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Research article

Provocation of left ventricular outflow tract obstruction using nitrate inhalation in hypertrophic cardiomyopathy: Relation to electromechanical delay

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ABSTRACT

Background: Left ventricular outflow tract obstruction (LVOT) is an independent predictor of adverse outcome in hypertrophic cardiomyopathy (HCM). It is of major importance that the provocation modalities used are validated against each other.

Aim: To define the magnitude of LVOT gradients provocation during both isosorbide dinitrate (ISDN) inhalation and treadmill exercise in non-obstructive HCM and analyze the correlation to the electromechanical delay using speckle tracking.

Methods: We studied 39 HCM pts (64% males, mean age 38 ± 13 years) regional LV longitudinal strain and electromechanical delay (TTP) was analyzed at rest using speckle tracking. LVOT gradient was measured at rest and after ISDN then patients underwent a treadmill exercise echocardiography (EE) and LVOT gradient was measured at peak exercise.

Results: The maximum effect of ISDN on LVOT gradient was obtained at 5 minutes, it increased to a significant level in 12 (31%) patients, and in 14 (36%) patients using EE, with 85.6% sensitivity & 100% specificity. Patients with latent obstruction had larger left atrial volume and lower E/A ratio compared to the non-obstructive group ($p < 0.01$). LVOTG using ISDN was significantly correlated with that using EE ($p < 0.0001$), resting LVOTG ($p < 0.0001$), SAM ($p < 0.0001$), EF% ($p < 0.02$) and regional electromechanical delay but not related to global LV longitudinal strain. Using multivariate regression, resting LVOTG ($p = 0.006$) & TTP mid septum ($p = 0.01$) were found to be independent predictors of latent LVOT obstruction using ISDN.

Conclusion: There is a comparable diagnostic value of nitrate inhalation to exercise testing in provocation of LVOT obstruction in HCM. Latent obstruction is predominantly dependent on regional electromechanical delay.

Keywords: LVOT obstruction provocation, electromechanical delay, hypertrophic cardiomyopathy

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What is already known about this subject?

In hypertrophic cardiomyopathy (HCM) left ventricular outflow tract obstruction (LVOT) is dynamic, being greater in situations of increased LV contractility, reduced preload and afterload. It is an independent predictor of adverse outcome. Exercise echocardiography has been validated to incite LVOT obstruction in non-obstructive HCM patients.

What does this study add?

In non-obstructive HCM, ISDN inhalation is a reliable screening method for the detection of LVOT obstructions in clinical practice, and ***equivalent to exercise testing***. Latent obstruction is directly correlated to resting regional LV electromechanical delay. The prolonged electromechanical activation of mid-septal segment is a key determinant to inducible obstruction in HCM population and can be used to predict LVOT gradient provocation.

How might this impact on clinical practice?

Assessment of LVOT gradients with ISDN might be a bedside routine component of the evaluation of non-obstructive HCM. So it may broaden management options by identifying symptomatic patients not able to do exercise and otherwise regarded as potential candidates for septal reduction therapy.

INTRODUCTION

Obstruction to left ventricular outflow (LVOT) is an important pathophysiological component of hypertrophic cardiomyopathy (HCM).[1–3] When present under resting (basal) conditions, or developed during exercise, obstruction in HCM is an important cause of symptoms and disease progression. It is an independent predictor of adverse clinical consequences and identifies a subgroup of patients in whom septal reduction interventions such as surgical myectomy or alcohol septal ablation may be considered therapeutic options.[4,5]

LVOT gradient in HCM is dynamic, being greater in situations of increased LV contractility, reduced preload and afterload.[6] Its measurements are highly dependent on a standardized environment and mainly caused by narrowing of the LVOT due to septal hypertrophy and systolic anterior movement (SAM) of the mitral leaflets.[6]

Current consensus suggests the use of exercise echocardiography to reveal stress-induced LVOT obstruction in HCM patients.[7,8] However, the question is whether or not it is possible to perform exercise treadmill testing in all HCM patients. Therefore, it is of major importance that the provocation modalities used are validated against each other.

On the other hand, recent studies have documented the positive association of intraventricular delay with LVOT gradient in HCM patients with obstruction under basal condition.[9,10] However no studies have examined the relation of electromechanical behavior to latent obstruction using provocation tests. This relation may provide additional information for characterizing subgroups of patients at increased risk of cardiovascular event.

Therefore, in this study, we compared the results of echocardiographic measurements of LVOT gradients at rest and during both isosorbide dinitrate inhalation (ISDN) and treadmill exercise in non-obstructive HCM and analyzed the correlation to the electromechanical activation delay using speckle tracking.

