Quantitative Myocardial Perfusion in Fabry Disease

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Abstract

**Background:** Fabry disease (FD) is an X-linked lysosomal storage disease resulting in tissue accumulation of sphingolipids. Key myocardial processes that lead to adverse outcomes in FD include storage, hypertrophy, inflammation and fibrosis. These are quantifiable by multi-parametric Cardiovascular Magnetic Resonance (CMR). Recent developments in CMR perfusion mapping allow rapid in-line perfusion quantification permitting broader clinical application, including the assessment of microvascular dysfunction. We hypothesized that microvascular dysfunction in FD would be associated with storage, fibrosis and oedema.

**Methods:** A prospective, observational study of 44 FD patients (49 years, 43% male, 24 (55%) with left ventricular hypertrophy (LVH)) and 27 healthy controls with multi-parametric CMR including vasodilator stress perfusion mapping. Myocardial blood flow (MBF) was measured and its associations with other processes investigated.

**Results:** Compared to LVH- FD, LVH+ FD had higher LV ejection fraction (73% vs 68%), more LGE (85% vs 15%) and a lower stress MBF (1.76 vs 2.36ml/g/min). The reduction in stress MBF was more pronounced in the subendocardium than subepicardium. LVH-FD had lower stress MBF than controls (2.36 vs 3.00ml/g/min, p=0.002). Across all FD, LGE and low native T1 were independently associated with reduced stress MBF. On a per-segment basis stress MBF was independently associated with wall thickness, T2, ECV and LGE.

**Conclusions:** FD patients have reduced perfusion, particularly in the subendocardium with greater reductions with LVH, storage, edema and scar. Perfusion is reduced even without LVH suggesting it is an early disease marker.
Clinical perspective

Fabry disease (FD) is a slowly progressive multisystem storage disease. Progressive cardiac involvement is the primary cause of premature death. Therapy is available but expensive. Myocardial phenotype development and pathways is not well understood and the impact of treatment and the timing of initiation is uncertain. Recently, cardiovascular magnetic resonance has begun to unravel phenotype development because, as well as hypertrophy and fibrosis (using late gadolinium enhancement), storage can now be measured (using T1 mapping) and edema/inflammation (using T2 mapping). Microvascular dysfunction is also thought also to play a role. CMR perfusion mapping can now quantify this – both concurrently with the other assessments and without using ionizing radiation, more easily permitting the assessment of early disease.

We performed multi-parametric CMR in FD including perfusion mapping. Compared to healthy volunteers, patients with FD had reduced stress myocardial blood flow (MBF). This occurred even before hypertrophy. It was most marked subendocardially, was worse when there was storage and, regionally, where there was fibrosis. This implies that microvascular dysfunction is an early disease feature and could contribute to the progression from storage to fibrosis (and hence heart failure and arrhythmia). Because it may relate to endothelial rather than myocyte storage, it may be more readily treatable and is a candidate surrogate endpoint in therapeutic trials of enzyme and novel therapies.
Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease caused by mutations in the gene encoding the α-galactosidase A enzyme (GLA). This results in the inability to break down sphingolipids and their accumulation in organs including the heart, skin, kidneys and brain (1). Myocardial deposition of sphingolipids is gradual, taking decades, causing left ventricular hypertrophy (LVH) and often arrhythmias, heart failure and death (2,3). Treatment includes oral chaperone therapy (OCT) or intravenous enzyme replacement therapy (ERT) to restore enzymatic activity, reduce sphingolipids and prevent organ dysfunction (4–6). Multi-parametric cardiovascular magnetic resonance (CMR) can characterize several processes within the cardiac FD phenotype development with an initial sphingolipid storage phase, detected as low myocardial T1 (7), triggered LVH with focal and then more widespread inflammation leading to fibrosis (8). Inflammation and fibrosis typically start in the basal inferolateral wall and can be visualized with late gadolinium enhancement (LGE) (9,10) with edema detected using T2 mapping and inferred as inflammation and myocyte death by detected troponin release (11). LVH, apparently from triggered hypertrophy is more marked in males and often results pseudo-normalization in myocardial T1 (8). These processes: storage, cell response, inflammation and fibrosis are consistent with other organ involvement in FD. FD also causes endothelial storage and microvascular dysfunction (12,13), but this has not been well characterized in the FD heart.

