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# Contemporary View of Magnetic Resonance Imaging in Fabry Disease

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**Abstract**

**Purpose** Fabry disease is a rare lysosomal storage disorder, whose main cause of death is cardiac. CMR provides relevant information that contributes to diagnosis, enabling staging of the disease and an appropriate start of therapy. This review intends to highlight the main strengths of this technique, where a relatively robust scientific evidence supports its use.

**Recent Findings** CMR is useful in Fabry disease in a number of aspects. On the one hand, it helps characterize myocardial involvement, enabling accurate chamber size quantification and tissue characterization, by means of LGE, and more recently T1 mapping. Early and appropriate diagnosis of the cardiac disease can guide the start of ERT. Secondly, it has prognostic value, improving risk stratification for device therapy.

**Summary** An integrative approach of conventional and new CMR techniques is desirable for early detection of subclinical disease, appropriate disease staging, risk stratification, and therapy guiding. T1 mapping is a particularly promising tool in this field.

**Keywords** Fabry disease · Cardiac magnetic resonance · Left ventricular hypertrophy · Late gadolinium enhancement · T1 mapping · T2 mapping

## Introduction

Fabry disease (FD) is a rare lysosomal storage disorder due to a deficit in $\alpha$-galactosidase. As a result, glycosphingolipids accumulate in a variety of tissues, which involve a wide range of symptoms and clinical presentations. Because of its X-linked inheritance, men are usually more severely affected at an earlier age, although women present with a more unpredictable course that range from being asymptomatic to severely diseased [1]. Cardiac, renal, and neurological involvement drive the prognosis, being cardiac disease the leading cause of death [2]. The typical presentation is a similar phenotype to hypertrophic cardiomyopathy, also with an increased risk of atrial and ventricular arrhythmias that may lead to sudden cardiac death [3]. Since an enzyme replacement therapy (ERT) has been available for several years, cardiac imaging plays an important role for a correct diagnosis and start of treatment indication. Echocardiography is the first-line cardiac assessment technique, but cardiac magnetic resonance (CMR) is superior in many aspects, providing more accurate information on cardiac morphology and function. Additionally, recent advances in tissue characterization may have a meaningful impact on the management of the disease.

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## Diagnosis

### Morphology and Function

CMR is the recommended approach for volumetric and functional analysis in FD and for tissue characterization of the myocardium. Increased left ventricular (LV) wall thickness is the hallmark feature of FD, caused by glycolipid deposition in ventricular muscle fiber, involving papillary muscles,

trabeculations, and ventricular walls [4]. The classical Fabry cardiomyopathy presents as concentric hypertrophy (Fig. 1), although other phenotypes are also possible, including asymmetric, septal, posterior wall hypertrophy, or concentric remodeling [5]. CMR allows a more accurate measurement of LV mass (LVM) index compared to echocardiography [6]. The latter systematically overestimates LVM, and due to its higher variability also fails to detect longitudinal changes that aim to evaluate treatment response and can impact therapeutic decisions [7]. In addition, the spatial characteristics of left ventricular hypertrophy (LVH), including papillary muscles hypertrophy, can be well described by CMR [8]. In FD, they are reportedly disproportionally hypertrophied, representing up to 20% of the LVM (usually they are 8% of the LVM) [9]. Moreover, the contribution of papillary muscles to total LVM has been shown to be significantly increased in FD compared to other forms of LV hypertrophy (hypertrophic cardiomyopathy (HCM), amyloidosis, hypertensive heart, or aortic stenosis) and controls, not only in patients with established hypertrophy but also in early stages of the disease where LVH is still not present [10].

## Late Gadolinium Enhancement

Beyond its accuracy in chamber size quantification, the main strength of CMR is its capability for tissue characterization. Lipid accumulation, fibrosis, or inflammation are all pathological processes amenable to be detected with CMR, either with late gadolinium enhancement (LGE) and calculation of extracellular volume (ECV), both of which explore the extracellular compartment, or with native (non-contrast) T1 and T2 mapping, which represent a mixed signal of the myocyte and interstitium. The pattern and location of LGE can suggest a specific etiology within the group of non-ischemic cardiomyopathies [11]. Around 50% of FD patients have LGE, typically located in the basal infero-lateral wall in a midwall distribution [12, 13]; however, it can be associated with atypical locations, as apical or mid-ventricular LV LGE, usually matching myocardial hypertrophy [14]. Distribution of LGE can explain the regional differences of the LV hypertrophy and wall motion alterations [15]. The histological correlate of LGE in FD patients was initially thought to be fibrosis [16] and although it was thought to be a late phenomenon indicating irreversible damage, a significant proportion of patients (13–23%), mainly females, can present LGE without LV hypertrophy [17, 18], suggesting that the development of fibrosis do not necessarily require myocardial hypertrophy in female patients with FD. This finding is probably explained by the process of lyonization that takes place in females during the first weeks of life, determining a more variable presentation, with a later onset of symptoms but also a more unpredictable clinical course.