PATIENTS AND METHODS

Study population

A total of 165 HCM patients were prospectively evaluated between September 2011 to May 2013 at the Yacoub Research Unit, Menoufiya University, Egypt (as a part of BA-HCM National Program). All patients had non-dilated hypertrophic LV (maximal wall thickness $\geq$15 mm) in the absence of other cardiac or systemic diseases capable of producing the magnitude of hypertrophy evident.[11]

Of these patients, 126 were judged ineligible and were excluded from the study for the following reasons: particularly LVOT gradient at rest $\geq$ 30 mmHg, advanced age or heart failure "end-stage" phase with systolic dysfunction, prior septal myectomy, ICD implantation, excessive arrhythmic risk with prior documentation of ventricular tachyarrhythmias related to activity, recent exertional syncope, comorbid medical conditions that prohibited reliable exercise testing.

We evaluated the measurements of LVOT gradients obtained by two modalities (exercise treadmill and ISDN inhalation) in relation to LV deformation in a consecutive cohort of 39 HCM (age: 38 $\pm$ 8

years) after their informed consent, and approval of Ethics Committee of Menoufiya University Hospitals was obtained.

Resting echocardiography

Measurements were performed on Esaote Mylab 30 Gold ultrasound system (Esaote S.p.A, Florence, Italy) equipped with a 5 MHz phased-array transducer. Using standard techniques to obtain M-mode, 2-dimensional, and Doppler measurements, each patient had echocardiographic evaluations performed at rest: in left lateral decubitus, with assessment of LV dimensions (in systole and diastole), maximal LV wall thickness and LVOT gradient (via continuous wave Doppler to evaluate gradients derived from Doppler velocity profiles typical of subaortic obstruction) using Bernoulli equation ($PG = 4V^2$).

Each examination was completed with a sublingual spray application of isosorbide dinitrate (ISDN) (Isoket spray, Schwartz Pharma AG, Germany) 2.5 mg and LVOT gradient measurements were obtained after 2, 5, and 10 min. This dose is recommended for using in coronary artery disease (CAD).

Analysis of LV deformation

Tracking and subsequent strain calculations were performed with the software package Esaote-X-Strain based on a previously validated algorithm.[12] Scanning was performed longitudinally from the apex to acquire best apical views. Frame rate (70 ± 20 F/s), was adjusted depending on the heart rate. Longitudinal strain (εsys) was measured in the basal, mid and apical segments of antero-septal, posterior, posteroseptal, lateral, anterior and inferior wall. In order to reduce random noise, each sample was obtained by averaging more than one consecutive heart cycle (usually three).

To estimate LV electromechanical delay, time to peak strain (TTP) was measured from regional longitudinal strain curves for each ventricular segment (Figure 1), as time from the beginning of Q wave of ECG to the time to peak ε_{sys}.[12] LV dyssynchrony was defined as the standard deviation of the averaged time-to-peak-strain (TTP-SD).[12]

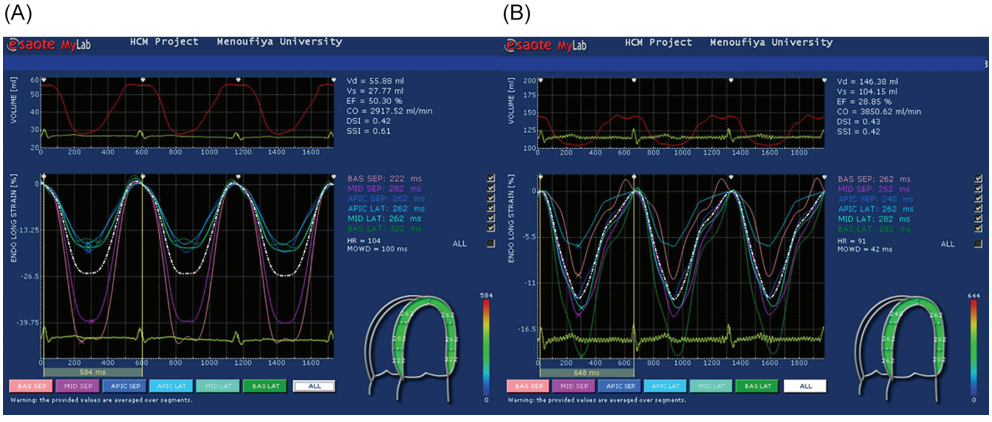

Figure 1. LV longitudinal strain curves in apical 3Ch of HCM patient: (A) Latent obstruction: electromechanical delay (TPP) between basal and mid segments is 60 ms in (B) Non obstructive: the difference between TTP of mid and basal septal segments is 0 ms.

