Detection of transient cardiac hypertrophy induced by isoproterenol in mice

H-W. Chen[1], K-C. Yang[1], C-F. Cheng[1], and C. Chang[1]

[1]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

Synopsis

Treatment of animals with isoproterenol (Iso) results in cardiac hypertrophy, myocyte necrosis and interstitial cell fibrosis. The objective of the present study was to examine the time course of the low-dose isoproterenol-induced transient cardiac hypertrophy in mice by using high temporal and spatial ECG-triggered fast FLASH cine MRI. Subtle changes of left ventricle (LV) morphology in transient hypertrophy were observed that would be helpful to gain better understanding of the compensatory and reparative response in reversible physiological hypertrophy.

Introduction

Left ventricle hypertrophy (LVH) is associated with significant excess mortality and morbidity. Cardiac hypertrophy can cause by either physiological or pathological stimuli. Physiological stimuli such as exercise lead to compensatory growth of the heart that is characterized by normal cardiac structure with improved cardiac function and reversible changes in cardiac gene expression pattern. Whereas, the pathological hypertrophy results in heart failure and myocyte fibrosis. Thus, there may be similarities and differences in physiological and molecular mechanisms underlying pathological and physiological LV hypertrophy. Cardiac MRI (CMR) not only has the capability of acquiring tomographic images of hypertrophied LV chamber with tissue contrast and border definition, but also provides high-resolution and nonoblique images with excellent and uniform contrast at endocardial borders, encompassing all levels and regions of the LV and permitting virtually complete reconstruction of the chamber. Therefore, CMR imaging has the potential to precisely measure LV mass and detect wall thickening in any area of the LV wall, even when these regions are quite limited size, and therefore can provide critical supplemental morphological information. In the present study, to better understand the process into physiological or pathological cardiac hypertrophy, we employed ECG-triggered FLASH cine MRI method and low-dose Iso (1.5mg/kg) induced transient LVH in mice to investigate the temporal relations between LV wall thickening and myocardial fibrosis.

Materials and Methods

MRI Protocols: Cine MRI was performed at D0, D2, D4, D7, D9 and D14 after mice were treated with Iso on a 7 T-PharmaScan (Bruker, Germany) under inhalation anesthesia applied by nose cone (1.7% isoflurane supplement by 1 l/min oxygen). ECG-triggered fast gradient echo (FLASH) cine sequence was used with the following imaging parameters: flip angle was 40°, echo time was 2.3 ms, repetition time 10.7 ms, field-of-view was 3 cm, Matrix=256*128 and slice thickness was 1 mm. The short axis is identified by first piloting the vertical long axis (VLA) plane from axial images, passing through the center of the mitral valve of the LV. On the VLA image, a horizontal long axis (HLA) plane is then obtained perpendicular to the VLA, again passing through the center of the mitral valve and apex. From the HLA, there will be derived two images of sagital and coronal planes passed through the apex.

Data Analysis: The image stack can provide volume information by summing the outer-cardial area on each slice to derive left ventricular volumes. Data analysis was performed using ParaVision 4.0 (Bruker, Germany). Left ventricular slice volumes were determined from end-diastolic images by multiplication of compartment area and slice thickness (1 mm). Total volumes were calculated as *Cine MRI* the sum of all slices.

Animals: A total of 6 mice (129), aged 10-12 wk and weight 26-33g, was used in the study. Isoproterenol hydrochloride (Sigma, St. Louis, Missouri) was prepared in isotonic phosphate buffer saline (PBS). Animals were assigned to receive Iso (1.5 mg/kg) and control mice received saline (6 ul/g).

Histology: Hearts were immersion fixed with 10% buffered formalin and axial cross sections were made of LV. These sections were stained with Masson trichrome

Results and Discussion

Fig.1 shows typical short axis cardiac MRI and histology sections. The images provide a qualitative indication of LV morphology. The LV walls after Iso injection were thickening (Fig.1b) at D4 in comparison with D0 (Fig.1a) and recovered LV walls were observed at D14 (Fig.1c). The corresponding histology showed some of Iso-treated group with slightly fibrosis (Fig.1h) but not in most of cases (Fig.1i). The results suggested that the LV wall thickening resulted from physiological hypertrophy. The temporal changes in LV mass reconstructed from short axis cardiac MRI sections after Iso-treated were shown in Fig.2. The changes in LV mass were paralleled to the LV walls. In comparison with control group, Iso-treated hypertrophy of surviving LV myocardium increase 16% in LV mass from D0 to D4. The shift of time-volume curves toward large volumes was associated with global or regional LV wall thickening, a sign of a failing heart after Iso-treatment. After D4, the LV mass of Iso-treated mice decreased and continued throughout. These mass-time curves demonstrate that the low-dose Iso-treated hypertrophy is not only transient but also reversible.

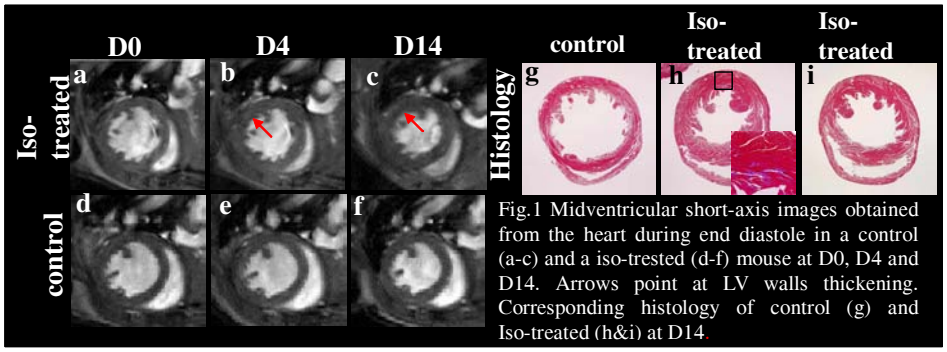

Fig.1 Midventricular short-axis images obtained from the heart during end diastole in a control (a-c) and a iso-trested (d-f) mouse at D0, D4 and D14. Arrows point at LV walls thickening. Corresponding histology of control (g) and Iso-treated (h&i) at D14.

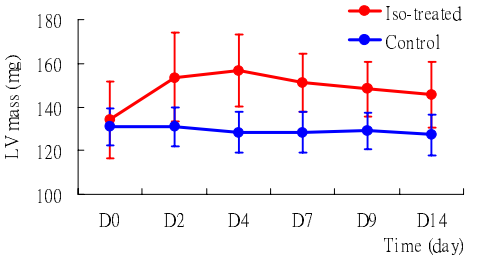

Fig.2 Time-mass curves of the LV mass in control (blue) and Iso-treated (red) mice. *y*-axis is the LV mass; *x*-axis is the time after treatment.

Conclusion

Our present study demonstrates that ECG-triggered FLASH cine sequence allows for serial and non-invasive imaging and calculation of the LV function in a mouse to study the transient cardiac hypertrophy induced by Iso injection. Treatment of mice with low-dose Iso provided an animal model for investigating in transient and reversible cardiac physiological hypertrophy.

Reference

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