



Clinical research

# Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease<sup>1</sup>

## Evidence for a disease specific abnormality of the myocardial interstitium

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### KEYWORDS

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**Aims** Anderson-Fabry Disease (AFD), an X-linked disorder of sphingolipid metabolism, is a cause of idiopathic left ventricular hypertrophy but the mechanism of hypertrophy is poorly understood. Gadolinium enhanced cardiovascular magnetic resonance can detect focal myocardial fibrosis. We hypothesised that hyperenhancement would be present in AFD.

**Methods and results** Eighteen males (mean 43±14 years) and eight female heterozygotes (mean 48±12 years) with AFD underwent cine and late gadolinium cardiovascular magnetic resonance. Nine male (50%) had myocardial hyperenhancement ranging from 3.4% to 20.6% (mean 7.7±5.7%) of total myocardium; in males, percentage hyperenhancement related to LV mass index ( $r=0.78$ ,  $P=0.0002$ ) but not to ejection fraction or left ventricular volumes. Lesser hyperenhancement was also found in four (50%) heterozygous females (mean 4.6%). In 12 (92%) patients with abnormal gadolinium uptake, hyperenhancement occurred in the basal infero-lateral wall where, unlike myocardial infarction, it was not sub-endocardial. In two male patients with severe LVH (left ventricular hypertrophy) and systolic impairment there was additional hyperenhancement in other myocardial segments.

**Conclusion** These observations suggests that myocardial fibrosis occurs in AFD and may contribute to the hypertrophy and the natural history of the disease.

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## Introduction

Anderson-Fabry Disease (AFD), an X-linked disorder of lysosomal metabolism, has recently become the subject of increased clinical interest with the demonstration that it is a relatively common cause of left ventricular hypertrophy in middle aged men.<sup>1</sup> Most of the cardiovascular manifestations of AFD are attributed to the deposition of glycosphingolipid (GB3) within myocytes, valves and vascular endothelium,<sup>2,3</sup> but there are data suggesting that GB3 storage alone is insufficient to account for the extent of myocardial abnormalities seen in AFD patients.<sup>4</sup>

Other diseases characterized by myocardial hypertrophy are associated with expansion of the cardiac interstitium and variable degrees of myocardial fibrosis.<sup>5</sup> If this were to be the case in AFD, then the efficacy of new treatment strategies based on enzyme replacement therapy may be limited. In order to investigate the extent of any myocardial interstitial abnormalities in AFD, we performed contrast enhanced CMR (cardiovascular magnetic resonance) in individuals with AFD using the interstitial tracer Gadolinium-DTPA.

## Methods

### Patients

This study complies with the Declaration of Helsinki and was approved by the local research ethics committees; and all patients gave written informed consent before entry. Eighteen male patients (43±14 years, range 12–67) with AFD and eight female heterozygotes (48±12, range 31–59 years) were studied. Patients were recruited from the cardiomyopathy clinic at St. George's Hospital and the Royal Free Hospital, London, United Kingdom. Patients had a variety of AFD symptoms including acroparaesthesia (*n*=17); hypohidrosis (*n*=7); abdominal pain (*n*=6); tinnitus (*n*=5) and angiokeratoma (*n*=9). The diagnosis of AFD in males was based on a plasma  $\alpha$ -galactosidase A ( $\alpha$ -Gal) activity of <1.0 nmol/h/ml (0.3±0.3, range 0.1–0.9, normal range 4.0–21.9). Of the eight females, four were obligate carriers, two had disease-causing mutations and in two the diagnosis was based on a renal biopsy. The females had a mean  $\alpha$ -Gal activity of 4.2±1.3 (range 2.7–6.6). All patients underwent 12-lead electrocardiography and 2-D/Doppler echocardiography prior to CMR. For the patient baseline characteristics, left ventricular wall thickness was determined as the greatest diastolic wall thickness in any segment when the heart was divided into four basal, four mid and two apical segments.