Exercise echocardiography (EE)

The EE was performed as a separate procedure at a later date. Patients underwent symptom-limited exercise testing on a treadmill, using a Modified Bruce protocol. Exercise was terminated when the predicted heart rate was achieved or when fatigue, dyspnea, chest pain, or hypotension developed. During exercise, a 12-lead ECG and blood pressure measurements were obtained every 3 min. Immediately after exercise, and within 1 min, the patient was placed in a semi-supine position and with a left lateral tilt to enable immediate imaging of apical views and measurement of subaortic gradient, which is in accordance with the guidelines for an exercise echocardiography.[13]

A significant latent obstruction developed by the two modalities was defined as a peak LVOT gradient ≥ 30 mmHg. Long-term medications (such as beta-blockers, calcium channel blockers, etc.) were discontinued from 24 to 72 hours before EE and ISDN testing because in some patients it was judged imprudent to discontinue drug therapy because of dependence on medication to control symptoms.

Statistical analysis

Data were presented as numbers and percentages or mean ± SD. Continuous variables were compared using the unpaired or paired Student t-test, as indicated. The distributions of qualitative data were compared using the chi-square or Fisher's exact test, as appropriate. Pearson's correlation coefficient was calculated to express the tightness of the relation between continuous variables. Statistical significance was defined by a P value < 0.05. All tests were bilateral. Variables that were statistically significant in univariate analysis were used in two multivariate analysis models. The first was a repeated measures ANOVA used to evaluate the change of pressure gradient from resting values to after 2, 5 and 10 minutes of using nitroglycerine. The second was a forward stepwise logistic regression analysis model used to detect independent predictors of latent LVOTO. Statistical analysis was performed using IBM SPSS statistical software for Mac, version 21.

RESULTS

LVOT gradient provocation using ISDN

The effect of nitroglycerine at 2, 5 and 10 minutes as regard LVOT gradient, HR and BP was depicted in (Table 1, Figure 1), the maximum effect of ISDN on LVOT gradient was obtained at 5 minute and it was compared with that of peak exercise.

Table 1. Hemodynamics during ISDN inhalation.

	LVOTO (mmHg)	HR (b/min)	SBP (mmHg)	DBP (mmHg)
Rest	12.7 ± 9.7	75 ± 17	120 ± 20	79 ± 14
Min 2	17 ± 16	80 ± 14	114 ± 18	75 ± 12
Min 5	25.8 ± 27*	85 ± 16*	106 ± 19*	74 ± 14
Min 10	18 ± 18	77 ± 14	112 ± 19	77 ± 12

*: $p < 0.01$ versus rest value. LVOTO: gradient across left ventricular outflow tract; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The ISDN test at 5 min increased LVOT gradient to significant level in 12 (31%) of 39 patients, and in 14 (36%) patients using exercise echocardiography (Table 2). 10 (83%) patients with a significant

Table 2. Clinical and conventional echocardiographic data.

	All HCM cohort (n = 39)	Latent obstruction 14 (36%)	Non-obstruction 25 (64%)	p-value
Age (year)	38 ± 13	39 ± 14	37 ± 13	0.9
Male	25 (64%)	8 (57%)	17 (66%)	0.5
Familial HCM	16 (41%)	5 (36%)	11 (44%)	>0.05
NYHA I	9 (23.1%)	4 (29%)	5 (20%)	0.05
NYHA II	22 (56.4%)	7 (50%)	15 (60)	>0.05
NYHA III/IV	8 (20.5%)	3 (21%)	5 (20%)	>0.05
AF	4 (10.2%)	0 (0%)	4 (16%)	>0.05
Asymmetric LVH	32 (82%)	12 (86%)	20 (80%)	>0.05
Concentric LVH	7 (18%)	2 (14%)	5 (20%)	>0.05
No/Mild MR	26 (66.7%)	7 (50%)	19 (76%)	0.07
Moderate MR	9 (23.1)	3 (21%)	6 (24%)	0.09
Severe MR	4 (10.2%)	4 (29%)	0 (0%)	0.03
SAM	11 (28.2%)	9 (64%)	2 (8%)	0.0001
LA (mm)	39.8 ± 7.6	40 ± 8.3	36 ± 3.4	0.8
LAV (ml)	72.4 ± 30	83 ± 83	64 ± 24	0.2
ESD (mm)	22.1 ± 5	21.4 ± 5.2	22.4 ± 5.2	0.2
EDD (mm)	36.4 ± 6	37.7 ± 6.6	35.5 ± 5.7	0.5
EF (%)	70.5 ± 7	75 ± 11	67 ± 10	0.03
SPT (mm)	26.4 ± 5.5	26 ± 7	27 ± 5	0.6
LVPW (mm)	15.4 ± 4	15.4 ± 3	15.3 ± 2.7	0.9
LVMI (gm/m^2)	224 ± 64	237 ± 67	218 ± 65	0.3
LVOTG (mmHg)	12.7 ± 9.7	69 ± 18	11.5 ± 7	0.001
E/A	1.25 ± 0.55	0.9 ± 0.26	1.4 ± 0.58	0.01
PAP (mmHg)	26 ± 8	24 ± 5	26 ± 9	0.5

