

Cardiac Involvement in Fabry Disease: From Electrocardiography to Recent Advances in Cardiovascular Imaging

Lício Cunha Volpolini,^{1,2} Cláudio Henrique Fischer,^{1,3} Valdir Ambrósio Moisés,¹ Márcia de Paula Cardinali,² Marco Antonio Curiati,^{1,4} Ana Maria Martins,^{1,4} Frederico José Mancuso,¹ Marly Uellendahl^{1,2}

Universidade Federal de São Paulo (UNIFESP),¹ São Paulo, SP – Brazil

DASA (Diagnósticos da América),² São Paulo, SP – Brazil

Hospital Israelita Albert Einstein,³ São Paulo, SP – Brazil

IGEIM (Instituto de Genética e Erros Inatos do Metabolismo),⁴ São Paulo, SP – Brazil

Abstract

Fabry disease is an X-linked lysosomal storage disorder caused by α -galactosidase A deficiency, leading to the progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in multiple organs. Cardiac involvement is the leading cause of morbidity and mortality, making early recognition of cardiomyopathy fundamental to optimizing treatment and improving prognosis. This review summarizes the current evidence on the role of electrocardiography, conventional and advanced echocardiography, and cardiac magnetic resonance (CMR) imaging in the assessment of cardiac involvement in Fabry disease. The main electrocardiographic findings, the structural and functional changes identified by echocardiography, including myocardial deformation by speckle tracking and myocardial work, as well as the contributions of magnetic resonance imaging to tissue characterization through late gadolinium enhancement (LGE), T1 and T2 mapping, extracellular volume (ECV), and feature tracking are discussed. The applications of these methods in the early detection of cardiomyopathy, differential diagnosis, risk stratification, monitoring of disease progression, and evaluation of treatment response are discussed. The integration of different imaging methods allows for a more comprehensive characterization of the pathophysiological mechanisms and stages of Fabry cardiomyopathy, contributing to early diagnosis, clinical decision-making, and longitudinal follow-up of these patients.

Introduction

Fabry disease is a hereditary lysosomal storage disorder characterized by the systemic accumulation of glycosphingolipids in multiple organs and tissues.^{1,2} The metabolic defect results from

deficient activity of α -galactosidase A, a lysosomal enzyme that catalyzes the hydrolytic cleavage of terminal galactose residues from globotriaosylceramide (Gb3).¹ Deficient α -galactosidase A activity leads to the progressive accumulation of Gb3 and related glycolipids within lysosomes, particularly in vascular endothelial cells, cardiomyocytes, and renal and neural cells, ultimately resulting in the multisystemic manifestations of the disease.^{1,2} In addition to lysosomal accumulation of Gb3, recent evidence demonstrates that secondary mechanisms, including lyso-Gb3 accumulation, inflammation, oxidative stress, mitochondrial dysfunction, and alterations in autophagy, play an important role in the progression of tissue damage and cardiomyopathy.^{1,3}

The disease is caused by pathogenic variants in the *GLA* gene, located on the X chromosome, which encodes the lysosomal enzyme α -galactosidase A.⁴ The estimated prevalence is approximately 1 case per 10,000 live births. However, this frequency varies widely depending on the population studied and the screening strategy employed. Neonatal screening studies and studies of at-risk populations have shown that the disease is significantly more frequent than previously estimated, especially in males and in carriers of late-onset variants of the *GLA* gene.^{3,4} Symptoms of Fabry disease typically begin in childhood and include neuropathic pain, gastrointestinal dysfunction, hypohidrosis, and intolerance to temperature fluctuations.⁵ Although Fabry disease presents with multisystemic manifestations, cardiac involvement represents its main cause of morbidity and mortality, making imaging methods fundamental for early diagnosis, risk stratification, and disease monitoring.^{3,6,7} This review aims to synthesize the current evidence regarding the role of electrocardiography, echocardiography, and cardiac magnetic resonance (CMR) in the assessment of cardiac involvement in Fabry disease. The central figure summarizes the natural history of Fabry cardiomyopathy and the integrated application of multimodal assessment in the different stages of the disease.

Keywords

Fabry Disease; Echocardiography; Magnetic Resonance Imaging; Electrocardiography; Cardiomyopathies

Mailing Address: Lício Cunha Volpolini •

Programa de Pós-Graduação em Cardiologia, Departamento de Medicina, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Rua Botucatu, 740, 5º andar, sala 503. Postal Code: 04023-062. São Paulo, SP - Brazil.

E-mail: licio_volpolini@yahoo.com.br

Manuscript received July 28, 2026; revised July 28, 2026; accepted July 28, 2026

Editor responsible for the review: Marcelo Tavares

DOI: <https://doi.org/10.36660/abcimg.20260095i>

Pathophysiology

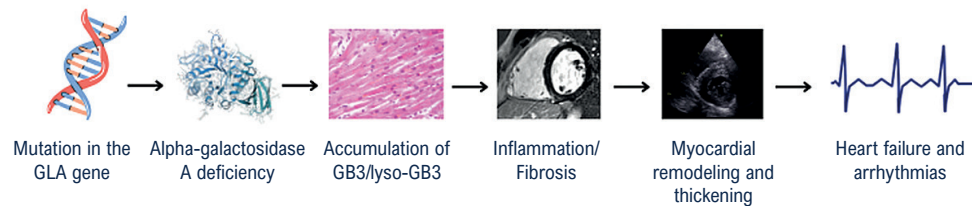
α -Galactosidase A is a lysosomal acid hydrolase responsible for the degradation of Gb3, a glycosphingolipid present in cell membranes. Under physiological conditions, this enzyme catalyzes the removal of the galactose terminal residue from the Gb3 molecule, allowing its degradation inside lysosomes.^{1,2,8,9} In Fabry disease, pathogenic variants in the *GLA* gene result in deficiency or absence of α -galactosidase A activity, interrupting the lysosomal degradation of Gb3

Central Illustration: Cardiac Involvement in Fabry Disease: From Electrocardiography to Recent Advances in Cardiovascular Imaging



Cardiac involvement in Fabry disease

NATURAL HISTORY



MULTIMODAL ASSESSMENT



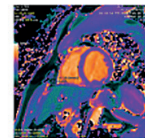
ELECTROCARDIOGRAPH

Short PR interval
Progressive expansion of the QRS
Repolarization abnormalities
Ventricular overload
QT Dispersion



ECHOCARDIOGRAM

Myocardial deformation
Myocardial work
Diastolic dysfunction
Myocardial thickening
Systolic dysfunction



CMR IMAGING

T1 Mapping
T2 Mapping
Gadolinium-induced late enhancement
Extracellular volume
Feature Tracking