Non-invasive imaging can quantify tissue perfusion - myocardial blood flow (MBF, ml/g/min) at rest and during vasodilator stress to detect microvascular dysfunction. Positron emission tomography (PET) has been the gold standard modality (14) but is limited by inferior spatial resolution, ionizing radiation use, availability and does not
provide multi-parametric detail (15,16). Recently, quantitative perfusion CMR has been developed with “perfusion mapping” (17) where fully automated analysis occurs inline on the scanner using the Gadgetron framework (18,19) generating perfusion maps similar to T1 or T2 maps – but where each pixel color represents local flow in ml/g/min. Initial validation results (e.g. against PET and coronary angiography) are good (20,21) and inter-subject repeatability is similar to the published PET literature.(22,23). CMR perfusion mapping, being fast and free from ionizing radiation has potential in a wide range of circumstances. In hypertrophic cardiomyopathy (HCM), microvascular dysfunction is known to occur, increasing with LVH and LGE and may be early, before hypertrophy (24,25). Microvascular dysfunction in HCM is linked to adverse outcomes (26). In FD, myocardial perfusion is reported as reduced in PET studies (27) and not changed by ERT (28,29) but the studies to date have been small and the relationship of such changes to storage, hypertrophy, inflammation and scar is unknown.

In this study we recruited FD patients for multi-parametric CMR including vasodilator perfusion mapping for microvascular dysfunction. We hypothesized that microvascular dysfunction is an early marker in FD and would be associated with storage, fibrosis and edema.
Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by the National Health Service Research Ethics Committee (NHS REC) and Health Research Authority (HRA) and conducted in accordance with the Declaration of Helsinki. All subjects provided written, informed consent. 44 patients with FD and a healthy control cohort (27 subjects) were recruited. All subjects underwent multi-parametric CMR. FD exclusion criteria were age <18 years, ischemic heart disease, severe chronic kidney disease (eGFR <30mmol/l), contraindication to MRI or adenosine. Patient cardiovascular history, symptoms and ERT status were assessed at the time of the CMR with a questionnaire. The healthy control cohort were volunteers who had no cardiac symptoms, medications or co-morbidities.

CMR scans

CMR scans were performed at 1.5 Tesla (Aera, Siemens Healthcare, Erlangen, Germany) using a standard clinical protocol (30). The protocol consisted of cine imaging, native T1 mapping (using a modified look-locker inversion recovery sequence, MOLLI), T2 mapping, stress and rest perfusion, late gadolinium enhancement (LGE) and post contrast T1 mapping. Synthetic extracellular volume fraction (ECV) was derived from the native and post contrast T1 maps (31). T1, T2 and ECV mapping were performed for basal, mid and apical short axis and three long axis slices.

Vasodilator stress perfusion was performed using a standard clinical approach. Adenosine (140 mcg/kg/min, increased to 175 microgram/kg/min for a further 2 minutes if less than 10% heart rate increase or no symptoms) was infused (30,32). A
gadolinium-based contrast agent (gadoterate meglumine, Dotarem, Guerbet, Paris, France) was injected into a peripheral vein at 4ml/s during peak vasodilator stress at a dose of 0.05mmol/kg. 60 images were acquired for basal mid and apical left ventricular (LV) short-axis slices. It was retrospectively confirmed that splenic switch off was achieved, indicating adequate stress (33). Rest perfusion images were acquired subsequently after an interval of 6-10 minutes. Perfusion mapping implemented using the Gadgetron streaming software image reconstruction framework is previously described (17,18).

**CMR analysis**

CMR was analyzed using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). For parametric map analysis, endo- and epicardial contours were manually drawn and the right ventricular (RV) insertion points identified. The borders were offset by 10% and a 16 segment American Heart Association (AHA) model (34) created for each parameter (e.g. T1, T2, stress and rest MBF, ECV), along with a global mean value (mean across all segments). Additionally, to measure possible transmural gradients, stress MBF was split into endocardial and epicardial MBF by adjusting the offsets to 50% of the myocardium. Normal ranges for T1 and T2 are sequence and scanner dependent. Normal ranges at our center have been established in accordance with the current SCMR consensus statement (35).

