Echocardiographic Assessment of Patients with Fabry Disease

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Fabry disease is an X-linked lysosomal storage disorder that results from a deficiency of α-galactosidase A. Increased left ventricular wall thickness has been the most commonly described cardiovascular manifestation of the disease. However, a variety of other structural and functional abnormalities have also been reported. Echocardiography is an effective noninvasive method of assessing the cardiac involvement of Fabry disease. A more precise and comprehensive characterization of Fabry cardiomyopathy using conventional and novel echocardiographic techniques may lead to earlier diagnosis, more accurate prognostication, and timely treatment. The aim of this review is to provide a comprehensive overview of the structural and functional abnormalities on echocardiography that have thus far been described in patients with Fabry disease and to highlight potential areas that would benefit from further research. (J Am Soc Echocardiogr 2018;■:■-■.)

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Fabry disease, also known as Anderson-Fabry disease or, historically, angiokeratoma corporis diffusum universale, is an X-linked lysosomal storage disorder that results from a deficiency of the lysosomal enzyme α-galactosidase A.[1] Its prevalence in males has been estimated at one in 117,000 worldwide but can be as high as one in 17,000 in certain communities as a result of founder effects.[2,3] The condition can be initially misdiagnosed because of its variable clinical manifestations, which include neuropathic pain, angiokeratomas, gastrointestinal symptoms, hypohidrosis, and corneal changes, as well as the development of renal, cardiovascular, and cerebrovascular disease.[1] Treatment depends on early recognition of the disease and timely institution of enzyme replacement therapy (ERT).[4]

Echocardiography is an effective noninvasive method of assessing the structural and functional consequences of Fabry disease on the heart.[5-8] Increased left ventricular (LV) wall thickness is the predominant cardiovascular manifestation of the disease, although atrial enlargement, valvular heart disease, aortic dilatation, and subclinical impairment in atrial and ventricular function can also be seen (Table 1). More precise characterization of Fabry cardiomyopathy using traditional and novel echocardiographic techniques may lead to earlier diagnosis, more accurate prognostication, and timely treatment. This review provides a comprehensive overview of the structural and functional abnormalities on echocardiography that have thus far been described in patients with Fabry disease and highlights potential areas that would benefit from further research.

INCREASED LV WALL THICKNESS

Increased LV wall thickness is the hallmark feature of Fabry disease and is caused by glycolipid deposition in ventricular muscle fibers (Figure 1).[9-11] Concentrically increased wall thickness is the predominant pattern of hypertrophy among patients with Fabry disease.[12,13] However, other patterns can also occur, including asymmetric septal hypertrophy, eccentric hypertrophy, and apical hypertrophy, leading to misdiagnosis.[12,14-20] In cohorts of patients initially diagnosed with hypertrophic cardiomyopathy (HCM), 3.9% to 12% are eventually found to have Fabry disease.[17] Similarly, the condition is discovered in up to 10% of selected patients with LV hypertrophy (LVH) but no obvious cause, such as systemic hypertension, asymmetric septal hypertrophy, apical hypertrophy, aortic valvular stenosis, or aortic valvular regurgitation.[21] A prior review effectively compared the clinical and imaging characteristics of conditions presenting with increased LV mass and wall thickness.[22] The differential diagnosis for patients with features of HCM or unexplained hypertrophy on echocardiography should therefore include Fabry cardiomyopathy, particularly when they present with late-onset disease.

In patients with Fabry disease who are left untreated, LV mass and wall thickness increase with age and stage of disease.[23-26] Although the prevalence of LVH is higher in male than female patients at any given age, a substantial proportion of female patients will still develop cardiac manifestations of Fabry disease.[24-26] Without treatment, male patients exhibit LVH at a younger age than female patients.[25] In a large international cohort of 714 patients with Fabry disease, the mean age of patients with LVH was 42.0 $\pm$ 14.5 years in men and 50.1 $\pm$ 12.0 years in women.[25] This delay in onset and

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Abbreviations

CS = Circumferential strain

DTI = Doppler tissue imaging

ERT = Enzyme replacement therapy

HCM = Hypertrophic cardiomyopathy

LS = Longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

MRI = Magnetic resonance imaging

RV = Right ventricular

RVH = Right ventricular hypertrophy

SR_{IVR} = Strain rate during isovolemic relaxation

progression of LVH in female patients is similarly observed in cohorts that exclude patients with underlying arterial hypertension.[27]

The development of LVH is associated with increased cardiovascular morbidity and mortality. In the cross-sectional study of 714 patients with Fabry disease, LVH was associated with more cardiac symptoms, arrhythmias, and valvular disease.[25] In the largest longitudinal study of 2,869 patients in the Fabry Registry who were observed in the natural history period before treatment, hypertension and LVH were the strongest predictors of major cardiovascular events, which included myocardial infarction, heart failure, and cardiac-related death.[28]

Other morphologic abnormalities of the left ventricle unrelated to increased wall thickness are rare in Fabry patients, although apical aneurysms[29,30] and noncompaction[31,32] have been reported.