NYHA: New York Heart Association; AF: atrial fibrillation; LVH: left ventricular hypertrophy, MR: mitral regurgitation; SAM:systolic anterior motion; LA left atrium; ESD: left ventricular end-systolic diameter, EDD: left ventricular end-diastolic diameter; EF: ejection fraction, MWT:maximal wall thickness, LVPW = posterior wall thickness, SPT: septal thickness; LVMI:left ventricular mass index, LVOTG left ventricular outflow tract gradient, DT: E/A: ratio of early to late diastolic mitral inflow velocity, PAP:pulmonary artery pressure.

obstruction during the NTG test also had a positive EE. Using EE as the 'gold standard', the sensitivity of NTG test was (85.7%) and the specificity was (100%). The results for pressure gradients in whole cohort were fairly lower in NTG compared to EE (25.8 ± 27 vs. 29 ± 28 mmHg, $P < 0.06$). Nevertheless, the correlation between the two measurements was high ($R2 = 0.856$, $p < 0.0001$), with small absolute individual differences (average 10 ± 3 mm Hg).

Exercise echocardiography

Measurement of LVOT gradients was possible in all patients during EE. LVOT gradients increased from 11(5–20 mmHg) at rest to 29 (8–96 mmHg) during EE ($p < 0.001$). In 34 (87.1%) of patients, the patients achieved the target heart rate. Two patients experienced a self-limiting episode of hypotension at peak EE. One patient experienced severe but transient dizziness, one patient stopped due to chest pain and two patients due to dyspnea or leg muscle fatigue. Patients were categorized into 2 groups according to presence of latent LVOT obstruction.

Comparisons between latent and non-obstructive groups

No differences in the prevalence of familial type, and functional classes between non-obstructive and latent obstruction groups (Table 2). There was a non-significant trend towards more males with latent obstruction compared to females ($p = 0.08$). No differences in LV wall thickness or cavity dimensions between the two groups. Patients with latent obstruction had larger left atrial & volume, higher prevalence of SAM, lower E/A ratio compared to the non-obstructive group ($p < 0.01$) and no difference in the severity of hypertrophy as assessed by LVMI.

At peak exercise 3/39 (7.6%) patients had a significant increase in mitral regurgitation grade, all in latent obstruction cohort. 11 (78.5%) had a peak LVOT gradient of >50 mmHg. These patients were more likely to have a higher prevalence of syncope/presyncope 4 (28.5%) compared to 2 (8%) in non-obstruction group, $p < 0.001$. The side effects of ISDN application were rare, only one patient had headache (with peak gradient of 52 mmHg).

LV electromechanical delay

No difference of regional or global longitudinal strain between patients with latent obstruction and non-obstruction group (Table 3). The TTP of mid anteroseptum, basal, mid anterior, basal and mid lateral wall segments were significantly prolonged in latent obstruction cohort ($p < 0.001$).

Table 3. LV longitudinal strain and regional electromechanical delay.

