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The Binary Endocardial Appearance Is a Poor Discriminator of Anderson-Fabry Disease From Familial Hypertrophic Cardiomyopathy

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Objectives We compared the frequency of a binary endocardial appearance in patients with hypertrophic cardiomyopathy (HCM) and Anderson-Fabry disease (AFD).

Background A recent study suggested that a binary endocardial appearance is a highly sensitive and specific discriminator of AFD from other causes of hypertrophic cardiomyopathy (HCM).

Methods Fourteen patients with AFD (55.4 ± 9.9 years, 9 men) and 14 patients with HCM (57.2 ± 10.9 years, 9 men) were randomly selected from a dedicated patient database. Two-dimensional echo images were blindly reviewed by 2 experienced echocardiographers.

Results Maximum left ventricular (LV) wall thickness, LV end-systolic dimension, fractional shortening, and left atrial size were similar in the 2 patient groups. The LV end-diastolic dimension was smaller in patients with HCM ($p = 0.04$). A binary sign was present in 8 of 28 patients (29%). The sensitivity and specificity of the binary sign as a discriminator of AFD from HCM were 35% and 79%, respectively. A binary sign was present in only 1 patient with LV wall thickness <15 mm.

Conclusions The binary endocardial appearance lacks sufficient sensitivity and specificity to be used as an echocardiographic screening tool. (J Am Coll Cardiol 2008;51:2058–61) © 2008 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM), defined as left ventricular hypertrophy (LVH) in the absence of a hemodynamic abnormality sufficient to cause the observed degree of myocardial thickening, has a population frequency of 1 in 500 persons (1). Several studies have suggested that between 2% and 4% of individuals fulfilling conventional echocardiographic criteria for HCM have Anderson-Fabry disease (AFD), an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A (α-Gal) (2,3). Current noninvasive screening methods for AFD require analysis of plasma or leucocyte α-Gal activity and direct sequencing of the encoding gene. A recent study has suggested that a binary appearance of the left ventricular endocardial border on 2-dimensional (2D) echocardiography is a highly sensitive and specific discriminator of AFD from HCM (4). The aim of the present study was to test this sign in a double-blind manner in a referral population of patients with HCM and AFD.

Methods

Patient population. Two groups of patients with HCM and AFD were randomly selected from a dedicated database of patients followed at The Heart Hospital, London, U.K. Patients were matched for age, gender and maximum left ventricular (LV) wall thickness. The diagnosis of HCM was based on the presence of a maximum LV wall thickness of ≥15 mm (1) or on familial diagnostic criteria when maximum LV wall thickness was <15 mm (5). The diagnosis of AFD was based on leucocyte α-Gal activity and deoxyribonucleic acid sequencing of the encoding gene. All AFD patients were

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receiving enzyme replacement therapy (Fabrazyme [Genzyme Corporation, Cambridge, Massachusetts] or Replagal [Shire Human Genetic Therapies, Inc., Cambridge, Massachusetts]) at the Lysosomal Storage Diseases Unit, The Royal Free Hospital, London, United Kingdom, or the National Hospital for Neurology and Neurosurgery, London, United Kingdom.

Echocardiography. All echocardiographic studies were performed using a General Electric Vivid 7 (Milwaukee, Wisconsin) or a Phillips Sonos 7500 (Best, the Netherlands) ultrasound system. The 2D images from the parasternal short-axis and the standard apical views were reviewed by 2 experienced echocardiographers blinded to the patients' diagnoses and clinical details. All data were stored as digital recordings. No off-line changes were made to imaging settings, including 2D gain and compression. The binary sign was defined as an echo-bright endocardium with an adjacent hyporeflective subendocardial layer, discriminating it from the myocardial midwall at end-diastole. The presence of the binary sign was noted, and in cases of disagreement consensus was reached with the help of a third experienced reviewer.

Left ventricular septal, posterior, and lateral wall thickness, left ventricular end-diastolic and -systolic dimensions, LV fractional shortening (FS), and left atrial diameter (LAD) were measured using established methods (6). Maximum wall thickness was defined as the greatest measured at any LV segment. Left ventricular outflow tract (LVOT) obstruction was defined as a peak pressure gradient of ≥30 mm Hg at rest or upon Valsalva provocation measured with continuous-wave Doppler. In cases with a maximum LV wall thickness of ≥13 mm, asymmetrical septal and concentric patterns were defined using basal septal to posterior wall thickness ratio with a cut-off value of 1.3.

