Kinetic modelling of ^{13}C Hyperpolarised Pyruvate Metabolism using Measured Arterial Input Function in Tumours

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Introduction

Intravenous (i.v.) administration of hyperpolarised ^{13}C pyruvate provides a means for quantifying pyruvate (PA)-lactate (LA) interconversion in living tissues via MRS/MRSI. This approach has potential for monitoring tumour cell viability and oxygenation following treatment. Mathematical models are required to extract kinetic parameters from the spectroscopy data. One or two-way exchange models utilising a hypothetical approximation to the actual arterial input function (AIF), e.g. a 'boxcar' function, have been commonly used to estimate the kinetic parameters of PA-LA interconversion from the data. Here, we develop methods for obtaining the direct AIF and determine the influence of the choice of AIF on estimates of the kinetic parameters associated with PA metabolism in tumours.

Methods

5ml/kg i.v. injections of ^{13}C-PA (using a custom MR compatible automated injector) were administered into anaesthetised BDIX rats, with a sub-cutaneously implanted P22 sarcoma. PA and LA signals were localised using a ^{13}C surface coil and slice selection. The ^{13}C time response curves were measured in slices containing the carotid artery and subsequently the tumour tissue. To validate the carotid artery measurements and to provide a direct AIF, separate experiments were performed where ^{13}C-PA was injected and the ^{13}C time response curve was measured in a well-mixed chamber embedded in a femoral artery cannula using automated blood withdrawal (Figure 1a). This signal was then corrected for pyruvate relaxation time, T_{1py}, residence time in the chamber and withdrawal rate. In separate experiments T_{1py} for PA and T_{1lac} for LA in blood were measured in the arterial cannula following the injection of either ^{13}C-PA or ^{13}C-LA. After 0.5ml blood withdrawal, blood flow was halted and the decaying portion of the signal was fitted to obtain the T_1 and the applied flip angle at that location. To determine whether PA-LA interconversion was a one- or two-way process, experiments (n=5) were performed where LA was injected and the signal measured at the tumour site and in the arterial cannula.

Results

Significant LA and PA signals were observed in the carotid slice (n=5), whereas only PA was observed in the arterial line (18 injections, n=8). This suggested that the LA signal in the carotid artery slice originated from the surrounding tissue and/or venous blood and that this method was not suitable for providing an AIF. A typical arterial pyruvate signal observed in the on-line cannula (direct AIF), a corrected direct AIF and carotid artery slice are shown in Figure 1b. The shapes of the carotid artery signal and the corrected direct AIF are clearly different. For the lactate experiments, a very weak PA signal was observed in only 2 of 5 animals; hence initially a one-way exchange model was used.

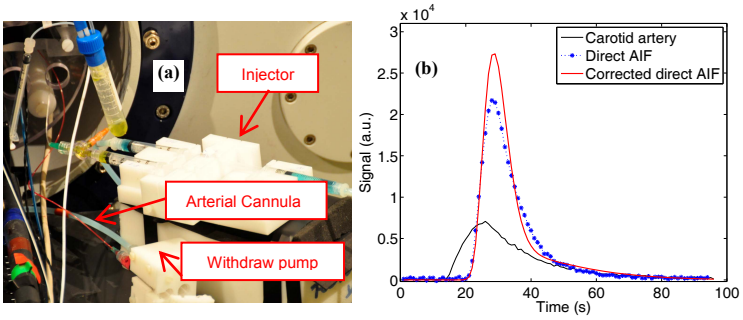

Figure 1: (a) Injection and withdrawal system (b) typical pyruvate signal in carotid artery slice, direct AIF and corrected direct AIF.

The influence of AIF on the fitted rate constant of PA to LA conversion (k_{pl}), T_{1pyr} and T_{1lac} values were determined for 4 different cases: 1- boxcar AIF (five parameters); 2 - boxcar AIF (four parameters + T_{1py}); 3 - PA as an input for the LA (a precursor-product relationship) and 4 – corrected direct AIF. The results of the fits for one representative example are presented in Figure 2 for cases 1, 3 and 4. Figure 3 shows the mean and the standard error for the fitted parameters (k_{pl}, T_{1lac} and T_{1py} where applicable) in all four cases. The boxcar model with all five variables underestimates k_{pl} in comparison to our direct AIF experimentally parameterised model. It also overestimates the relaxation rates of pyruvate (T_{1py}) and lactate (T_{1la}). It can also be seen that the rate constant k_{pl} is a relatively robust parameter and that case 3 might be the best approach if we are mainly interested in the estimation of k_{pl}. However, identification of the true AIFs will enable a more complete validation of this model and analysis of the biochemistry with absolute measures for all other parameters.

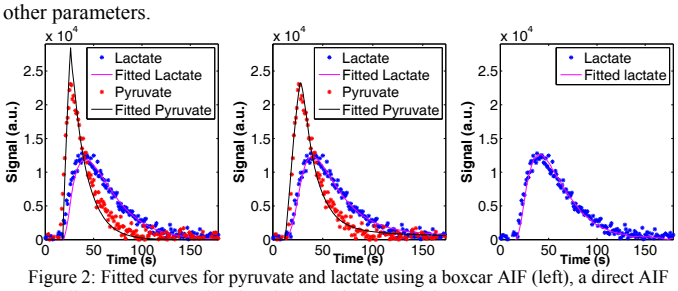

Figure 2: Fitted curves for pyruvate and lactate using a boxcar AIF (left), a direct AIF (middle) and pyruvate signal as the input function (right).

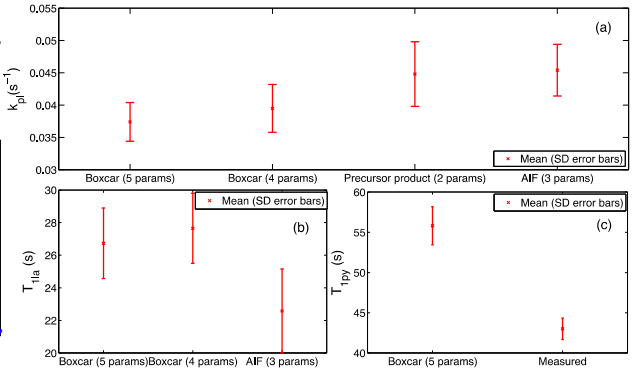

Figure 3: (a) mean and standard error of k_{pl} estimates using four different cases (n=9); (b) estimated T_{1lac} in three cases; (c) estimated (case 1) and measured value of T_{1pyr}.

Discussion

We have established a methodology to allow the direct estimation of the AIF in an arterial cannula following intravenous injection of hyperpolarised pyruvate/lactate in rats. We have compared parameter estimation from models using the direct AIF, an assumed boxcar function AIF and the pyruvate signal as an input function for lactate (precursor-product model). We found that use of the direct AIF and precursor-product model provided comparable estimates of k_{pl}. We have also determined T_{1pyr} values for pyruvate in arterial blood, under normal air-breathing conditions, and compared the measured value against estimated values using different AIFs. We have built a more complete model, which will allow further parameter estimation and will enable a more complete analysis of the biochemistry of PA metabolism in tumours and its response to changes in oxygenation.