Sublingual isosorbide dinitrate for the detection of obstruction in hypertrophic cardiomyopathy

David Zemánek1*, Pavol Tomášov2, 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 \( \geq 30 \text{ mmHg} \). 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 \pm 25.0 \text{ mmHg}), however, at ISDN plus 5 and 10 min, obstructions were found in 42 patients (55%, gradient 44.5 \pm 39.6 \text{ 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 \( \sim 25\% \) of patients, the usage of a provoking test can increase the number up to 70%.1 Evaluation of LVOT obstructions are clinically relevant, because it may be associated with symptoms and can be managed by specific surgical and nonsurgical interventions; additionally it is informative regarding prognosis.2–4 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 position 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 monoplane 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, the patients were placed in the left lateral decubitus position and the gradient was measured. All gradients were obtained within 1 min, which is in accordance with the guidelines for an exercise echocardiography. During exercise, a 12-lead ECG was run continuously and blood pressure measurements were obtained every 3 min. Long-term medications (such as beta-blockers, calcium channel blockers, etc.) were not discontinued during testing.

A significant obstruction was defined as a peak gradient of >30 mmHg. Statistical analysis of gradients was performed using the Student’s t-test. A P value < 0.05 was considered significant. Comparison of the prevalence of the obstruction at 2 min and at 5 and 10 min, in the ISDN test, was performed using the Pearson’s χ² test. All the measurements were documented.

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%) using exercise echocardiography (Table 2). All patients with a significant rest obstruction also had positive ISDN tests and exercise echocardiography tests; all patients with a significant obstruction during the ISDN test also had a positive exercise echocardiography. Using exercise echocardiography as the ‘gold standard’, the sensitivity of the rest measurement (27%) was significantly lower relative to the sensitivity of the ISDN test (76%; P < 0.01), with the same specificity (100%). 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.

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 positive inotropes, have drawbacks relative to routine 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.
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.10

The haemodynamic effect of ISDN is caused by the drop-off of the left ventricular preload and afterload. The effect of a sublingual spray application is delayed in HCM, in a similar way to its more common use in coronary artery disease. Further, the ISDN sublingual spray application has more rapid onset of its effect than sublingual and oral tablets.11 We found that measurements should be deferred, in most cases, up to 5–10 min; measurements taken earlier than 5–10 min after ISDN application can give false negative results. The nitroglycerine sublingual spray has similar haemodynamic effect and so we can expect the same result for it. However, it has a mildly different pharmacokinetics than ISDN so the time intervals and results may vary slightly.12

Despite the fact that the haemodynamic effects of nitrates on LVOT obstruction are well known, there are only occasional references in the medical literature dealing with the use of nitroglycerine or ISDN in HCM patients. One study documented an increased peak intraventricular gradient after sublingual nitroglycerine, but only in a small group (20 patients) and did not compare the result with other tests.13 Another study also evaluated a small cohort (16 patients), but it compared it with an unusual orthostatic test (using head-up tilt).14 Amyl nitrite is a more fully investigated vasodilator agent, especially in the USA. Its haemodynamic effect is similar to ISDN. However, in comparison to exercise echocardiography, a relatively poor correlation was observed in a study with 57 HCM patients. In this study, amyl nitrite was found to be similar to ISDN, with regard to ‘sensitivity’, when compared with exercise echocardiography, however, there were many more false-negative results compared with our results with ISDN.9 These results are similar to recently published data, which compare the Valsalva manoeuvre against exercise echocardiography. In this study, the Valsalva manoeuvre also lacked the specificity of exercise echocardiography.15

Despite the positive results and the simplicity of the ISDN test, there is still one issue that needs mentioning, which is the usefulness of the ISDN test for prediction of clinical improvement after gradient reduction procedures (i.e. surgical myectomy, alcohol septal ablation). On the other hand, all patients in our study with a positive ISDN test also had a positive exercise echocardiography, which is considered as ‘gold standard’ in this evaluation. Nevertheless, the indication for gradient reduction procedures is based on a complex evaluation including clinical symptoms and other echocardiographic findings.16

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
5. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. American Society of Echocardiography’s Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108.

Table 2 Results for obstruction in the left ventricular outflow tract

<table>
<thead>
<tr>
<th></th>
<th>Rest measurement</th>
<th>ISDN, 2 min</th>
<th>ISDN, 5–10 min</th>
<th>Exercise echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT peak gradient (mmHg)</td>
<td>18.6 ± 15.6</td>
<td>28.8 ± 25.0</td>
<td>44.5 ± 39.6</td>
<td>62.2 ± 43.2</td>
</tr>
<tr>
<td>Positive test (%)</td>
<td>19</td>
<td>38</td>
<td>55</td>
<td>71</td>
</tr>
</tbody>
</table>

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

Downloaded from https://academic.oup.com/ehjcimaging/article-abstract/12/9/684/2397209 by guest on 23 November 2018
response to acute sublingual administration of an isosorbide dinitrate tablet, iso-

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 52, 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 syndrome in literature. In this case, a 44-year-old female with no significant past medical history presented with exertional dyspnoea and chest pain. Electrocardiography showed atrial fibrillation and left bundle branch block. Echocardiography showed moderately severe mitral and tricuspid regurgitation. Coronary angiogram showed an incidental finding of ALCAPA (see Supplementary material online, Video S1). Multislice computed tomographic scan confirmed the diagnosis. She was surgically treated with a Button transfer procedure 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

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