# Left ventricular concentric hypertrophy and strain redirection in m.3243A>G mutation carriers: cardiomyopathy correlates with mutation load

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**Introduction:** The m.3243A>G mutation in the mitochondrial DNA (mtDNA) tRNALeu$^{(UUR)}$ gene is the most common heteroplasmic single mtDNA defect, present in ~1 in 300 of the population and causing disease in ~1 in 6000 individuals [1]. Cardiomyopathy is a frequent cause of morbidity and mortality in patients carrying the m.3243A>G mutation and often has a hypertrophic phenotype [2,3]. Cardiac involvement has been found in 20-30% of subjects with the full MELAS syndrome [4] but it has also been found in those with partial phenotype [5] and as the sole clinical feature in mutation carriers. A recent 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 [2,3]. However, it is recognized that this method lacks sensitivity to early changes, particularly in asymptomatic cases [6]. Moreover, previous studies have compared the cardiac morphology of m.3243A>G carriers by comparison to global reference ranges, rather than studying age-matched controls using the same methodology. Given the importance of identifying early structural and functional defects to enable early intervention, we used cardiac magnetic resonance imaging (MRI) to detect early changes in this genetic cardiomyopathy. Cardiac tagging [7] was used to measure myocardial circumferential strain and torsion through the cardiac cycle provides a further method of detecting antecedent changes.

**Methods:** Ten m.3243A>G mutation carriers (5m:5f, mean age 42.5 ± SD9y) were recruited under ethical permission and informed consent: 16 healthy control subjects (8m:8f, mean age 41.6 ± SD15y) were matched to provide baseline population data. Nine of the subjects underwent a needle biopsy of the mid-portion of left vastus lateralis skeletal muscle. The percentage level of m.3243A>G mutation load was measured as described [8]. It was not possible to obtain a muscle biopsy from subject 10. Written informed consent was obtained from all participants and institutional ethics was obtained. All subjects underwent a 2D echocardiogram and ECG. No significant abnormalities were found on ECG or echo and no previous diagnosis of heart failure had been made. *MR protocol:* All scans were performed using a 3T Philips Intera Achieva with a 6 channel cardiac coil. *(1) Cardiac morphology* High resolution, short axis cine-MRI was available for all subjects using methods reported previously [9] to provide measurements of LV mass, LV index (LV mass normalised to body surface area), and blood pool volumes, using a Philips Viewforum. The eccentricity ratio (LV mass/end diastolic volume) was calculated as a measure of concentric remodelling. Radial thickening was calculated from mean wall thicknesses at end systole and end diastole *(2) Cardiac tagging: T*agged images of the myocardium in the short axis were obtained throughout the cardiac cycle. A multishot turbo-field echo sequence with TFE factor 9 was used (TR/TE/FA/NEX = 4.9/3.1/10º/1, SENSE factor 2, FOV 350x350mm, voxel size 1.37x 1.37mm with an orthogonal grid with tag spacing of 7mm, fig 1). 2 adjacent slices of 10mm thickness were acquired at mid-ventricle with a 2mm gap. The Cardiac Image Modelling package (University of Auckland) was used to analyse the tagging data by aligning a mesh on the tags between the endo- and epi-cardial contours. Circumferential strain and the rotation of the two planes were calculated throughout the cardiac cycle. Torsion between the two planes (taken as the circumferential-longitudinal shear angle) was calculated according to the method in [10]. The ratio of peak torsion to peak endocardial torsion was calculated as a measure of strain distribution across the myocardial wall [7]. Longitudinal shortening was measured on a 4-chamber cine view as the percentage change in distance from the mitral plane to the apex between end-diastole and end-systole. Student t testing and Pearson correlations were performed with SPSS 17.0.

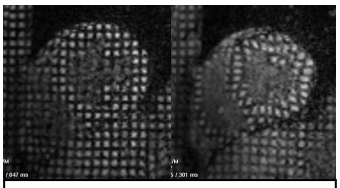

**Fig 1 :** Tagged images *(left)* end diastole and *(right)* end systole

**Table 1 :** A selection of cardiac parameters, *p < 0.05

| | Controls | Carriers |
|---|---|---|
| End diastolic volume (ml) | 143±32 | 103±23* |
| End systolic volume (ml) | 61±19 | 36±11* |
| Longitudinal shortening (%) | 18.1±2.8 | 14.5±4.0* |
| Peak torsion (degrees) | 6.0±1.4 | 7.3±1.3* |

