Hypertrophic remodelling and subendocardial dysfunction in mitochondrial DNA point mutation carriers without known cardiac involvement

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Target Audience MR cardiac physicists and clinicians interested in the early detection of cardiac disease, especially in mitochondrial mutation carriers.

Purpose The m.3243A>G mutation in mitochondrial DNA is present in ~1 in 300 of the population and causes disease in ~1 in 6000 individuals [1]. Cardiomyopathy is a cause of morbidity and mortality in patients and often has a hypertrophic phenotype. A study of cardiac manifestation in a population-based cohort of patients with the m.3243A>G mtDNA mutation detected left-ventricular hypertrophy in 56% of cases by two-dimensional-echocardiography [2]. However, this method lacks sensitivity to early changes, particularly in asymptomatic cases [3]. Previous studies have compared patients to global reference ranges, rather than studying age-matched controls. Detection of early structural and functional defects would enable timely intervention.

We hypothesized that abnormalities of left ventricular mechanics and bioenergetics would be detectable in patients carrying the m.3243A>G mutation without known cardiac involvement, and that such abnormalities would be related to markers of disease burden.

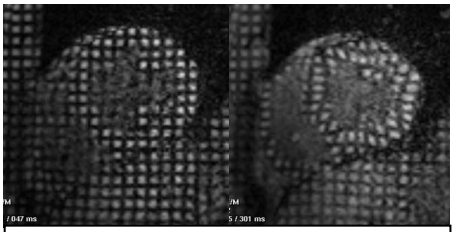

Fig 1 : Tagged images at *(left)* end diastole and (*right)* end systole

Methods *Subjects:* Twenty-two adult patients with disease due to the m.3243A>G mutation (11 males, age 42.5 ± 12.2 y, BMI 23.1 ± 5.1 kg/m^2), but no known cardiac involvement, were recruited. The absence of cardiac involvement was determined by clinical history and examination with normal ECG and echocardiogram. All 22 patients were matched with healthy controls for gender and age (42.8 ± 13.4 y, BMI 26.6 ± 4.8 kg/m^2), with normal ECG and no history of cardiovascular or metabolic disease. Ethical approval and informed consent were obtained. *MRI protocol : S*cans were performed using a 3T Philips Achieva with a 6 channel cardiac coil. (1) *Cardiac morphology:* High resolution, short axis cine-MRI was analysed using methods reported previously [4] to provide measurements of LV mass, LV mass index (LV mass normalised to body surface area), and blood pool volumes, using a Philips Viewforum. The M/V ratio (LV mass/end diastolic volume) was calculated as a measure of concentric remodelling. (2) *Cardiac tagging:* Tagged images of the myocardium in the short axis were obtained throughout the cardiac cycle. A multishot turbo-field echo sequence with turbo factor 9 was used (TR/TE/FA/NEX = 4.9/3.1/10^o/1, SENSE factor 2, FOV 350x350mm, voxel size 1.37x 1.37 mm with an orthogonal grid with tag spacing of 7 mm). The Cardiac Image Modelling package (University of Auckland) was used to analyse the tagging data. Circumferential strain and the rotation of the planes were calculated throughout the cardiac cycle. Torsion between two mid-ventricular planes (taken as the circumferential-longitudinal shear angle) was calculated and the ratio of peak torsion to peak endocardial strain was calculated as a measure of strain distribution across the myocardial wall [5]. Longitudinal shortening was measured as the percentage change in distance from the mitral plane to the apex between end-diastole and end-systole. *Cardiac spectroscopy:* A 10cm diameter ^{31}P surface coil (Pulseteq, UK) and a 7cm slice-selective, cardiac gated 1D-CSI sequence were used with spatial pre-saturation of skeletal muscle. 16 coronal phase-encoding steps were used, each 10mm thick (TR = heart rate, 96 averages, 20 mins). The first spectral line without skeletal muscle contamination was selected. Quantification was performed using AMARES (jMRUI), and the PCr/ATP ratios were calculated and corrected for blood contamination, saturation and coil excitation profile as detailed in [4]. *Clinical measures:* m.3243A>G mutation load was determined in urinary epithelial cells. Student t testing and Pearson correlations were performed with SPSS 17.0.

Table 1 : Cardiac morphology, tagging and energetics results

Parameter	Controls	Patients
Blood pressure (mmHg)	128±11/75±9	116±13/77±8
Weight (kg)	77 ± 13	66 ± 16
LV mass (g)	109 ± 20	119 ± 28
LV mass index (g/m^2)	59 ± 7	70 ± 12 ‡
Wall thickness in systole (mm)	10.9 ± 1.9	13.5 ± 3.1‡
Wall thickness in diastole (mm)	6.9 ± 1.1	9.8 ± 2.9 $
M/V ratio (-)	0.81 ± 0.14	1.28 ± 0.33 *
Peak torsion (^{o})	5.9 ± 1.4	8.0 ± 2.7 #
Torsion to endocardial strain ratio (rad)	0.46 ± 0.10	0.62 ± 0.21 #
Longitudinal shortening (%)	18.2 ± 2.3	15.1 ± 1.5 *
PCr/ATP ratio (-)	1.92 ± 0.20	1.51 ± 0.34 *
# p < 0.03, ‡ p<0.01, $ p<0.001, * p <0.0001		

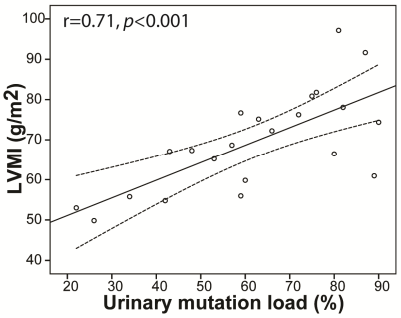

Fig 2 : Left ventricular mass index vs urinary mutation load

Results Table 1 gives the results for cardiac morphology, tagging and energetics. Patients were found to have a significantly raised LV mass index, with increased wall thicknesses and M/V ratio, all indicative of concentric remodeling. Peak torsion was significantly higher in the patients, and longitudinal shortening was lower. The PCr/ATP ratio was significantly reduced in the patient group but does not correlate with changes in other cardiac measurements. There was a significant correlation between urinary mutation load and both LVMI (r=0.71, p<0.001, figure 2) and peak endocardial circumferential strain (r=-0.59, p< 0.03).

Discussion The findings in patients compared with the controls are: 1) LVMI is greater and is a more sensitive indicator of subtle cardiac hypertrophy than LV mass; 2) concentric remodeling occurs in the absence of hypertension or diabetes mellitus; 3) altered systolic myocardial strains occur, with reduced longitudinal shortening and increased peak torsion, in the absence of global systolic or diastolic dysfunction, indicating relative subendocardial impairment; 4) changes in cardiac morphology and strains are associated with increased mtDNA mutation load and NMDAS score; and 5) PCr/ATP ratio is reduced, but the ratio does not identify individuals with structural or functional myocardial abnormalities.

Conclusions MR methods are able to detect early changes in morphology, torsion and energetics in m.3243A>G mutation patients without known cardiac involvement, potentially making them useful biomarkers of disease for therapy trials.

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