Arq Bras Cardiol: Imagem cardiovasc. 2026;39(3):e20260095

Schematic representation of the natural history of Fabry cardiomyopathy, from α -galactosidase A deficiency and Gb3/lyso-Gb3 accumulation to myocardial remodeling and its clinical manifestations, highlighting the complementary role of electrocardiography, echocardiography, and CMR imaging in the multimodal assessment of cardiac involvement. CMR: Cardiac Magnetic Resonance; Gb3: globotriaosylceramide; lyso-Gb3: globotriaosylsphingosine; ECV: Extracellular Volume.

and promoting its progressive accumulation in various cell types, particularly endothelial cells, vascular smooth muscle cells, podocytes, renal tubular cells, and cardiomyocytes.^{1,9,10} Intracellular Gb3 storage begins in intrauterine life in individuals with the classic form of the disease and precedes the appearance of clinical manifestations by many years.^{1,10}

In addition to lysosomal Gb3 storage, part of this molecule undergoes deacylation, originating globotriaosylsphingosine (lyso-Gb3), a soluble metabolite currently recognized as one of the main mediators of the pathophysiology of the disease. Lyso-Gb3 levels are markedly elevated in Fabry disease and exert several biological effects, including stimulation of cardiomyocyte hypertrophy, fibroblast activation, inflammation, vascular remodeling, and extracellular matrix deposition, thereby contributing to the progression of cardiomyopathy.^{1-3,11}

Recent evidence demonstrates that tissue damage in Fabry disease does not result exclusively from lysosomal storage of glycosphingolipids. The interaction between lyso-Gb3 accumulation, activation of inflammatory pathways, oxidative stress, mitochondrial dysfunction, and alterations in autophagy favors progressive myocardial remodeling, culminating in left ventricular hypertrophy, myocardial fibrosis, diastolic dysfunction, arrhythmias, and heart failure.^{1-3,6}

Fabry cardiomyopathy develops gradually and can be understood as a sequence of events beginning with intracellular glycosphingolipid storage, followed by early metabolic and inflammatory changes, myocardial remodeling, left ventricular hypertrophy, fibrosis, and, ultimately, ventricular dysfunction and heart failure. This pathophysiological model helps explain how cardiovascular

imaging can detect structural and functional abnormalities at different stages of the disease, often before the appearance of overt clinical manifestations.^{3,6,7,12}

Clinical Manifestations

Symptoms of the classic form of Fabry disease usually begin in childhood or adolescence and include neuropathic pain (acroparesthesia), angiokeratomas, hypohidrosis, intolerance to heat, cold, and exercise, as well as recurrent gastrointestinal manifestations.^{3,5,9,10} Small-fiber neuropathy is one of the most characteristic neurological manifestations of the disease and frequently precedes the involvement of other organs.^{10,13} Ophthalmological findings, such as cornea verticillata, and otological manifestations, including sensorineural hearing loss, tinnitus, and vertigo, are also frequent and may represent early signs of the disease.^{10,13}

Cerebrovascular involvement may occur early and represents a significant cause of morbidity. Ischemic strokes, transient ischemic attacks, and ischemic white matter lesions, frequently identified by brain magnetic resonance imaging, can occur decades earlier than in the general population, especially in men with the classic form of the disease.^{10,13,14}

Renal involvement results from the progressive deposition of Gb3 in podocytes, and tubular/vascular cells, initially manifesting as microalbuminuria and proteinuria, progressing to chronic kidney disease and end-stage renal failure when left untreated.^{9,10,13}

Although Fabry disease has multisystemic manifestations, cardiac involvement is currently the leading cause of morbidity and mortality. The progressive accumulation of Gb3 and the biological effects of lyso-Gb3 contribute to left ventricular hypertrophy, myocardial remodeling, fibrosis, valvular heart disease, microvascular disease, conduction abnormalities, and arrhythmias, leading to a substantial increase in the risk of heart failure, sudden cardiac death, and cardiovascular events.^{3,6,7,12,15,16}

Electrocardiography

Progressive accumulation of Gb3 in cardiomyocytes, the conduction system, and the microvasculature promotes early electrophysiological changes that can often be detected on the electrocardiogram before the development of left ventricular hypertrophy, making electrocardiogram an important tool for the early recognition of cardiac involvement in Fabry disease.^{6, 17-19}

One of the classic electrocardiographic changes in the disease is a shortened PR interval, measured from the onset of the P wave to the onset of the QRS complex. Initially attributed to the presence of accessory pathways, electrophysiological studies have shown that most patients do not present with anomalous atrioventricular bundles, suggesting that this finding results mainly from increased conduction velocity through the atrioventricular node and atrial conduction abnormalities related to glycosphingolipid deposition.¹⁸⁻²⁰

More recent studies have shown that, in the early stages of the disease, especially in the absence of left ventricular hypertrophy, the apparent shortening of the PR interval results

predominantly from a reduction in the duration of the P wave, reflecting early atrial involvement before ventricular remodeling is established.^{19,21}

As cardiomyopathy progresses, left ventricular hypertrophy develops, the main cardiac phenotype of Fabry disease, often mimicking sarcomeric hypertrophic cardiomyopathy or hypertensive cardiomyopathy. The progressive increase in ventricular mass is associated with an increase in QRS complex voltage and the appearance of electrocardiographic criteria for left ventricular hypertrophy, although its sensitivity remains limited.^{15,16,21}

In more advanced stages, infiltration of the His-Purkinje system and the development of myocardial fibrosis favor widening of the QRS complex, intraventricular blocks, and atrioventricular conduction disturbances. ST segment and T wave changes reflect repolarization disturbances resulting from myocardial infiltration, fibrosis, and microvascular dysfunction, and are associated with the progression of cardiac involvement.^{6,17-19}

Even in the absence of left ventricular hypertrophy, patients with Fabry disease may present with prolonged corrected QT interval (QTc), increased QT dispersion and Tpeak-Tend interval dispersion, reflecting greater ventricular electrical heterogeneity and a predisposition to the development of ventricular arrhythmias.²¹

More recently, Figliozzi *et al.* developed an electrocardiographic score comprising four parameters — the Sokolow–Lyon index, P-wave duration/PR-segment ratio, QRS duration, and QTc — that can estimate the probability of reduced native T1 on CMR imaging, potentially enabling early identification of myocardial glycosphingolipid storage before the development of left ventricular hypertrophy.²¹