LV volume analysis was performed by contouring each short axis slice in diastole and systole. Papillary muscles were excluded from the LV volume and included as LV mass. The maximal diastolic wall thickness was measured. LVH was defined as a maximum wall thickness greater than 12mm, as measured by CMR (36).
LGE was assessed for each myocardial segment. A region of interest was manually drawn in visually normal myocardium and LGE identified automatically for pixels 5-standard deviations above the mean signal intensity of the normal myocardium (37). The presence or absence of LGE was then noted for each segment and globally.

Statistical analysis

Statistical analysis was performed in SPSS (IBM SPSS statistics, Version 25.0). Continuous variables are presented as mean±standard deviation; categorical as absolute values and percentages. Patients were divided into those with and without LVH and analyzed compared to volunteers using ANOVA or Kruskal-Wallis for parametric and non-parametric variables, respectively, and chi-square for categorical variables. Pairwise comparisons between groups were performed using Bonferroni adjustment. A p value of <0.05 and was considered significant.

A simple linear regression analysis was performed to determine the factors that contribute to stress MBF. Subsequently, the variables that were significantly associated were used in a multiple linear regression analysis. The analysis was performed on a “per patient” basis, inputting the age, sex, treatment status, indexed EDV, indexed LV mass, LVEF, mean T1, T2, ECV, the presence of LGE and LVH. An analysis was also performed on a “per segment” basis. In this analysis, the effect of each CMR variable on stress MBF was considered on an AHA segment basis. Wall thickness, native T1, T2, ECV and percentage of LGE were treated as continuous variables. A mixed effects linear regression controlled for subject dependency.
Results

44 patients (19 male, 43%), mean age 49 years were recruited. A total of 30 patients (44%) were on treatment (ERT or OCT (9 patients)). 24 patients (55%) had LVH and 23 patients (52%) were positive for LGE. Compared to controls, patients had higher indexed LV mass (90.6 vs 52.3g/m², p<0.001), EF (70% vs 65%, p=0.007), lower septal T1 (959 vs 1015ms, p<0.001) and higher septal T2 (49.3 vs 47.5ms, p=0.025 (Table 1). The control cohort (n=27) were age matched to the FD patients who did not have LVH (38.1 vs 42.3 years, p=0.264). Patients with LVH were older than those without LVH (54.6 vs 42.3 years, p=0.006) and a greater proportion were male (62.5 vs 20%, p=0.003). They had a higher EF (72.8 vs 66.7%, p=0.03) and a higher LV mass (117.4 vs 58.43g/m², p<0.001) than patients without LVH (Table 2). Compared to controls, a greater proportion of LVH negative patients were female but no other significant differences (Table 2). Of the LVH negative patients, 7 (35%) had low septal T1 (based on one septal segment classification). The cardiac phenotype of patients on ERT was more advanced than those on no therapy, with higher LV mass (115 vs 60 g/m2), lower T1 (933 vs 1000ms), and a higher proportion of LGE (77% vs 21%). The OCT group was a mixture of patients who had previously been on long-term ERT (all patients on ERT had been receiving therapy for >1 year) and new-starters, with the shortest duration of therapy 6 months (the drug has only been recently introduced). Their cardiac phenotype was intermediate between ERT and no therapy patients: LV mass 77g/m2, T1 959ms, LGE 38%.

Cardiovascular risk factors were similar between LVH positive and negative patients with only atrial fibrillation (AF) being statistically higher in the LVH positive group 5
Hypertension was present in 4 (17%) vs 3 patients (15%), p=0.88, hyperlipidaemia 4 (17%) vs 1 patient (5%), p=0.21, renal impairment 3 (13%) vs 1 patient (5%), p=0.40, stroke 1 (4%) vs 2 patients (10%), p=0.46 for LVH positive and LVH negative patients respectively. Similarly a minority of patients had symptoms. The most common was palpitations which was present in 8 (33%) LVH positive and 4 (20%) LVH negative patients. 6 (25%) LVH positive patients and 1 (5%) of LVH negative patients complained of breathlessness. 4 (17%) LVH positive patients and 2 (10%) LVH negative patients complained of chest pain. The majority of patients were New York Heart Association functional class I (30/44, 68%), 12 patients were class II (27%) and 2 (5%) patients had mobility limited by musculoskeletal problems.

