Title: Diagnosis and Treatment of the Cardiovascular Consequences of Fabry Disease.

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Abstract

Fabry Disease (FD) has been a diagnostic challenge since it was first recognised in 1898, with patients traditionally suffering from considerable delay before a diagnosis is made. Cardiac involvement is the current leading cause of death in FD. A combination of improved enzyme assays, availability of genetic profiling, together with more organised clinical services for rare diseases, has led to a rapid growth in the prevalence of FD. The earlier and more frequent diagnosis of asymptomatic individuals before development of the phenotype has focussed attention on early detection of organ involvement and closer monitoring of disease progression. The high cost of enzyme replacement therapy at a time of constraint within many health economies moreover, has challenged clinicians to target treatment effectively. This article provides an outline of FD for the general physician and summarises the aetiology and pathology of FD, the cardiovascular (CV) consequences thereof, modalities used in diagnosis, and then discusses current indications for treatment, including pharmacotherapy and device implantation.

Abbreviations

FD – Fabry disease

CV – Cardiovascular

LVH – left ventricular hypertrophy

ECG – electrocardiogram

LV – left ventricle

CMR – cardiac magnetic resonance

TTE – transthoracic echocardiography

LGE – late gadolinium enhancement

ERT – enzyme replacement therapy

MIBG – ^{123}I-meta-iodobenzylguanidine

OCT – oral chaperone therapy

HCM – hypertrophic cardiomyopathy

ICD – internal cardio-defibrillator

Introduction

FD is a rare X-linked lysosomal storage disorder caused by a deficiency in the enzyme α-galactosidase A (AGAL-A) with a prevalence that has increased dramatically within the Western world as a result of intensive targeted screening (1 in 2500). [1] Although point mutations and other defects, including small deletions, insertions and splicing defects, have been isolated within the AGAL-A gene (Xq22.1), the number of genetic variants and the differences in their effect on enzyme activity has complicated attempts to establish a clear genotype-phenotype correlation. With the additional effects of potential modifier genes and environmental factors, clinical presentation can be highly variable, even within the same family. Developments in therapy have transformed the progression and natural history of FD, such that cardiovascular (CV) disease has surpassed renal failure as the leading cause of morbidity and mortality. This article aims to provide an outline of FD to the general physician that reviews current concepts in aetiopathology of CV involvement of FD, the main presenting features and contemporary modalities for diagnosis, before discussing indications for treatment.

Aetiology

AGAL-A is a lysosomal glycohydrolase that is responsible for the hydrolytic cleavage of galactose residues in glycosphingolipids. Deficiency of this enzyme leads to intracellular accumulation of glycosphingolipids with a terminal α-galactosyl moiety, in particular globotriaosylceramide (Gb3) and globotriaosylsphingosine (lysoGb3). There is not however, a direct cause-and-effect relationship between genetic defect, residual enzyme activity, plasma levels of Gb3 and lysoGb3, and clinical effects. [2] For example, heterozygote females

can have significant residual AGAL-A activity, yet present with severe organ damage. On the other hand, hemizygotes who lack AGAL-A activity can have evidence of accumulation of Gb3 at birth or even in utero but no clinical consequences until young adulthood. Left ventricular hypertrophy (LVH) is a characteristic feature of CV involvement in FD, yet the amount of Gb3 deposited in the heart corresponds only to a fraction of the total myocardial mass (around 1-3%). Moreover, while enzyme replacement therapy (ERT) can normalise Gb3 levels in the myocardium, the effects on patient-reported outcomes are less clear. [3] This suggests that substrate accumulation either does not cause immediate adverse effects or that a number of other pathways are likely to be involved (**Figure 1**). One possibility is that a biologically-active intermediary, for example sphingosine-1-phosphate, amplifies CV remodelling in response to changes in Gb3 levels. [4] Another is that Gb3 and in particular lyso-Gb3 may be pro-inflammatory, provoking interstitial fibrosis and myocyte apoptosis, reflected in elevated levels of high sensitivity troponin. [5,6]