	Latent obstruction 14 (36%)	Non-obstruction 25 (64%)	p-value
ε_{sys} septum (%)	−12.2 ± 10.6	−10.6 ± 7.7	0.7
ε_{sys} lateral (%)	−14.2 ± 8.3	−11.2 ± 6.4	0.4
ε_{sys} anterior (%)	−11.8 ± 7	−9.5 ± 5.7	0.7
ε_{sys} inferior (%)	−9.9 ± 4.9	−9.6 ± 5	0.7
ε_{sys} Global (%)	**−12.6 ± 5.5**	**−10 ± 5**	**0.6**
TTP basal AS	382 ± 78	339 ± 83	0.66
TTP mid AS	413 ± 90	333 ± 95	0.001
TTP apical AS	367 ± 124	314 ± 77	0.2
TTP mean septum	**384 ± 71**	**335 ± 97**	**0.1**
TTP basal lateral	451 ± 116	389 ± 88	0.01
TTP mid lateral	440 ± 121	373 ± 77	0.01
TTP apical lateral	385 ± 161	330 ± 111	0.06
TTP mean lateral	**408 ± 106**	**364 ± 81**	**0.09**
TTP basal anterior	453 ± 158	339 ± 126	0.002
TTP mid anterior	431 ± 168	329 ± 114	0.002
TTP apical anterior	400 ± 118	323 ± 109	0.1
TTP mean anterior	**419 ± 132#**	**331 ± 106**	**0.01**
TTP basal inferior	398 ± 135	363 ± 114	0.4
TTP mid inferior	403 ± 130	357 ± 88	0.26
TTP apical inferior	393 ± 131	314 ± 95	0.07
TTP mean inferior	**398 ± 113**	**357 ± 88**	**0.11**
TTP basal PS	363 ± 35	336 ± 30	0.5
TTP mid PS	385 ± 27	359 ± 27	0.78
TTP-SD	**71 ± 36**	**65 ± 33**	**0.58**

ε_{sys}: peak systolic strain; TTP: time to peak strain; AS: antero-septal; PS: postero-septal.

The electromechanical activation of basal septal segment (382 ± 78 ms) was considerably earlier than mid-septal activation (413 ± 90 ms) in patients with latent obstruction (43 ± 76 ms, $p < 0.01$) compared to non obstructive group (323 ± 83 ms) for basal septum and 339 ± 95 ms for mid septum (22 ± 27 ms, p = NS). However, intraventricular dyssynchrony (TTP-SD) was not considerably different between the two groups (p = ns).

Relation of LVOT gradient to clinical and echocardiograpgic variables

The peak gradient for the whole cohort using EE was 29 ± 28 mmHg. It showed direct correlation to resting LVOT gradient ($r = 0.766$, $p < 0.0001$, EF% ($r = 0.357$, $p < 0.02$) and regional electromechanical delay (Table 4). Moreover, it showed strong correlation to PG at 5 min ISDN inhalation($r = 0.876$, $p < 0.0001$). Similarly, PG at 5 minutes after ISDN when taken separately, it was significantly correlated with resting LVOTG ($r = 0.77$, $p < 0.0001$), SAM ($r = 0.76$, $p < 0.0001$), EF% ($r = 0.36$, $p < 0.02$). The PG provocation was considerably related to TTP of mid septum ($p < 0.005$), TTP of apical septum ($p < 0.01$), basal lateral ($p = 0.002$), and mid lateral ($p < 0.002$). The difference between TTP of basal and mid anteroseptal was 33 ± 18 ms and there was modest correlation between PG provocation and the magnitude of difference between basal and mid-septal and ($r = 0.37$, $p < 0.024$); nevertheless, this PG was not correlated to global LV dyssynchrony. Variables with significant relation in univariate analysis, were introduced in a regression analysis model to detect independent predictors of obstruction using ISDN inhalation. TTP mid septum ($p = 0.018$) and resting LVOTG ($p = 0.006$) were found to be independent predictors of latent LVOT obstruction using NTG (Figures 2–5).

Table 4. Relation of left ventricular outflow gradient to regional electromechanical delay.

TTP	Basal AS	Mid AS	Apical AS	Basal lateral	Mid lateral	Apical lateral	Basal anterior	Mid anterior
EE	R = 0.082	r = 0.43	r = 0.28	r = 0.42	r = 0.41	r = 0.204	r = 0.371	r = 0.244
	P = 0.63	p = 0.008	p = 0.084	p = 0.009	p = 0.011	p = 0.220	p = 0.020	p = 0.135
ISDN	R = 0.07	r = 0.45	r = 0.38	r = 0.49	r = 0.49	r = 0.312	r = 0.283	r = 0.190
	P = 0.69	p = 0.005	p = 0.018	p = 0.002	p = 0.002	p = 0.057	p = 0.081	r = 0.25

TTP	Apical anterior	Basal inferior	Mid inferior	Apical inferior	Basal PS	Mid PS	TTP-SD
EE	R = 0.36	r = 0.14	r = 0.239	r = 0.279	r = 0.36	r = 0.244	r = 0.052
	P = 0.025	p = 0.404	p = 0.142	p = 0.086	p = 0.025	p = 0.135	p = 0.772
ISDN	R = 0.26	r = 0.143	r = 0.259	r = 0.185	r = 0.223	r = 0.250	r = 0.089
	P = 0.109	p = 0.384	p = 0.111	p = 0.259	p = 0.171	p = 0.125	p = 0.569

TTP: time to peak strain; EE: exercise echo; ISDN: isosorbide dinitrate; AS: anteroseptal, PS: posteroseptum.; TTP: time to peak strain; SD: standard deviation.

