Non-invasive quantification of hepatic metabolic rate of oxygen (HMRO2) by MRI

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Fig. 1: Relationship between physiologic parameters in oxygen demand and supply

INTRODUCTION: The liver receives 25% of the total resting cardiac output and consumes 20% of the total resting oxygen consumption (1). Thus, hepatic metabolic rate of oxygen, $HMRO_2$, is an important marker for liver function. Unfortunately, *in vivo* measurement of $HMRO_2$ in humans has proven challenging. There were occasional reports in the literature using invasive methods (e.g. hepatic biopsy or catheter) to determine $HMRO_2$ (2, 3), but none has been used widely. The goal of our study is to develop a global $HMRO_2$ method that is non-invasive (no exogenous agent), relatively fast (<15 min), and can be used on a standard 3T MRI. This work was built upon our previous technical development studies to measure oxygen metabolic rate in the brain (4).

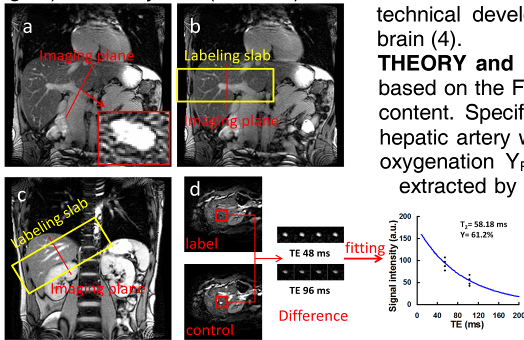

Fig 2. Representative results of HMRO2 scans

THEORY and PULSE SEQUENCES: The theory of measuring $HMRO_2$ is based on the Fick principle, in which global $HMRO_2$ can be quantified from arterio-venous difference in oxygen content. Specifically for the hepatic system, the liver receives oxygen supply from two types of vessels: 1) hepatic artery with flow rate of F_{HA} and oxygen saturation fraction Y_{HA}; 2) portal vein with flow rate of F_{PV} and oxygenation Y_{PV} (Fig. 1). When the oxygen molecules pass through capillaries, a fraction of them will be extracted by tissue (Fig. 1) for its use, the rate of which is HMRO2. The rest will be drained through hepatic veins which has a flow rate of F_{HV} (=F_{HA}+F_{PV}) and an oxygenation of Y_{HV} (Fig. 1). The $HMRO_2$ can then be calculated as:

$$HMRO_2 = \frac{[F_{PV} \cdot Y_{PV} + F_{HA} \cdot Y_{HA} - (F_{PV}+F_{HA}) \cdot Y_{HV}] \cdot C_a}{V} \quad [1]$$

where the term in the bracket represents the calculation of the arterio-venous differences as depicted in Fig. 1, C_a is the oxygen-carrying capacity of blood, V is the volume of the liver (which can be measured from anatomic scans). Y_{HA} in Eq. [1] represents arterial oxygenation and can be assumed to be 98% or measured using a pulse oximetry.

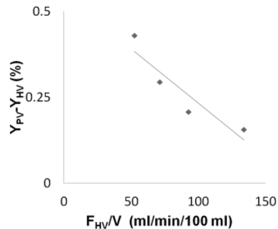

Fig 3. Y_{PV}-Y_{HV} is negatively correlated with F_{HV} per liver volume.

Thus, in Eq. [1], the parameters that need to be determined experimentally are F_{PV}, F_{HA}, Y_{PV}, and Y_{HV}. In our method, F_{PV} is measured with phase contrast (PC) MRI applied at the point where portal vein enters the liver (Fig. 2a). F_{HA} in principle can be determined in a similar manner. Unfortunately, hepatic arteries are known to show large variations in size and number across individuals and could not be reliably measured in every participant. Thus, we assumed it to be 1/3 of the flow in the portal vein, based on literature (5). Y_{PV} and Y_{HV} are assessed by a recently developed technique, T_2-Relaxation-Under-Spin-Tagging (TRUST) MRI. TRUST MRI is based on the principle that T_2 relaxation time of the blood has a well-known and calibratable relationship with Y, thus one can measure pure blood T_2 and then convert T_2 to Y using a calibration plot. TRUST separates pure blood signal by subtracting label and control images under spin-tagging principle (Fig. 2b). The label and control scans are T_2 weighted through different T_2 preparation pulses. The monoexponential fitting of the blood signal to the T2-preparation duration, TE, then gives the T_2 value of the blood (Fig. 2d).