Clinical Presentation of Cardiovascular Involvement in FD

CV symptoms are present in most FD patients but are non-specific, including breathlessness, chest pain, palpitations, dizziness and syncope. [7] Breathlessness is often due to LVH, impaired LV filling and atrial dilatation, which are markers of diastolic dysfunction and predispose to atrial arrhythmia. Chest pain is a frequent complaint; however, the incidence of atherosclerotic coronary artery disease is low. The more likely explanation for “angina” in FD is a combination of coronary microvascular dysfunction, increased myocardial oxygen demand from the hypertrophied myocardium and small vessel disease. [8] Symptoms such as palpitations, dizziness and syncope are extremely common. Although involvement of the conduction system is an early feature of FD and a major proportion of the CV deaths are

attributable to 'sudden cardiac events', there is very little correlation of these symptoms with life-threatening rhythm abnormalities. The incidence of arrhythmia in FD is variably reported, with atrial arrhythmia (commonly atrial fibrillation) occurring in approximately 13% and ventricular arrhythmias in 5-30% of FD patients. [9] This variable incidence is likely to reflect the limitations of short-term 24-48-hour monitoring, particularly since the use of implantable loop recorders that can record the heart rhythm long-term resulted in frequent modification of drug therapy and increased device implantation for arrhythmia in one small study. [10] Mild aortic root dilatation and valvular dysfunction also occur in FD, although both of these are often mild and rarely require clinical intervention. [11]

Diagnostic Testing

Most patients identified through screening lack the classical signs of FD, including acroparesthesia, heat intolerance, angiokeratomas, and cornea verticillata but present with involvement of a single organ system, for example cryptogenic stroke, proteinuria or LVH. [1] Late presentation of some patients led to the concept of a 'cardiac' variant, although recent evidence suggests that these individuals often have attenuated involvement of other organ systems. [12] The difficulty for clinicians in patients presenting with LVH is that, while this is a pathognomonic feature of CV involvement in FD, it most commonly is due to other diseases such as hypertension. In those cohorts with unexplained LVH, especially when concentric and symmetrical, physicians must be wary of the possibility of undiagnosed FD.

ECG: Electrophysiological changes are thought to precede both structural and functional effects of FD on the heart. [13] Shortening of the PQ interval with reduced P wave duration,

shortening of the QRS duration and prolongation of the QT/QTc interval have been identified in FD patients without LVH compared to healthy controls, although there is considerable overlap. Increasing age in FD patients is associated with prolongation of the PR interval and broadening of the QRS complex. Both LVH by Sokolow-Lyon criteria and QRS prolongation correlate closely with the presence of sphingolipid storage assessed using T1 mapping and LVH measured on cardiac magnetic resonance (CMR) imaging, while ST/T wave inversion in V5-6 is common in those with inferolateral fibrosis and rare in those without[14] (**Figure 2**). ECG changes may be a marker for progression of CV disease and maximal treatment benefit may be obtained before onset of abnormalities. [15]

Echocardiography: Transthoracic echocardiography (TTE) is useful in detection of LVH, systolic and diastolic dysfunction, valvular abnormalities and proximal aortic root dilatation in FD. Since many patients do not have LVH at the time of diagnosis however, standard echocardiography has limitations in diagnosing cardiac involvement, although 2D speckle tracking analysis of myocardial deformation (strain; strain rate) is a more sensitive method of detection and response to treatment. [16] In fact, impairment of global longitudinal strain (GLS) has been identified before the onset of overt 'Fabry cardiomyopathy' and is associated with impaired exercise capacity. [17] While CMR has replaced TTE as the gold standard for quantifying LVH, echocardiography is the preferred modality for measuring diastolic dysfunction, which is present before the onset of LVH in FD, with reduced early myocardial relaxation velocity (e') and late diastolic relaxation velocity (a') but elevated early mitral filling velocity (leading to increased E/e' ratio; a marker of high LV end-diastolic filling pressure), (**Figure 3(a) and (b)**). Although these alterations can occur in a wide variety of other pathologies, such as hypertension and HCM, in FD they become more pronounced with the onset of LVH. Often recognised as a barometer of ventricular diastolic function, atrial reservoir and contractile function for example, falls with cardiac involvement in FD and

improves with treatment. [18] Prominent papillary muscles have also been noted in FD on echocardiography that are not only disproportionate to the degree of LVH but may also develop before sphingolipid storage can be detected on T1 mapping. [19]

