In vivo cardiac MRI detects differential response to partial and complete Akt1 deficiency

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Introduction

The PKB/Akt family of intracellular protein kinases regulates cellular growth, proliferation, survival and metabolism. It is known that Akt1/PKBα controls heart size and function. Akt1/PKBα knockout mice and their cardiomyocytes were shown to be smaller than their wild type equivalent (Chen et al., 2001; Easton et al., 2005). Akt1/PKBα knockout mice were reported to be resistant to development of exercise-induced physiological hypertrophy and their contractile function is impaired in Akt1/PKBα deficient animals after exercise training (De Bosch et al., 2006).

Methods

Three male PKBalpha/Akt1 wild type (+/+), 3 heterozygote (+/-) and 3 knockout (-/-) mice on C57Bl/6 background were imaged at 10 weeks old. Imaging was performed at 9.4T (Bruker BioSpec, Germany) using a linear resonator for excitation and an actively decoupled 2-cm surface coil for detection. Body temperature was maintained around 36.0ºC, and anesthesia was maintained using 1.25% isoflurane in oxygen inhaled through a nose cone. During scanning, heart rate and respiration were monitored using a fiber optic, MR compatible system (Small Animal Imaging Inc., Stony Brook, NY, USA). Baseline left ventricular (LV) structure and function were assessed using retrospectively reconstructed FLASH cine scans with the aid of navigator scans (IntraGateFLASH, Bruker, Germany). Six short-axis slices were acquired from base to apex, with slice thickness 1mm, FOV 2x2mm; matrix 256x128 with zerofilling to 256x256. Baseline left ventricular mass (LV Mass), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), stroke volume (SV) were measured from the cine images using Segment. Mass-to-volume (MVR) was calculated as a ratio of LVM to EDV. LV Mass/ body mass is a parameter for hypertrophy.

	Wild type (n=3)	*Heterozygote (n=3)*	*Knockout (n=3)*
Weight (g)	27 ± 0.6	23 ± 1.3*	20.6 ± 0.3*
Heart rate (bpm)	507 ± 6	405 ± 20*	405 ± 23*
Temperature (ºC)	36 ± 0.2	36.2 ± 0.3	36.1 ± 0.2
LV Mass (µl)	86.2 ± 1.8	96.5 ± 6.3	72.2 ± 4.2*
LV Mass (mg)	90.5 ± 1.8	101.4 ± 6.6	75.8 ± 4.4*
EDV (ml)	47.1 ± 3.4	40.3 ± 3.9	37.8 ± 3
ESV (ml)	17.1 ± 1.6	12.9 ± 1.2	17.8 ± 2
SV (ml)	30 ± 2.8	27.4 ± 2.9	20 ± 3.4
EF (%)	63.5 ± 2.7	67.8 ± 1.3	52.6 ± 6.2
CO (ml/min)	15.2 ± 1.6	11.2 ± 1.6	8.0 ± 0.9*
MVR (mg/µl)	1.9 ± 0.1	2.5 ± 0.1*	1.9 ± 0.1
LV Mass/body mass (mg/g)	3.4 ± 0.1	4.4 ± 0.3*	3.4 ± 0.14

Table 1. Baseline LV structure for PKBalpha/Akt1 wild type, heterozygote and knockout (*P<0.05).

Results

Cine FLASH (Fig. 1) confirmed that LV mass in knockout mice was reduced, consequently also cardiac output (CO) was reduced (Table 1). Relative to the body mass, LV mass was not reduced in these mice, since the knockout mice are smaller in general. Additionally, heart monitoring during anesthesia shows a lower heart rate in knockout and heterozygotes. Mass-to-volume (MVR) and LV Mass/body mass are significantly increased, which indicated hypertrophy. Under anesthesia, the heart rate of both heterozygote and wild type appeared reduced.

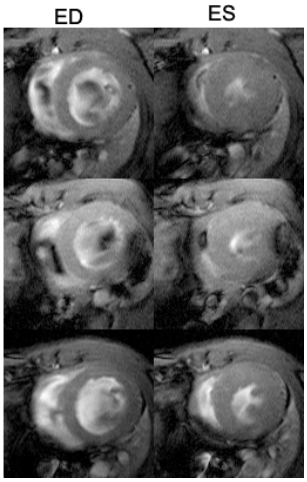

Fig 1. White-blood mid-ventricular short-axis end-diastolic (ED) and end-systolic (ES) of PKBalpha/Akt1 wild type (+/+), heterozygote (+/-) and knockout (-/-) mice.

Discussion

Here, we showed in vivo, that LV mass and cardiac output are reduced in knockout animals. This reduction is consistent with the reduced body weight. Surprisingly, cardiac hypertrophy observed here by MRI of heterozygote mice, and noted also previously by ultrasound, was resolved in the full Akt1 knockout. Previous studies (De Bosch et al., 2006) were performed with echocardiography, without ability of 3D cardiac data. These results raise the possibility for a compensatory role for Akt2 and 3 under conditions of total Akt1 deficiency.