## T1 Mapping

Recently, the advent of T1 mapping sequences has contributed to a more refined evaluation of diffuse myocardial disease, providing a quantifiable and reproducible measure of the myocardial signal. While most cardiomyopathies present with increased T1 [19] (edema, amyloid infiltration, fibrosis), the fact that fat presents a very low T1 signal suggests that T1 mapping could be used as a diagnostic tool to help discriminate FD from other causes of LVH, and even more interesting, as a non-invasive surrogate measure for myocardial glycosphingolipid accumulation. Native T1 mapping at 1.5 T was found to be significantly decreased in FD patients compared to healthy controls and subjects with concentric remodeling or LV hypertrophy [20]. Another group [21, 22] reported similar findings, distinguishing FD from other conditions with no overlap when LVH was present. Notably, even in the absence of LVH, 40% of Fabry patients showed abnormal native T1 values, underscoring its ability for early detection of myocardial involvement (Fig. 2). In a relatively broad Fabry patients cohort evaluated with T1 mapping (182 patients), native T1 was normal in children, dropping with age and reaching levels below the normal threshold in adulthood, suggesting subclinical sphingolipids accumulation. Both in children and adults, the drop in native T1 levels with age is steeper in men compared with women [23]. Noticeably, myocardial

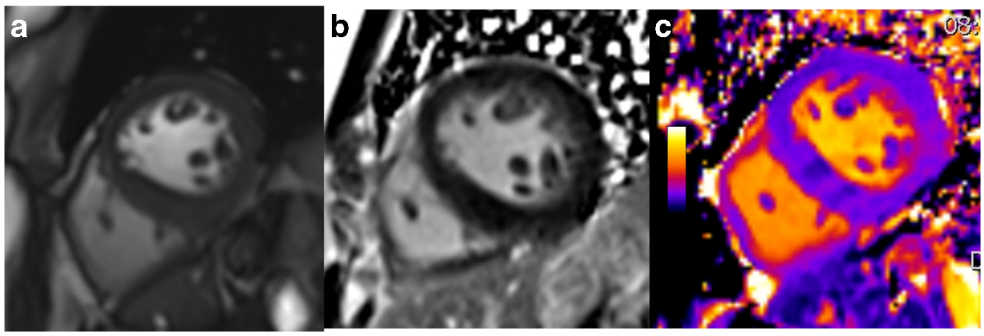


**Fig. 1** 45-year-old male with global concentric LVH and hypertrophied papillary muscles in CINE images, corresponding to a classical FD phenotype (**a**). No LGE was observed in this patient (**b**), but native T1 values were decreased compared to local controls (1032 ms, lower limit of normality 1140 ms)

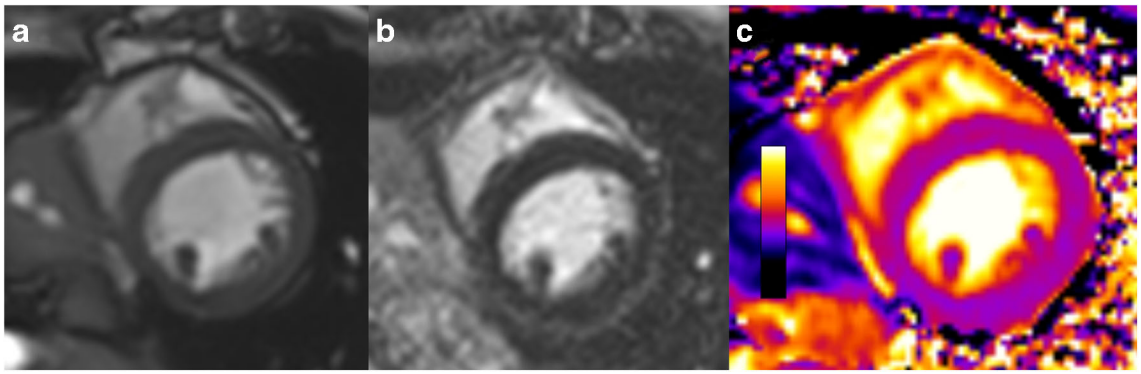


**Fig. 2** 39-year-old male, younger sibling of the patient in Fig. 1, who has developed neither LVH (**a**) nor LGE (**b**). He started ERT at the age of 21 due to gastrointestinal symptoms. Although conventional CMR sequences do not detect cardiac involvement, native T1 was low (1038 ms) in a similar range as his brother (**c**)