Conventional Echocardiography

Transthoracic echocardiography is the first-line imaging modality for the cardiac evaluation of Fabry disease because of its wide availability, safety, and ability to characterize cardiac morphology, geometry, and function, as well as to enable longitudinal monitoring of cardiomyopathy progression and response to treatment. However, conventional echocardiographic parameters may remain normal in the early stages, so normal findings do not exclude subclinical cardiac involvement.^{3,7,22,23}

Increased thickness of the ventricular walls and left ventricular mass constitutes the most characteristic echocardiographic manifestation of Fabry cardiomyopathy. Left ventricular hypertrophy most commonly presents with a concentric pattern, with a relatively uniform increase in the thickness of the interventricular septum and posterior wall. However, asymmetrical, septal, or apical patterns can also occur, especially in more advanced stages, and may mimic sarcomeric hypertrophic cardiomyopathy or hypertensive heart disease.^{7,12,16,22,24}

Increased ventricular thickness is generally earlier and more pronounced in men, although women can also present with fibrosis and significant cardiac involvement, even without an evident increase in thickness.^{1,3,6,25}

Hypertrophy and prominence of the papillary muscles are frequent morphological findings and can significantly contribute to increased left ventricular mass. Although disproportionate papillary muscle enlargement has been proposed as a possible early marker of Fabry cardiomyopathy, this finding is not specific and should be interpreted in conjunction with the clinical context and other imaging parameters.^{7,22,23}

The binary aspect of the endocardium was initially described as a marker of Fabry disease, but it has low reproducibility and little specificity, and is not currently recommended as an isolated diagnostic criterion.^{7,22,23,26}

Left Ventricular Ejection Fraction (LVEF) generally remains preserved until advanced stages, even in the presence of significant hypertrophy. However, normal ejection fraction values do not exclude myocardial dysfunction, since alterations in longitudinal function, ventricular relaxation, and myocardial mechanics may precede the reduction of overall systolic function. As fibrosis and ventricular remodeling progress, ventricular cavity dilation, reduced ejection fraction, and heart failure may develop.^{6,7,12,16}

Impaired myocardial relaxation can be identified early in Fabry disease, particularly through reduced diastolic mitral annular velocities on tissue Doppler imaging. With the progression of cardiomyopathy, increased ventricular mass, reduced myocardial compliance, and the development of fibrosis contribute to the worsening of diastolic dysfunction, which may result in elevated filling pressures and increased left atrial volume. Conventional mitral flow parameters have limited sensitivity for identifying early involvement and should be interpreted in an integrated manner with mitral annulus velocities by tissue Doppler and myocardial deformation parameters.^{7,12,22,27}

Fabry disease should integrate parameters of mitral flow, tissue Doppler, left atrial volume, and other echocardiographic markers. The 2025 ASE update incorporated new parameters and a revised algorithm for assessing diastolic function and estimating filling pressures. However, further studies are needed to evaluate the applicability and performance of these recommendations specifically in patients with Fabry disease.²⁸⁻³⁰

Valvular involvement results primarily from thickening and infiltration of the leaflets and subvalvular apparatus, most frequently affecting the mitral and aortic valves. Mild valvular regurgitation is relatively common, while hemodynamically significant lesions are uncommon. The right ventricle may also exhibit increased wall thickness and hypertrophy, generally associated with greater severity of left ventricular hypertrophy and more advanced stages of cardiomyopathy. Despite these structural changes, conventional right ventricular systolic function often remains preserved.^{7,12,16,22}

Dilation of the aortic root and ascending aorta has also been described, particularly in men, possibly related to the accumulation of glycosphingolipids in the vascular wall and connective tissue remodeling. Although generally subtle, assessment of aortic dimensions should be included in the routine echocardiographic examination of patients with Fabry disease.^{7,22}

Speckle Tracking Echocardiography and Myocardial Deformation

Speckle tracking echocardiography allows for the quantitative assessment of myocardial deformation and can identify subclinical functional changes before ejection fraction reduction and, in some patients, before the development of left ventricular hypertrophy. Unlike tissue Doppler imaging, this technique is less dependent on the insonation angle and allows for the analysis of the longitudinal, circumferential, and radial components of ventricular deformation, in addition to the evaluation of atrial and right ventricular function. Pioneering studies with myocardial Doppler demonstrated reduced velocities and deformation indices in patients with Fabry disease, contributing to the recognition of early functional impairment.^{12,27} Subsequently, studies that include speckle tracking broadened the characterization of cardiac mechanics and demonstrated biventricular and atrial changes even in the presence of preserved conventional systolic function.^{22,31-33}

Left Ventricular Longitudinal Strain

Global Longitudinal Strain (GLS) assesses myocardial shortening along the longitudinal axis of the left ventricle and is the most studied strain parameter in Fabry disease. Early myocardial Doppler studies demonstrated impaired longitudinal function despite preserved ejection fraction, while later speckle tracking studies confirmed reduced GLS and regional changes in strain, even in patients without evident left ventricular hypertrophy.^{12,22,27,31,34}

The reduction in longitudinal strain shows a heterogeneous distribution and tends to be more pronounced in the basal segments, particularly in the inferolateral wall, a region characteristically associated with the development of myocardial inflammation and fibrosis. However, the apical segments are not completely spared, unlike the pattern of relative apical sparing frequently observed in cardiac amyloidosis. The regional reduction in strain may be related to the presence of Late Gadolinium Enhancement (LGE) and the progression of myocardial damage, although changes in deformation may also occur before fibrosis is detectable by CMR.^{22,32,33}

Radial and Circumferential Strain of the Left Ventricle

Radial strain represents myocardial thickening towards the center of the ventricular cavity during systole. Initial studies using myocardial Doppler demonstrated a reduction in radial strain, even in women with preserved left ventricular mass, while subsequent analyses by speckle tracking showed impairment of radial strain before the development of left ventricular hypertrophy and independently of the ventricular geometric pattern.^{27,35}

Circumferential strain represents myocardial shortening around the ventricular circumference and predominantly reflects the mechanics of the mid-wall myocardial fibers. In Fabry disease, regional changes in circumferential strain and a reduction in the physiological gradient from base to apex have been described even in patients without left ventricular hypertrophy. However, findings regarding global circumferential strain are less consistent, and some studies have not demonstrated significant differences compared to healthy individuals.^{22,24,36}

Left Atrial Strain

Analysis of left atrial strain allows for the evaluation of its reservoir, conduit, and contraction functions, and can identify atrial involvement before the development of significant dilation. Boyd *et al.* demonstrated increased atrial volume and reduced left atrial compliance before the onset of ventricular hypertrophy, providing early evidence of early atrial involvement in Fabry disease.³⁷