Regression equations for predicting LVOTO

The multivariate regression analysis enables prediction of LVOT provocation using ISDN inhalation through measurement TTP of mid septum, using the following regression equation: **$Y = 0.143\ X - 14.3$**, where Y is LVOTO with provocation and X is TTP of mid septum segment. Additionally, using resting pressure gradient (in mm), the latent gradient can be derived as follow: **$Y = 1.25X + 10$**, where Y is latent obstruction at 5 min ISDN and X is the resting obstruction.

DISCUSSION

This study is to our knowledge the first work that compares the use of two stress modalities, ISDN and EE, in the evaluation of latent LVOT obstruction and its relation to LV electromechanical delay in HCM.

The present study demonstrates a comparable diagnostic value of nitrate inhalation to exercise testing in provocation of LVOT obstruction in HCM. Latent LVOT obstruction is not related to global longitudinal strain but directly correlated to LV short axis function, as evaluated by ejection fraction, presence of SAM and predominantly dependent on regional electromechanical delay. Electro-mechanical activation of mid-septal segment is the key determinant of LVOT gradient provocation in this population.

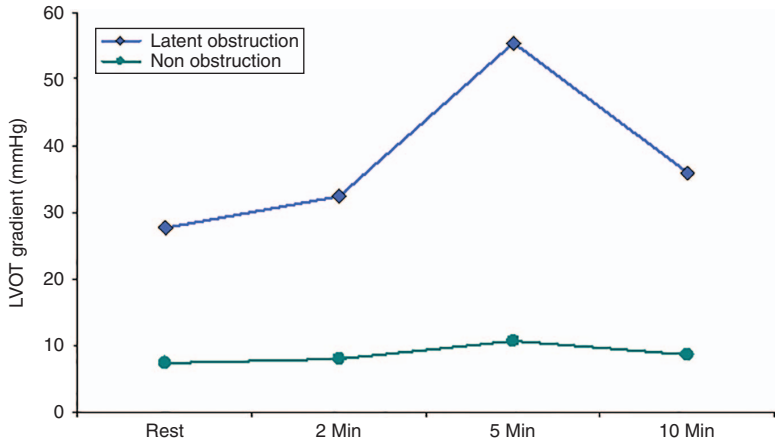

Figure 2. Estimated marginal means of pressure gradient after ISDN: comparison of patients with and without obstruction.

LVOT obstruction provocation using ISDN

Generally most pharmacologic and physiologic provoking tests that previously applied have drawbacks relative to routine clinical practice.[14–19] The haemodynamic effect of ISDN is caused by the reduction of LV preload and afterload. Its effect is delayed in HCM, in a similar way to its more common use in CAD. Further, the ISDN sublingual spray application has more rapid onset of its effect than sublingual and oral tablets.[6,20]

In the present study, we demonstrated that measurements of peak LVOT gradient, in most cases, is achieved after 5 min of ISDN application; measurements taken earlier can give false negative results. The peak gradient showed direct correlation to LVOT gradient at peak EE and it showed 86% sensitivity and 100% specificity. Concordantly, Zemánek et al.[20] analyzed 77 consecutive HCM patients, measuring the LVOT gradient at rest, using ISDN and with EE. The ISDN test had a sensitivity of 76% and the specificity of 100% relative to EE.

While Marwick et al.[15] compared the ability of amyl nitrite and exercise testing to provoke outflow tract gradients in 57 HCM patients, a lower specificity and a relatively poor correlation was observed compared to exercise testing. Another study also evaluated a small cohort (16 patients), but it compared it with an unusual orthostatic test (using head-up tilt).[21] Orthostasis testing was able to identify all patients with obstructive HCM and demonstrated a diagnostic value similar to nitrate application.

