CARDIOVASCULAR MEDICINE

Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with α galactosidase A

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Objective: To measure coronary flow reserve (CFR), an index of microvascular function, in Anderson-Fabry disease (AFD) at baseline and after enzyme replacement therapy (ERT).
Methods and results: Mean (SD) myocardial blood flow (MBF) at rest and during hyperaemia (adenosine 140 μg/kg/min) was measured in 10 male, non-smoking patients (53.8 (10.9) years, cholesterol 5.5 (1.3) mmol/l) and in 24 age matched male, non-smoking controls (52.0 (7.6) years, cholesterol 4.5 (0.6) mmol/l) by positron emission tomography (PET). Resting and hyperaemic MBF and CFR (hyperaemic/resting MBF) were reduced in patients compared with controls (0.99 (0.17) *v* 1.17 (0.25) ml/g/min, $p < 0.05$; 1.37 (0.32) *v* 3.44 (0.78) ml/g/min, $p < 0.0001$; and 1.41 (0.39) *v* 3.03 (0.85), $p < 0.0001$, respectively). This coronary microvascular dysfunction was independent of cholesterol concentrations. PET was repeated in five patients after 10.1 (2.3) months of ERT; resting and hyperaemic MBF and CFR were unchanged after ERT (0.99 (0.16) *v* 0.99 (0.16) ml/g/min; 1.56 (0.29) *v* 1.71 (0.3) ml/g/min; and 1.6 (0.37) *v* 1.74 (0.28), respectively; all not significant).
Conclusions: The results of the present study show that patients with AFD have very abnormal coronary microvascular function. These preliminary data suggest that ERT has no effect on coronary microvascular dysfunction. Further work is necessary to determine whether treatment at an earlier stage in the course of the disease may improve coronary microvascular function in patients with AFD.

Anderson-Fabry disease (AFD) is a multisystem disorder caused by an X-linked deficiency of lysosomal α galactosidase A that results in renal, cardiac, and cerebrovascular disease and premature death.[1] Patients with AFD have angina despite angiographically normal coronary arteries. Recent studies have also shown progressively deteriorating left ventricular (LV) systolic function and myocardial scarring in patients with AFD cardiomyopathy.[2 3] We hypothesised that these clinical abnormalities may be caused by coronary microvascular dysfunction.

The objectives of this study were to measure coronary flow reserve (CFR), an index of coronary microvascular function, in a consecutive cohort of patients with AFD by using positron emission tomography (PET) and to determine the effect of enzyme replacement therapy (ERT) on microvascular abnormalities.

METHODS

Patient and controls

Ten non-smoking male patients with AFD (mean (SD) age 53.8 (10.9) years, range 43–82 years; cholesterol 5.5 (1.3) mmol/l) referred to the Heart Hospital, London, UK were studied. The diagnosis of AFD was based on the identification of an α galactosidase A gene mutation and a low plasma α galactosidase A (mean (SD) 0.45 (0.35) nmol/h/ml, range 0.04–0.99 nmol/h/ml). Nine patients were identified through screening of patients presenting with unexplained LV hypertrophy; six of these patients have been reported on previously.[4] One patient was referred with an established diagnosis of AFD (patient 6) and one was identified through family screening (patient 10). At the time of diagnosis, none of these patients was receiving ERT.

All patients underwent ECG and two dimensional Doppler echocardiography by previously described methods.[5] LV mass was calculated by M mode echocardiography with the Devereux formula and indexed to body surface area.[6] Nine patients had symptoms or signs suggestive of myocardial ischaemia and underwent coronary angiography to exclude coronary artery disease.

Twenty four healthy non-smoking age matched men (52.0 (7.6) years, cholesterol 4.5 (0.6) mmol/l) with normal ECG and no evidence of cardiac disease served as controls for the myocardial blood flow (MBF) and CFR data.

Enzyme replacement therapy

Five patients (table 1) received Fabrazyme (Genzyme Corporation, Cambridge, Massachusetts, USA) at a dose of 1 or 2 mg/kg every two weeks as part of a separate randomised study. Follow up PET was obtained 17.1 (1.9) months after the baseline scan while patients were being treated. Plasma globotriaosylceramide (neutral glycosphingolipid) concentrations were measured by tandem mass spectrometry before and after ERT.[7]

The study was approved by the local research ethics committees and all participants gave written informed consent. Radiation exposure was approved by the UK Administration of Radioactive Substances Advisory Committee.