Global stress MBF was lower in FD than controls (2.04 vs 3.00 ml/g/min, p<0.001) but there was no difference in rest MBF (0.85 vs 0.86, p=0.85). Stress MBF was lower when there was LVH (1.76 vs 2.36 ml/g/min, p=0.005), but stress MBF was also lower in LVH negative FD compared to controls (2.36 vs 3.00ml/g/min, p=0.002, Figures 1 and 2). It is possible that chest pain and / or breathlessness may have been symptoms of microvascular dysfunction and these patients had a lower stress MBF than those with no symptoms (1.68 vs 2.11ml/g/min, p=0.039).

Stress MBF in FD was lower in the endocardium than epicardium (1.84 vs 2.13 ml/g/min, p=0.022) but not in controls (3.10 vs 2.85 ml/g/min, p=0.271). However, this was only significant in patients with LVH (1.88 vs 1.50 ml/g/min, p=0.013); in LVH negative patients epicardial and endocardial stress MBF was not significantly different (2.44 vs 2.25 ml/g/min, p=0.2078) (Figure 3).
To predict FD global stress MBF, a simple linear regression analysis was performed including age, sex, ERT/OCT treatment, indexed EDV, EF, indexed LV mass, presence of LGE, LVH (yes/no), T1, T2 and ECV. Of these, age, T1, T2, ECV, LGE and LVH were significantly associated and used for the multivariate model. In this, independently associated variables were (order of association strength): the presence of LGE and low T1 ($R^2$ for the model 0.572, $p<0.001$, Table 3).

To predict FD segmental stress MBF (including 704 segments), a multivariate model included wall thickness, native T1, T2, ECV and LGE, controlling for within subject dependency. The thickest myocardium was associated with the lowest stress MBF (Figure 4). Additionally, high T2, high ECV and the presence of LGE were independently associated with a lower myocardial stress MBF (Table 4).
Discussion

These data show that patients with Fabry disease have lower stress myocardial blood flow than healthy controls even in those patients without LVH. Perfusion appears to track disease severity with LVH, inflammation (elevated T2) and scar (elevated ECV and LGE) being associated with reduced segmental MBF (Figure 1).

Whilst there have been a few small studies to date that have used quantitative PET to measure MBF in patients with FD, this is the first in which CMR has been used to quantify perfusion in the context of a multi-parametric assessment. Furthermore, this is the largest study of perfusion in FD across all modalities and for the first time includes LVH negative patients with an age matched control group. Our results support the PET findings that found reduced stress perfusion in FD (28,29). These studies also sought treatment effect, and although one study was negative, the other found a correlation between pre-treatment relative wall thickness and post-treatment changes in flow reserve, hypothesizing that patients treated early may gain more benefit from ERT. Such findings could be explored in greater detail using multi-parametric CMR as it enables quantification of LVH, storage, inflammation and fibrosis in addition, now, to perfusion (7,9,11).

The findings of our study suggest that this reduction in stress MBF occurs early in the FD disease course and is related to features of myocardial disease severity. This early reduction in stress MBF is interesting. The current study did not have the statistical power to detect if it was associated with myocardial storage before LVH – further work will be needed. It is however possible that abnormalities in microvascular
perfusion, if related to endothelial storage and dysfunction, could precede myocyte storage and be the earliest sign of myocardial involvement in FD. Another explanation could be that our detection of myocardial storage with low T1 has a threshold effect whereby a certain amount of storage needs to occur before T1 lowers, but our imaging is more sensitive to detect MBF abnormalities. Such dysfunction may also contribute to FD patient symptoms that are hard to pin down, such as fatigue and reduced cardiopulmonary exercise test performance. Endothelial cells may be more amenable or faster to de-sphingation (clearance of sphingolipids) than myocytes (a scenario familiar in the kidney with podocytes (38)) so the investigation of ERT effect in pre-LVH disease would be particularly interesting mechanistically. This in turn could be a useful surrogate endpoint in drug studies and may provide insights into drivers of hypertrophy and basal lateral inflammation/scar.

