Exploring detection limits of cardiac ischemia using dynamic imaging of hyperpolarized 13C pyruvate

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Purpose: Hyperpolarized[1] ^{13}C pyruvate has been shown to be a promising tool for assessing metabolic alterations during cardiac ischemia. A decrease in pyruvate dehydrogenase (PDH) activity has been observed using this technique[2,3]. Using dynamic spatial-spectral imaging techniques[4], heterogeneity of myocardial metabolism can be studied and ischemic regions identified. Kinetic information on the underlying metabolic activities can be obtained by fitting the metabolite time series, extracted voxel by voxel from the dynamic images, with kinetic models to derive enzymatic rates. However, kinetic modeling is challenged by a tradeoff between Signal-to-Noise Ratio (SNR) and spatial resolution. In this work, we considered through simulation the detection limit of hyperpolarized ^{13}C metabolic imaging in identifying local myocardial ischemia depending on ischemic transmurality, SNR and image resolution. A numerical signal model based on a short axis view of the rat heart was implemented to simulate *in vivo* hyperpolarized ^{13}C dynamic images with a range of SNRs and spatial resolutions and a kinetic model of the conversion of pyruvate to bicarbonate was used to extract enzymatic reaction rates.

Methods: ^{13}C dynamic images of pyruvate and bicarbonate with a range of bicarbonate SNRs (3,6,10,12) and resolutions (2-0.25 mm) were simulated in Matlab using a mask obtained from *in vivo* high resolution ^{1}H images of the rat heart in short axis view (Fig. 1a). A temporal resolution of Δt=3s was chosen in the dynamic series. Transmural ischemia (18%, 40%, 64% and 100% transmurality) was simulated in the myocardial anterior segment in agreement with the left ventricle segmentation proposed by the American Heart Association[4] (AHA) (segment 3 in Fig. 1b). A kinetic model based on the modified Bloch equations[5] (Eqs.1 and 2) considering one-side exchange (pyruvate → bicarbonate) was implemented in Matlab. (1) $\frac{dP}{dt} = -(k_{pb} + r_{1p}) * P + U$, (2) $\frac{dB}{dt} = k_{pb} * P - r_{1b} * B$, where P and B are the hyperpolarized signal of pyruvate and bicarbonate, respectively. k_{pb} is the apparent rate constant of the metabolic conversions and $r_{1p} = \frac{1}{T_{1p}}$, $r_{1b} = \frac{1}{T_{1b}}$ with T_{1p} and T_{1b} decay time constants of the hyperpolarized signal of pyruvate and bicarbonate. U is the input function here modeled as a γ-variate function (Eq. 3). (3) $U = A(t - t_{arrival})^{alpha} * e^{\frac{(t-t_{arrival})}{beta}}$ where A, alpha and beta are parameters that characterize the shape of the input function, and $t_{arrival}$ is the time point of arrival of the pyruvate bolus. Eqs.1 and 2 were simultaneously solved using Matlab assuming zero signal at t=0 for all metabolites. The values for k_{pb} used to generate the synthetic ^{13}C dynamic curves were chosen in agreement with[7] where it was suggested that 45 min after reperfusion, the conversion of pyruvate to bicarbonate was reduced to 16.6% the control value. To study the percentage of transmural ischemia that is possible to detect using the kinetic model described above, a t-test was used to compare the values of k_{pb} obtained from all pixels using the kinetic model in the anterior segment of the left ventricle (ischemic segment) and those in a healthy segment for each simulated image. P values < 0.05 were considerate significant.

Results & Discussion: A representative series of simulated ^{13}C dynamic images is shown in Fig. 2 (2 mm resolution). In Fig.3 the resolution and the bicarbonate SNR needed to detect 18%, 40%, 64% and 100% transmurality in the anterior segment of the left ventricle are shown. Results suggest that for a bicarbonate SNR of 6 it is feasible to discern ischemia with 18% transmurality from healthy myocardium only if 0.75 mm resolution is achieved, whereas 1 mm resolution is sufficient to detect ischemia with 40% and 64% transmurality.

Conclusion: In this work we studied the percentage of transmural ischemia that is possible to be detected using pixel wise kinetic modelling of the data. The choice of the optimal SNR and resolution is crucial to discern ischemic myocardium from healthy myocardium. This study gives guidance for choosing the optimal tradeoff between SNR and resolution for hyperpolarized ^{13}C dynamic imaging when myocardial ischemia is studied.

References: **1.** Ardenkjaer-Larsen JH, et al. *Proc. Natl. Acad. Sci. U. S. A.* Sep 2 2003;100(18):10158-10163. **2.** Schroeder MA, et al. *Cardiovascular Research.* Apr 1 2010;86(1):82-91. **3.** Golman K, et. al. *Magnetic Resonance in Medicine.* May 2008;59(5):1005-1013. **4.** Lau AZ, et al. *Magnetic Resonance in Medicine.* Nov 2010;64(5):1323-1331. **5.** Cerqueira MD, et al. *J. Am.Soc. Echocardiogr.* May 2002;15(5):463-467. **6.** Day SE, et al. *Nat. Med.* Nov 2007;13(11):1382-1387. **7.** Lau AZ, et. al. *Magnetic Resonance in Medicine.* Jul 2012.

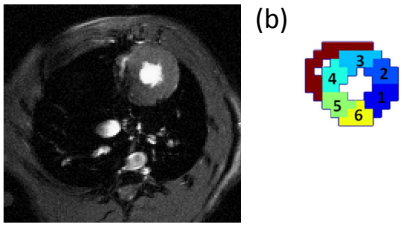

Figure 1: (a) Representative in vivo high resolution ^{1}H image of the rat hart in short axis view. (b) An example of AHA left ventricle segmentation for 2mm resolution. Segment (1) inferiolater, (2) anterolateral, (3) anterior, (4) anteroseptal, (5) inferoseptal, (6) inferior.

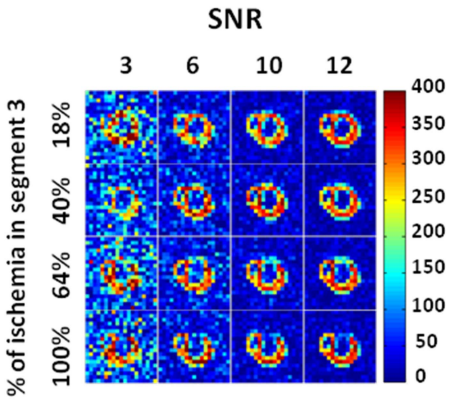

Figure 2: A representative series of simulated ^{13}C dynamic images for bicarbonate metabolism at t=42s. The resolution in this example is 2 mm.

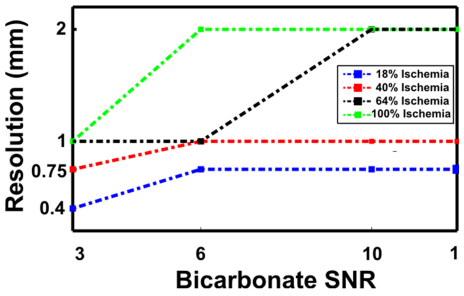

Figure 2: Minimum resolution required to observe significant difference in k_{pb} between ischemic and healthy myocardium for a range of SNR. 4 different percentage of trasmurality were simulated in the anterior segment of the left ventricle.