Cardiac MRI reveals progressive abnormalities in heart shape and function in the R6/2 mouse model of Huntington's disease

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Introduction

Huntington's disease (HD) is a progressive neurological disorder characterised by psychiatric and motor abnormalities caused by a single gene. It is invariably fatal and no effective cure has yet been found. The gene is not brain specific and there is increasing evidence of peripheral as well as CNS pathology. The incidence of cardiac disease is similar between HD patients and non-HD patients, but the death rate amongst HD patients is 30% compared to 2% of non-HD patients [2]. Here we examined the R6/2 mouse [3], widely used as an animal model of HD, with *in vivo* assessment of cardiac function and morphology using MRI.

Methods

Ten R6/2 (CAG 250) transgenic mice were scanned along with ten wildtype littermate controls (WT) at 13 weeks and again at 16 weeks. Scans were performed using a Bruker BioSpec 47/40 spectrometer at 4.7T with a 2cm circular surface coil. A 4-chamber view image was acquired to position 7 short-axis (SA) slices following the LV axis (figure 1). Mice were anaesthetised with 1-2% isoflurane and ECG triggering was used for prospective gating of all sequences. SA slices were acquired using FLASH (TR/TE 11/2.8ms, 30° FA, 6 NEX, 13-16 cine frames). Saturation slices placed over the atria and major vessels were used for black blood imaging. The LV was delineated manually on SA slices for each frame using the freely-available software Segment (http://segment.heiberg.se). It was noted during dissection after the experiments were finished that the R6/2 hearts had a 'bent' appearance. To quantify this, we parametrised a bending angle for the LV axis by fitting lines to upper and lower blocks of slices and calculating the angle between them (figure 2). Lines were fitted to the centroids of LV sections and taken as the median across phases of the cardiac cycle.

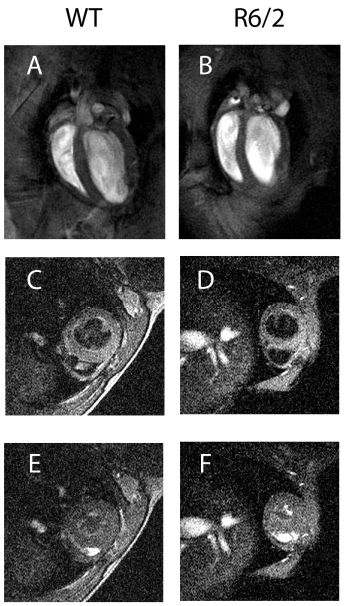


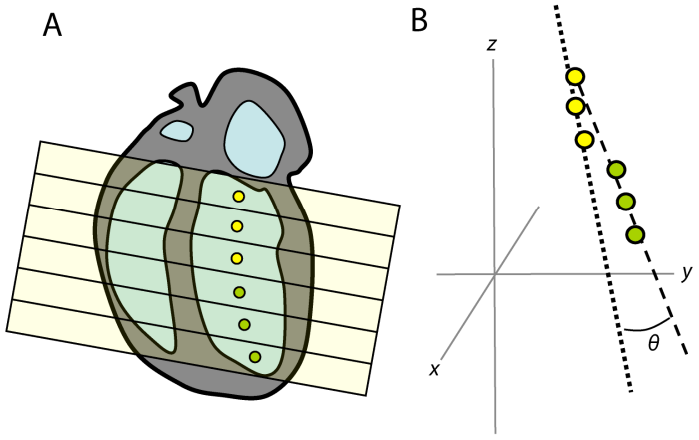
Figure 1 4 chamber (A,B) and SA (C-F) views of the mouse heart in diastole (A-D) and systole (E, F) for WT and R6/2 transgenic mouse hearts. All images are shown from mice aged 16 weeks.

Results

One R6/2 mouse died after the first scan so was excluded from the study. Morphological and functional parameters (end diastolic/systolic volume EDV/ESV, stroke volume, SV, cardiac output CO, ejection fraction EF) are shown in table 1. Significance was determined using two-tailed Student's *t*-tests. At 13 weeks, R6/2 hearts have lower EDV and ESV though EF and CO are not significantly different. At 16 weeks, the differences between WT and R6/2 mice are larger and more significant, affecting SV, CO and EF. The bending angle we have defined is not significantly larger until 16 weeks suggesting a progressive rather than congenital shape difference.

Conclusions

We have shown that the R6/2 transgenic mouse heart shows deterioration in functional and morphological parameters at 13 weeks that are worse at 16 weeks. Combined with MRI assessment, the R6/2 mouse can be used to investigate potential therapeutics acting on the heart. Further examination of this model may shed light on the mechanisms leading to the higher death rate from cardiac disease amongst HD patients.



	13 weeks				16 weeks			
	WT		R6/2		WT		R6/2	
EDV/µl	45	(1)	37	(2)**	46	(1)	29	(2)***
ESV/µl	21	(2)	15	(1)*	18	(2)	9	(1)***
SV/µl	24	(1)	22	(1)	28	(1)	21	(1)***
CO ml/min	7	(0.5)	6	(0.4)	8	(0.5)	6	(0.4)***
EF %	54	(3)	60	(3)	61	(3)	71	(2)**
Angle °	13	(2)	14	(2)	11	(1)	15	(1)*

Table 1 Parameters measured at 13 and 16 weeks shown as mean (SEM). Significant differences between WT and R6/2 at each age are marked as *, ** and *** for $p < 0.05, 0.01, 0.001$ respectively.

Figure 2 (left) Assessment of shape changes with disease. A: centroids of each LV slice on SA sections used to fit lines (B) to calculate the 'bending angle' of the LV.

References [1] Walker FO (2007) Lancet 369 (9557) 218-228 [2] van der Burg *et al* Lancet Neurol 2009 8(8) 765-774 [3] Mangiarini L 1996 Cell 87 (3) 493-506