Structural changes in the myocardial microvasculature have been explored using biopsy. Chimenti et al compared endomyocardial biopsies of 13 FD patients with angina to a control cohort of FD patients with no chest pain (39). Although the endothelial cells were swollen and proliferating due to storage, arteriolar luminal narrowing was also due to hypertrophy and hyperplasia of the smooth muscle cells and increased fibrosis within the intimal and medial layers. Additionally, this pattern was more often associated with perivascular myocardial fibrosis surrounding the most affected vessels. There was less luminal narrowing in those patients without angina. The results of our study are consistent with such processes. We have shown non-invasively that myocardial segments with increased hypertrophy, sphingolipid deposition (low T1) and fibrosis (high ECV and LGE) have the lowest myocardial perfusion. There is currently no treatment proven to be effective in microvascular
dysfunction in either Fabry disease or hypertrophic cardiomyopathy. With the use of perfusion mapping, it would now possible to assess the efficacy of ERT/OCT on improving the microvasculature. In another model of LVH - hypertension, there is the suggestion that the combination of angiotensin-converting enzyme (ACE) inhibitors and thiazide diuretics improve microvascular function and this has been shown in hypertensive rat models and small human studies (40,41).

CMR has another advantage over PET with the resolution to better discriminate transmyocardial perfusion gradients. Here, FD impairment in perfusion was more pronounced in the subendocardium. It has been shown in healthy animal models that vasodilatory flow in the subendocardium is relatively reduced compared to the subepicardium and this is more pronounced in heart failure models due to chronic subendocardial fibrosis (42). It is therefore plausible that a chronic fibrosis that preferentially affects the sub-endocardium is responsible for the more pronounced perfusion abnormalities in FD patients with LVH and this would fit with the described histological findings.

**Limitations**

This is a single time-point observational study with inherent limitations. Whilst the perfusion abnormalities detected likely reflect microvascular dysfunction other explanations such as a specific impaired response to adenosine cannot be ruled out. Additionally, without biopsy, we make assumptions that the CMR tissue characterization from these patients reflects storage, edema and fibrosis. This is, however, consistent with previous studies.
Conclusion

CMR perfusion mapping permits the detection of impaired myocardial perfusion in FD patients compared to healthy controls, even before the onset of LVH. Global perfusion impairment is associated with storage and LGE, with regional impairment associated also with T2 and LVH. Microvascular dysfunction is clearly an early disease marker and may be a useful parameter to distinguish the relative contribution of storage in vascular cells, particularly endothelium vs myocytes. Perfusion mapping readily allows the quantification of MBF in Fabry disease patients in a way that can be readily integrated within the clinical workflow and may be useful as a marker in clinical studies.
Acknowledgements