Positron emission tomography

All patients and controls underwent PET to measure MBF at rest and during adenosine induced hyperaemia (140 μg/kg/

Abbreviations: AFD, Anderson-Fabry disease; CFR, coronary flow reserve; ERT, enzyme replacement therapy; LV, left ventricular; MBF, myocardial blood flow; PET, positron emission tomography

Table 1 Patient characteristics

Patient	Age at study (years)	Chest pain	NYHA class	Syncope	Palpitations	Max LVWT (mm)	FS (%)	LVMI (g/m^2)	CFR
1	46	+	II	+	+	25	40	263	1.58
2*	58	−	I	+	+	26	26	407	2.60
3*	81	−	III	−	+	18	23	228	2.31
4	49	+	II	−	−	17	35	192	2.09
6*	55	+	II	−	+	15	36	222	2.24
7*	49	+	II	−	+	16	39	180	2.74
8	45	+	I	−	+	20	51	248	1.27
9*	54	−	I	−	−	24	42	314	2.27
10	43	−	I	−	−	15	33	93	1.28
12	58	+	II	+	+	20	27	407	1.83

*Five patients with follow up positron emission tomography after enzyme replacement therapy.
+, present; −, absent.
CFR, coronary flow reserve; FS, fractional shortening; LVMI, left ventricular mass index; Max LVWT, maximum left ventricular wall thickness; NYHA, New York Heart Association.

min intravenously). Images were recorded with an ECAT 931-08/12 15 slice tomograph with a 10.5 cm axial field of view (CTI/Siemens, Knoxville, Tennessee, USA). Resting and hyperaemic MBF were measured with oxygen-15 labelled water ($H_2{}^{15}O$) as previously reported.[8] Arterial blood pressure was recorded by automatic cuff sphygmomanometer at one minute intervals and the ECG was monitored continuously throughout the procedure.

PET data analysis

All emission and transmission data were reconstructed with a Hanning filter with a cut off frequency of 0.5 units of the reciprocal of the sampling interval of the projection data resulting in an image resolution of 8.4 × 8.3 × 6.6 mm full width at half maximum at the centre of the field of view. Myocardial and blood pool images were then generated directly from the dynamic $H_2{}^{15}O$ study as previously reported.[9] Regions of interest were drawn within the left atrium and ventricular myocardium on consecutive image planes. These were projected on to the dynamic $H_2{}^{15}O$ images to generate blood and tissue time activity curves. Arterial and tissue activity curves were fitted to a single tissue compartment tracer kinetic model to give values of MBF (ml/g/min).[9] Coronary resistance (mm Hg/ml/min/g) was calculated as the ratio of mean arterial pressure to MBF and CFR was calculated as the ratio of hyperaemic MBF to resting MBF.

Statistical analysis

Continuous variables were compared by the paired Student's *t* test (Statview version 5.0; SAS institute Inc, Cary, North Carolina, USA). Linear regression was determined to assess the relation between cholesterol concentrations, LV mass index, MBF, and CFR. Data are reported as mean (SD) values. A probability value of $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

Table 1 shows the clinical characteristics of the patients. Six (60%) patients had exertional chest pain. None of the nine patients had angiographically significant coronary artery disease. Three patients had rate responsive dual chamber permanent pacemakers: one for LV outflow tract gradient reduction and two for heart block. None of the patients had a PR interval less than 120 ms. Two patients had non-sustained ventricular tachycardia on Holter monitoring (patients 2 and 3) and two were in atrial fibrillation (patients 5 and 11). Seven years before the diagnosis of AFD, patient 1 had coronary sinus pH assessed during dipyridamole infusion.[10] The peak change in coronary sinus pH during hyperaemia was −0.086 units, indicating severe myocardial ischaemia.

Serum cholesterol was higher in the patients than in controls (mean difference 0.97 mmol/l, 95% confidence interval 0.3 to 1.6, p = 0.006). Patients also had higher high density lipoprotein cholesterol concentrations than did controls (1.7 (0.5) mmol/l *v* 1.1 (0.4) mmol/l, respectively, p = 0.002). Low density lipoprotein cholesterol (3.1 (0.8) mmol/l *v* 3.7 (1.3) mmol/l, respectively, p = 0.2) and triglyceride concentrations (1.4 (0.7) mmol/l *v* 1.8 (1.6) mmol/l, respectively, p = 0.5) did not differ between patients and controls.