### Cardiovascular magnetic resonance

The technique has been described in detail.<sup>6</sup> In brief, a short axis stack of cine images was quantified by planimetry to determine myocardial mass. A bolus of 0.1 mmol/kg gadolinium-DTPA was administered intravenously and late contrast enhanced imaging using inversion recovery acquired.<sup>7</sup> All images were taken twice with a phase swap to exclude artefact. The location of any regions of hyperenhancement was noted by consensus of two observers using a standard 17 segment model.<sup>8</sup> The extent of hyperenhancement was quantified by planimetry and expressed as a percentage of the total myocardial mass.

**Table 1** Patient baseline characteristics

Characteristic	Male ( <i>n</i> =18)	Female ( <i>n</i> =8)
Age years	43±14 (range 12–67)	48±12 (range 31–59)
ECG abnormal	16 (89%)	6 (75%)
T wave changes	14 (78%)	6 (75%)
LVH <sup>a</sup>	12 (67%)	2 (25%)
Short PR	2 (11%)	0
atrial fibrillation	1 (6%)	0
LVWT <sup>b</sup> (mm)	15.3±5 (range 10–29)	11.3±4 (range 7–18)
Max LVWT >13mm	12 (67%)	2 (25%)
NYHA <sup>c</sup> Class		
I	10 (56%)	7 (88%)
II+	8 (44%)	1 (13%)
Palpitations	6 (33%)	2 (25%)
Chest pain	5 (28%)	1 (13%)
Syncope	3 (17%)	0

<sup>a</sup>LVH=left ventricular hypertrophy.

<sup>b</sup>LVWT=left ventricular wall thickness.

<sup>c</sup>NYHA=New York Heart Association.

### Statistics

All continuous values are shown as mean±SD. Non-Parametric Wilcoxon rank comparisons were made to compare measures of LV function and mass in the presence/absence of hyperenhancement. Linear correlations coefficients were assessed between extent of hyperenhancement and parameters of LV function using SPSS v 9.0 (SPSS Inc, Chicago, Illinois). A *P* value of <0.05 was considered significant.

## Results

### Patient baseline characteristics

Patient baseline data are displayed in **Table 1**. Eight patients (seven male) had undergone coronary angiography on clinical grounds which was normal (no narrowing greater than 30%) in all cases. These patients included the 6 patients with the most hypertrophy and the highest percentage gadolinium hyperenhancement. 14 (53%) had LVH (left ventricular hypertrophy) with maximum LV wall thickness >13 mm. There was mild mitral regurgitation (*n*=4), mild TR (*n*=1), mild AR (*n*=1) and rest outflow tract obstruction (*n*=2).

### CMR

Myocardial hyperenhancement was present in nine males and four females, one of whom had a normal echo (2D, M-mode and colour flow) and ECG. The mean percentage of myocardium involved was 6.7%±5.1, (range 1.2 to 20.6%) with more hyperenhancement in males (mean 7.7% males vs 4.6% females). Percentage hyperenhancement in males related to LV mass index (*r*=0.78,

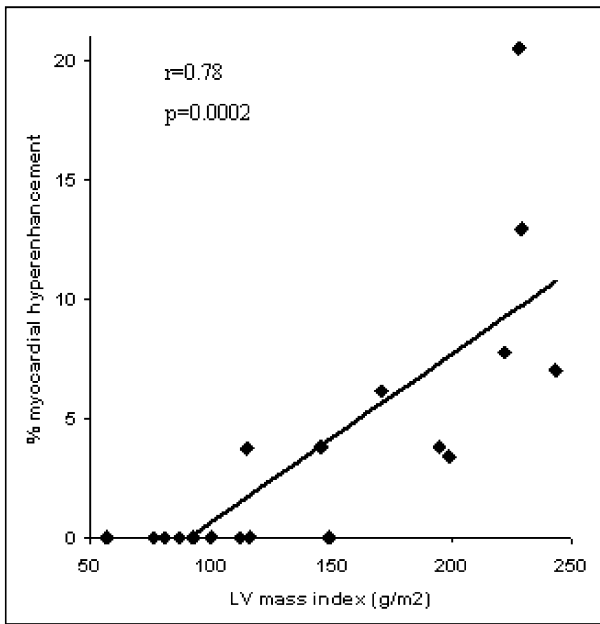


Fig. 1 Scatter plot of the relationship between myocardial mass index and the extent of myocardial enhancement.