segments are affected by a varying degree of T1 shortening, being the inferior and infero-septal segments, the ones with the highest differences between HCM and FD. ECV however showed no difference between patients and controls, consistent with the fact that FD is an intracellular (lysosomal) storage disease. The use of native T1 thus offers the possibility of accurate myocardial characterization and early diagnosis without the need for contrast use, with particularly of use in this population, who frequently present with impaired renal function.

The diagnostic value of T1 mapping was also recently assessed at 3 T [24]; in line with previous studies, it showed lower values of both left and right ventricles, providing incremental diagnostic value beyond age, sex, and conventional imaging features. Right ventricular involvement in FD is common, typically manifesting as hypertrophy and/or myocardial dysfunction; native T1 is also reduced and correlates positively with LV native T1 value [25].

### Deformation analysis

Functional impairment of myocardium in FD has been previously described with speckle-tracking echocardiography [26] in patients with and without LVH. Deformation analysis stands therefore as an alternative tool for early diagnosis. Feature-tracking global longitudinal strain (GLS) correlated with LVM and native T1 in a recent study with 221 patients. In LVH− FD (early disease), impairment of GLS was associated with a reduction in native T1, suggesting that mechanical dysfunction and sphingolipid accumulation occur before the onset of LVH [13]. These results were not reproduced by a contemporary study, which, although included a reduced sample (N 18), showed significant differences in circumferential strain (GCS), but not in GLS, between LVH+ and LVH− [27]. Native T1 has shown a stronger correlation with increased LVM compared to GLS [28]. The use of feature tracking is limited due to the fact that reproducibility still remains problematic, with considerable intervendor and regional variability, being GCS the most robust measure. For the time being, T1 mapping may be a more reproducible and technically feasible routine measure than deformation analysis.

## Therapy Guidance

Since 2001, specific $\alpha$-galactosidase replacement therapy is available. Initial studies evaluating its efficacy showed a significant reduction in LVM and strain assessed with echocardiography after 12 months of ERT [29, 30]. However, this morphological and functional improvement seems to be conditioned by initiation at an appropriate stage of the disease, before irreversible damage has occurred. Several studies from the same group have shown that 12-month ERT fails to induce regression of LVH as well as improvement in regional function in patients with LGE and only patients without LGE show significant associations of ERT with favorable changes in LV mass and radial and longitudinal deformation parameters [15, 31]. Similar results after 3-year follow-up suggest that cardiac disease progression is unchanged by ERT once LGE is present [32]. Migalastat, an oral pharmacological chaperone of $\alpha$-galactosidase, has also been shown to reduce LVM and also decrease LGE and cardiac biomarkers (TnT and NT-ProBNP), although these results need to be confirmed in a larger cohort [33–35].

Currently, the start of ERT is recommended as soon as early clinical signs of renal, cardiac, or brain involvement. Focusing on cardiac findings, ERT should be started when LVH is present (> 12-mm wall thickness) without or with minimal fibrosis by LGE [36]. Advanced cardiac disease with extensive myocardial fibrosis is considered criteria for not starting ERT if cardiac disease is the sole treatment indication. As abovementioned, fibrosis can precede the development of LVH; therefore, early detection of myocardial lipid accumulation is highly desirable for a timely intervention that prevents further worsening of cardiac function while avoiding