Two patients had acroparaesthesia, one had hypohidrosis, and one had renal dysfunction (creatinine clearance 52 ml/min). None of the patients was hypertensive and one had non-insulin dependent diabetes mellitus. No angiokeratomas were noted in any of the patients. All patients had a maximum LV wall thickness ⩾ 13 mm (17 (4.0) mm, range 14–26 mm). Nine patients had concentric LV hypertrophy and one had asymmetric septal hypertrophy. At the time of study no patient had LV outflow tract obstruction; the mean LV end systolic, end diastolic, and left atrial diameters were 33 (0.9), 5.2 (0.8), and 4.7 (1.1) mm, respectively. The mean LV mass index was 234 (81.3) g/m^2 (range 141–407 g/m^2).

MBF and CFR

Heart rate and mean arterial blood pressure were similar in controls and AFD patients at rest and during adenosine infusion. The rate pressure product (systolic blood pressure × heart rate) was similar in the controls and patients during all study conditions.

Resting and hyperaemic MBF and CFR were significantly reduced in AFD patients compared with controls (0.99 (0.17)

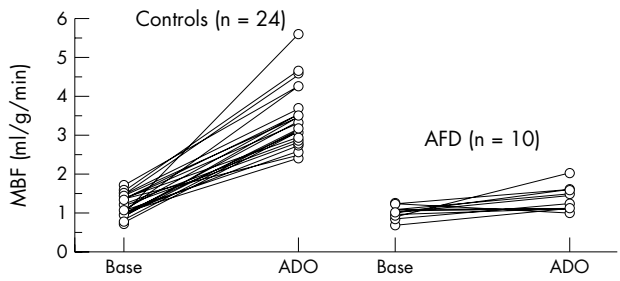

Figure 1 Myocardial blood flow (MBF) at rest (Base) and during adenosine induced hyperaemia (ADO) in patients with Anderson-Fabry disease (AFD) and controls.

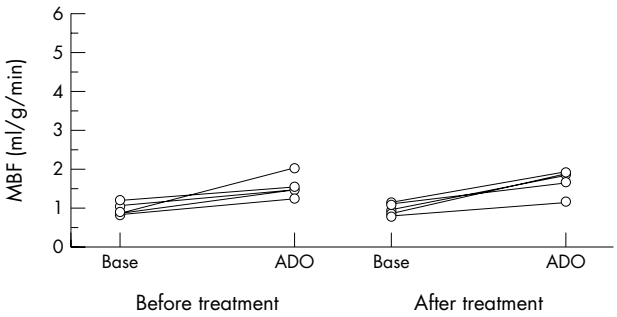

Figure 2 MBF at rest and during ADO before and after enzyme replacement therapy with Fabrazyme.

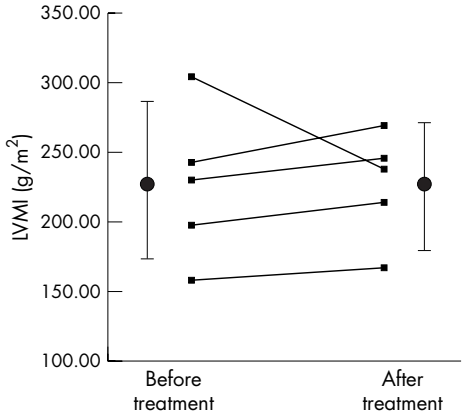

Figure 3 Left ventricular mass index (LVMI) before (226.3 (54.1) g/m^2) and after (226.7 (39.0) g/m^2, not significant) enzyme replacement therapy with Fabrazyme. Cumulative data are presented as mean (SD).

v 1.17 (0.25) ml/g/min, $p < 0.05$; 1.37 (0.32) *v* 3.44 (0.78) ml/g/min, $p < 0.0001$; and 1.41 (0.39) *v* 3.03 (0.85), $p < 0.0001$, respectively) (fig 1, table 1). This reduction in coronary microvascular function was independent of cholesterol and high density lipoprotein cholesterol concentrations. Resting coronary resistance was comparable in patients and controls (82.2 (27.8) *v* 89.3 (31.2) mm Hg/ml/min/g, respectively, not significant). The minimum resistance during hyperaemia was higher in AFD patients than in controls (65.1 (16.9) *v* 26.5 (6.0) mm Hg/ml/min/g, $p < 0.0001$). No correlation was found between LV mass index and resting or hyperaemic MBF or CFR.