Subsequently, Pichette *et al.* demonstrated, using speckle tracking, impairment of all three phases of left atrial function and improvement in strain parameters following enzyme replacement therapy, representing an important milestone in the assessment of atrial strain in Fabry disease.³⁸ Subsequent studies confirmed the reduced atrial strain and suggested that left atrial dysfunction may reflect a combination of intrinsic atrial myopathy, ventricular diastolic dysfunction, and increased filling pressures, potentially being associated with the development of atrial fibrillation and adverse clinical events.³⁹⁻⁴²

Right Ventricular Strain

Speckle tracking allows the identification of subclinical changes in right ventricular systolic function that may not be recognized by conventional echocardiographic parameters. Initial studies with myocardial Doppler did not demonstrate a significant reduction in the longitudinal strain rate of the right ventricle, possibly due to the characteristics of the studied population and the methodological limitations of the technique.¹²

With the development of speckle tracking, Lillo *et al.* demonstrated reduced global right ventricular longitudinal strain and right ventricular free wall longitudinal strain in patients with Fabry disease and cardiac involvement, while these parameters remained preserved in patients without evidence of cardiac involvement.⁴³ Subsequent studies have demonstrated an association between reduced right ventricular free wall strain, greater severity of cardiac phenotype, and the occurrence of cardiovascular events. However, this association did not remain independent after adjustment for global left ventricular longitudinal strain and indexed left atrial volume, suggesting that right ventricular involvement accompanies the severity of cardiomyopathy, with no current evidence of incremental prognostic value in relation to left heart parameters.^{32,33,44}

Right Atrial Strain

Evaluation of the right atrium constitutes a more recent area of echocardiographic characterization in Fabry disease. Lillo *et al.* demonstrated reduced reservoir and contraction functions of the right atrium, even in patients without left ventricular hypertrophy, suggesting that right atrial involvement may be part of the early cardiac phenotype of the disease.²⁹

Echocardiogram with Myocardial Work

Myocardial work is a noninvasive echocardiographic approach that integrates left ventricular longitudinal strain with estimated systolic blood pressure through pressure-strain loop analysis, allowing assessment of ventricular mechanics while accounting for the influence of afterload. In Fabry disease, recent studies have demonstrated alterations in global and regional myocardial

work indices, with differences related to the presence of left ventricular hypertrophy and the stage of cardiac involvement. Regional analysis also revealed a heterogeneous distribution of myocardial work, adding information to the evaluation by GLS (Figure 1).^{45,46} Although promising, myocardial work still needs validation in multicenter studies before its routine incorporation.

CMR Imaging

CMR Imaging plays a central role in the evaluation of Fabry cardiomyopathy, allowing for comprehensive characterization of ventricular morphology, volumes, and function, as well as non-invasive assessment of myocardial tissue composition. Its high spatial resolution and multiparametric characterization capabilities enable the identification of different components of the pathological process, including intracellular storage of glycosphingolipids, hypertrophy, inflammation, edema, and fibrosis, contributing to differential diagnosis, disease staging, prognostic stratification, and therapeutic monitoring.^{6,7,23,47,48} The most common morphological manifestation is left ventricular hypertrophy, usually with a concentric pattern, although asymmetric patterns and other phenotypic variants may also occur. CMR is the reference standard for quantifying ventricular volumes, myocardial mass, and biventricular function, allowing more precise characterization of the distribution of hypertrophy and identification of structural abnormalities that may not be adequately detected by echocardiography.^{7,23,25,49}

LGE enables the identification of areas of extracellular space expansion related to focal myocardial fibrosis. The classic pattern of Fabry cardiomyopathy consists of mesocardial or subepicardial LGE, predominantly located in the basal and mid- inferolateral wall segments, generally with preservation of the subendocardium (Figure 2A). This pattern was initially characterized by Moon *et al.*, and constitutes an important marker of advanced heart disease, although other distributions may be observed, especially in patients with more extensive myocardial remodeling.^{7,23,49,50}

Fabry disease was subsequently demonstrated by Moon *et al.*, who directly compared CMR images with macroscopic and histological analysis of the heart. Regions with LGE showed extensive collagen deposition, confirming that late enhancement corresponds to focal myocardial fibrosis and not to intracellular storage of glycosphingolipids.⁵¹ In the study, the LGE-enhanced segments showed approximately 62% collagen, compared to 4% in the non-enhanced segments.

The presence and extent of LGE are associated with the progression of cardiomyopathy, a higher risk of ventricular arrhythmias, and adverse cardiovascular events. Myocardial fibrosis is also an important determinant of treatment response, as patients with established fibrosis have less potential for regression of hypertrophy and functional recovery after initiation of specific therapy. This finding reinforces the importance of diagnosis and treatment before the development of irreversible myocardial damage.^{7,23,52-54}

T1 Mapping

Native T1 mapping represented one of the major advances in the evaluation of Fabry cardiomyopathy, allowing for quantitative characterization of the myocardium without the need for contrast administration (Figure 2B). Unlike most