In the present study, latent LVOT obstruction was significantly correlated with resting LVOTG, SAM and EF%. SAM and mitral-septal contact, usually produced by the leading edge of AML,[22–24] is

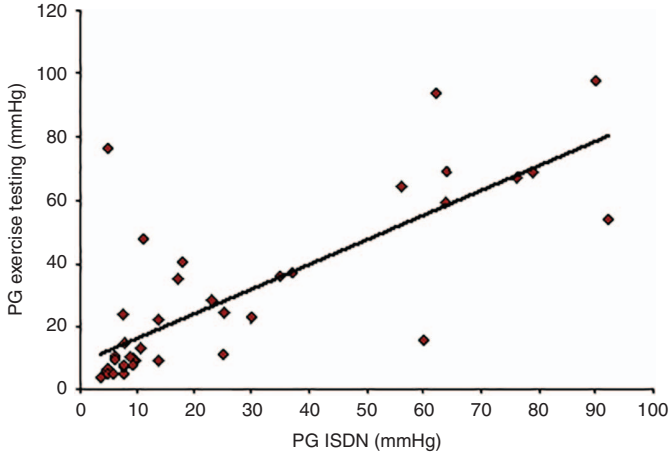

Figure 3. Relationship of pressure gradient provocation using ISDN versus exercise testing ($r = 0.76$, $p < 0.0001$).

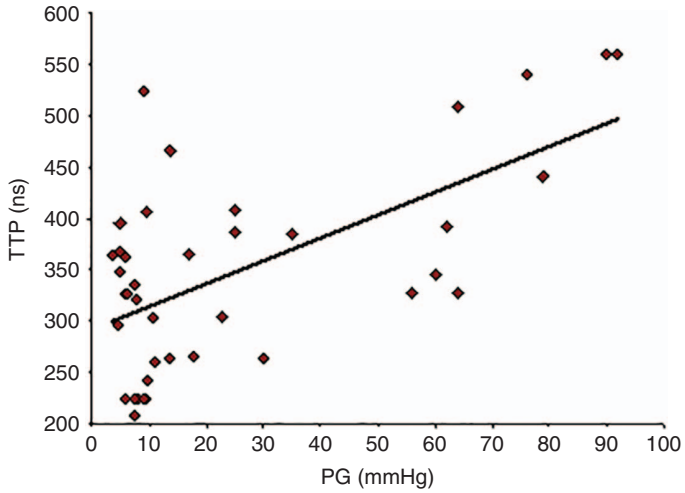

Figure 4. Relationship of LVOT gradient using ISDN to mid-septal electromechanical delay ($r = 0.45$, $p < 0.005$).

responsible for obstruction to LV outflow in 95% of cases.[24] It may also occur in the absence of SAM[25] due to muscular apposition or anomalous insertion of the anterolateral papillary muscle directly into AML.[26] In our study SAM was responsible for 64% of patients with latent obstruction.

From previous studies, determinants of SAM and outflow obstruction include the vigorous LV ejection, as well as the unusual chamber geometry and morphology.[25,26] This forceful contraction reduces outflow tract cross-sectional area to which the hypertrophied septum contributes and usually associated with exaggerated anterior displacement of the mitral valve apparatus and papillary muscles. This could explain our findings of strong relationship of latent obstruction to LVEF%.

In the present study, we did not found important relation between LVOT provocation and resting global longitudinal strain and no difference of longitudinal strain between obstructive and non-obstructive HCM. This is true despite direct correlation of inducible LVOT gradient to LVEF%, which confirms the divergence of long axis and short axis systolic function in this heterogenous disease.

This is discordant to the findings reported by van Ramshorst et al.[27] who reported immediate decrease in septal strain after alcohol septal ablation, which was strongly related to a decrease in LVOT gradient after 6 months. They considered the reduction in septal strain as an early determinant for long-term success of the ASA procedure. However, the behavior of regional LV strain and its change during provocation may be not the same, which is not examined in their treated group.

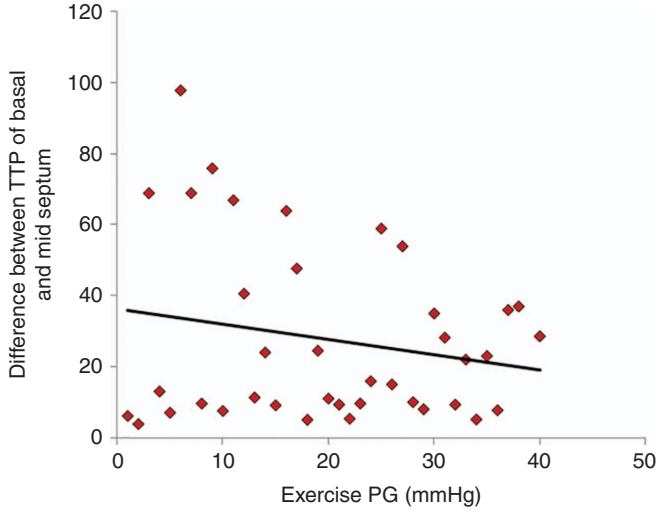

Figure 5. Relationship of PG provocation to difference between basal and mid-septal TTP ($r = 0.37$, $p < 0.02$).