Response to ERT

In patients who underwent a repeat PET plasma globotriaosylceramide had decreased with ERT (mean change 5.3 μg/ml, 95% confidence interval 0.5 to 10.1, $p = 0.04$). Resting and hyperaemic MBF and CFR before and after 10.1 (2.3) months of ERT were similar (0.99 (0.16) *v* 0.99 (0.16) ml/g/min; 1.56 (0.29) *v* 1.71 (0.3) ml/g/min; and 1.6 (0.37) *v* 1.74 (0.28), respectively; all not significant) (fig 2). Resting coronary resistance was similar before and after ERT (83.9 (18.9) *v* 90.2 (26.5) mm Hg/ml/min/g, respectively, not significant). The minimum resistance during hyperaemia was unchanged after ERT (56.9 (14.7) *v* 52.8 (18.7) mm Hg/ml/min/g, not significant). LV mass index did not change (mean change 0.4 (37.8) g/m^2, range −66.3 to +26.4, not significant) (fig 3). LV cavity dimensions did not change (mean change in end systolic cavity dimension 0.1 (0.3) mm; mean change in end diastolic cavity dimension 0.1 (0.2) mm; both not significant). Fractional shortening tended to decease (mean pre-ERT fractional shortening 34.8 (6.7)%, mean post-ERT fractional shortening 31.4 (6.3)%, $p = 0.08$). Maximum LV wall thickness did not change (mean change 0.02 (0.3) mm, not significant).

DISCUSSION

This study shows that patients with AFD have a substantial reduction in hyperaemic MBF and CFR compared with normal controls. The significance of these findings for individual patients remains to be determined, but the severity of the microvascular dysfunction suggests that these abnormalities may have a substantial influence on the natural history of AFD.

Mechanisms of microvascular dysfunction

Symptoms and signs suggestive of myocardial ischaemia in the absence of coronary disease are common in patients with cardiomyopathies and in patients with LV hypertrophy secondary to pressure overload. Reductions in CFR similar to those seen in this study have been observed in all these conditions, although different mechanisms are involved. In patients with hypertrophic cardiomyopathy, remodelling of the intramural arterioles is important,[11 12] whereas in aortic stenosis increased perivascular fibrosis and intramyocardial pressure and reduced diastolic filling are the dominant mechanisms for microvascular dysfunction.[13 14]

In AFD, several mechanisms may contribute to microvascular dysfunction. AFD cardiomyopathy is characterised by globotriaosylceramide deposition in myocytes, conduction tissue, vascular endothelium, and valve tissue. This is accompanied by secondary changes such as myocyte hypertrophy and fibrosis,[15] which cause raised coronary vascular resistance and increased myocardial oxygen demand. Although endothelial globotriaosylceramide deposits may lead to microvascular dysfunction, a recent publication has shown that patients with AFD have *enhanced* nitric oxide independent endothelial function measured by forearm venous plethysmography.[16] It is unknown whether similar abnormalities would be seen the in coronary microvasculature.

Response to ERT

In this study plasma concentrations of globotriaosylceramide were significantly reduced with ERT but no improvements in coronary microvascular function or LV mass were seen. However, interpretation of this observation is limited by the small size of the cohort and by the fact that the cohort was considerably older and had more severe cardiac disease than did patients in previous trials of ERT.[17–19] Along with an improvement in AFD symptoms these trials have shown a reduction in LV mass and an improvement in systolic function with ERT. To understand the impact of ERT on coronary microvascular function a larger study conducted over a longer time is required.

Conclusion

This study showed that microvascular dysfunction is important in the pathophysiology of AFD cardiomyopathy. Further studies are required to assess the impact of ERT on microvascular function.

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IMAGES IN CARDIOLOGY

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Aortopulmonary fistula in an acute aortic syndrome

A 67 year old man with an aortic prosthetic tube implanted after being diagnosed with an ascending aortic aneurysm and secondary severe aortic insufficiency complained of progressive dyspnoea, orthopnoea, and episodes of intense, sharp interscapular pain unrelated to exercise irradiating to the precordium. He developed severe hypoxaemia which required orotracheal intubation and mechanical ventilation. Transoesophageal echocardiography detected a pseudoaneurysm (Ps) with a diameter of 12 cm around the aortic tube (AoT) with thrombus inside. A fistula connecting the pseudoaneurysm with the right pulmonary artery (RPA) was suggested by the initial image (upper panel, arrow) and was demonstrated by colour Doppler (lower panel). Emergency surgery was indicated, but suddenly the patient had a profuse serohaematic secretion through the endotracheal tube, suffered severe hypotension and hypoxaemia that did not respond to treatment, and he died.

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