**Results:** There were no significant differences between controls and m.3243A>G in systolic or diastolic blood pressure. Left ventricular mass (LV mass) was not significantly different between patients and controls (fig 2a): however, LV index was significantly increased in m.3243A>G carriers (fig 2b). End-systolic and end-diastolic volumes are found to be significantly reduced in m.3243A>G (table 1). The eccentricity ratio was significantly greater for carriers than controls, indicating concentric remodeling (fig 2c). Within the control group there was significant correlation between the diastolic blood pressure and eccentricity ratio (r = 0.49, p = 0.02), though not within the m.3243A>G group. The maximum longitudinal shortening found at systole was reduced by an average of 20% in the m.3243A>G patients compared to controls (table 1) and correlated significantly with the eccentricity ratio (r =-0.82, p = 0.004, fig 2d): impaired longitudinal shortening occurs in association with concentric remodeling. Peak cardiac torsion is found to be significantly raised in m.3243A>G subjects compared to controls (table 1). The percentage level of m.3243A>G mutation load significantly correlated with the torsion to endocardial strain ratio (r = 0.71, p < 0.05, fig 2e). In particular those m.3243A>G patients with mutation loads higher than 50% (ratio = 0.68 ± 0.05) had a significantly higher ratio than their own age-matched controls (ratio = 0.43 ± 0.10, p<0.001) or the whole control group (0.49 ± 0.13, p < 0.01): 6/10 m.3243A>G patients have abnormally high torsion to endocardial strain ratios. Overall, this suggests a directional change in myocardial shortening in MELAS patients in association with the concentric left ventricular hypertrophy, towards a more oblique angle (producing torsion) and away from the longitudinal axis. As mutation load increased radial thickening decreased in the m.3243A>G patients (r = -0.80, p = 0.01, fig 2f).

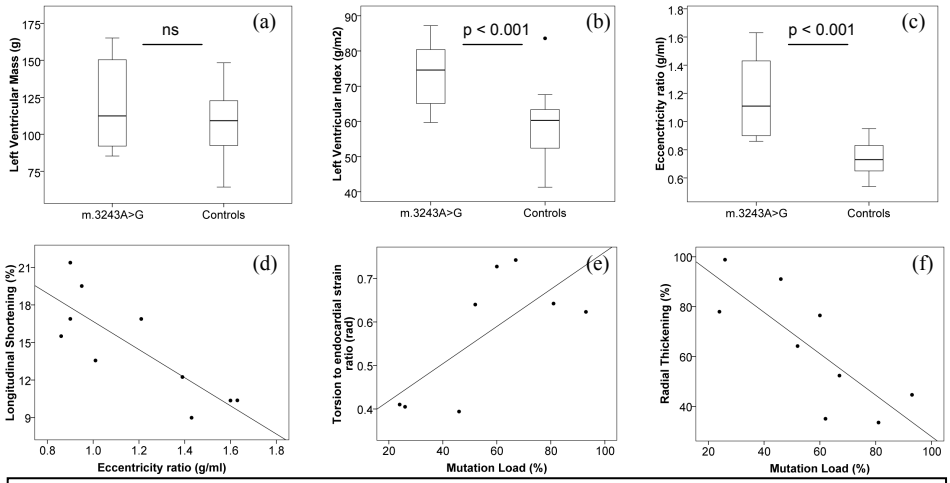


**Fig 2 :** *Top :* Comparison between m.3243A>G mutation carriers and control subjects for (a) left ventricular mass (b) left ventricular index (mass/BSA), and (c) eccentricity ratio (mass/EDV). *Bottom :* For the m.3243A>G mutation carriers, correlation between (d) eccentricity ratio and longitudinal shortening, (e) TSR and mutation load, (f) radial thickening and mutation load

**Conclusion :** In conclusion, cardiac hypertrophy is found in patients with the m.3243A>G mutation and there is an associated re-orientation of intramyocardial strains, both of which are closely related to the underlying mutation load. MR imaging and tagging provides a sensitive evaluation of the early structural abnormalities in m.3243A>G patients and reveals a close relationship between the degree of cardiac dysfunction and underlying genetic abnormality.

**Acknowledgements :** Carol Smith, Louise Morris, Tim Hodgson

**References:** [1] Chinnery *Ann. Neurol.***48:**188 (2000) [2] Majamaa-Vollti *BMC Cardiovasc. Disord.* **2**:12 (2002) [4] Hirano *J.Child Neurol.* **9**:4 (1994), [5] Antozzi *Card. Res.* **35:**184 (1997), [6] Myerson *Hypertension* **40**: 673 (2002), [7] Lumens *AJP Heart Circ Physiol.* **291**, H1573 (2006), [8] Taylor in *Organelle Diseases,* Chapman and Hall (2007) [9] Jones *J.Intern. Med.* **267**: 394 (2010), [10] Buchalter *Circ.* **81**: 1236 (1990).