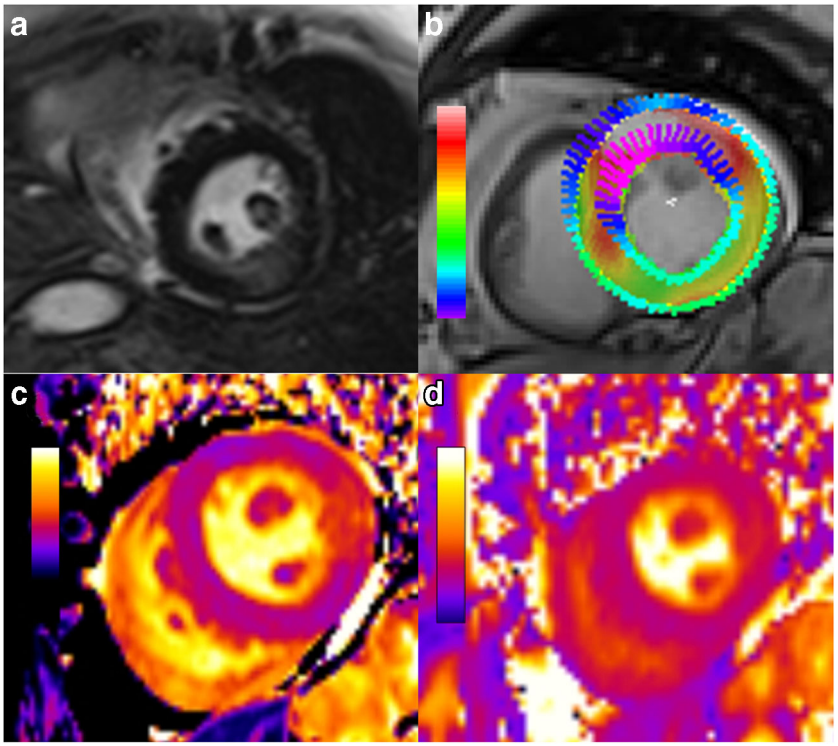


**Fig. 3** Panel **a** shows typical FD faint midwall LGE in the basal infero-lateral wall, corresponding to a 55-year-old female, with severe LVH, more pronounced in the apical segments. Mechanical dysfunction in the inferior, infero-lateral, and infero-septal walls is evident in deformation analysis (GCS, panel **b**). Further characterization is provided by T1 and T2 mapping sequences (**c** and **d**): septal T1 is 1060 ms (low) and T2 is 36 ms (normal). However values in the area of LGE are significantly increased, being T1 1291 ms and T2 47 ms, probably reflecting inflammation ± fibrosis in that location

**Table 1** Bullet points summarizing the clinical utility of CMR-derived measures

| | Diagnosis | Therapy | Prognosis |
|---|---|---|---|
| LV mass | • No specific hypertrophy pattern<br>• Hypertrophy of papillary muscles suggests FD | • Initiation of therapy<br>• Surrogate endpoint for the efficacy of therapy | • Association with arrhythmia and ventricular arrhythmia risk |
| LGE | • Midwall basal infero-lateral LGE typical of FD | •Absence identificates those patients with a favorable response more likely | • Association with MVA and composite cardiac adverse events |
| T1mapping | • Low native T1 suggests FD irrespective of LV hypertrophy<br>• Potential use for early diagnosis of myocardial involvement | • Promising as a surrogate endpoint for the efficacy of therapy (not explored yet) | |
| Deformation | • Possible use for early diagnosis of myocardial involvement | • Promising as a surrogate endpoint for the efficacy of therapy (not explored yet) | |

patient exposure to undesired adverse events. Noteworthy, these recommendations are based on expert consensus, as the supporting evidence is scarce (mentioned in the preceding paragraph) and does not include randomized studies that compare different strategies. The suggestion that early detection of myocardial lipid deposits by means of T1 mapping could improve patient selection for initiation of ERT, although feasible from a physiopathological perspective, needs to be tested in prospective studies comparing different approaches, optimally demonstrating better outcomes with early initiation of ERT. Unfortunately, the conductance of adequately powered clinical trials evaluating therapy in FD is hindered by sample size and ethical and economic issues.

Once ERT has been initiated, monitoring of disease progression is required to evaluate efficacy. The highly precise information that CMR provides, together with the limited sample size that Fabry studies usually include despite collaboration of high-volume centers, supports the use of CMR measures as a surrogate endpoint for the evaluation of the efficacy of ERT or newer therapeutic alternatives [37]. Myocardial mass and deformation parameters reflecting impaired myocardial function have been used as surrogates in previous studies that assessed the impact of both agalsidase (alpha and beta) and migalastat on the myocardium. Additionally, native T1 provides quantifiable and reproducible information and is highly sensitive to small changes in myocardial composition; it appears therefore as an attractive tool in the future for longitudinal monitoring of FD therapy, although to date it has never been used for follow-up.