$P=0.0002$ , Fig. 1), and patients with hyperenhancement had a higher mass than those without (188 vs 100 g/m<sup>2</sup>,  $P=0.001$ ). There were no relationships between hyperenhancement and end-diastolic, end-systolic left ventricular diameters or to ejection fraction.

In 12 of the 13 (92%) patients with abnormal gadolinium uptake, the hyperenhancement occurred in basal infero-lateral wall. The subendocardium was not involved in 8 patients, Fig. 2, unlike the hyperenhancement associated with myocardial infarction that always involves the subendocardium.<sup>9</sup> In three males, extensive hyperenhancement in this region was associated with a wall motion abnormality and wall thinning, Fig. 3. The two patients with the most severe LVH (maximum wall thickness of 29 mm and 28 mm) had hyperenhancement elsewhere in the myocardium, Fig. 4. One male patient did not follow the typical pattern and had hyperenhancement in the inferior wall but not the basal lateral wall.

### Discussion

Hyperenhancement during gadolinium CMR occurs because gadolinium chelated to DTPA diffuses into the interstitial space between cells but not across cell

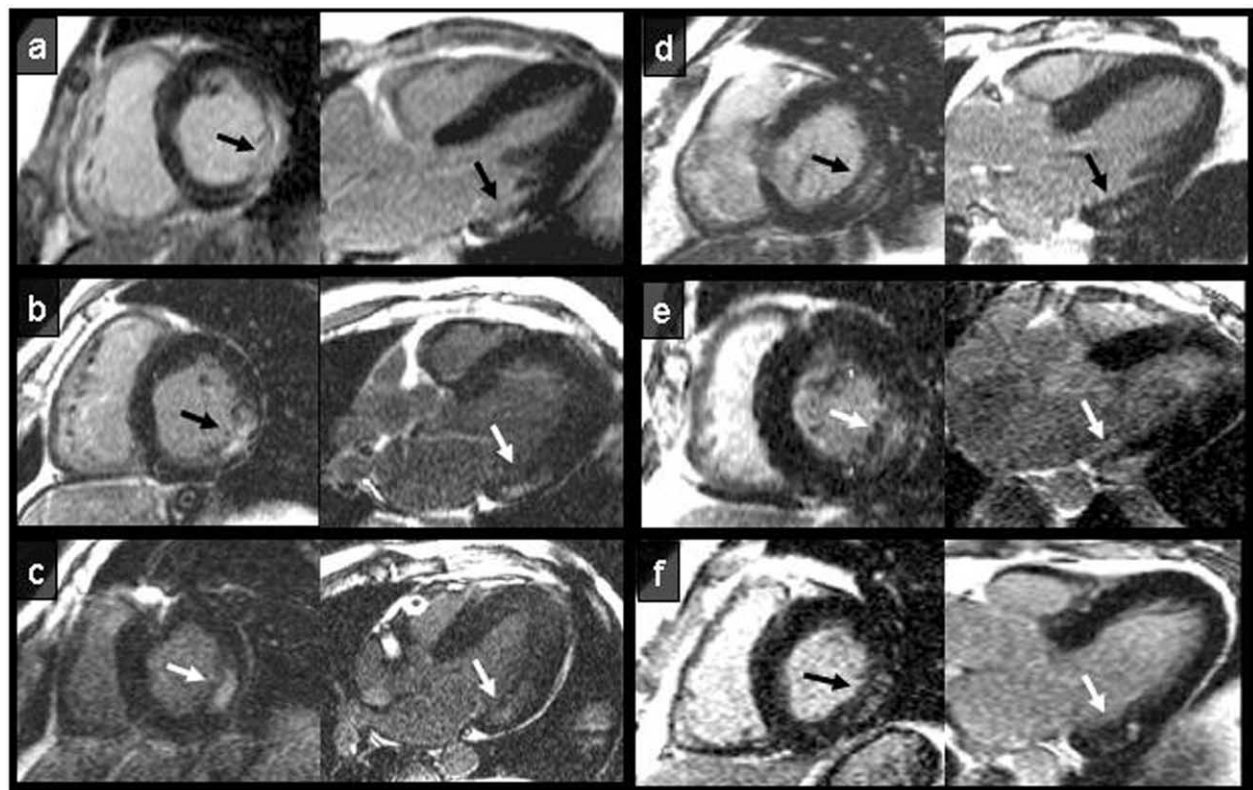
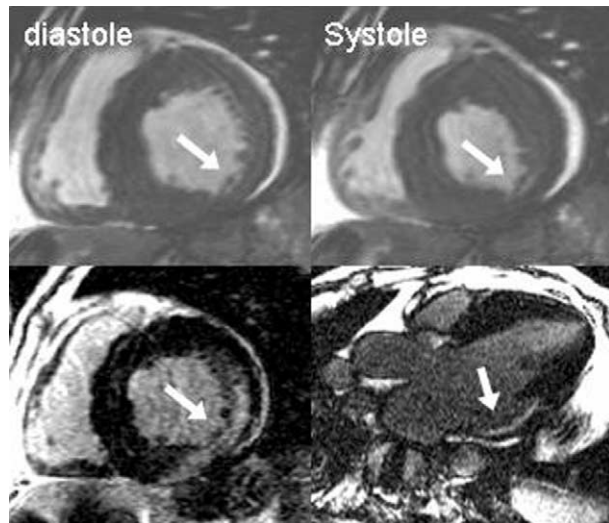
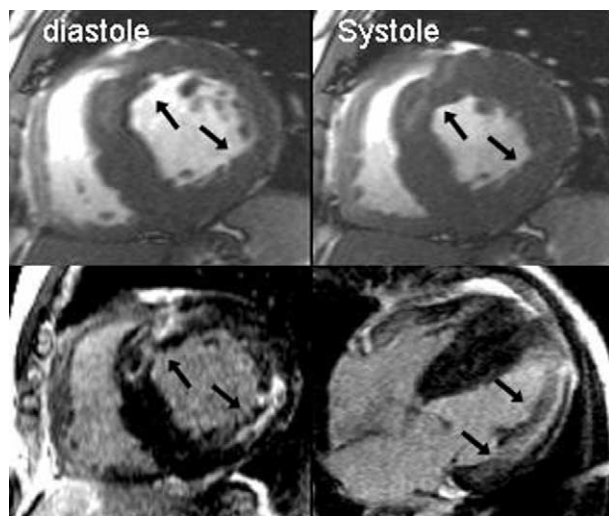


Fig. 2 Six Cases of basal infero-lateral hyperenhancement in AFD without wall motion abnormalities. Short (left column) and long axis views. Patient (a) is female, the rest male. Six cases are shown to demonstrate the consistency of the finding.



**Fig. 3** Basal infero-lateral hyperenhancement associated with wall thinning in AFD. A 57-year-old man with basal infero-lateral wall thinning and akinesis demonstrated on cine imaging (top). There was hyperenhancement (lower) in the same area. Coronary angiography was normal.



