In vivo 2D mapping of cardiac high energy phosphates in the mouse

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Introduction

^{31}P MRS studies of the human heart have shown that certain cardiac diseases are associated with a decrease of the normal PCr/ATP ratio of 1.8-2.0[1,2]. It is, therefore, of particular interest to determine this parameter also in transgenic mouse models of cardiomyopathies. *In vivo* ^{31}P MRS of the small mouse heart has yet been used only at relative low magnetic field strength (up to 4.7 T) with limited spatial resolution not allowing energetic measurements in different areas of the murine heart[3,4]. In the present study, we examined for the first time acquisition-weighted 2D ^{31}P CSI in the mouse heart at a field strength of 9.4 T and employed this 2D approach to analyze cardiac energetics of a recently described murine hypertrophy model characterized by ventricular dilatation and interstitial fibrosis[5].

Methods

Experiments were performed at a vertical Bruker DRX Wide Bore NMR Spectrometer operating at frequencies of 400.1 MHz for ^{1}H and 161.97 MHz for ^{31}P measurements. *In vivo* experiments (MRI, 2D CSI) were performed under isofluran anaesthesia (1.5 %) at 37 °C using a Bruker Microimaging unit (Mini 0.5) equipped with an actively shielded 57-mm gradient set (200 mT/m maximum gradient strength, 110 µs rise time at 100% gradient switching) and a double tuned ^{1}H/^{31}P 38-mm birdcage resonator. After evaluation of cardiac function using an ECG- and respiratory-triggered cine FLASH sequence (FOV 3×3 cm^2, *in plane* resolution 117×117 µm^2, slice thickness 1 mm, 6-8 contiguous slices), cardiac energetics was determined by an acquisition-weighted (sine-bell) 2D ^{31}P CSI sequence (16×16 matrix, voxel size: *in plane* 1.8×1.8 mm^2 × slice thickness of the heart, flip angle 45°, repetition time 250 ms, total acquisition time 75 min). Spectra of tissue extracts from excised, snap-frozen hearts were recorded using a 10-mm ^{1}H/^{31}P dual probe.

Results and Discussion

As shown below for the anterior wall of the left ventricle and the septum, ^{31}P MR spectra of good quality could be acquired from the entire thorax of the mouse with high spatial resolution at defined regions of the heart (Fig. 1). Spectra of the septum and the anterior wall showed some contamination with signals from the blood (Fig. 1, spectra 1 *vs.* 2). 2D data sets were quantified after application of appropriate correction factors (blood + partial saturation) using a self-developed software module (LabVIEW) in direct correlation to the morphological ^{1}H MR image. Analysis of a transgenic cardiomyopathy model (double mutant: cardiospecific iNOS overexpression and lack of myoglobin (TGiNOS/myo$^{-/-}$)[5]) revealed that cardiac dysfunction (EF: 53.9±3.8%) was associated with an impaired energy homeostasis (PCr/ATP 1.54±0.18) over the entire left ventricle (WT: EF 69.7±3.5%, PCr/ATP 2.06±0.22, n=5, P<0.05). The spectroscopic data acquired *in vivo* were validated against ^{31}P MR spectra of perchloric acid extracts from the same hearts (PCr/ATP: 1.87±0.21 (WT), 1.39±0.17 (TGiNOS/ myo$^{-/-}$), n=5, P<0.05).

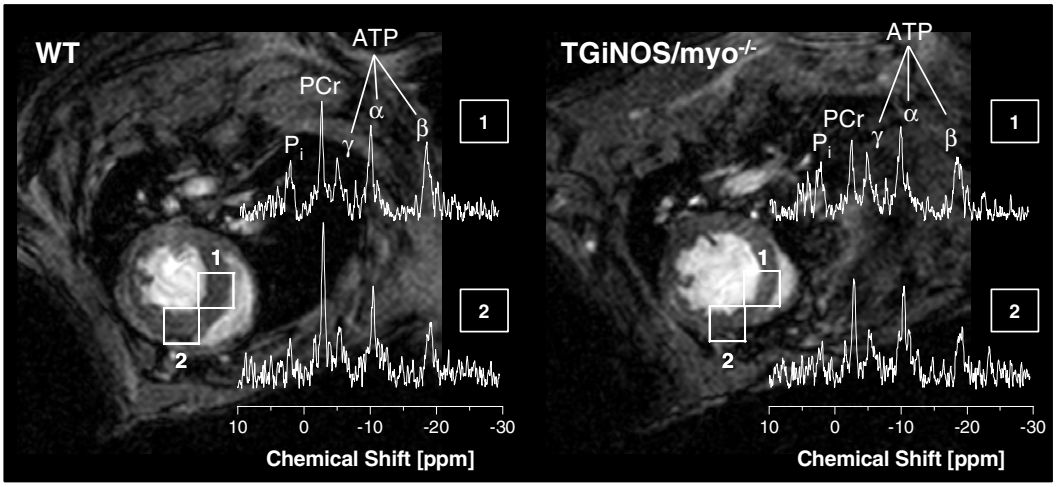

Figure 1: Axial ^{1}H MR images (FOV 3×3 cm^2) in diastole and corresponding spatially localized ^{31}P MR spectra of WT (left) and TGiNOS/myo$^{-/-}$ (right) mice. Representative spectra of the septum (1) and the anterior wall (2) show that impaired cardiac function in TGiNOS/myo$^{-/-}$ mice is accompanied by a decreased PCr/ATP ratio. Voxel size of ^{31}P MR spectra: *in plane* 1.8×1.8 mm^2 × slice thickness of the heart (6-8 mm); total acquisition time of the full 2D ^{31}P CSI data set was 75 min; exponential line broadening of 20 Hz.

In conclusion, the presented method allows the noninvasive, repetitive measurement of cardiac anatomy and function together with the regional energy state in transgenic mouse models in one experiment.

References

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