**Table. 2** Overview of studies providing evidence on the use of CMR in FD

| Publication | Year | Technique | Patients | Main contribution to current knowledge |
|---|---|---|---|---|
| Wu JC et al. [5] | 2010 | CMR | 139 | Concentric LVH is the predominant cardiac pathology in FD. |
| Hazari H et al. [6] | 2018 | CMR vs echo | 32 | Due to higher variability, echo fails to detect small longitudinal changes compared to CMR. |
| Kozor R et al. [7] | 2016 | CMR | 89 | CMR detects cardiac involvement in 48% of this Fabry cohort. |
| Kozor R et al. [8] | 2015 | CMR | 40 | The volumetric contribution of papillary muscles and trabeculations in Fabry disease is markedly increased relative to healthy controls. |
| Kozor R et al. [10] | 2017 | CMR | 478 | Disproportionate hypertrophy of papillary muscles in LVH+ hearts occurred in FD compared to other forms of LVH. Papillary muscles were also increased in LVH− in FD. |
| Moon J et al. [12] | 2003 | CMR | 36 | First study to describe the typical pattern of midwall LGE in the basal inferolateral wall in FD |
| Vijapurapu R et al. [13] | 2018 | CMR | 298 | GLS in FD correlates with an increase in LVMi, storage, and the presence of ECG abnormalities. |
| Deva DP et al. [14] | 2016 | CMR | 39 | Describes the morphological spectrum of LVH in FD as well as the patterns of myocardial scarring |
| Niemann et al. [17] | 2011 | CMR | 104 | Fibrosis and loss of myocardial function do not necessarily require myocardial hypertrophy in female patients with FD. |
| Nordin S et al. [18] | 2018 | CMR | 135 | Prehypertrophic phenotype in FD: low native T1, structural, functional, and ECG changes |
| Sado DM et al. [21] | 2013 | CMR | 227 | First study to describe low native T1 as a specific diagnostic tool for FD. It also shows subclinical cardiac involvement in patients without LVH. |
| Thompson RB et al. [20] | 2013 | CMR | 75 | Confirms the diagnostic value of native T1 for the early detection of cardiac FD |
| Nordi S et al. [23] | 2018 | CMR | 182 | Proposes three stages of FD based on multiparametric CMR approach: the accumulation phase, inflammation and myocyte hypertrophy phase, and fibrosis and impairment phase. |
| Karur GR et al. [24] | 2018 | CMR | 60 | First study to evaluate the use of native T1 as a diagnostic tool at 3T. |
| Wilson HC et al. [27] | 2018 | CMR | 18 | FD patients with LVH have reduced native T1 and more positive circumferential strain compared to those without. |
| Weidemman F et al. [29] | 2003 | CMR | 16 | ERT can decrease left ventricular hypertrophy and improve regional myocardial function. |
| Beer M [31] | 2006 | CMR | 35 | First study to point out that ERT might not be of use in advanced cardiac FD, defined by the presence of LGE. |
| Weidemann F et al. [32] | 2009 | CMR | 32 | The use of LGE predicts the response to ERT. The annual increase in LGE was an independent predictor of ventricular arrhythmia. |
| Krämer J et al. [42] | 2014 | CMR | 73 | This study reported that the annual increase in LGE was an independent predictor of ventricular arrhythmia. |
| Hanneman K et al. [43] | 2018 | CMR | 82 | LGE has prognostic value, being predictive of ventricular arrhythmia and outcomes in FD |
| Spinelli L et al. [47] | 2018 | CMR | 24 | Myocardial inflammation prompted by sphingolipids deposition may play a role in the pathogenesis of FD |
| Nordin S et al. [46•] | 2016 | CMR | 165 | Elevated T1 and T2 mapping values related to areas of LGE, supporting the inflammatory substrate of the disease. |

## Prognosis and Relation with Outcomes

As previously mentioned, cardiac disease is the leading cause of death in FD, being sudden cardiac death (SCD) the most common presentation (62% of all reported deaths) [38]. Male sex, age, classical phenotype, and chronic kidney disease are known prognostic factors for adverse events [39–41]. However, they are clearly insufficient for an adequate prognostic stratification, which is of the utmost importance as it has a direct impact on therapeutic decisions: on the one hand, the initiation of ERT (previously discussed) and on the other hand, device therapy for SCD prevention. LVH has been associated with an increased risk of overall arrhythmia and ventricular arrhythmia [14, 42]. The significance of myocardial fibrosis, by means of LGE, was first evaluated by Krämer et al. [43]; in a cohort of 73 FD patients, they observed malignant ventricular arrhythmias (MVAs) in 13 LGE+ patients, while none of the LGE− had MVAs. Logistic multivariate

regression analysis revealed that the annual increase in fibrosis during follow-up was the only independent predictor of MVAs. Another small study reproduced similar findings, with an HR 7.35, 95% CI, 2.09–25.89, $p = 0.002$ for the occurrence of a combined endpoint of ventricular tachycardia, bradycardia, heart failure, and cardiac death [44]. Two other small studies failed to find a significant association between LGE and cardiac events, probably due to limited sample sizes and variability of evaluated endpoints [14, 42]. It is also important to emphasize that the abovementioned studies assigned arrhythmic endpoints through 24-h Holter ECG monitoring, which is probably insufficient and often miss clinically relevant arrhythmias [45]. Inherent limitations of LGE, not able to detect reversible interstitial myocardial involvement, make the use of T1 mapping promising, although no data of its potential added prognostic value have been published yet.

