Cardiac Fabry disease with late gadolinium enhancement is a chronic inflammatory cardiomyopathy – evidence from multi parametric mapping by cardiovascular magnetic resonance

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Abbreviations

FD	Fabry disease
LVH	Left ventricular hypertrophy
CMR	Cardiovascular magnetic resonance
LGE	Late gadolinium enhancement
HCM	Hypertrophic cardiomyopathy
MOLLI	Modified Look-Locker Inversion recovery
cMI	Chronic myocardial infarction
BIFL	Basal inferolateral

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutations in α-galactosidase A. Sphingolipid accumulates in organs including the heart, causing left ventricular hypertrophy (LVH) and myocardial fibrosis. Cardiac involvement is the leading cause of death in FD. Cardiovascular magnetic resonance (CMR) provides insights with late gadolinium enhancement (LGE) characteristically occurring in the basal inferolateral (BIFL) wall.[1] Histological correlation in advanced disease indicates that this is focal fibrosis, although hybrid imaging with PET/MR has suggested this could be inflammation.[2]

CMR can now measure three magnetic tissue properties (T1,T2,T2*) and display them as color maps. T1 is low in FD due to sphingolipid accumulation.[3] However, the link between storage and LGE remains obscure. T2 mapping is sensitive to inflammation and edema in acute myocardial infarction and myocarditis.[4,5] We hypothesized that inflammation contributes to LGE in FD, and is measurable using T2 mapping and troponin.

This is a single centre, single time point study using CMR and blood biomarkers in FD (n=47, all gene-positive, males and females) versus hypertrophic cardiomyopathy (HCM; n=28, gene-positive, asymmetrical LVH with LGE), chronic myocardial infarction (cMI, n=30, 6 months post-reperfused ST-elevation MI) and normal controls (n=60). Ethical approval was obtained. All participants underwent CMR, performed at 1.5 Tesla (Avanto, Siemens). T1 (MOLLI, 5s(3s)3s sampling) and T2 (WIP 448B, Siemens) mapping were acquired on pre-contrast images. Conventional 2D LGE was acquired with phase sensitive inversion recovery. High-sensitivity troponin T was measured in FD.

Seven FD cases did not receive gadolinium due to patient preference. Of the remaining cases, 18 had LGE (14/21 males – all LVH positive; 4/19 females – 3 LVH positive). All LGE was in the BIFL wall, 8 with additional LGE elsewhere. The median LGE extent was 18g (25^{th} percentile 12g, 75^{th} percentile 24g).

T1 in the remote myocardium in FD was lower than in HCM, cMI and controls (934±61ms vs 1021±40ms, 1003±41ms, 1015±36ms; $p<0.001$). T1 was elevated in LGE areas in all diseases but with lesser elevation in FD compared to HCM and cMI (1096±93ms, 1180±66ms, 1138±52ms; $p<0.05$). However, the increase over remote T1 was higher in FD (204±90ms, 158±62ms, 135±57ms; $p<0.05$).

Remote area T2 was normal in all groups (51±3ms, 51±3ms, 48±2ms, controls 49±2ms). However, LGE T2 was very high in FD compared to HCM and cMI (64±7ms, 55±4ms, 54±3ms; $p<0.001$) and higher than normal in every FD case (range 55-81ms). The BIFL T2 was normal in cases without LGE, although slightly higher than controls (51±3ms vs 49±2ms, $p=0.006$).

Of the FD patients, 89%(42/47) had troponin measured, of which 40%(17/42) were elevated (median troponin 10ng/L, 25^{th} percentile 1ng/L, 75^{th} percentile 32ng/L, range 3-93ng/L; normal reference 0-14ng/L). Troponin elevation only occurred when there was LGE (83% vs 0%, $p<0.001$) and was strongly LVH related (94% vs 4%, $p<0.001$). T2 in the BIFL wall correlated with log troponin ($r_s=0.82$, $p<0.001$) and LV mass ($r_s=0.69$, $p<0.001$) but not LGE extent ($r_s=0.42$, $p=0.08$). In multivariate analysis, the strongest predictor of troponin was T2 in the BIFL wall ($B=2.4$, $p<0.001$).

We believe that the best explanation of these results – which combine blood and imaging biomarkers – is that LGE in the BIFL wall is not ‘scar’, but inflammation, supporting the former PET/MR data. Given that sampling was at a single (random) time point, the inflammation would appear chronic, suggesting FD with LGE is not only a storage disease but also a chronic inflammatory cardiomyopathy. Inflammation may be the pathological link in phenotype development – a concept that opens new avenues of therapy. Both blood troponin levels and T2 mapping are potential biomarkers for monitoring candidate therapies and risk stratification. We suspect that inflammation plays a wider role in cardiomyopathies,

and that T2 and troponin should be further researched in FD and other diseases. Limitations of our study include no histological validation, and no additional inflammatory markers.

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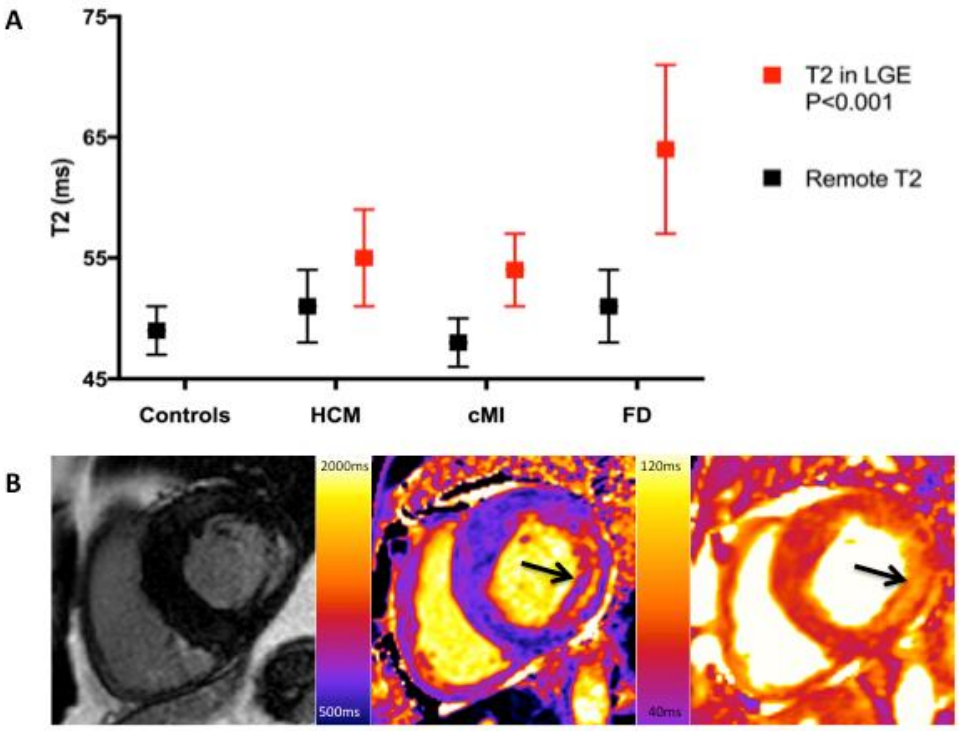

Figure 1A: Mean T2 values in the remote myocardium and LGE area in all groups. Error bar =1 standard deviation.
1B: Corresponding LGE, T1 and T2 map in FD.

Figure 1A: Mean T2 values in the remote myocardium and LGE area in all groups. Error bar = 1 SD. 1B: Corresponding LGE, T1 and T2 map in Fabry disease (FD).