In Vivo ^{17}O MRS Imaging for Assessing Myocardial Oxygen Metabolism in Rat Heart at 9.4T

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Introduction Besides brain, heart is another highly aerobic organ consuming large amount of oxygen. The oxygen metabolism, which is tightly associated with the energy generation in the form of ATP, is essential for supporting myocyte contraction/relaxation in performing mechanical work in hearts. It is, thus, important to exploit imaging approaches capable of noninvasively mapping the myocardial oxygen metabolic rate (MVO_2) in living hearts. Although the established ^{15}O-PET has been successful in imaging cerebral oxygen metabolic rate ($CMRO_2$) in human and large animal, its applicability in imaging MVO_2 has not been established, especially in small animals with a much smaller heart size, which could beyond the ultimate spatial resolution of ^{15}O-PET. Recently, *in vivo* ^{17}O MRS imaging (MRSI) approach [1] has been successfully applied at ultrahigh field for imaging and quantifying $CMRO_2$ in three dimensions in rat and cat brains with a few minutes inhalation of ^{17}O-labeled oxygen gas ($^{17}O_2$) [2-3]. In the present study, we exploit the feasibility of 3D ^{17}O MRSI for noninvasively assessing and imaging MVO_2 in the rat heart with a brief (2-3 minutes) inhalation of $^{17}O_2$ at 9.4T under basal and high workload conditions.

Method Artificial ventilation and gaseous anesthesia (2 % isoflurane in a mixture of 70% nitrous oxide and 30% oxygen) were applied to rat heart studies conducted on a 9.4T horizontal animal magnet (Magnex Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA). In general, it is challenging to obtain a superior ^{17}O MR signal-to-noise ratio (SNR) in the rat heart due to its small organ size and deep location in the chest. To overcome this limitation and achieve adequate sensitivity for obtain 3D ^{17}O MRSI within a short imaging time of ~10 s, we have utilized a RF coil configuration consists of two electrically decoupled coils. A small ^{17}O surface coil (~1 cm diameter) with electric isolation was inserted into the rat chest via thoracotomy and placed between the chest wall and the heart; and a half-volume ^{1}H RF coil was wrapped around rat body while the animal was in prone position. Fourier series window (FSW) approach was applied to acquire 3D ^{17}O MRSI data with following acquisition parameters: spectral width=30 kHz; FOV=3×3×2.5 cm^3, 9×9×5 phase encodes, image voxel size = 123 μl (equivalent to nominal voxel size of 31 μl); 11 s per 3D MRSI volume. A 2-3 minutes of $^{17}O_2$ (89% ^{17}O enrichment) inhalation was used for imaging MVO_2 under either basal or high workload condition via bolus injection of 40μg/kg dobutamine and dopamine.

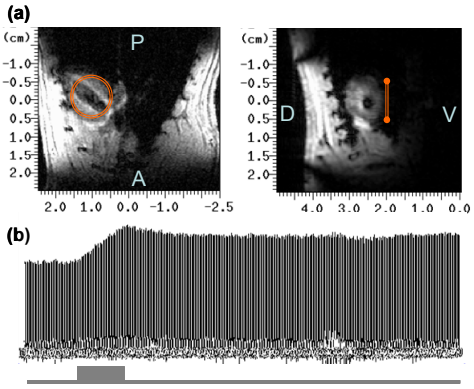

Fig. 1 (a) ^{1}H MRI of rat chest and heart in axial (left panel) and sagittal (right panel) orientation, and the ^{17}O surface coil location. (b) Stack plot of global heart ^{17}O water signals acquired before, during (grey bar) and after the inhalation of $^{17}O_2$ gas.