## Pathophysiology and New Insights in the Disease

Understanding the pathophysiological processes that underlie a disease is a necessary step for accurate diagnosis and development of effective new therapeutic approaches. In FD, sphingolipid storage over time appears to trigger pathological myocardial processes such as infiltration, replacement fibrosis, and inflammation, and CMR constitutes the primary imaging modality for myocardial tissue characterization. As previously mentioned, the histological correlation of the frequently observed midwall LGE pattern in the basal infero-lateral wall in advanced disease is focal fibrosis [16]. However, recent research has reported abnormally high values of native T1 and T2 in the LGE+ areas [46•] (Fig. 3). Accumulation of glycosphingolipids in Fabry myocytes triggers a proinflammatory response by the human immune system. Accordingly, immune-mediated myocarditis was retrospectively detected in up to 56% of FD patients who had a previous endomyocardial biopsy [47]. Studies with hybrid PET/CMR suggest that focal 18F-FDG uptake represents an early sign of disease-related myocardial damage [48] and is associated with impaired left ventricular longitudinal function [49]. All these findings support the hypothesis that inflammation plays a role in the genesis of myocardial damage, being FD not only a storage disease but also chronic inflammatory cardiomyopathy [46•].

Myocardial inflammation is now amenable to be measured quantitatively with CMR. The combination of T1 and T2 mapping offers interesting and complementary information, as native T1 (as abovementioned) is low in FD due to lipid accumulation, while T2 mapping (by the amount of water content in the tissue) increases with inflammation. In a recent study which evaluated T1 and T2 mapping in FD versus sarcomeric HCM, chronic myocardial infarction, and controls, Fabry patients showed abnormally high native T1 and T2 values strictly confined to LGE-positive areas. Interestingly, the increase over remote T1 and T2 was higher in FD than in the other groups. In multivariate analysis, the strongest predictor of increased troponin was T2 values in the infero-basal wall [46•].

In conclusion, the combination of different CMR sequences provides complementary information that can help us understand the processes occurring in the myocardium in the different stages of the disease. A multiparametric CMR approach, together with biomarkers, was recently used to characterize a wide FD population (182 children and adults) [23]. According to the results, the authors proposed three stages of myocardial phenotype development based on native T1 values, LVH, and LGE. The initial *accumulation phase*, in which only subtle morphological changes are present, native T1, is below normal ranges. It shows progressive fall, being faster in men than in women and is associated with ECG changes. In the second phase, *myocyte hypertrophy and inflammation phase*, LVH is manifest showing a sex dimorphism: male hypertrophy is far more extreme than in women. Native T1 in women falls until LVH appears (there is a balance between sphingolipid storage and myocyte hypertrophy) but in men, T1 increases/pseudonormalizes due to the presence of true hypertrophy of the LV. In the third and last one, *fibrosis and impaired phase*, fibrosis and thinning occur, which are reflected by extensive LGE, LV impairment, and normalization of T1 values. Although these proposed stages are hypothesis generating and reflect a single-center experience and a transversal (not longitudinal) evaluation of the patients, it represents a nice example of how information provided by CMR help us better understand and classify the disease.