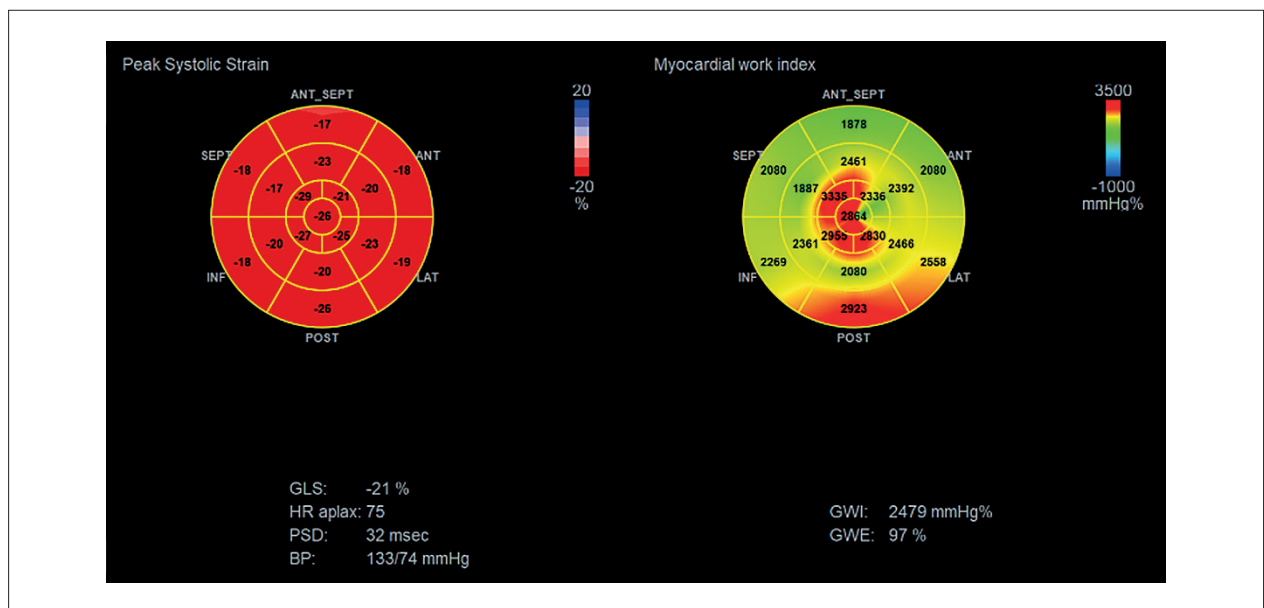


Figure 1 – Assessment of left ventricular mechanics via advanced echocardiography in a patient with Fabry disease. On the left, a polar map of systolic longitudinal strain, demonstrating a GLS of -21% . On the right, a polar map of myocardial work, with a global work index (GWI) of $2479 \text{ mmHg\%}$ and a global myocardial work efficiency (GWE) of 97% . Image from the authors' collection.

cardiomyopathies associated with ventricular hypertrophy, in which native T1 is usually elevated, Fabry disease is typically characterized by reduced T1 values, attributed to the intracellular storage of glycosphingolipids.^{23,55-58}

The pioneering studies by Sado et al. and Thompson et al. demonstrated that a reduction in native T1 has a high capacity to differentiate Fabry disease from other causes of left ventricular hypertrophy and may be present even before the development of detectable hypertrophy or fibrosis. Thus, native T1 constitutes a sensitive marker of early myocardial storage and may allow the identification of cardiac involvement in subclinical phases of the disease.⁵⁵⁻⁵⁷

However, normal T1 values do not exclude cardiac involvement. In regions with inflammation, edema, and fibrosis, particularly in the inferolateral wall, the increased water content and extracellular matrix can elevate T1 and counterbalance the reducing effect of intracellular storage, producing apparently normal values, a phenomenon called T1 pseudonormalization. In advanced stages, T1 may even present elevated values in regions with extensive fibrosis.^{6,7,23,59,60}

T1 values should be interpreted according to the equipment, the technique used, and local reference values.^{6,23,58}

T2 Mapping and Myocardial Inflammation

T2 mapping allows for the quantitative assessment of myocardial fluid content and constitutes a non-invasive marker of edema and inflammation. In Fabry disease, elevated T2 values are observed predominantly in the inferolateral wall, frequently in association with areas of LGE, suggesting the presence of chronic inflammatory activity superimposed on glycosphingolipid storage and myocardial fibrosis.

Regional T2 elevation is associated with the presence of LGE, elevated troponin, and greater severity of cardiomyopathy, and should be interpreted in conjunction with other CMR imaging parameters.^{7,23,59,60}

Extracellular Volume

Myocardial Extracellular Volume (ECV), calculated from T1 values obtained before and after contrast administration, together with hematocrit, allows estimation of the fraction of myocardium occupied by extracellular space. Unlike native T1, which in Fabry disease is typically reduced due to intracellular storage of glycosphingolipids, ECV generally remains within normal limits in the initial phases, reflecting the predominantly intracellular nature of the storage process.^{55,56,58}

With the progression of cardiomyopathy and the development of myocardial injury, inflammation, and fibrosis, expansion of the extracellular space and regional or global increase in the ECV may occur. These changes are observed mainly in regions with LGE, particularly in the inferolateral wall, and may contribute to characterizing the extent of interstitial remodeling.^{6,23,47,59}

ECV should be interpreted in conjunction with T1, T2, and LGE, as normal values do not exclude early involvement and may coexist with regional abnormalities.^{6,7,47}

Strain by CMR Imaging

Myocardial deformation analysis by feature tracking in CMR imaging allows quantification of the longitudinal, circumferential, and radial components of strain from conventional cine sequences, without the need for additional acquisitions. In

Fabry disease, alterations in myocardial deformation can be identified even in the presence of preserved ejection fraction and are associated with the severity of cardiac involvement. Zhao *et al.* demonstrated a reduction in longitudinal and radial strain of the left ventricle, with progressive impairment according to the stage of cardiomyopathy; however, circumferential strain showed less uniform behavior. Despite its potential for functional characterization and monitoring of disease progression, differences between programs, analysis methods, and reference values still limit its routine clinical application, and longitudinal studies are needed to define its prognostic value and its usefulness for therapeutic monitoring.^{47,48,61}

Conclusion

The integration of electrocardiography, echocardiography, and CMR enables early diagnosis, risk stratification, and longitudinal monitoring of Fabry cardiomyopathy. Emerging techniques, including myocardial work and CMR feature tracking, show promising potential but require further validation before their routine clinical implementation.

Author Contributions

Conception and design of the research and analysis and interpretation of the data: Volpolini LC, Mancuso FJ, Uellendahl M; acquisition of data: Volpolini LC, Cardinali MP, Uellendahl M; statistical analysis and writing of the manuscript: Volpolini LC; critical revision of the manuscript for intellectual content: Volpolini LC, Fischer CH, Moises VA, Curiati MA, Martins AM, Mancuso FJ, Uellendahl M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo under the protocol number 51118615.6.0000.5505. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

During the preparation of this work, the authors used artificial intelligence to improve the text and for translation purposes, and not for the creation of the content itself. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