Statistical analysis. Continuous variables are presented as mean ± SD and categoric data as proportion or percentage. Two-tailed unpaired Student *t* test was used to compare continuous variables. Comparisons of percentages between groups were performed using the Fisher exact test. A value of $p < 0.05$ was considered to be significant.

The kappa (κ) statistic was used to describe interobserver agreement. To assess intraobserver agreement, 10 randomly selected studies were reviewed after 6 months by 1 echocardiographer. A value of >0.6 was considered to indicate good agreement between analyses.

Results

The study population comprised of 14 patients with AFD (mean age 55.4 ± 9.9 years, 9 men and 5 women) and 14 patients with HCM (mean age 57.2 ± 10.9 years, 9 men and 5 women) (Table 1).

Two (14%) AFD patients had a normal LV wall thickness (<13 mm), 3 (21%) had a maximum LV wall thickness of 13 to 14 mm, and 9 (64%) had a wall thickness of ≥15 mm. The LVH was concentric in all AFD patients with the exception of a 40-year-old man with eccentric hypertrophy of the LV basal posterior wall. No patient with AFD had LVOT obstruction.

Four HCM patients (29%) had a maximum wall thickness of 13 to 14 mm and 10 (71%) had a wall thickness of ≥15 mm. Thirteen of the 14 patients (93%) with familial HCM had asymmetric septal hypertrophy; the remainder had concentric LVH. Four of the 14 patients (29%) had resting or provocable LVOT obstruction.

Abbreviations and Acronyms

AFD = Anderson-Fabry disease
α-Gal = α-galactosidase A
FS = fractional shortening
HCM = hypertrophic cardiomyopathy
LAD = left atrial diameter
LV = left ventricular
LVH = left ventricular hypertrophy
LVOT = left ventricular outflow tract

Maximum LV wall thickness, left ventricular end-systolic dimension, FS, and LAD were similar in the 2 patient groups. An LVOT obstruction tended to be more common ($p = 0.09$) and the left ventricular end-diastolic dimension was smaller ($p = 0.04$) in patients with HCM (Table 1).

The presence of a binary endocardial appearance was noted in 9 of 28 patients (32%) by the first reviewer and in 5 of 28 patients (18%) by the second reviewer. Disagreement between the 2 investigators was found in 6 of 28 (21%) of the cases, with a κ statistic of 0.44. After consensus was reached, a binary sign was considered to be present in 8 of 28 patients (29%). Intraobserver disagreement was 30%, with a calculated κ statistic of 0.35.

Table 1 Demographic and Echocardiographic Data

Parameters	AFD	HCM	p Value
n	14	14	
Men/women	9/5	9/5	1.0
Age (yrs)			
Men	52.1 ± 10.7 (39–68)	53.4 ± 10.4 (41–71)	0.73
Women	61.4 ± 4.8 (54–67)	64 ± 8.9 (50–71)	0.58
All	55.4 ± 9.9 (39–68)	57.2 ± 10.9 (41–71)	0.65
Max LVWT (mm)	15.8 ± 3.6 (10–22)	15.7 ± 2.1 (13–20)	0.95
Binary sign	5/14 (35%)	3/14 (21%)	0.67
LVEDD (mm)	47.3 ± 4.4	43.6 ± 4.7	0.04
LVESD (mm)	29.2 ± 3.3	28.2 ± 4.8	0.53
FS (%)	0.38 ± 0.05	0.35 ± 0.06	0.27
LAD (mm)	42.6 ± 6.8	41.7 ± 5.7	0.72
LVOTO	0/14 (0%)	4/14 (29%)	0.09
LVH	12/14 (86%)	14/14 (100%)	0.48
Concentric LVH	11/12* (92%)	1/14 (7%)	>0.001
ASH	0/12* (0%)	13/14 (92%)	>0.001

Concentric LVH defined as septal to posterior wall thickness <1.3 mm. *Of those patients with LVH.

AFD = Anderson-Fabry disease; ASH = asymmetrical septal hypertrophy, defined as septal to posterior wall thickness ≥1.3 mm; FS = fractional shortening; HCM = hypertrophic cardiomyopathy; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVH = left ventricular hypertrophy ≥13 mm; LVOTO = left ventricular outflow tract obstruction >30 mm Hg; LVWT = left ventricular wall thickness.

Table 2 Sensitivity and Specificity of the Binary Endocardial Appearance

		Maximum LVWT		
		<15 mm	≥15 mm	Overall
AFD	No. of patients	5	9	14
	Binary sign	1	4	5
	Sensitivity	20%	44%	35%
HCM	No. of patients	4	10	14
	Binary sign	0	3	3
	Specificity	100%	70%	79%

Abbreviations as in Table 1.