Results and Discussion Figure 1a shows the ^{1}H images of rat chest, including heart and other adjacent tissues. The position of the ^{17}O surface coil is also marked in the images (orange line and circle), indicating its close proximity to the heart for detecting localized ^{17}O signal mainly attributed by the myocardium. Figure 1b illustrates a stack plot of global myocardial ^{17}O water ($H_2{}^{17}O$) signals with superior sensitivity acquired before, during and after an inhalation of $^{17}O_2$ gas using extremely high temporal resolution of 3 s per spectrum. There are three distinct phases reflecting the $H_2{}^{17}O$ signal changes. The first phase (prior inhalation) measures the ^{17}O natural abundance water signal from myocardium and this signal is useful to calibrate the absolute $H_2{}^{17}O$ concentration in myocardium and quantify MVO_2. The second phase shows a rapid accumulation of myocardial $H_2{}^{17}O$ content, which is likely dominated by the ^{17}O-labeled waters generated by the myocardial $^{17}O_2$ metabolism in mitochondria; and the accumulation rate should tightly correlated to the MVO_2. The third phase shows the $H_2{}^{17}O$ signal decay after the termination of $^{17}O_2$ inhalation due to the washout of the $H_2{}^{17}O$ water from myocardium; and the decay rate (k = 0.56 min^{-1} for this measurement) is related to the myocardial blood perfusion. The pattern of the three phases observed in the rat heart is similar with that of rat brain [3]. Although significant research efforts are necessary for establishing a MVO_2 quantification method, for preliminary testing purpose we adapted the 2nd-order polynomial fitting algorism [4] previously developed for calculating $CMRO_2$ in the rat brain to estimate MVO_2 value. It resulted in a global myocardial MVO_2 of 1.9 μmol/g/min in the rat studied herein.

Figure 2 illustrates the results from another rat study, showing the co-registered ^{1}H heart image (Fig. 2a) and one representative 3D ^{17}O MRSI of ^{17}O natural abundance water signal mainly from myocardium. An excellent ^{17}O sensitivity is evident for imaging the myocardial natural abundance $H_2{}^{17}O$ *in situ* using the 3D MRSI with a temporal imaging resolution of 11 s. Figures 2c and 2d illustrate the stack plots of myocardial ^{17}O water signals detected from a single voxel cycled in Fig. 2b before, during and after a 2-3 min inhalation of $^{17}O_2$ under: (c) basal and (d) high workload conditions, respectively. The estimated MVO_2 and $H_2{}^{17}O$ decay rate, k, measured in the voxel located inside myocardium were 1.4 μmol/g/min and 0.34 min^{-1} under basal condition, and 2.7 μmol/g/min and 0.60 min^{-1} under high workload condition, suggesting an approximately 100% increase in both myocardial oxygen consumption rate and perfusion with increased myocardial workload. This result demonstrates a tight coupling between metabolic and perfusion changes in the heart; and it also reveals that the *in vivo* ^{17}O MRSI approach is sensitive for imaging the myocardial metabolic and perfusion changes at high field.

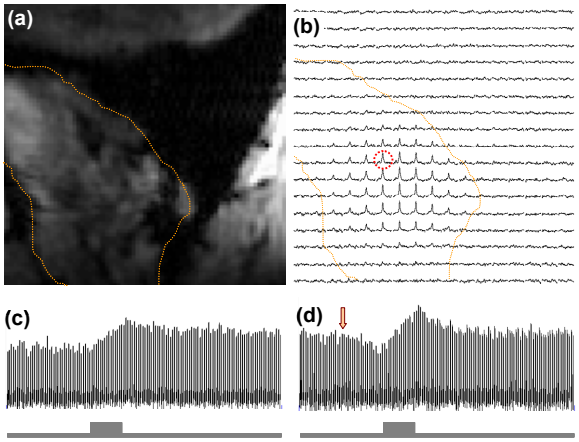

Fig. 2 (a) ^{1}H MRI of rat chest and heart outlined by the orange line. (b) One representative 2D ^{17}O spectra image of myocardial ^{17}O natural abundance water taken from 3D MRSI data. (c) and (d) Stack plots of myocardial ^{17}O water signals of a single voxel (red circle) acquired before, during (grey bar) and after an 2-3 min $^{17}O_2$ gas inhalation under (c) basal and (d) higher workload conditions, respectively (the orange arrow indicates the start of high workload).

Conclusions This preliminary study demonstrates the unique utility of high-field *in vivo* ^{17}O MRSI approach for noninvasively assessing MVO_2 in small animals; and the high sensitivity for obtaining 3D MVO_2 images with a few minutes of $^{17}O_2$ inhalation. It is highly feasible to establish a noninvasive imaging modality using *in vivo* ^{17}O MRSI and proper quantification modeling for simultaneously imaging MVO_2 and myocardial perfusion. This should provide new opportunities for studying myocardial bioenergetics associated with cardiac function and dysfunction.

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References [1]Mateescu et al, *ISMRM*, p659, 1989; [2]Zhu et al, *NMR Biomed,* 2005; [3]Zhu et al, *PNAS,* 2002; [4]Zhang et al, *JCBFM*, 2004.