## Conclusion

CMR is an essential tool for an adequate evaluation of cardiac involvement in FD. This review emphasizes the use of conventional parameters (LVM and LGE) and new ones (T1 and T2 mapping, to a lesser extent strain) for an accurate diagnosis, therapy guide and risk evaluation, and prognosis (summarized in Table 1). An integrative approach of these parameters is desirable for early detection of subclinical disease and an appropriate disease staging that may help to guide timely therapeutic interventions. Unfortunately, due to the rarity of the disease, most of the fields covered in this review lack the desirable level of evidence, with only few studies with limited sample size being available (Table 2) and most recommendations being supported only by expert consensus.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. Kampmann C, Linhart A, Baehner F, Palecek T, Wiethoff CM, Miebach E, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int J Cardiol. 2008;130:367–73.
2. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015;52:353–8.
3. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart. 2007;93:528–35.
4. 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;31:639–49.
5. Wu JC, Ho CY, Skali H, Abichandani R, Wilcox WR, Banikazemi M, et al. Myocardial disease cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and a -galactosidase A activity. Eur Heart J. 2010;31: 1088–97.
6. Hazari H, Belenkie I, Kryski A, White JA, Oudit GY, Thompson R, et al. Comparison of cardiac magnetic resonance imaging and echocardiography in assessment of left ventricular hypertrophy in Fabry disease. Can J Cardiol. 2018;34:1041–7.
7. Kozor R, Grieve SM, Tchan MC, Callaghan F, Hamilton-Craig C, Denaro C, et al. Cardiac involvement in genotype-positive Fabry disease patients assessed by cardiovascular MR. Heart. 2016;102: 298–302.
8. Kozor R, Callaghan F, Tchan M, Hamilton-Craig C, Figtree GA, Grieve SM. A disproportionate contribution of papillary muscles and trabeculations to total left ventricular mass makes choice of cardiovascular magnetic resonance analysis technique critical in Fabry disease. J Cardiovasc Magn Reson. 2015;17:22.
9. Niemann M, Liu D, Hu K, Herrmann S, Breunig F, Strotmann J, et al. Prominent papillary muscles in Fabry disease: a diagnostic marker? Ultrasound Med Biol. 2011;37:37–43.
10. Kozor R, Nordin S, Treibel TA, Rosmini S, Castelletti S, Fontana M, et al. Insight into hypertrophied hearts: a cardiovascular magnetic resonance study of papillary muscle mass and T1 mapping. Eur Heart J Cardiovasc Imaging. 2017;18:1034–40.
11. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005;26:1461–74.
12. • 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;24:2151–5. **First study to describe the typical pattern of midwall LGE in the basal inferolateral wall in FD**.
13. Vijapurapu R, Nordin S, Baig S, Liu B, Rosmini S, Augusto J, et al. Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease. Heart. 2018.
14. • 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 J Cardiovasc Magn Reson. 2016;18:14. **Describes the morphological spectrum of LVH in FD as well as the patterns of myocardial scarring**.
15. Koeppe S, Neubauer H, Breunig F, Weidemann F, Wanner C, Sandstede J, et al. MR-based analysis of regional cardiac function in relation to cellular integrity in Fabry disease. Int J Cardiol. 2012;160:53–8.
16. 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;8:479–82.
17. Niemann M, Breunig F, Beer M, Machann W, Ertl G, Wanner C, et al. Differences in Fabry cardiomyopathy between female and male patients. 2011;4:592–601.
18. Nordin S, Kozor R, Baig S, Abdel-Gadir A, Medina-Menacho K, Rosmini S. Cardiac phenotype of prehypertrophic Fabry disease. Circ Cardiovasc Imaging. 2018;11:e007168.
19. Puntmann VO, Peker E, Chandrashekhar Y, Nagel E. T1 mapping in characterizing myocardial disease: a comprehensive review. Circ Res. 2016;119:277–99.
20. • Thompson RB, Chow K, Khan A, Chan A, Shanks M, Paterson I, et al. $T_1$ mapping with cardiovascular MRI is highly sensitive for Fabry disease independent of hypertrophy and sex. Circ Cardiovasc Imaging. 2013;6:637–45. **Confirms the diagnostic value of native T1 for the early detection of cardiac FD**.
21. •• Sado DM, White SK, Piechnik SK, Banypersad 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;6:392–8. **First study to describe low native T1 as an specific diagnostic tool for Fabry disease. It also shows subclinical cardiac involvement in patients without LVH**.
22. 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;16:99.
23. •• 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. 2018. **This study includes a broad FD population of a variety of ages, that underwent a multiparametric CMR. As a result the authors propose a novel staging of the disease..**
24. • Karur GR, Robison S, Iwanochko RM, Morel CF, Crean AM, Thavendiranathan P, et al. Use of myocardial T1 mapping at 3.0 T to differentiate Anderson-Fabry disease from hypertrophic cardiomyopathy. Radiology. 2018;288:398–406. **First study to evaluate the use of native T1 as a diagnostic tool at 3T**.
25. Pagano JJ, Chow K, Khan A, Michelakis E, Paterson I, Oudit GY, et al. Reduced right ventricular native myocardial T1 in Anderson-Fabry disease: comparison to pulmonary hypertension and healthy controls. PLoS One. 2016;11:e0157565.
26. 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;31:301–13.