Cardiovascular Magnetic Resonance Imaging: CMR is the gold standard for assessment of structural disease and characterisation of myocardial involvement by detection of late gadolinium enhancement (LGE) and by measuring T1 and T2 relaxivity in FD. LGE is found where there is expansion of the extracellular space between myocytes, which in FD spares the sub-endocardium and is often seen in a characteristic distribution in the basal inferolateral wall. [20] LGE has been shown by histological correlation to represent focal fibrosis in advanced FD and is a marker of adverse prognosis, (**Figure 4(a)**). T1 and T2 mapping are magnetic resonance rate constants (measured in milliseconds) that vary according to tissue characteristics and appear to be of particular use in FD. Analysis results in an image of the myocardium where each pixel is given a specific colour depending on the T1 or T2 time in that area. (**Figure 4(b)**). Native T1 values (pre-contrast administration) are low, representing glycosphingolipid accumulation in 85% of FD patients with LVH and up to 59% of LVH-negative patients, suggesting that storage occurs earlier in the disease process than the hypertrophic response. [21,22,23,24] Although the presence of LGE is associated with a worse response to ERT and adverse prognosis, it is not yet known whether early treatment targeted to those with a low T1 value in the absence of LGE or LVH improves outcome compared to treating when ECG changes or hypertrophy are also present. The presence of LGE typically increases T1 values ('pseudonormalisation') in the basal inferolateral wall but studies have highlighted the possibility of oedema and inflammation in this area demonstrated by an elevated T2 time[25] and by using hybrid positron emission tomography/CMR, [23] both of which are associated with troponin rise (a marker of myocyte inflammation).

Exercise ECG: A major consequence of CV involvement in FD is effort intolerance, with a lower maximum working capacity, lower maximum heart rate, and more frequent ventricular ectopy during exercise in those with evidence of myocardial fibrosis. [26] Initiation of ERT before the development of fibrosis appears to preserve exercise capacity, although does not improve effort intolerance in those in whom fibrosis has already developed. [27]

Myocardial Perfusion Imaging and Coronary Angiography: FD patients with typical angina commonly have normal coronary arteries but have evidence of stress induced perfusion defects (**Figure 5**). Recent studies have also identified luminal narrowing of intramural arteries as a result of sphingolipid triggered smooth muscle and endothelial hypertrophy, suggesting that compromise in the microvascular circulation may be the cause of symptoms. [8] There has been a growing interest in reduced cardiac sympathetic nervous activity in FD measured using ^{123}I-meta-iodobenzylguanidine (MIBG) scintigraphy within the inferolateral LV wall, prior to the onset of LVH and fibrosis. [28] This nuclear imaging technique also shows promise in facilitating the early detection of cardiac involvement in FD.

Biomarkers: Elevated cardiac biomarkers, such as troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) may precede LVH and although not diagnostic can support the presence of cardiac involvement in FD. [6,29] Elevated serum troponin correlates with the extent of LGE[5,29] and may be a marker of disease severity.

Treatment

Medical Treatment: Medical management is directed toward minimising the impact of end-organ damage as far as possible. Despite a lack of studies showing benefit, smoking cessation, increase in physical activity and optimal management of conventional risk factors,

including dyslipidaemia, hypertension and diabetes, is recommended. There is evidence to suggest that strict blood pressure control may be beneficial in delaying progression of LVH, with angiotensin converting enzyme inhibitors used first line in view of co-existing renal dysfunction. [30] Symptoms of heart failure, angina and arrhythmia are common in advanced FD and can be difficult to manage, with medical therapy following current standard practice.

Treatment of Arrhythmia: Compromise of conduction tissue early in the disease process can lead to multiple cardiac arrhythmias, including supraventricular tachycardia, atrial tachycardia, atrial fibrillation (AF) and ventricular tachycardia (VT). Treatment for AF is often managed with a rhythm control strategy in the first instance, since the arrhythmia is tolerated poorly in those with LVH and impaired diastolic filling. Rate-limiting medications, such as beta-blockers or calcium-channel blockers, should be administered with caution and close monitoring due to the increased risk of conduction disease and bradycardia in these patients. The use of the CHA_2DS_2-VAS_c scoring system is not recommended in FD for initiation of anticoagulation. [31] Given the high incidence and risk of stroke in FD, lifelong anticoagulation is recommended in those with AF, even if sinus rhythm has been achieved. There is currently no FD specific guidance for choice of anticoagulant.