BINARY SIGN

A binary appearance of the LV endocardial border on echocardiography refers to a hyperechogenic endocardial surface adjacent to a relatively hypoechogenic subendocardial layer (Figure 2). In patients with Fabry disease, this correlated with a characteristic pattern of glycosphingolipid compartmentalization on histological examination.[33] The hyperechogenic component includes a thickened endocardium as a result of glycolipid-enriched smooth muscle cells, followed by a subendocardial empty space containing free glycosphingolipids and an inner subendocardial layer of severely affected myocardium. The hypoechogenic component represents middle to outer layers of myocardium that are relatively spared from glycolipid deposition.[33] This "binary sign" was once thought to represent a hallmark feature of Fabry cardiomyopathy, as it occurred in 83% of patients in one cohort.[33] However, it appeared at much lower prevalence rates in subsequent studies.[34-37] In one prospective study, only 20% of patients exhibited the sign, although it tended to occur more frequently in patients with increased LV wall thickness and more advanced disease, suggesting that the high prevalence of the finding in initial studies reflected an ascertainment bias.[33-35,37] In follow-up studies, it performs with an estimated sensitivity of 15.4% to 28% and a specificity of 73.3% to 80%, making it an unreliable marker of Fabry cardiomyopathy.[34,36,37]

PROMINENT PAPILLARY MUSCLES

Papillary muscle thickening and hyperechogenicity have been found to accompany other mitral valve abnormalities,[12,38,39] and abnormalities in its structure and function have been proposed as a mechanism of mitral regurgitation in patients with Fabry disease (Figure 3).[40,41] In contrast to Fabry disease, patients with HCM had anterior displacement of the anterolateral papillary muscles or direct insertion of the papillary muscle into the mitral valve.[39] The hypothesis of enlarged papillary muscles in Fabry disease was further tested in a study of 101 consecutive patients with concentric LVH of various etiologies, including 28 with Fabry disease, 30 with Friedreich ataxia, 34 with isolated arterial hypertension, and nine with amyloidosis, compared with 50 healthy control subjects.[42] As a group, patients with Fabry disease had a significantly larger absolute papillary muscle area than those with Friedreich ataxia or amyloidosis and a higher ratio of papillary muscle size to LV circumference than hypertensive and amyloid patients. Nevertheless, a finding of prominent papillary muscles alone has not been shown to distinguish Fabry disease from other etiologies of LVH in individual patients.

RIGHT VENTRICULAR HYPERTROPHY AND FUNCTIONAL IMPAIRMENT

Right ventricular hypertrophy (RVH) was first described on echocardiography in a case report of a patient with marked biventricular hypertrophy (Figure 1).[43] Subsequent cohort studies have reported rates of RVH ranging from 31% to 71%.[44-47] RVH prevalence increases with age, and unlike LVH, RVH appears to affect males and females similarly.[44,45] Patients with LVH on the basis of increased LV mass and wall thickness were the most likely to exhibit coexisting RVH.[44-47]

Right ventricular (RV) systolic function in patients with Fabry cardiomyopathy tends to be preserved and higher than in those with amyloid cardiomyopathy with similar degrees of RVH.[47,48] However, systolic and diastolic dysfunction has been observed in patients presumably with more advanced Fabry disease. In a study of 58 patients with Fabry disease, one exhibited RV systolic dysfunction, and 47% of the 45 patients who had adequate RV diastolic measurements showed diastolic impairment.[45] In another study in which 46 of 129 patients with Fabry disease demonstrated RVH, 13 of them showed severe RV systolic dysfunction, and six of them exhibited severe RV diastolic impairment.[44]

Furthermore, patients may exhibit subclinical RV functional impairment on speckle-tracking strain imaging despite normal systolic and diastolic function on conventional two-dimensional and Doppler echocardiography.[49] Increased RV fibrosis and wall thickness (>7 mm) have been associated with abnormal RV strain.

ATRIAL ENLARGEMENT AND REDUCED COMPLIANCE

Histologic studies before the use of echocardiography showed glycolipid deposition in atrial cells,[50-52] which may cause atrial enlargement and a predisposition to atrial arrhythmias.[25] The few case reports that provide atrial measurements describe patients with normal-sized atria[53] as well as those with left atrial enlargement[54] or biatrial enlargement.[43] However, in cohort studies, the mean left atrial size on echocardiography is greater in patients with Fabry disease than in age-matched control subjects,[26] and the prevalence of atrial enlargement has been estimated to be approximately 30% (Figure 4A).[55]

Nevertheless, atrial enlargement is often at most mild to moderate. In a large cohort of 180 patients, only a single patient exhibited severe left atrial dilatation that occurred in the setting of severe mitral valve