Relation of latent obstruction to electromechanical delay

It is known that, optimal hemodynamics which includes decreasing pressure gradient of LVOT and increase cardiac output is obtained by coordinated contraction. The present study is first one that investigated the relationship between LVOT obstruction and regional LV electromechanical heterogenity. Latent LVOT obstruction was directly correlated to delayed electromechanical activation especially of mid-septal segment; it was associated with early basal septal activation when compared to non-obstruction cohort.

Several mechanisms can be proposed to clarify the relation of LVOT obstruction to regional electromechanical delay. First, the earlier mechanical activation of basal septal segment is resulting in proximal septal bulge which morphologically narrows LVOT. The narrow LVOT increases flow velocity which produces local pressure drop by the Venturi effect, drawing AML toward LVOT. Second, the delayed mid-septal activation will create a large angle of strike and increase the drag forces on to the AML. Third, the presence of SAM, of mitral leaflet in 67% of this population, is associated with delayed mechanical activation of its attached lateral wall segments. This will contribute to the further narrowing of LVOT in patients with inducible obstruction. The significance of these factors can be confirmed by recent study of surgical septal myectomy, which revealed that LVOT enlarged, ejection flow became more parallel to mitral leaflet, and the LVOT gradient is decreased after successful septal reduction.[7]

In the present study, however, LVOT obstruction appeared to be induced not only through SAM of mitral leaflet, but rather by the delayed protrusion of mid septum during systole, because TTP of mid septum was manifest as the only determinant of latent obstruction in this study, beyond resting pressure gradient.

Recently, LVOT obstruction can be provoked not only in HCM but also in other various conditions, including acute myocardial infarction,[27,28] Takotsubo cardiomyopathy,[28,29] and even sigmoid septum.[29,30] These conditions are also associated with increase of regional electromechanical delay and LV dyssynchrony.

Additionally, in the current study, despite the absence of intraventricular conduction defects by surface ECG in our HCM cohort, heterogenous myocardial systolic activation was detected in patients with latent obstruction and correlated to LVOT gradient. These results are not surprising considering a previous study by D'Andrea et al.[9] demonstrated that LV intraventricular delay using Doppler myocardial imaging (DMI) in HCM was directly correlated to LVOT gradient, and DMI intra-V-Del was the most powerful independent predictor of sudden cardiac death ($p < 0.0001$) in the subsequent 5 years. This information provided significant incremental prognostic value when compared with clinical information and other instrumental data.

Previous studies have demonstrated an adverse impact of latent LVOT obstruction on survival.[2–4] However, higher risk in this cohort cannot be explained simply by presence of obstruction, but probably because of the underlying mechanism and hidden electromechanical dysfunction behind inducible obstruction in this population.

Therefore, myocardial heterogeneity in HCM could represent an anatomical and electrical substrates that may on one hand determine a non-uniform systolic activation of LV wall and on the other hand establish a basic unit in dynamic LVOT obstruction.

Study limitations

The main limitations of the study are:

(1) Sample size was small.
(2) It was not possible to obtain good quality recordings of changes in mid-cavity obliteration during the exercise test and compare it with dynamic LVOT gradient.
(3) 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).
(4) LVOT Measurements during exercise or in the standing position after exercise are likely higher than our measurements after exercise in the supine position. However, careful consideration was paid for measuring LVOTO immediately after exercise and within one minute. As it was not possible to obtain good quality recordings suitable for LV tracking using speckle tracking which is 2D strain imaging mainly dependent on good image quality.

CONCLUSION

Over 30% of patients with apparently non-obstructive cardiomyopathy have obstruction with provocation. ISDN inhalation is equivalent to exercise testing for the detection of LVOT obstruction. It is a reliable screening method in clinical practice, and equivalent to exercise testing. Latent obstruction is directly correlated to resting regional electromechanical delay. The prolonged electromechanical activation of mid-septal segment is a key determinant to inducible obstruction in HCM population and can be used to predict LVOT gradient provocation. Assessment of subaortic gradients with ISDN might be a bedside routine component of the evaluation of non-obstructive HCM. So it may broaden management options by identifying symptomatic patients not able to do exercise and otherwise regarded as potential candidates for septal reduction therapy.

Author contributions

HB had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: HB, NF, TA,. Acquisition of data: HB, NF. Analysis and interpretation of data: HB, NF, TA, WI. Drafting of the manuscript: HB,NF, WI. Critical revision of the manuscript for important intellectual content: MY, RY, TA.

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Competing interests

No authors have any interests to declare.

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