**Fig. 4** Basal infero-lateral hyperenhancement with hyperenhancement elsewhere in the LV. In 2 patients, hyperenhancement was present in the basal-lateral wall, but also elsewhere. In this 47-year-old male, there is impaired systolic function (EF 47%) with massive hypertrophy (mass index 228, normal range up to 113). There are regional wall motion abnormalities associated with hyperenhancement. Coronary angiography was normal.

membranes. In fibrosis and interstitial expansion, there is a greater extracellular space and distribution kinetics are slower compared with normal myocardium. In myocardial infarction, these two effects result in a higher relative concentration of gadolinium in areas of the heart where extracellular tissue is abnormal.<sup>10,11</sup> Recent studies have demonstrated focal gadolinium enhancement in a number of non-ischemic cardiac diseases including hypertrophic cardiomyopathy,<sup>6,12</sup> dilated car-

diomyopathy<sup>13</sup> and glycogen storage disease type IIIa,<sup>14</sup> where it is thought to represent myocardial fibrosis. In one case of HCM, the relationship between fibrosis and myocardial enhancement has been confirmed.<sup>15</sup> The few studies that have examined cardiac histology in AFD<sup>4,16–18</sup> have focussed on the classical intra-myocyte concentric lamellar inclusions bodies within lysosomes, but at least one study has suggested that sphingolipid accumulation alone is insufficient to account for the extent of myocardial abnormalities seen in patients with AFD,<sup>4</sup> whilst myocardial fibrosis has been demonstrated in isolated case reports<sup>19,20</sup> and exertional angina and thallium perfusion defects can occur despite complete epicardial revascularisation.<sup>21</sup> The demonstration of myocardial hyperenhancement in this study suggests that, in addition to the accumulation of sphingolipid within myocytes, interstitial expansion is also prominent pathological feature of AFD.

The underlying mechanism for interstitial expansion in AFD is unknown. In other myocardial diseases characterised by myocardial hypertrophy, interstitial expansion and fibrosis are caused by activation of various neuro-hormones and growth factors, as well as cell loss and necrosis. AFD may be similar with intracytoplasmic storage being the trigger for pathway activation resulting in a similar end phenotype with myocardial fibrosis and its associated clinical manifestations of diastolic and systolic dysfunction and arrhythmia. To the best of our knowledge, the curious predilection for the basal infero-lateral segments of the left ventricle that was seen in over 50% of the patients has not been described previously in any other cardiac disease. This region of the heart is usually supplied by the circumflex and or right coronary arteries, but in this study, of the 7 out of 12 patients with basal hyperenhancement studied by angiography, none had angiographic evidence of epicardial coronary artery disease. It is possible that factors such as regional wall mechanics or microvascular anatomy may influence enzyme deficiency with the myocardium, but this too seems unlikely given the fact that all myocardial cells in male patients should be equally affected by a deficiency of  $\alpha$ -Gal. Whatever the explanation, the presence of myocardial hyperenhancement suggests that fibrosis plays an important role in disease progression in AFD, potentially contributing to the clinical manifestations.<sup>22</sup> It also has important implications for the treatment of AFD, as enzyme replacement therapy may be less effective in patients with extensive areas of myocardial scarring, thereby providing an argument for the early initiation of therapy before fibrosis has developed.

The limitations of this study include a lack of histological correlations and an incomplete exclusion of coronary artery disease. Although only 8 (31%) patients underwent coronary angiography, this was skewed towards patients with hyperenhancement. Seven out of the eight (88%) catheters were in patients with myocardial hyperenhancement. So over half (53%) of the patients with hyperenhancement were studied angiographically. The distribution of hyperenhancement also suggests a disease specific phenomenon and it seems improbable that is

related to unrecognised epicardial coronary artery disease. The behaviour of gadolinium-DTPA is well described in coronary artery disease where it acts as an extra-cellular tracer. It is possible that myocytes in AFD behave differently and allow intracellular accumulation of gadolinium-DTPA, but is unlikely. Further study will be required to determine the clinical correlates of myocardial enhancement in Anderson-Fabry disease.