Those with advanced FD are known to have an increased risk of bradyarrhythmia requiring pacing and ventricular arrhythmia requiring implantable cardio-defibrillators (ICDs). [26] There are however, no criteria to guide implantation of cardiac devices for primary prevention like those available in HCM, with FD specifically excluded from the risk prediction tool for sudden cardiac death (SCD). Consequently, implantation of such devices in FD tends to occur on a secondary prevention basis, following clinically significant bradyarrhythmia, symptomatic ventricular arrhythmia or aborted SCD.

Disease-Modifying Therapy: There is considerable development in this area, with a number of new treatment options in development at present, including gene therapy with the potential for long-term cure. [32] The latter is outside the scope of this article, which will focus on current available enzyme replacement and oral chaperone therapies.

Enzyme replacement therapy: Treatment of FD is primarily directed at replacing the deficient or absent enzyme, AGAL-A. Traditionally, ERT is the primary therapy for FD and involves intravenous infusion of either recombinant or gene-activated preparations of the deficient AGAL-A (agalsidase beta, Fabrazyme, Sanofi-Genzyme, USA and agalsidase alpha, Replagal, Shire, USA). Currently, ERT is commenced as cardiac, renal or neurological involvement from FD becomes evident. The indications and contra-indications for therapy are described in Table 1. [33] Efficacy in Fabry 'cardiomyopathy' is mixed, with benefit from early initiation but limited impact in advanced disease. [3] For example, in male patients with cardiac involvement based on increased LV mass (LVMi >50g/m^2), there was both a reduction in LV mass with reduction in anginal symptoms and improved self-reported activity. [34] On the other hand, other studies have shown no advantage if LGE is present. [3]

Oral Chaperone Therapy: Migalastat (Amicus Therapeutics, USA) is a newer small molecule pharmacological chaperone (OCT) that reversibly binds to the active site of AGAL-A. It stabilises specific forms of mutant enzyme and facilitates appropriate trafficking to lysosomes where AGAL-A catabolises sphingolipid. [35] All FD patients over the age of 16 years who have an amenable mutation can be considered for migalastat as a potential alternative to intravenous ERT. Its use is contraindicated in renal impairment however, with an eGFR less than 30ml/min, and during pregnancy or breast-feeding. Use of OCT has been associated with improvements in CV disease, with small studies showing a reduction in LV mass and wall thickness on transthoracic echocardiography. [36,37]

Transplantation: Cardiac transplantation is a viable option for those with severe, life limiting cardiovascular involvement. Patients who remain symptomatic (NYHA functional class 4) despite optimal medical therapy (including implantation of a biventricular pacemaker, if appropriate) may be considered for potential transplantation, although the presence of renal dysfunction can be a frequent limitation to acceptance. FD does not appear to develop in the allograft, presumably due to residual enzyme activity in the donor organ.

Conclusion

CV disease is the most frequent cause of death in FD and has a major impact on quality of life. Clinical presentation is variable, and symptoms do not always correlate with extent of disease. As such a combination of clinical, biochemical and imaging features are crucial in correctly identifying patients with cardiac involvement, assessing severity and determining treatment. Novel imaging and blood biomarkers are emerging that enable earlier diagnosis, opening a potential window for early therapy at which time the inevitable cascade of irreversible cardiovascular damage may be potentially averted.

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Abbreviations

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ECG – electrocardiogram

LV – left ventricle

CMR – cardiac magnetic resonance

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MIBG – ^{123}I-meta-iodobenzylguanidine