METHODS: *Experiment:* A total of 9 healthy subjects (5 females, age=27±3 years old) were studied on a Philips 3T system to evaluate four aspects of the proposed technique. In 4 subjects, the completed $HMRO_2$ protocol was applied to estimate the normal $HMRO_2$ values. In 5 subjects, the reproducibility of PC MRI in portal vein was assessed. In 4 and 3 subjects, respectively, the reproducibility of TRUST MRI in portal vein and hepatic vein was assessed. For PC MRI on the portal vein, the following parameters were used: single slice, voxel size = 0.5*0.5*5 mm^3, FOV =280*280 mm, maximum velocity encoding = 40 cm/s, scan duration 1'40". TRUST MRI on portal vein was performed using the following parameters: voxel size = 1.96*1.96*5 mm^3, FOV = 220*220 mm,TR = 16000 ms, TE = 15 ms, TI = 800 ms, labeling slab thickness = 200 mm, labeling offset = 0 mm and 2 different T2 weightings, with TE= 48 and 96 ms, duration 5'32". TRUST on the hepatic vein used a similar protocol except that TI = 600 ms. *Data analysis*: For the phase-contrast data, a ROI was manually drawn on the velocity map to delineate the portal vein and the flux of all voxels inside the ROI were summed to yield the total flow in the vessel. For TRUST data, after the control and label images were realigned and subtracted. An ROI of 9 voxels were used for monoexponential fitting to obtain T_2. The T_2 was converted to oxygenation level using a calibration plot (6).

Parameter	Value
F_{PV}(ml/min)	920.4±271.7
Y_{PV}(%)	0.72±0.05
Y_{HV}(%)	0.45±0.15
Liver volume (ml)	1479.7±382.8
$HMRO_2$ (μmol/min/100 ml)	222.2±12.0

Table 1. Summary of results of HMRO2 measurements.

Measure	CoV
F_{PV}	0.08±0.03
Y_{PV}	0.06±0.04
Y_{HV}	0.18±0.12

Table 2. Coefficient of Variation (CoV) of repeated measures.

RESULTS and DISCUSSION: Fig. 2a shows the slice location of the PC MRI when applied on the portal vein, with the resulting image displayed in the inset. F_{PV} was obtained by summation of all voxels encompassing the vessel. Figs. 2b and 2c illustrate the locations of imaging slice and labeling slab in the portal vein TRUST and hepatic vein TRUST scans, respectively. A representative dataset for hepatic vein TRUST is shown in Fig. 2d. The subtraction of the control and label images yielded pure vessel signal, which decays exponentially with increasing TE (Fig. 2d). The time-constant of the decay curve corresponds to blood T_2 (Fig. 2d). Table 1 lists a summary of each experimental measure as well as the final $HMRO_2$ values (N=4). Our $HMRO_2$ values are in good agreement with literature that cited a normal value of 166 to 250 μmol/min/100 ml. It is also interesting to note that there appears to be correlation between flow and oxygen extraction fraction, in that an individual who has higher flow rate tends to have a smaller extraction fraction, defined by Y_{PV}-Y_{HV} (Fig. 3). This correlation has also been seen in the brain physiology literature (4).Coefficient of variation (CoV) of each of the experimental measures is listed in Table 2. As can be seen, the flow and oxygenation measures in the portal vein were more reliable (as indicated by smaller CoV) compared to hepatic vein. To our knowledge, the present work represents the first effort to quantify hepatic oxygen metabolism using completely non-invasive procedures. These preliminary results demonstrate a proof-of-principle for the proposed approach and provide a basis for further technical development in future research. In particular, the impact of the assumption on hepatic arterial flow (assumed to be 1/3 of portal vein at present) should be more carefully evaluated.

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