## Conclusions

Patients with AFD have focal enhancement during gadolinium CMR which is evidence that interstitial abnormalities, including myocardial fibrosis may be important in the natural history of cardiovascular disease in AFD. Prospective studies are required to determine the relevance of these findings to the treatment of AFD with enzyme replacement therapy.

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## References

- Sachdev B, Takenaka T, Teraguchi H et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002; **105**:1407–11.
- Desnick RJ, Ioannou YA, Eng CM.  $\alpha$ -Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill; 1995.
- Eng CM, Guffon N, Wilcox WR et al. Safety and efficacy of recombinant human alpha-galactosidase A-replacement therapy in Fabry's disease. *N Engl J Med* 2001; **345**:9–16.
- Elleder M, Bradova V, Smid F et al. Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. *Virchows Arch A Pathol Anat Histopathol* 1990; **417**:449–55.
- Anderson KR, Sutton MG, Lie JT. Histopathological types of cardiac fibrosis in myocardial disease. *J Pathol* 1979; **128**:79–85.
- Moon JCC, McKenna W, McCrohon JA et al. Towards clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol* 2003; **41**:1561–7.
- Simonetti OP, Kim RJ, Fieno DS et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology* 2001; **218**:215–23.
- Cerqueira MD, Weissman NJ, Dilsizian V et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; **105**:539–42.
- Reimer KA, Jennings RB. The 'wavefront phenomenon' of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; **40**:633–44.
- Kim RJ, Chen EL, Lima JAC et al. Myocardial Gadolinium-DTPA Kinetics determine MRI Contrast Enhancement and Reflect the Extent and Severity of Myocardial Injury After Acute Reperfused Infarction. *Circulation* 1996; **94**:3318–26.
- Flacke SJ, Fischer SE, Lorenz CH. Measurement of the gadopentetate dimeglumine partition coefficient in human myocardium in vivo: normal distribution and elevation in acute and chronic infarction. *Radiology* 2001; **218**:703–10.
- Choudhury L, Mahrholdt H, Wagner A et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **40**:2156–64.
- McCrohon JA, Moon JCC, Prasad SK et al. Differentiation of Heart Failure Related to Dilated Cardiomyopathy and Coronary Artery Disease using Gadolinium Enhanced Cardiovascular Magnetic Resonance. *Circulation* 2003; **108**:54–9.
- Moon JC, Mundy HR, Lee PJ et al. Images in cardiovascular medicine. Myocardial fibrosis in glycogen storage disease type III. *Circulation* 2003; **107**:e47.
- Moon JCC, Reed E, Sheppard M et al. The Histological Basis of Myocardial Hyperenhancement by Gadolinium Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy. *JACC* in press.
- Faraggiana T, Churg J, Grishman E et al. Light- and electron-microscopic histochemistry of Fabry's disease. *Am J Pathol* 1981; **103**:247–62.
- Ferrans VJ, Hibbs RG, Burda CD. The heart in Fabry's disease. A histochemical and electron microscopic study. *Am J Cardiol* 1969; **24**:95–110.
- von Scheidt W, Eng CM, Fitzmaurice TF et al. An atypical variant of Fabry's disease with manifestations confined to the myocardium. *N Engl J Med* 1991; **324**:395–9.
- Funabashi N, Toyozaki T, Matsumoto Y et al. Myocardial fibrosis in fabry disease demonstrated by multislice computed tomography: comparison with biopsy findings. *Circulation* 2003; **107**:2519–20.
- Case 2-1984. A 47-year-old man with coronary-artery disease and variable neurologic abnormalities. *N Engl J Med*. 1984; **310**:106–14.
- Desnick RJ, Gordon RE, Eng CM et al. Fabry disease: an unusual cause of severe coronary disease in a young man. *Ann Intern Med* 1992; **117**:221–3.
- Linhart A, Palecek T, Bultas J et al. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000; **139**:1101–8.