbide dinitrate (ISDN) for the evaluation of HCM LVOT obstructions and determine if the results were time dependent.

Methods
Between April 2007 and December 2009, 80 consecutive HCM patients were evaluated at our centre. The patients enrolled in the study met the following criteria: (i) wall thickness >15 mm and (ii) absence of a significant valvular disease (except mitral regurgitation related to HCM), coronary artery disease, and any other known cause of the left ventricular hypertrophy (amyloidosis, etc.).
The above-mentioned patients underwent a clinical examination, ECG, and a two-dimensional echocardiography (Sonos 7500, Philips, Andover, MA, USA). Echocardiography images were obtained in the parasternal long- and short-axis views and apical two- and four-chamber views, using a standard transducer positions by a single operator. The parameters of the left ventricle (LV, end-diastolic, end-systolic diameter, wall thickness) and left atrium (dimension and calculated volume) were measured in the parasternal long axis or apical four-chamber view. The hypertrophy was calculated according to the recommendation of the American Society of Echocardiography. The volume of the LV, left atrium, and the ejection fraction of the LV were calculated using a simplified Simpson’s method in a mono-plane projection. The peak gradient was measured using continuous-wave Doppler and calculated using a modified Bernoulli equation. Each examination was concluded with a sublingual spray application of isosorbide dinitrate (Isoket spray, Schwartz Pharma AG, Germany) 2.5 mg and measurements were obtained after 2, 5, and 10 min. This dose is recommended for using in coronary artery disease.

The exercise echocardiography was performed as a separate procedure at a later date. Patients underwent symptom-limited exercise testing on a treadmill, using a standard Bruce or a modified Bruce protocol according to their level of fitness. Immediately after the exercise, using a standard transducer positions by a single operator. The most frequently used, the Valsalva manoeuvre, has only limited evidence for reproducibility. Amyl nitrite or infusion of positive inotropes, has led to its use in clinical practice. For example, the most frequently used, the Valsalva manoeuvre, is very easy, but it requires the patient’s cooperation, it is not reproducible and results in a deterioration of the image quality. Measurement after position change, from supine to upright, has only limited evidence for reproducibility. Amyl nitrite has a similar vasodilator effect as ISDN, which leads to afterload reduction; however, it is not routinely available in many countries and has psychoactive effects, which has led to its use.

### Results

We prospectively evaluated 80 patients suffering from HCM. Two patients were excluded for their inability to participate in exercise testing due to comorbidities, and one patient was excluded for a rest gradient >100 mmHg, and symptoms of severe heart failure. As a result, 77 patients were enrolled. Clinical characteristics of patients are summarized in Table 1. A significant rest LVOT obstruction was measured in 15 patients (19%), the ISDN test increased the number to 42 patients (55%), and to 55 patients (71%) after exercise testing. Only 22 patients (29%) from the group were without LVOT obstruction.

### Discussion

The exercise echocardiography is still considered as the best method for evaluation of LVOT obstruction related to HCM not only for its high sensitivity, but also for the physiological simulation of real-life situations. However, this test is time consuming and requires the appropriate equipment. Other obstruction-provoking tests, such as the Valsalva manoeuvre, the upright position, a post-extrasystolic measurement, inhalation of amyl nitrite or infusion of pressure gradients (18.6 ± 15.6 vs. 44.5 ± 39.6 mmHg, P < 0.001). The results were also confirmed for pressure gradients (18.6 ± 15.6 vs. 44.5 ± 39.6 mmHg, P < 0.001).

Another objective was evaluation of the LVOT obstruction during the minute following ISDN application. An obstruction was only observed in 29 patients 2 min after ISDN application, compared with 42 patients after 5 or 10 min (P < 0.05). A statistically significant difference was also observed for the gradient in the LVOT (28.8 ± 25.0 vs. 44.5 ± 39.6, P < 0.001). The side effects of ISDN application were rare, only two patients had headache and another one had transient dizziness (with peak rest gradient of 76 mmHg).

Exercise echocardiography confirmed its ‘gold standard’ role for detection of LVOT obstructions. Obstructions were found in 55 of 77 patients and the LVOT gradient was also significantly higher than at rest or after the ISDN test. These results are presented in Table 2. The final distribution of LVOT obstructions for our group of patients is as follows: only 15 patients (19%) have LVOT obstruction at rest, in opposite to 42 patients (55%) after ISDN or 55 patients (71%) after exercise testing. Only 22 patients (29%) from the group were without LVOT obstruction.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM group</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (male, %)</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
</tr>
<tr>
<td>Septum (mm)</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
</tr>
<tr>
<td>LVH/BSA</td>
</tr>
<tr>
<td>MET</td>
</tr>
<tr>
<td>Clinical symptoms (%)</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LVEDD, end-diastolic diameter of the left ventricle; LV, left ventricle; LVH, left ventricular hypertrophy; BSA, body surface area; MET, metabolic equivalent task.
as a recreational drug. In addition, amyl nitrite has frequent unpleasant side effects (flush, dizziness). Catecholamines, such as isoproterenol or dobutamine, are effective provoking agents, but they require continuous ECG monitoring due to pro-arrhythmogenic effects.  

