Multi-modal cardiac MRI monitoring of the effect of isoproterenol on myocardial perfusion, function and morphology

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Introduction

Calcium overload induced by chronic administration of isoproterenol (IP), a β-adrenoreceptor agonist, is used in animal models to study the mechanisms of cardiac hypertrophy and failure (1). Cine MRI has been used in the past to show cardiac hypertrophy produced IP in mice (2-4).

To better understand the mechanisms involved in the morphologic changes induced by IP, time-dependent changes in myocardial perfusion were assessed in rats *in vivo* along with morphologic and functional parameters using multimodal cardiac MRI during continuous administration of IP.

Materials and Methods

A group of 10 healthy male Wistar rats (age 10 weeks) received continuous administration of IP (5mg/kg/day) and ascorbic acid (10mg/kg/day, used to stabilize IP) by an implanted mini-osmotic pump (Alzet). A control group (N=8) received only ascorbic acid at the same dose. Three MRI examinations were performed at day 1, 2 and 7 after pump implantation. Animals were positioned prone on an actively decoupled surface coil (Rapid Biomedical, Rimpar, Germany) and inserted into a 4.7T/30 horizontal Magnet (Bruker, Ettlingen, Germany). ECG and breath were monitored and used for double-gating using a Rapid Biomedical ECG trigger unit.

A cine-MRI sequence (FOV 4cm, slice thickness 2mm, matrix size 128x128, TE=1.2ms, TR=5.1ms, approx. 35 phases per cardiac cycle) was used to determine cardiac function along three planes carefully positioned perpendicular to the main cardiac axes. A gradient-echo FAIR Look-Locker arterial spin labeling technique (5) was used to assess myocardial perfusion at all three stages (FOV 4cm, slice thickness 3mm, matrix size 128x64). Cardiac morphology and function were measured using an ellipsoid model based on manually delineated ventricular areas (short axis) and ventricular lengths (long axis).

Results

IP group LV mass was increased after 1 day, and maintained throughout the study. Similarly, the wall thickness was increased in the IP group with a peak at day 2 and a tendency to more basal values at day 7. In contrast, EDV in the IP group was only increased at day 7. LVEF was increased in the IP group (90 ± 4 %, all stages pooled) versus the control group (68 ± 9 %) over the entire time range observed. Similarly, cardiac output was increased by 35% at all measurement stages, whereas stroke volume progressively increased up to day 7. All MBF values were comparatively high. IP MBF was dramatically increased at day 1 and returned to values similar to those found in the control group between day 1 and day 2.

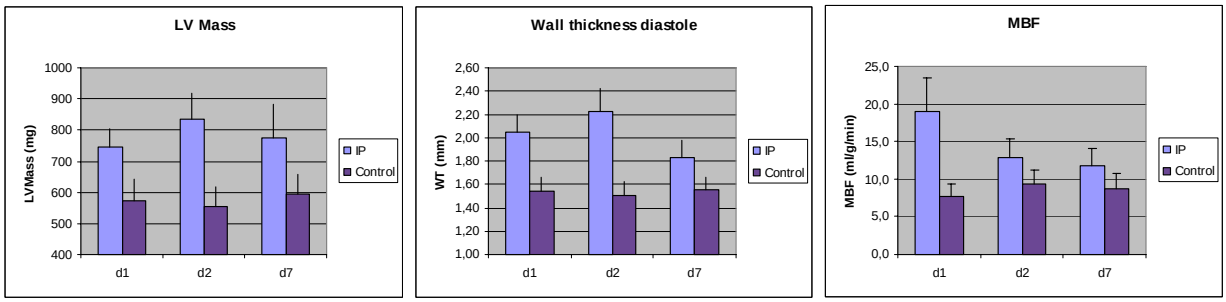

Figure 1: Longitudinal changes in cardiac morphology and myocardial perfusion (means±SD) with IP infusion

Discussion

These results show that isoproterenol dramatically increases cardiac work inducing morphologic changes in the heart within the first 24 hours of isoproterenol administration. The high initial MBF indicates high myocardial oxygen demand during this period as well as the beginning of ventricular adaptation at day 2, since MBF subsequently returns to almost normal values, whereas cardiac output remains high. The increase in EDV and evidence of wall thinning by 7 days of IP infusion indicate dilatation of the left ventricle. The globally high MBF values are likely to be a consequence of both isoflurane anesthesia and ascorbic acid, which is a potent antioxidant.

Conclusion

Longitudinal multimodal MRI has shown that IP administration results in rapid hypertrophy, and a chronic increase in cardiac function. The maintenance of function is unexpected as chronic infusion of IP at the levels of this study should result in downregulation of β-adrenergic receptors (6). The dramatic increase in MBF with onset of IP infusion is not sustained, and this indicates a mismatch between cardiac function and perfusion that might play a major role in the process of ventricular adaptation.

References: (1) Boluyt MO et al, Am J Physiol. 1995;269(2 Pt 2):H638-47. (2) Slawson SE et al, Magn Reson Med. 1998;39(6):980-7. (3) Asemu et al., Proc. ISMRM 2007. (4) Chen et al, Proc ISMRM 2007 (5) Kober F et al, Magn Reson Med. 2004;51(1):62-7. (6) Brouri F et al, Eur J Pharmacol. 2002 :5 ;456 :69-75