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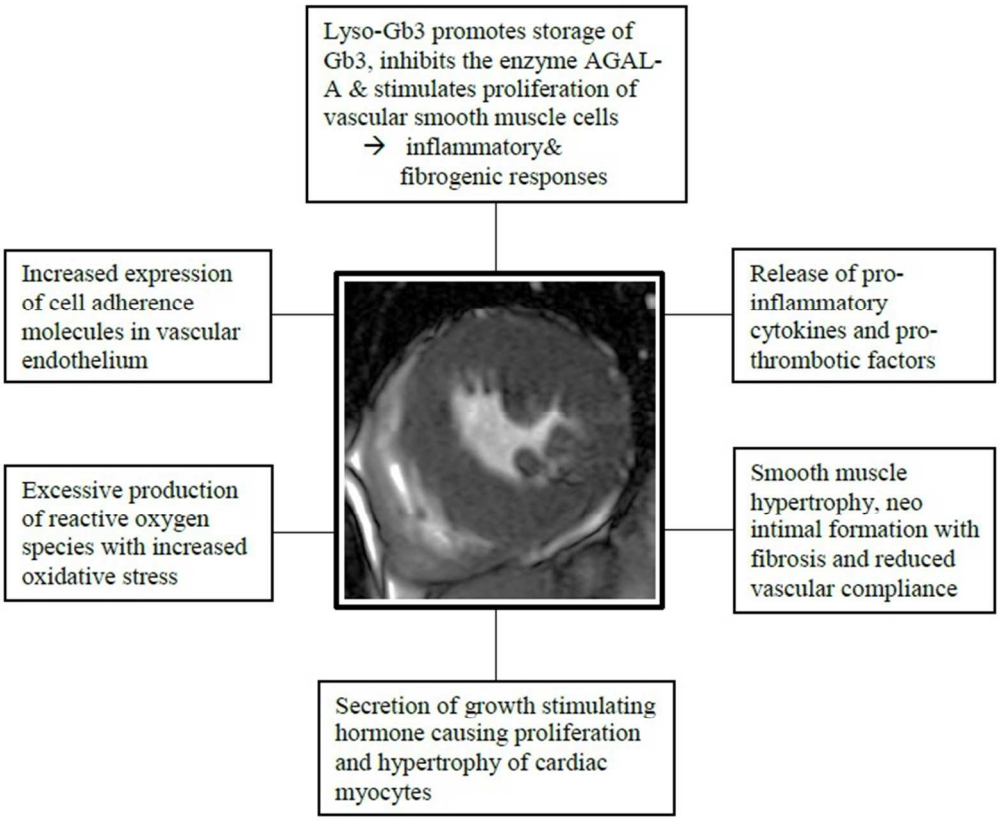

Figure 1: Metabolic pathways involved in the development of cardiovascular complications in Fabry disease.

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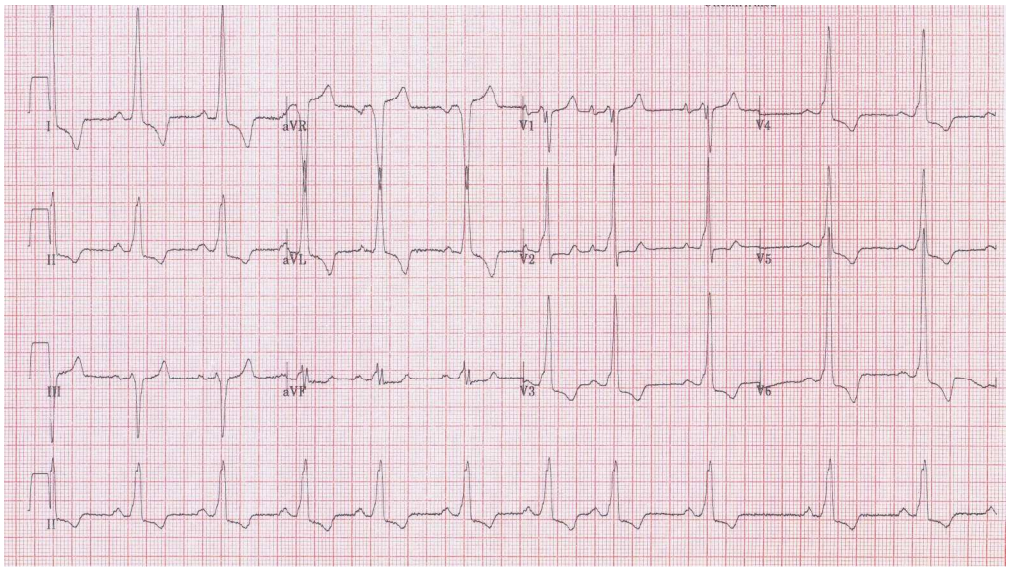

Figure 2: Typical ECG Changes in Fabry Cardiomyopathy – these include conduction abnormalities (broad QRS, shortened or prolonged PR interval), T-wave changes and ECG criteria for LVH.

