Journal of the American College of Cardiology Vol. 58, No. 1, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00

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Exercise-Induced Left Ventricular Outflow Tract Obstruction in Symptomatic Patients With Anderson-Fabry Disease

To the Editor: Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disorder caused by mutations in the gene encoding alpha-galactosidase A. The resultant deficiency in alpha-galactosidase A leads to progressive intracellular accumulation of neutral glycosphingolipids throughout the body, causing multiorgan dysfunction (1,2). The most common cardiac abnormality is progressive left ventricular (LV) hypertrophy associated with dyspnea and angina (1,2). Left ventricular outflow tract obstruction (LVOTO) has not been thought to be an important mechanism of symptoms because previous studies have reported a very low incidence of LVOTO under resting conditions in patients with AFD (1,2). We report a case series in which patients with AFD and drug-refractory exertional symptoms underwent exercise echocardiography to determine the mechanism of their functional limitation.

The cohort consisted of 14 patients (6 male [43%]; mean age 54.3 ± 10 years, range 38 to 74 years) with AFD who had moderate to severe cardiac symptoms without resting LVOTO (<30 mm Hg) on routine echocardiography. Two-dimensional, M-mode, and Doppler echocardiography were performed in accordance with the American Society of Echocardiography guidelines (3).

Left ventricular cavity dimensions were measured in end-diastole (LVedd) and end-systole. Ejection fraction was calculated using the Teichholz method (3). Papillary muscles were classified as hypertrophic if either the vertical or horizontal diameter of at least 1 of the 2 papillary muscles was more than 1.1 cm in the short-axis views (4). Maximal LV wall thickness was defined as the greatest thickness in any segment measured in end-diastole (3). The LV mass was calculated and indexed for body surface area (3). Relative wall thickness was calculated with an upper limit of normal of 0.43 (3). Systolic anterior motion (SAM) was defined as incomplete if there was any movement of the mitral valve leaflets (MVLs) or chordae toward the ventricular septal endocardium without septal contact and as complete when there was contact with the ventricular septum during systole. Left ventricular outflow tract gradients (LVOTGs) were measured using continuous-wave Doppler in the apical 5-chamber view. Mitral regurgitation was graded as absent, trivial, mild, moderate, or severe. Groups were compared with *t* tests for independent samples and Fisher exact tests.

All cardiac medications were discontinued for a minimum of 5 half-lives before the exercise study. LVOTGs were measured in the supine and upright position. Patients performed symptom-limited upright exercise on a bicycle ergometer using a ramp protocol with simultaneous echocardiography during exercise and recovery. The highest gradient measured was taken as the peak LVOTG. Latent obstruction was defined as a peak LVOTG ≥50 mm Hg during or after exercise. Patients unable to perform exercise underwent measurement of the LVOTG following the administration of sublingual glyceryl trinitrate.

All patients were symptomatic at the time of evaluation. The clinical and echocardiographic characteristics of the cohort are shown in Table 1. The mean ejection fraction was 63 ± 8% with a mean indexed LVedd of 24 ± 2 mm/m^2. Twelve patients (86%) had a dilated left atrium (mean area 23 ± 3 cm^2, range 19 to 30 cm^2). Thirteen (93%) had increased indexed LV mass (mean 135 ± 42 g/m^2, range 88.9 to 226.2 g/m^2). The relative wall thickness was increased in 13 patients (93%) (mean 0.62 ± 0.2, range 0.32 to 1.0).

Thirteen patients (93%) underwent exercise stress echocardiography. One patient (7%) was unable to exercise, and the LVOTG was assessed following sublingual glyceryl trinitrate. Six patients developed dynamic LVOTO ≥50 mm Hg during exercise (latent obstruction) (Fig. 1). In 5 patients, the mechanism of obstruction was complete SAM of the MVLs. In 1 patient, the LVOTG was the result of a

Table 1 Clinical and Echocardiographic Characteristics

Patient #	Age at Evaluation, yrs	Sex	Mutation	ERT	LVEDD, mm	LVEDD/BSA, mm/m^2 (Normal Range 24–32)	MLVWT, mm	Papillary Muscle Hypertrophy	LVH Pattern	Peak Gradient, mm Hg
1	63	F	c.1025delG	yes	43	23	14	+	ASH	15
2	38	F	P343L	yes	53	29	9	+	Nil	6
3	43	M	R301Q	yes	49	21	15	+	Concentric	145
4	49	F	G208H	yes	45	26	12	−	Concentric	14
5	56	F	N215S	yes	40	20	15	+	ASH	152
6	50	M	N215S	yes	42	19	22	+	Concentric	101
7	44	F	R301G	yes	39	21	14	+	Concentric	56
8	74	M	N215S	yes	39	19	20	−	Concentric	95
9	59	F	R301X	yes	48	24	15	+	Concentric	20
10	61	F	A377D	yes	51	29	19	+	Apical	34
11	46	M	358del6	yes	48	26	14	+	Concentric	20
12	53	M	I317T	yes	50	27	18	+	Concentric	23
13	65	F	R301G	yes	44	26	16	+	Concentric	58
14	59	M	N215S	yes	47	22	14	−	ASH	15

ASH = asymmetrical septal hypertrophy; BSA = body surface area; ERT = enzyme replacement therapy; LVEDD = left ventricular end-diastolic dimension; LVH = left ventricular hypertrophy; MLVWT = maximal left ventricular wall thickness.