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Sources of funding

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Disclosures

None
References


Figure 1. Multiparametric CMR assessment in patients with Fabry disease and controls. Left to right – Steady state free precession cines, native T1 maps, T2 maps, stress myocardial blood flow (MBF) maps, late gadolinium enhancement (LGE). (A): Healthy control – no left ventricular hypertrophy (LVH), normal T1, normal T2, normal stress MBF, no LGE. (B) Fabry disease (FD), no LVH, low T1 (sphingolipid storage), normal T2, no LGE (B). (C) FD patient with severe LVH, storage (some pseudonormalization of T1 in LGE areas), high T2 in LGE areas, and extensive LGE. MBF falls with increasing disease severity, particularly in the endocardium.
Figure 2. Box and whisker plots demonstrating stress myocardial blood flow (MBF) in Fabry disease (FD) and controls. Each box displays the median and interquartile ranges (IQR) for MBF. The whiskers represent 1.5 x the IQR. Outliers (>1.5x the IQR) are indicated by the circles. Controls have higher MBF than Fabry disease (FD) patients, even without left ventricular hypertrophy (LVH, p=0.002) and FD patients with LVH have lower stress MBF than FD LVH- (p=0.005) and controls (p<0.001).
Figure 3. Endocardial (orange) and epicardial (blue) stress myocardial blood flow in Fabry disease and controls. Each box displays the median and interquartile ranges (IQR) for MBF. The whiskers represent 1.5 x the IQR. Outliers (>1.5x the IQR) are indicated by the circles. There is an epicardial to endocardial perfusion gradient in Fabry disease (FD) patients with left ventricular hypertrophy (LVH+, p=0.013). There is no significant gradient in healthy controls (p=0.271), or FD patients without LVH (LVH-, p=0.208).
Figure 4. Box and whisker plots demonstrating stress myocardial blood flow (MBF) in each myocardial segment compared to wall thickness. Each box displays the median and interquartile ranges (IQR) for MBF. The whiskers represent 1.5 x the IQR. Outliers 1.5-3x the IQR are indicated by the circles and >3 x IQR by the star. As wall thickness increases, the stress myocardial blood flow (MBF) falls (p<0.001).
<table>
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<td>n=27</td>
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<td>Age (years)</td>
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<td>14 (51.8)</td>
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<td>Height (cm)</td>
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<td>173.2 +/- 10.3</td>
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<td>Weight (kg)</td>
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<td>78.1 +/- 14.3</td>
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<td>26.8 +/- 6.3</td>
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<td>LGE, n (%)</td>
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<td>Septal T1 (ms)</td>
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<td>Stress MBF (ml/g/min)</td>
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Table 1. Characteristics of patients with Fabry disease and controls. Characteristics of Fabry disease (FD) patients and controls. Data is presented as mean +/- standard deviation unless stated. Abbreviations: BSA – body surface area, ERT – enzyme replacement therapy, LVEDVi – Left ventricular end diastolic volume indexed for...
BSA, LVESVi – left ventricular end systolic volume indexed for BSA, LVEF – left ventricular ejection fraction, LGE – late gadolinium enhancement, MBF – myocardial blood flow.
Table 2. A comparison between Fabry disease (FD) patients with and without left ventricular hypertrophy and controls. The FD patients are split into those with left ventricular hypertrophy (LVH+) and those without (LVH-). Data is presented as mean +/- standard deviation unless stated. The P value for trend is calculated using ANOVA or Kruskal-Wallis for parametric and non-parametric variables, respectively.
and chi-square for categorical variables. Pairwise comparisons between groups performed using Bonferroni adjustment.

* p<0.05 Vs FD LVH-, † p<0.05 vs Controls.
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Table 3. Multiple linear regression model for the dependent variable global stress myocardial blood flow. Global stress MBF was independently influenced by a low T1 time and the presence of late gadolinium enhancement (LGE). Age, T1, T2 and ECV were continuous variables; LGE was a categorical variable. Abbreviations: left ventricular hypertrophy (LVH), extracellular volume fraction (ECV). R² 0.572 for the model. p<0.001.
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<th>Beta</th>
<th>Standard error</th>
<th>95% CI Lower Bound</th>
<th>95% CI Upper Bound</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.630</td>
<td>0.526</td>
<td>1.597</td>
<td>3.662</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>-0.031</td>
<td>0.006</td>
<td>-0.043</td>
<td>-0.020</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>-0.000</td>
<td>0.000</td>
<td>-0.001</td>
<td>0.001</td>
<td>0.662</td>
</tr>
<tr>
<td>T2</td>
<td>-0.013</td>
<td>0.005</td>
<td>-0.023</td>
<td>-0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>ECV</td>
<td>0.021</td>
<td>0.005</td>
<td>0.010</td>
<td>0.031</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE</td>
<td>-0.005</td>
<td>0.002</td>
<td>-0.043</td>
<td>-0.020</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 4. Mixed effects linear regression model, controlling for within subject dependency, for the dependent variable segmental stress myocardial blood flow. Wall thickness, native T1, T2, extracellular volume fraction (ECV) and percentage late gadolinium enhancement (LGE) per segment were treated as continuous variables. Wall thickness, T2, ECV and LGE were independently associated with stress MBF.