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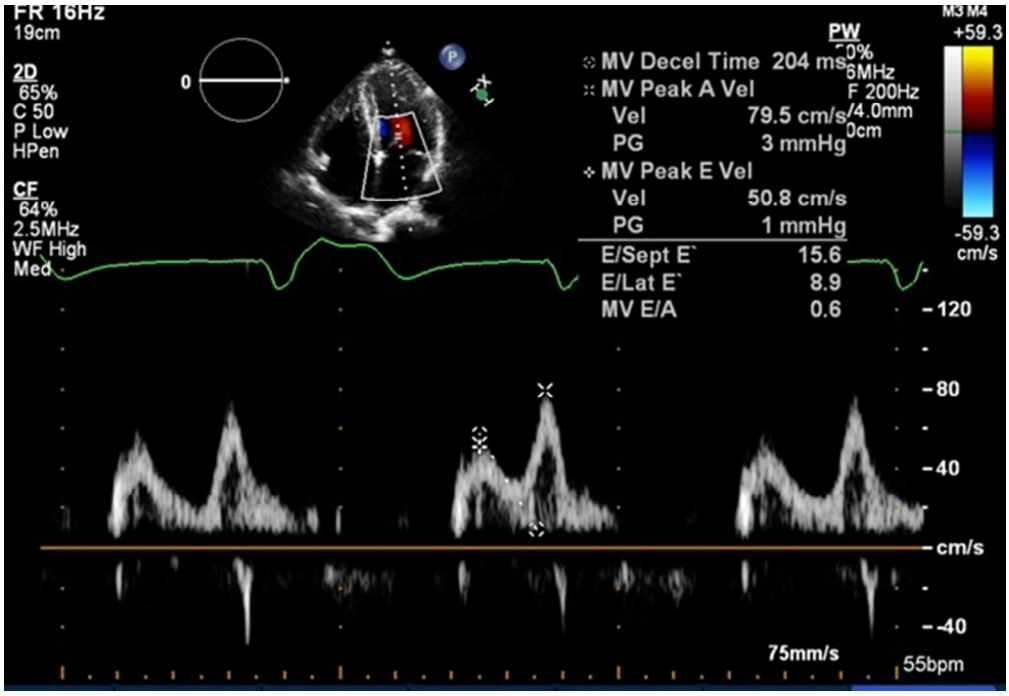

Figure 3(a): Pulsed Doppler echocardiogram demonstrating reduction in velocity of early filling (E wave) through the mitral valve and relative increase in dependence on atrial filling (A wave), which contributes to effort intolerance in Fabry patients.

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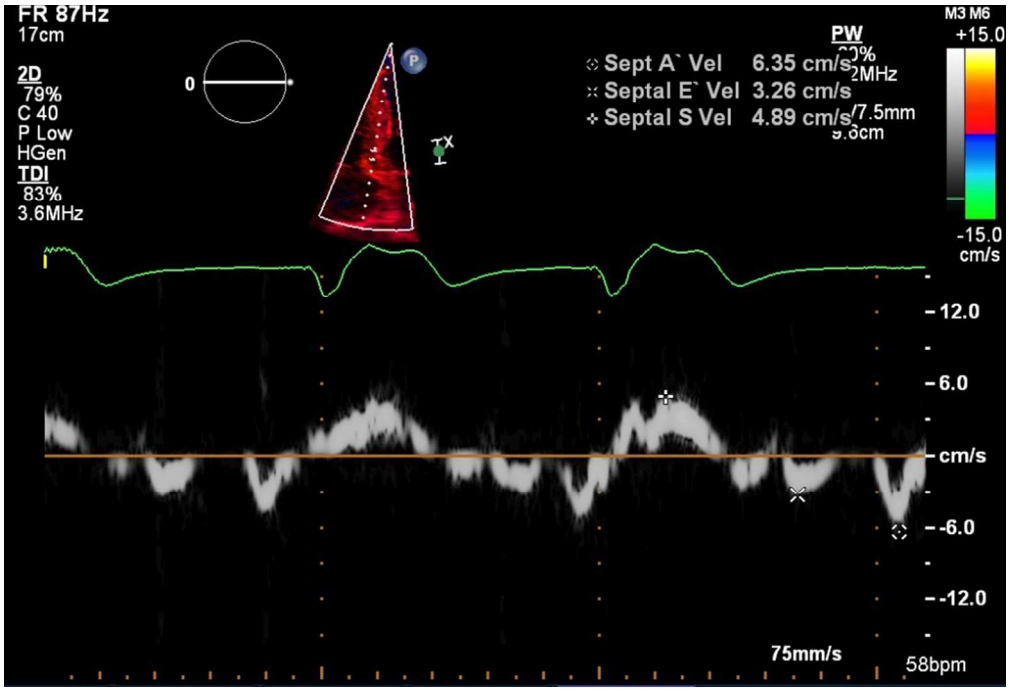