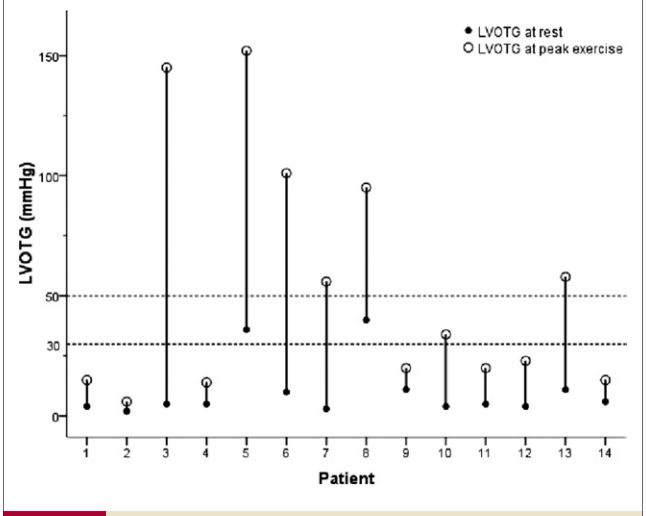

Figure 1 **Rest and Stress LVOTG**

LVOTG = left ventricular outflow tract gradient.

narrow LV outflow tract, the presence of a tendon running between the septum and the papillary muscles, and contact between MVLs and septum. A significant change in the grade of mitral regurgitation was found in 1 patient (from trivial to moderate/severe on exercise).

In the cohort of 14 patients, the 6 patients with latent LVOTO had smaller LV cavities compared with those of the 8 patients without latent LVOTO (mean LVedd/body surface area 21.5 mm/m^2 and 26.2 mm/m^2, respectively, p = 0.007; mean relative wall thickness 0.73 and 0.53, respectively, p = 0.02). Patients with latent LVOTO did not differ from patients without latent LVOTO in terms of mean age (55.3 vs. 53.5 years, p = 0.95), sex (50% vs. 38% male, p = 0.99), mean ejection fraction (60.1% vs. 65.7%, p = 0.44), mean maximal LV wall thickness (17.0 vs. 14.4 mm, p = 0.11), mean indexed LV mass (132.8 vs. 135.8 g/m^2, p = 0.90), papillary muscle hypertrophy (83% vs. 75%, p = 0.99), and incomplete SAM of the MVLs at rest (67% vs. 13%, p = 0.09).

Three of the 6 patients with exercise-induced LVOTO were treated with calcium antagonists or beta-blockers; 2 patients underwent dual-chamber pacemaker implantation for conduction disease and refractory symptoms secondary to LVOTO. Two patients (both women) went on to have surgical septal myectomy (1 of these patients failed dual-chamber pacing) with subsequent LVOTG reduction and clinical and functional improvement.

To the best of our knowledge, we documented for the first time the presence of provocable LVOTO in symptomatic patients with AFD with cardiac involvement and successful surgical septal myectomy procedures in 2 women affected with the disease. The reason for the low prevalence of LVOTO under resting conditions in patients with AFD is uncertain, but it probably relates to differences in LV and mitral valve anatomy in comparison with hypertrophic cardiomyopathy. Patients with provocable LVOTO in this study had smaller LV cavities compared with those without latent LVOTO, and we therefore speculate that it is the reduction in cavity size caused by exercise and papillary muscle hypertrophy that predisposes some patients with AFD to LVOTO.

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doi:10.1016/j.jacc.2011.03.020

Please note: This research was supported by grants from the European Society of Cardiology (to Dr. Calcagnino) and the Spanish Society of Cardiology (to Dr. Cardona). This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme. Dr. O'Mahony received a travel grant from Shire HGT. Dr. Mehta has received educational and research grants and has participated on the advisory boards for Shire HGT, Actelion, Genzyme Inc., and Amicus. Dr. Hughes received travel, educational, and research grants and has participated in advisory boards from Shire HGT, Amicus Therapeutics, and Genzyme Inc. Dr. Murphy received unrestricted educational grants from Shire HGT and Genzyme Inc. Dr. Lachmann received honoraria from Genzyme Inc. and unrestricted educational grants from Shire HGT and Genzyme Inc. Dr. Elliott has received unrestricted educational grants and speaker fees from Shire HGT and Genzyme Inc. All other authors have reported that they have no relationships to disclose.

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Key Words: Anderson-Fabry disease ■ exertional symptoms ■ provocable left ventricular outflow tract obstruction.