Right ventricular failure in the R6/2 mouse model of Huntington's disease is unmasked by dobutamine

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Target audience

Researchers working on phenotyping of genetic mouse models of disease, users of HD animal models, cardiac pathology models, clinicians working with HD patients.

Purpose

Huntington's disease (HD) is a hereditary disorder of the central nervous system characterised by psychological, neurological and physiological symptoms. Although primarily considered as a disease of the CNS, the mutant protein responsible for disease is expressed throughout the body. Despite similar rates of cardiac disease amongst patients and the general population, HD sufferers are more likely to die from heart failure [1]. Recently cardiac MRI has been used to investigate cardiovascular function in a mouse model of HD, the R6/2 mouse [2]. A progressive dysfunction with reduced left ventricular (LV) volume was found, though with a preserved LV ejection fraction (LVEF). Additionally it was shown that there were changes in the shape of the heart by measuring bending of the LV, but no analysis of the right ventricle (RV) was reported [2]. Visual inspection of the data in our lab showed that at a late stage of disease, some mice suffered a substantial impairment of RV systolic function (RVEF).

The aim of this study was to determine whether the RV was also involved in R6/2 cardiac pathology, to characterise this over time and to examine if these effects could be unmasked earlier in the disease using dobutamine stress test.

Methods

Two experiments were performed: the first to evaluate the functional parameters longitudinally in transgenic mice that were not exposed to dobutamine, the second to evaluate the difference in the effect of dobutamine on WT and R6/2 mice at an early timepoint.

Experiment 1 Five R6/2 mice were scanned at three time points, designed to capture an initial period before severe symptoms developed (t_1=7±0.5 wk; mean ± sd) and two later scans reflecting different stages of pathology. The second scan (t_2=15±0.5wk) was performed when the bodyweight had risen and fallen to the same point as the initial scan, and the third timepoint when the bodyweight was 75% of the initial weight (t_3=17±1.3 wk). Anaesthesia was induced with 3% isoflurane in 1l/min O_2 and maintained with 1-2% isoflurane in 1l/min O_2. Images were acquired at 4.7 T using a Bruker BioSpec 47/40 system (FISP, TR/TE 7ms/2.4ms, 13-20 frames, 3.5 cm FOV, 256 matrix, 1 mm slice thickness, bandwidth 64kHz, flip angle 20°, NEX 2). Slices were arranged to cover the whole RV as well as the whole LV following [3].

Experiment 2 Six R6/2 mice and six WT controls were scanned at 10 weeks of age, corresponding to the last timepoint before the transgenic phenotype starts to show and body weight starts to decrease. In addition to the protocol described above, dobutamine stress was performed after an *in situ* intraperitoneal injection of dobutamine (12 µg/g i.p)**.** For 30 minutes following injection three short axis mid-ventricular slices were acquired repeatedly.

Results

Experiment 1 showed a decrease in LV mass with the progression of the disease (*t1:* 76±9µl *t2:* 65±7µl* *t3:* 58±9µl; *=p<0.05 comparison with previous time point, paired *t*-test). In agreement with [2], LVEF was unaffected, but the RV measurements shown in Figure 2, which were not considered in [2], demonstrated a deterioration of RV function with time. Experiment 2 revealed that at 10 weeks of age LV mass was still unaffected (WT: 84±15µl R6/2: 79%14 µl). No significant difference in LVEF (WT: 73%±4 R6/2: 69%±5) or RVEF (WT: 74%±5 R6/2: 75%±4) was present between WT and R6/2 at baseline. Under stress, RVEF dropped significantly to pathological values in the R6/2 mice while it did not in the WT controls, as shown in Figure 3. There was not a significant difference in the effect dobutamine on LV function between groups.

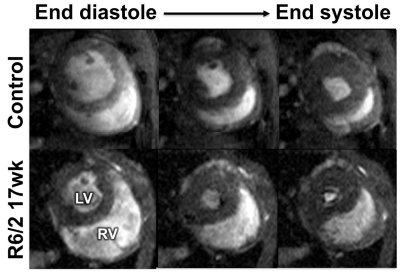

Figure 1 Short axis slices through systole showing impaired RV function in R6/2 mice.

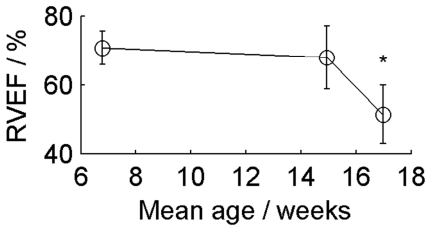

Figure 2 Decrease in RVEF of R6/2 mice as disease progresses, from experiment 1. *=p<0.05 (paired *t*-test comparison with previous timepoint; error bars show ±SEM).

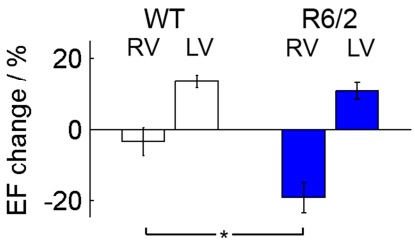

Figure 3 Changes in RV and LV ejection fraction due to dobutamine stress test, from experiment 2. *=p<0.05 (two samples *t*-test; error bars show ±SEM).

Discussion and conclusions

These data add to previous findings of LV pathology in the R6/2 mice by showing that RV function is also impaired. Importantly, these changes can be unmasked in young, otherwise asymptomatic animals with the beta-adrenergic agonist dobutamine. This finding suggests that cardiac abnormalities are not a symptom of generalised muscle loss seen in HD but represent specific cardiac dysfunction in this model. More detailed study of the mechanisms behind these changes may help elucidate the increased mortality seen in HD patients from heart disease.

References

[1] Van der Burg et al. *Lancet Neurol* 2009 8(8): 765–74 [2] N I Wood et al. *Journal of Huntington's Disease* 2012 1(1): 65–72
[3] F Weissmann et al, *Am J Physiol Heart Circ Physiol.* 2002 Sep;283(3):H1065-71.