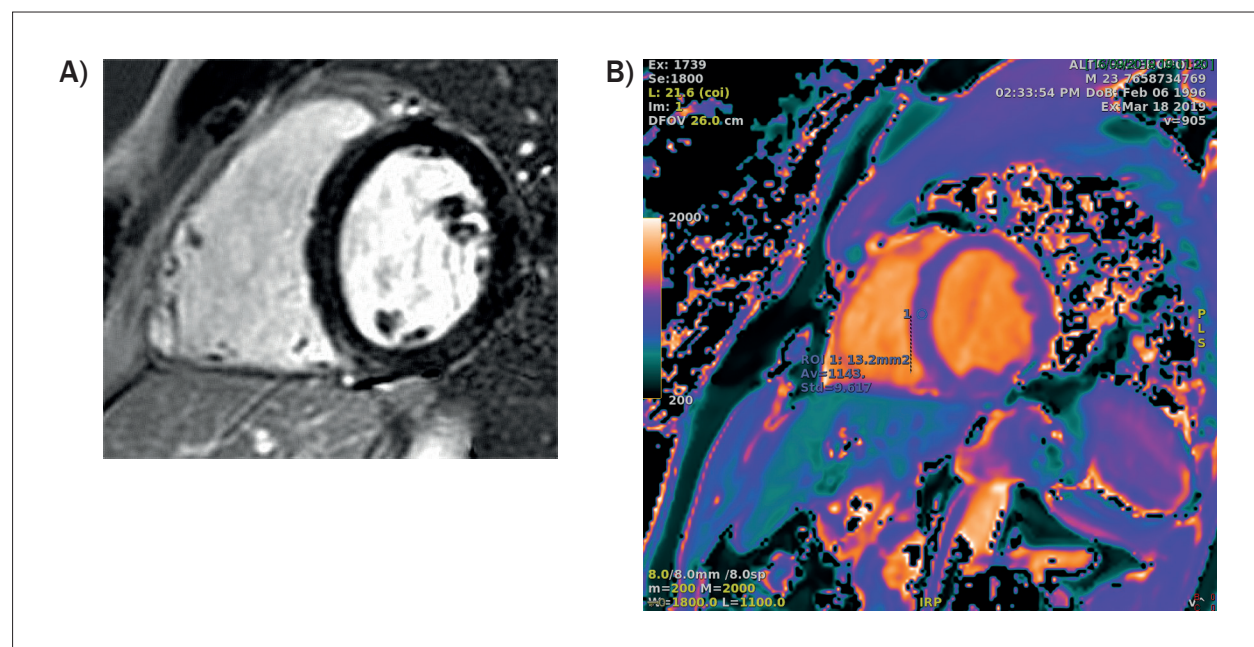


Figure 2 – Myocardial tissue characterization via CMR imaging in patients with Fabry disease. (A) Short-axis LGE image demonstrating mid-wall enhancement in the inferolateral wall of the left ventricle, consistent with myocardial fibrosis. (B) Short-axis native T1 map of the myocardium, used for the quantitative assessment of myocardial tissue properties. Images from the authors' collection.

References

1. Kok K, Zwiers KC, Boot RC, Overkleef HS, Aerts JMFG, Artola M. Fabry Disease: Molecular Basis, Pathophysiology, Diagnostics and Potential Therapeutic Directions. *Biomolecules*. 2021;11(2):271. doi: 10.3390/biom11020271.
2. Amodio F, Caiazza M, Monda E, Rubino M, Capodicasa L, Chiosi F, et al. An Overview of Molecular Mechanisms in Fabry Disease. *Biomolecules*. 2022;12(10):1460. doi: 10.3390/biom12101460.
3. Pieroni M, Namdar M, Olivetto I, Desnick RJ. Anderson-Fabry Disease Management: Role of the Cardiologist. *Eur Heart J*. 2024;45(16):1395-409. doi: 10.1093/eurheartj/ehae148.
4. Monda E, Diana G, Graziani F, Rubino M, Bakalakos A, Linhart A, et al. Impact of GLA Variant Classification on the Estimated Prevalence of Fabry Disease: A Systematic Review and Meta-Analysis of Screening Studies. *Circ Genom Precis Med*. 2023;16(6):e004252. doi: 10.1161/CIRCGEN.123.004252.
5. Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, et al. Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry. *Pediatr Res*. 2008;64(5):550-5. doi: 10.1203/PDR.0b013e318183f132.
6. Nordin S, Kozor R, Medina-Menacho K, Abdel-Gadir A, Baig S, Sado DM, et al. Proposed Stages of Myocardial Phenotype Development in Fabry Disease. *JACC Cardiovasc Imaging*. 2019;12(8 Pt 2):1673-83. doi: 10.1016/j.jcmg.2018.03.020.
7. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovic AC, et al. Cardiac Involvement in Fabry Disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2021;77(7):922-36. doi: 10.1016/j.jacc.2020.12.024.
8. Sweeley CC, Klionsky B. Fabry's Disease: Classification as a Sphingolipidosis and Partial Characterization of a Novel Glycolipid. *J Biol Chem*. 1963;238:3148-50.
9. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic Defect in Fabry's Disease. Ceramidetrihexosidase Deficiency. *N Engl J Med*. 1967;276(21):1163-7. doi: 10.1056/NEJM196705252762101.
10. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy. *Ann Intern Med*. 2003;138(4):338-46. doi: 10.7326/0003-4819-138-4-200302180-00014.
11. Aerts JM, Groener JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, et al. Elevated Globotriaosylsphingosine is a Hallmark of Fabry Disease. *Proc Natl Acad Sci U S A*. 2008;105(8):2812-7. doi: 10.1073/pnas.0712309105.
12. Weidemann F, Breunig F, Beer M, Sandstedt J, Störk S, Voelker W, et al. The Variation of Morphological and Functional Cardiac Manifestation in Fabry Disease: Potential Implications for the Time Course of the Disease. *Eur Heart J*. 2005;26(12):1221-7. doi: 10.1093/eurheartj/ehi143.
13. Germain DP. Fabry Disease. *Orphanet J Rare Dis*. 2010;5:30. doi: 10.1186/1750-1172-5-30.
14. Fellgiebel A, Müller MJ, Ginsberg L. CNS Manifestations of Fabry's Disease. *Lancet Neurol*. 2006;5(9):791-5. doi: 10.1016/S1474-4422(06)70548-8.
15. Goldman ME, Cantor R, Schwartz MF, Baker M, Desnick RJ. Echocardiographic Abnormalities and Disease Severity in Fabry's Disease. *J Am Coll Cardiol*. 1986;7(5):1157-61. doi: 10.1016/s0735-1097(86)80238-8.
16. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudová J, Karetová D, et al. New Insights in Cardiac Structural Changes in Patients with Fabry's Disease. *Am Heart J*. 2000;139(6):1101-8. doi: 10.1067/mhj.2000.105105.