Figure 3(b): Tissue Doppler echocardiogram demonstrating reduction in early myocardial relaxation at the annulus. In conjunction with the mitral early filling, this value contributes to calculation of E/e' that reflects impaired myocardial compliance.

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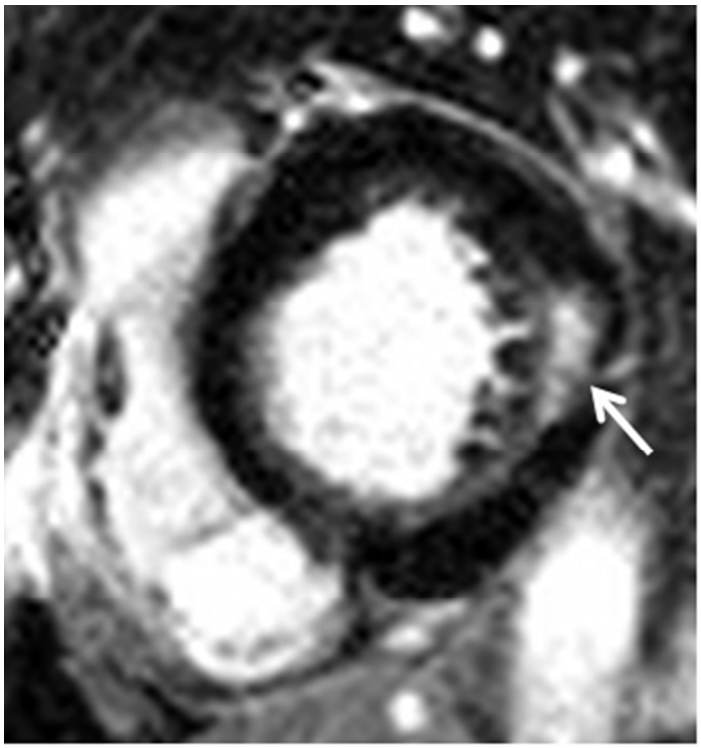

Figure 4 (a): Cardiovascular magnetic resonance image of the left ventricle in short axis demonstrating late gadolinium enhancement in the basal inferolateral wall (see arrow).

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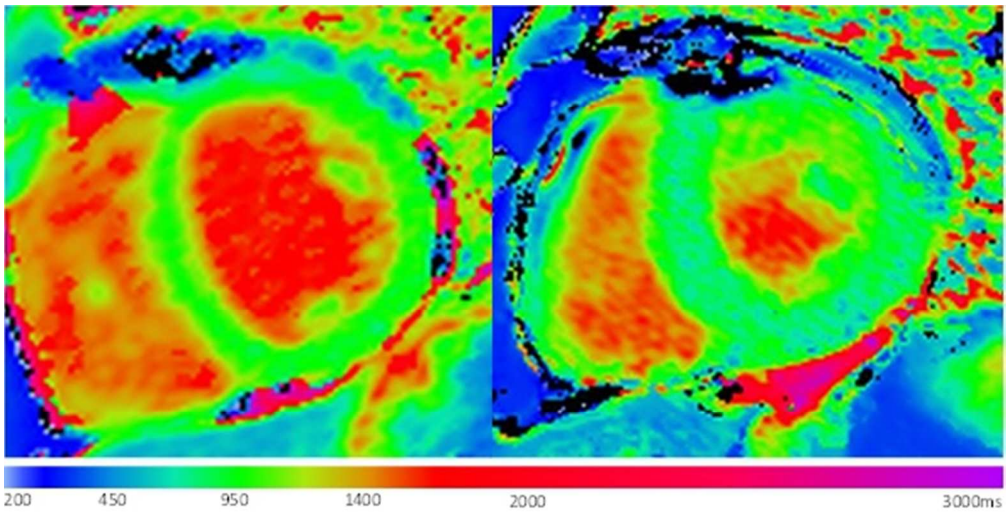