The haemodynamic effect of ISDN is caused by the drop-off of LVOT peak gradient (mmHg) 18.6 ± 15.6  Positive test (%) 19

| Table 2 Results for obstruction in the left ventricular outflow tract |
|------------------|------------------|------------------|------------------|
|                  | Rest measurement | ISDN, 2 min      | ISDN, 5–10 min   | Exercise echocardiography |
| LVOT peak gradient (mmHg) | 18.6 ± 15.6 | 28.8 ± 25.0 | 44.5 ± 39.6 | 62.2 ± 43.2 |
| Positive test (%) | 19              | 38              | 55              | 71              |

ISDN, isosorbide dinitrate; LVOT, left ventricular outflow tract.

In conclusion, the sublingual spray application of ISDN is a reliable screening method for the detection of LVOT obstructions in clinical routine. The measurement should be delayed 5–10 min after the application of ISDN. Early testing can lead to the false-negative results. Simple application, wide availability, and standardized dose are some of the key advantages related to its clinical use. Patients with a negative ISDN test should undergo an exercise echocardiography.

Conflict of interest: none declared.

Funding

This study was supported by grant MZOFNM 2005 from Ministry of Health, Czech Republic and by grant NT 11401-5 from the Internal Grant Agency, Ministry of Health, Czech Republic.

References

response to acute sublingual administration of an isosorbide dinitrate tablet, iso- 

left ventricular obstruction increased by nitroglycerin in elderly patients with 
hypertension and concentric left ventricular hypertrophy. Arch Med Coeur Vaiss 
1999;83:1155–60.

left ventricular outflow tract obstruction in patients with hypertrophic 
cardiomyopathy. Comparison of orthostasis testing and nitrate application. Int J 

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

mitral apparatus as potential cause of left ventricular outflow tract obstruction in 

Multislice computed tomography demonstrating anomalous left coronary 
artery from the pulmonary artery

Abdullah Icli, Melih Erdinc, Halil Mutlu*, Oguz Karahan, and Halil Kahraman

Department of Medicine, Baystate Medical Center, 759 Chestnut Street S2, Springfield, MA 01155, USA

* Corresponding author. Tel: +1 413 794 4320; fax: +1 413 794 1767; Email: histanbul@yahoo.com

Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare 
congenital anomaly that is often referred to as Bland–White–Garland syn-
drome in literature. In this case, a 44-year-old female with no significant past 
medical history presented with exertional dyspnoea and chest pain. Electrocardi-
ography showed atrial fibrillation and left bundle branch block. Echocardiogra-
phy showed moderately severe mitral and tricuspid regurgitation. Coronary angiogram showed an incidental finding of ALCAPA (see Sup-
plementary material online, Video S1). Multislice computed tomographic scan 
confirmed the diagnosis. She was surgically treated with a Button transfer pro-

cedure and pericardial patching, 28 mm saddle mitral ring annuloplasty and De 
Vega tricuspid annuloplasty. Control coronary artery angiography performed 
after surgery showed patent left coronary circulation and resolved collateral 
supply (see Supplementary material online, Video S2 and Video S3).

ALCAPA has an estimated incidence of 1 in 300 000 live births1 (between 
0.24 and 0.46% of all congenital cardiac anomalies).2 The embryological 
anomaly is a failure of the normal communication of the left coronary bud in the aorta with an abnormal connection to the pulmonary 
bud. Ninety per cent of these patients are symptomatic within first several months of life.2 Ninety per cent of the patients who survive 
into adulthood will die of sudden cardiac death at a mean age of 35 years.3 The oldest reported patient in English literature is 72 years 
old.2 Myocardial ischaemia in the anterior territory is the cause of death in most cases. The diagnosis of ALCAPA requires a high level 
of suspicion. Doppler echocardiography may be sufficient to diagnose ALCAPA. ALCAPA has a high mortality rate without surgery.

Figure 1 This preoperative multislice cardiac computer tomography with three-dimensional construction demonstrated the dilated 
right coronary artery, left coronary artery, and anomalous left coronary artery originating from the pulmonary artery.

Supplementary data
Supplementary data are available at European Journal of Echocardiography online.

References
3. Singh TP, Carli MF, Sullivan NM, Leenen MF, Morrow WR. Myocardial flow reserve in long term survivors of repair of anomalous left coronary artery from pulmonary 

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com