17. Ferrans VJ, Hibbs RC, Burda CD. The Heart in Fabry's Disease. A Histochemical and Electron Microscopic Study. *Am J Cardiol*. 1969;24(1):95-110. doi: 10.1016/0002-9149(69)90055-1.
18. Sheth KJ, Thomas JP Jr. Electrocardiograms in Fabry's Disease. *J Electrocardiol*. 1982;15(2):153-6. doi: 10.1016/s0022-0736(82)80010-1.
19. Namdar M. Electrocardiographic Changes and Arrhythmia in Fabry Disease. *Front Cardiovasc Med*. 2016;3:7. doi: 10.3389/fcvm.2016.00007.
20. Roudebush CP, Foerster JM, Bing OH. The Abbreviated PR Interval of Fabry's Disease. *N Engl J Med*. 1973;289(7):357-8. doi: 10.1056/NEJM197308162890709.
21. Figliozzi S, Camporeale A, Boveri S, Pieruzzi F, Pieroni M, Lusardi P, et al. ECG-Based Score Estimates the Probability to Detect Fabry Disease Cardiac Involvement. *Int J Cardiol*. 2021;339:110-7. doi: 10.1016/j.ijcard.2021.07.022.
22. Yeung DF, Sirrs S, Tsang MYC, Gin K, Luong C, Jue J, et al. Echocardiographic Assessment of Patients with Fabry Disease. *J Am Soc Echocardiogr*. 2018;31(6):639-49.e2. doi: 10.1016/j.echo.2018.01.016.
23. Cameli M, Pieroni M, Pastore MC, Brucato A, Castelletti S, Crotti L, et al. The Role of Cardiovascular Multimodality Imaging in the Evaluation of Anderson-Fabry Disease: From Early Diagnosis to Therapy Monitoring. *Eur Heart J Cardiovasc Imaging*. 2025;26(5):814-29. doi: 10.1093/ehjci/jeaf038.
24. Bass JL, Shrivastava S, Grabowski GA, Desnick RJ, Moller JH. The M-Mode Echocardiogram in Fabry's Disease. *Am Heart J*. 1980;100(6 Pt 1):807-12. doi: 10.1016/0002-8703(80)90060-5.
25. Niemann M, Herrmann S, Hu K, Breunig F, Strotmann J, Beer M, et al. Differences in Fabry Cardiomyopathy between Female and Male Patients: Consequences for Diagnostic Assessment. *JACC Cardiovasc Imaging*. 2011;4(6):592-601. doi: 10.1016/j.jcmg.2011.01.020.
26. Pieroni M, Chimenti C, De Cobelli F, Morgante E, Del Maschio A, Gaudio C, et al. Fabry's Disease Cardiomyopathy: Echocardiographic Detection of Endomyocardial Glycosphingolipid Compartmentalization. *J Am Coll Cardiol*. 2006;47(8):1663-71. doi: 10.1016/j.jacc.2005.11.070.
27. Weidemann F, Breunig F, Beer M, Sandstedt J, Turschner O, Voelker W, et al. Improvement of Cardiac Function during Enzyme Replacement Therapy in Patients with Fabry Disease: A Prospective Strain Rate Imaging Study. *Circulation*. 2003;108(11):1299-301. doi: 10.1161/01.CIR.0000091253.71282.04.
28. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314. doi: 10.1016/j.echo.2016.01.011.
29. Lillo R, Cianci A, Meucci MC, Iannaccone G, Di Brango C, Tusa F, et al. Right Atrial Strain in Anderson-Fabry Disease. *Front Cardiovasc Med*. 2025;12:1496534. doi: 10.3389/fcvm.2025.1496534.
30. Nagueh SF, Sanborn DY, Oh JK, Anderson B, Billick K, Derumeaux G, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure with Preserved Ejection Fraction Diagnosis: An Update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2025;38(7):537-69. doi: 10.1016/j.echo.2025.03.011.
31. Morris DA, Blaschke D, Canaan-Kühl S, Krebs A, Knobloch G, Walter TC, et al. Global Cardiac Alterations Detected by Speckle-Tracking Echocardiography in Fabry Disease: Left Ventricular, Right Ventricular, and Left Atrial Dysfunction are Common and Linked to Worse Symptomatic Status. *Int J Cardiovasc Imaging*. 2015;31(2):301-13. doi: 10.1007/s10554-014-0551-4.
32. Spinelli L, Bianco A, Riccio E, Pisani A, Iaccarino G. Cardiac Involvement in Anderson-Fabry Disease. The Role of Advanced Echocardiography. *Front Cardiovasc Med*. 2024;11:1440636. doi: 10.3389/fcvm.2024.1440636.
33. Roy A, O'Shea C, Dasí A, Patel L, Cumberland MJ, Nieves D, et al. Early Atrial Remodeling Drives Arrhythmia in Fabry Disease. *Circ Arrhythm Electrophysiol*. 2025;18(7):e013352. doi: 10.1161/CIRCEP.124.013352.

