Temporal evolution of cardiac function in mice with myocardial hypertrophy and heart failure

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Introduction
Heart failure (HF) is a progressive disease, which forms a considerable burden to patients in terms of suffering and to society in terms of costs. HF is often caused by systemic hypertension or aortic valve stenosis, resulting in a pressure overload of the left ventricle (LV). Thoracic aortic constriction (TAC) in mice is considered an important murine model to study this pathology. Many preclinical studies utilizing this animal model have focused on end-stage HF. To gain valuable information on various aspects of the disease process and their relevance for the progression of the disease, it is also of great interest to specifically study the transition from compensated hypertrophy to decompensated, end-stage HF. Therefore, the aim of this study was to characterize the temporal evolution of cardiac function in mice in a model of mild constriction of the aorta, resulting in compensated hypertrophy, as well as in a model of severe constriction causing end-stage HF.

Methods

Experiments: C57BL/6 mice (♂, age 12 weeks) underwent a transverse aortic constriction (TAC) to induce LV pressure overload. Animals were subjected to a mild (using a 25G needle, Ø 0.50mm; n=3) or severe constriction (using a 27G needle, Ø 0.42mm; n=9). Age-matched littermates (n=4) were used as controls. MRI measurements were performed at multiple time points starting 1 week post surgery until the age of 22 or 25 weeks. Cardiac function was characterized from cine MR images acquired at 9.4T. Images were obtained using an ECG triggered and respiratory gated FLASH sequence in 2 long-axis and 5 short-axis slices. Short-axis interslice distance was optimized to cover the complete LV. Imaging parameters were: TR = 3.7 ms, TE = 1.8 ms, NSA = 6, α = 15°. FOV = 3x3 cm², matrix = 192x192, slice thickness = 1 mm, number of cardiac frames = 15-18. Data analysis: The myocardial wall was segmented semi-automatically in the cine MR images using CAAS MRV FARM (Pie Medical Imaging, The Netherlands) to obtain LV and right ventricular (RV) volume, and the LV and RV ejection fraction. LV tissue density was assumed to be 1.04 g cm⁻³ to calculate LV mass. LV mass was normalized to tibia length to obtain an independent measure of hypertrophy. An ANOVA for repeated measures or a 1-way ANOVA followed by Tukey’s HSD post-hoc test (SPSS 16.0) was used to test for statistical significance, with p-values less than 0.05 considered statistically significant.

Results

All mice in the control group and the mild aortic constriction group finished the complete experimental protocol. Three of the mice with a severe stenosis of the aorta died in the period 4-10 weeks post surgery, most probably due to acute decompensated HF. Figure 1 shows typical examples of short and long axis images obtained in the different experimental groups. Note increased wall thickness in the animals with an aortic constriction, and LV dilation in the animals with a severe constriction. Mice with a mild stenosis of the aorta showed a small increase of LV mass normalized to tibia length as compared to controls (p>0.05, Figure 2a). LV EF was slightly depressed as compared to controls (p>0.05, Fig. 2b). For both parameters no changes over time were observed (p>0.05). Animals subjected to a severe constriction showed a progressive increase of LV mass (p<0.001) accompanied by a progressive decline of EF (p<0.001). Starting from the age of 16 weeks akinesia was detected in a subset of these mice (n=3) at the apical side of the heart (black arrow, Fig. 1) accompanied by dilation of the LV wall. Moreover, a progressive decline of RV EF was observed in mice with a severe constriction (Figure 2c, p<0.001). Furthermore, lung edema was observed in the mice with a severe aortic constriction, indicated by an increased lung-to-body weight ratio as compared to controls and animals with a mild constriction (p<0.01, Fig. 2d).

Conclusion

In this study two different degrees of aortic constriction in mice were used to obtain murine models of compensated hypertrophy, and of decompensated HF. MRI measurements were performed to quantify the temporal evolution of right and left ventricular function in these models. Mice with a mild aortic constriction showed myocardial hypertrophy and a depressed LV ejection fraction. Only mice subjected to a severe constriction showed progressive LV hypertrophy accompanied by a decline in LV function. Moreover, these mice showed a progressive decline of RV function, which was accompanied by pulmonary edema. Taken together, these results are in accordance with end-stage, overt HF. The different disease progression between both animal models opens unique opportunities to study interventions, and to study different aspects of myocardial hypertrophy during the transition from compensated hypertrophy towards overt HF.

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References