The sensitivity and specificity of the binary sign as a discriminator of AFD from HCM were 35% and 79%, respectively (Table 2). Among patients with LVH ≥15 mm, the sensitivity was higher (44%), but with a lower specificity (70%). A binary sign was present in only 1 patient with LV wall thickness <15 mm.

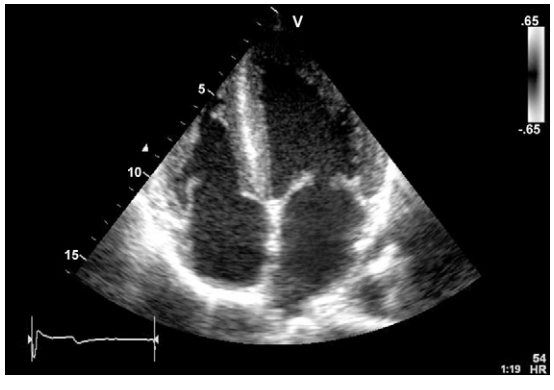

Figure 1 Apical View of a Patient With Anderson-Fabry Disease

Left ventricular hypertrophy is present with no binary endocardial appearance.

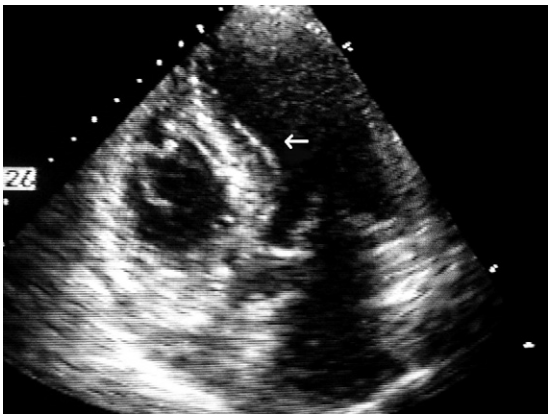

Figure 2 Apical View in a Hypertrophic Cardiomyopathy Patient

A binary endocardial appearance **(arrow)** is seen.

Discussion

Anderson-Fabry disease accounts for between 2% and 4% of cases of otherwise unexplained LVH (2,3). Correct diagnosis is important, because patient and family counseling differs from typical autosomal dominant familial HCM and potentially beneficial enzyme replacement therapy is available (7,8). The identification of AFD in HCM patients can be challenging, particularly in affected women, who frequently have leucocyte α-Gal activity within the normal range (9). Genetic testing overcomes this problem but is costly and impractical in large referral practices. The use of endomyocardial biopsies as a screening tool to detect characteristic histologic abnormalities is limited by its invasive nature and potential hazards.

As this study confirms, there are a number of features that should raise suspicion of AFD on transthoracic echocardiography. Left ventricular hypertrophy is typically concentric, and cardiac valves are often abnormal with leaflet thickening and redundancy (10). Indexes of global systolic function remain normal until the late stage of the disease, but early regional posterior-lateral wall abnormalities may be present (11). Finally, resting LVOT obstruction is uncommon in AFD cardiomyopathy (12). However, these features are nonspecific and can be seen in patients with other causes of LVH, including mutations in cardiac sarcomeric protein genes.

Recently, Pieroni et al. (4) reported a high prevalence of a binary endocardial appearance in the left ventricle (and less commonly in the right ventricle). They suggested that this is caused by increased glycosphingolipid in the subendocardial layers of the myocardium. In their study, this feature had a sensitivity of 94% and a specificity of 100% in patients with AFD cardiomyopathy and a maximum LV wall thickness of ≥15 mm; the sign was less sensitive in patients with milder hypertrophy but remained highly specific. In the present study, the overall sensitivity was only 35% (Fig. 1), rising to 44% in patients with a maximum LV wall thickness of ≥15 mm. Importantly, this feature was present in 21% of patients without AFD (Fig. 2) and there was poor inter- and intraobserver agreement, reflecting the inherent subjectivity of the binary sign using conventional 2D grayscale analysis and the likelihood that in many cases the "sign" is no more than an ultrasonic artefact.

The study design required that no adjustment of gain and compression was made between reviews, but we anticipate that the binary sign is also likely to be affected by image quality, gain settings, imaging software, and the characteristics of individual ultrasound systems. In conclusion, the binary endocardial appearance is poorly reproducible and lacks sufficient sensitivity and specificity to be used as an echocardiographic screening tool for AFD.

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