34. Huang S, Wang J, Zhang W, Gao F, Chen Y, Shui W, et al. Clinical Study of Left Ventricular Structure and Function in Patients with Anderson-Fabry Disease Before and after Enzyme Replacement Therapy. *J Clin Ultrasound*. 2024;52(1):20-9. doi: 10.1002/jcu.23592.
35. Spinelli L, Giugliano G, Imbriaco M, Esposito G, Nappi C, Riccio E, et al. Left Ventricular Radial Strain Impairment Precedes Hypertrophy in Anderson-Fabry Disease. *Int J Cardiovasc Imaging*. 2020;36(8):1465-76. doi: 10.1007/s10554-020-01847-z.
36. Labombarda F, Saloux E, Milesi G, Bienvenu B. Loss of Base-to-Apex Circumferential Strain Gradient: A Specific Pattern of Fabry Cardiomyopathy? *Echocardiography*. 2017;34(4):504-10. doi: 10.1111/echo.13496.
37. Boyd AC, Lo Q, Devine K, Tchan MC, Sillence DO, Sadick N, et al. Left Atrial Enlargement and Reduced Atrial Compliance Occurs Early in Fabry Cardiomyopathy. *J Am Soc Echocardiogr*. 2013;26(12):1415-23. doi: 10.1016/j.echo.2013.08.024.
38. Pichette M, Serri K, Pagé M, Di LZ, Bichet DG, Poulin F. Impaired Left Atrial Function in Fabry Disease: A Longitudinal Speckle-Tracking Echocardiography Study. *J Am Soc Echocardiogr*. 2017;30(2):170-9.e2. doi: 10.1016/j.echo.2016.10.014.
39. Saccheri MC, Cianciulli TF, Licidio WC, Lax JA, Beck MA, Morita LA, et al. Comparison of Left Atrial Size and Function in Hypertrophic Cardiomyopathy and in Fabry Disease with Left Ventricular Hypertrophy. *Echocardiography*. 2018;35(5):643-50. doi: 10.1111/echo.13829.
40. Frumkin D, Mattig I, Laule N, Al Daas M, Canaan-Kühl S, Knebel F, et al. Comparative Analysis of Phasic Left Atrial Strain and Left Ventricular Posterolateral Strain Pattern to Discriminate Fabry Cardiomyopathy from Other Forms of Left Ventricular Hypertrophy. *Echocardiography*. 2021;38(11):1870-8. doi: 10.1111/echo.15224.
41. Mattig I, Steudel T, Klingel K, Barzen C, Frumkin D, Spethmann S, et al. Right Heart and Left Atrial Strain to Differentiate Cardiac Amyloidosis and Fabry Disease. *Sci Rep*. 2024;14(1):2445. doi: 10.1038/s41598-024-52890-y.
42. Lillo R, Meucci MC, Del Franco A, Monda E, Iannaccone G, Ditaranto R, et al. Evolution of Cardiac Damage Staged with Echocardiography in Fabry Disease. *J Am Heart Assoc*. 2025;14(11):e041627. doi: 10.1161/JAHA.124.041627.
43. Lillo R, Graziani F, Panaioli E, Mencarelli E, Pieroni M, Camporeale A, et al. Right Ventricular Strain in Anderson-Fabry Disease. *Int J Cardiol*. 2021;330:84-90. doi: 10.1016/j.ijcard.2021.02.038.
44. Meucci MC, Lillo R, Mango F, Lombardo A, Lanza GA, Parisi V, et al. Right Ventricular Strain in Fabry Disease: Prognostic Implications. *Int J Cardiol*. 2023;374:79-82. doi: 10.1016/j.ijcard.2022.12.047.
45. Fan J, Ma C, Wang H, Zhou B. The Value of Myocardial Work in Patients with Left Ventricular Hypertrophy. *Int J Cardiovasc Imaging*. 2023;39(6):1105-13. doi: 10.1007/s10554-023-02818-w.
46. Wang H, Yang Y, Liu L, Zhao Y, Li Y, Zhang W, et al. Evaluation of Global and Regional Myocardial Work by Echocardiography in Patients with Fabry Disease. *Orphanet J Rare Dis*. 2024;19(1):383. doi: 10.1186/s13023-024-03396-3.
47. Camporeale A, Diano A, Tondi L, Pica S, Pasqualin G, Ciabatti M, et al. Cardiac Magnetic Resonance Features of Fabry Disease: From Early Diagnosis to Prognostic Stratification. *Rev Cardiovasc Med*. 2022;23(5):177. doi: 10.31083/j.rcm2305177.
48. Umer M, Kalra DK. Cardiac MRI in Fabry Disease. *Front Cardiovasc Med*. 2023;9:1075639. doi: 10.3389/fcvm.2022.1075639.
49. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, et al. Cardiovascular Magnetic Resonance Demonstration of the Spectrum of Morphological Phenotypes and Patterns of Myocardial Scarring in Anderson-Fabry Disease. *J Cardiovasc Magn Reson*. 2016;18:14. doi: 10.1186/s12968-016-0233-6.
50. Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, et al. Gadolinium Enhanced Cardiovascular Magnetic Resonance in Anderson-Fabry Disease. Evidence for a Disease Specific Abnormality of the Myocardial Interstitium. *Eur Heart J*. 2003;24(23):2151-5. doi: 10.1016/j.ehj.2003.09.017.
51. Moon JC, Sheppard M, Reed E, Lee P, Elliott PM, Pennell DJ. The Histological Basis of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in a Patient with Anderson-Fabry Disease. *J Cardiovasc Magn Reson*. 2006;8(3):479-82. doi: 10.1080/10976640600605002.
52. Weidemann F, Niemann M, Breunig F, Herrmann S, Beer M, Störk S, et al. Long-term Effects of Enzyme Replacement Therapy on Fabry Cardiomyopathy: Evidence for a Better Outcome with Early Treatment. *Circulation*. 2009;119(4):524-9. doi: 10.1161/CIRCULATIONAHA.108.794529.
53. Hanneman K, Karur GR, Wasim S, Wald RM, Iwanochko RM, Morel CF. Left Ventricular Hypertrophy and Late Gadolinium Enhancement at Cardiac MRI are Associated with Adverse Cardiac Events in Fabry Disease. *Radiology*. 2020;294(1):42-9. doi: 10.1148/radiol.2019191385.
54. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, et al. Two-Dimensional Speckle Tracking as a Non-Invasive Tool for Identification of Myocardial Fibrosis in Fabry Disease. *Eur Heart J*. 2013;34(21):1587-96. doi: 10.1093/eurheartj/ehs098.
55. Sado DM, White SK, Piechnik SK, Baniyarsad SM, Treibel T, Captur G, et al. Identification and Assessment of Anderson-Fabry Disease by Cardiovascular Magnetic Resonance Noncontrast Myocardial T1 Mapping. *Circ Cardiovasc Imaging*. 2013;6(3):392-8. doi: 10.1161/CIRCIMAGING.112.000070.
56. Thompson RB, Chow K, Khan A, Chan A, Shanks M, Paterson I, et al. T₁ Mapping with Cardiovascular MRI is Highly Sensitive for Fabry Disease Independent of Hypertrophy and Sex. *Circ Cardiovasc Imaging*. 2013;6(5):637-45. doi: 10.1161/CIRCIMAGING.113.000482.
57. Pica S, Sado DM, Maestrini V, Fontana M, White SK, Treibel T, et al. Reproducibility of Native Myocardial T1 Mapping in the Assessment of Fabry Disease and Its Role in Early Detection of Cardiac Involvement by Cardiovascular Magnetic Resonance. *J Cardiovasc Magn Reson*. 2014;16(1):99. doi: 10.1186/s12968-014-0099-4.
58. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical Recommendations for Cardiovascular Magnetic Resonance Mapping of T1, T2, T2* and Extracellular Volume: A Consensus Statement by the Society for Cardiovascular Magnetic Resonance (SCMR) Endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19(1):75. doi: 10.1186/s12968-017-0389-8.
59. Nordin S, Kozor R, Bulluck H, Castelletti S, Rosmini S, Abdel-Gadir A, et al. Cardiac Fabry Disease with Late Gadolinium Enhancement is a Chronic Inflammatory Cardiomyopathy. *J Am Coll Cardiol*. 2016;68(15):1707-8. doi: 10.1016/j.jacc.2016.07.741.
60. Augusto JB, Nordin S, Vijapurapu R, Baig S, Bulluck H, Castelletti S, et al. Myocardial Edema, Myocyte Injury, and Disease Severity in Fabry Disease. *Circ Cardiovasc Imaging*. 2020;13(3):e010171. doi: 10.1161/CIRCIMAGING.119.010171.
61. Zhao L, Zhang C, Tian J, Saiedi M, Ma C, Li N, et al. Quantification of Myocardial Deformation in Patients with Fabry Disease by Cardiovascular Magnetic Resonance Feature Tracking Imaging. *Cardiovasc Diagn Ther*. 2021;11(1):91-101. doi: 10.21037/cdt-20-897.



This is an open-access article distributed under the terms of the Creative Commons Attribution License