27. Wilson HC, Ambach SD, Madueme PC, Khoury PR, Hopkin RJ, Jefferies JL. Comparison of native T1, strain, and traditional measures of cardiovascular structure and function by cardiac magnetic resonance imaging in patients with Anderson-Fabry disease. Am J Cardiol. 2018;122:1074–8.
28. Reid AB, Miller CA, Jovanovic A, Woolfson P, Abidin N, Steeds RP, et al. Native T1 mapping versus CMR feature tracking (FT) derived strain analysis for the assessment of cardiac disease manifestation in Anderson Fabry. J Cardiovasc Magn Reson. 2016;18(Suppl 1):Q43.
29. Weidemman F, Breunig F, Beer M, Sandstede 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;108:1299–301.
30. Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. J Inherit Metab Dis. 2003;26:617–27.
31.•• Beer M, Weidemman F, Breunig F, Knoll A, Koeppe S, Machann W, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol. 2006;97:1515–8. **First study to point out that ERT might not be of use in advanced cardiac FD, defined by the presence of LGE**.
32.• 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;119:524–9. **Long-terms study that confirms the use of LGE to predict the response to ERT**.
33.• Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N Engl J Med. 2016;375:545–55. **First phase III study that evaluates the new chaperone migalastat**.
34. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017;54:288–96.
35. Muntze J, Salinger T, Gensler D, Wanner C, Nordbeck P. Treatment of hypertrophic cardiomyopathy caused by cardiospecific variants of Fabry disease with chaperone therapy. Eur Heart J. 2018;39:1861–2.
36. Biegstraaten M, Arngrímsson R, Barbey F, Boks L, Cecchi F, Deegan PB, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015;10:36.
37. Puntmann VO, Valbuena S, Hinojar R, Petersen SE, Greenwood JP, Kramer CM, et al. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I - analytical validation and clinical qualification. Cardiovasc Magn Reson. 2018;20:67.
38. Baig S, Edward NC, Kotecha D, Liu B, Nordin S, Kozor R, et al. Ventricular arrhythmia and sudden cardiac death in Fabry disease: a systematic review of risk factors in clinical practice. Europace. 2018;20:f153–61.
39. Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, et al. Characterization of classical and nonclassical Fabry disease: a multicenter study. J Am Soc Nephrol. 2017;28:1631–41.
40. Lenders M, Schmitz B, Stypmann J, Duning T, Brand SM, Kurschat C, et al. Renal function predicts long-term outcome on enzyme replacement therapy in patients with Fabry disease. Nephrol Dial Transplant. 2017;32:2090–7.
41. Weidemann F, Niemann M, Störk S, Breunig F, Beer M, Sommer C, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J Intern Med. 2013;274:331–41.
42. Arends M, Biegstraaten M, Hughes DA, Mehta A, Elliott PM, Oder D, et al. Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: analysis of prognostic factors. PLoS One. 2017;12(8):e0182379.
43.•• Krämer J, Niemann M, Störk S, Frantz S, Beer M, Ertl G, et al. Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. Am J Cardiol. 2014;114:895–900. **This study reported that the annual increase in LGE was an independent predictor of ventricular arrhythmia**.
44.•• Hanneman K, Karur GR, Wasim S, Morel CF, Iwanochko RM. Prognostic significance of cardiac magnetic resonance imaging late gadolinium enhancement in Fabry disease. Circulation. 2018;138:2579–81. **Confirms the prognostic value of LGE, being predictive of ventricular arrhythmia and outcomes in FD**.
45. Weidemann F, Maier SK, Störk S, Brunner T, Liu D, Hu K, et al. Usefulness of an implantable loop recorder to detect clinically relevant arrhythmias in patients with advanced Fabry cardiomyopathy. Am J Cardiol. 2016;118:264–74.
46.• 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;68:1707–8. **Prospective study showing elevated T1 and T2 mapping values related to areas of LGE, supporting the inflammatory substrate of the disease**.
47. Frustaci A, Verardo R, Grande C, Galea N, Piselli P, Carbone I, et al. Immune-mediated myocarditis in Fabry disease cardiomyopathy. J Am Heart Assoc. 2018;7:e009052.
48. Nappi C, Altiero M, Imbriaco M, Nicolai E, Giudice CA, Aiello M, et al. First experience of simultaneous PET/MRI for the early detection of cardiac involvement in patients with Anderson-Fabry disease. Eur J Nucl Med Mol Imaging. 2015;42:1025–31.
49.• Spinelli L, Imbriaco M, Nappi C, Nicolai E, Giugliano G, Ponsigliano A, et al. Early cardiac involvement affects left ventricular longitudinal function in females carrying α- galactosidase a mutation: role of hybrid positron emission tomography and magnetic resonance imaging and speckle-tracking echocardiography. Circ Cardiovasc Imaging. 2018;11:e007019. **This study suggests that myocardial inflammation prompted by sphyngolipids deposition may play a role in the pathogenesis of FD**.