Figure 4 (b): Cardiovascular magnetic resonance image of the left ventricle short axis slice demonstrating changes on T1 in a patient with FD (right panel) and a healthy control (left panel).

Colour map demonstrating T1 relaxation times (ms) seen within the left ventricle. The colour scale shows that low T1 values are represented by the patchy blue colouration within the image and the blood pool with high T1 times in orange/red. The T1 map on the left is taken from a healthy control patient demonstrating normal myocardial T1 time (predominantly green/yellow colouration). The image on the right is taken from a patient with FD and shows a patchy distribution of low T1 throughout the myocardium representing sphingolipid deposition (blue colouration).

156x79mm (96 x 96 DPI)

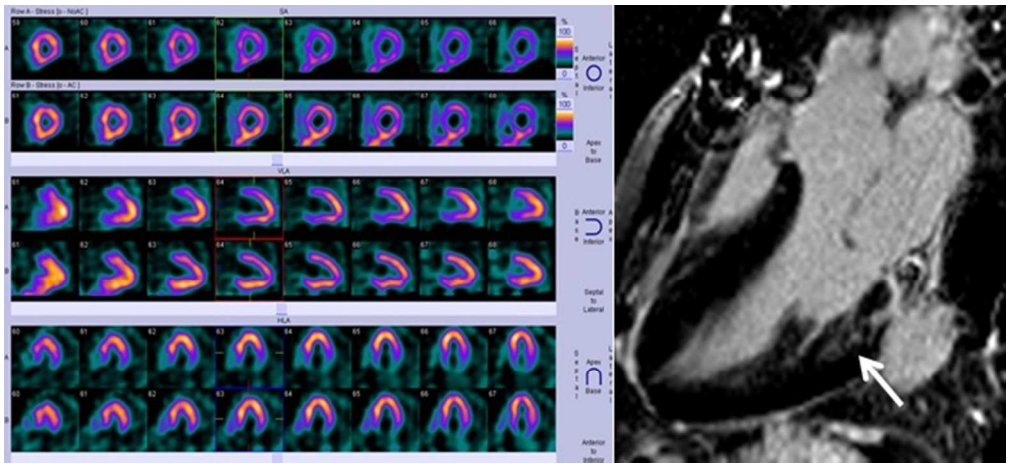

Figure 5: Single photon emission computed tomogram demonstrating abnormal stress perfusion in a patient with LVH and normal coronary arteries.

The SPECT images (left panel) show moderate reduction in tracer uptake within the basal lateral wall both at rest and stress, indicating a fixed perfusion defect. This corresponds with the area of late gadolinium enhancement seen in the basal inferolateral wall (see arrow) of the cardiac MRI image (right panel).

184x84mm (96 x 96 DPI)

Table 1: Current indications & contraindications to ERT (adapted from Biegstraten et al., 2015.(33))

Indications for ERT		Contraindications for ERT	Recommend stopping ERT
Cardiac	LVH	Advanced cardiac or renal disease	Non-compliance
	Cardiac fibrosis (demonstrated by LGE)	End-stage FD with life expectancy <1 year	Severe ERT infusion reactions
	Arrhythmia		Lack of response
Renal	Microalbuminuria		End-stage FD with life expectancy <1 year
	Proteinuria		
	Renal impairment (eGFR<90ml/min)		
Neuro-logical	White matter lesions		
	Stoke/TIA		
Other	Hearing loss		
	Abdominal discomfort		
	Neuropathic pain		