Method for robust pH measurement using hyperpolarized bicarbonate and carbon dioxide

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Introduction: In the presence of carbonic anhydrase (CA) enzyme activity, the pH of the local environment can be estimated using the Henderson-Hasselbalch equation if the HCO3-/CO2 ratio (~10 at normal physiological pH) is known. It has been demonstrated that in some tumors the extracellular HCO3-/CO2 ratio can be measured in vivo by following the infused hyperpolarized 13C-bicarbonate, and in the heart the intracellular HCO3-/CO2 ratio can be measured in vivo by following metabolism of hyperpolarized [1-13C]pyruvate (1-4). In these studies, H13CO - 13CO2 signals have been measured by applying MRS with a small tip angle RF pulse that tip the spins of both species equally. Thus, a much smaller, possibly inadequate SNR of the 13CO2 resonance may prevent accurate measurement of pH. Theoretically it is possible to excite the 13CO2 resonance independently with a chemically selective RF pulse of larger tip-angle (to achieve higher SNR), while the other resonances of interest (including H13CO3) are acquired with a smaller tip angle. Even when repeated measurements are required to obtain temporally or spatially resolved data, this method would still result in accurate pH measurement since the ratio between the two pools is rapidly restored by CA-mediated exchange (CA has an extraordinarily high turnover rate, near 106 s-1 in human red blood cells) (5), and the robustness of the measurement would be improved due to the higher SNR for 13CO2.

In this study, a pulse-acquire MRS pulse sequence which interleaved a conventional small tip angle pulse and a spectrally selective pulse was designed and tested in a phantom and in vivo pig hearts, with the aim of measuring intracellular pH using hyperpolarized H13CO3 and 13CO2 signals.

Methods: Hardware and Agents: All studies were performed using a 3T GE MR750 scanner (GE Healthcare, Waukesha, WI). A micro-strip dual-mask 1H,13C volume coil (8 cm ID.) was used for the phantom experiments (Magvalle, San Francisco, CA). A custom build 1H transmit/receive surface coil (5) was used in the animal studies. A HyperSense DNP polarizer (Oxford Instruments, Abingdon, UK) was used to polarize the substrates (5). NaH13CO3 (Isotec, Miamisburg, OH) was prepared in glycerol with OX63 radical (Oxford Instruments) as previously described (4). Neat [1,2-13C2] pyruvic acid (Isotec) was doped with 15mM of OX63 radical and 1mM Gd chelate (Prohance®, Bracco International). Phantom Experiments: A pulse-acquire pulse sequence was modified to allow toggling of the excitation RF pulses between a 100 ms spectrally selective pulse (150 Hz pass-band/104 stop-band) and a 200μs hard pulse on consecutive transients. Pre-polarized H13CO3 (~4ml/15mM in H2O) was mixed with buffered CA enzyme (Sigma Aldridge, St. Louis, MO) solution (4ml/500mM phosphate buffer, pH=7.25, 6μg CA), and dynamic MRS experiment with the interleaved sequence was performed on ~5ml of the mixture (TR=2s, 40° selective pulse, 10° hard pulse). In vivo Experiments: Cardiac gated, dynamic MRS data was acquired from pig hearts in vivo using the same pulse sequence following infusion of ~15 ml/85mM of pre-polarized [1,2-13C2] pyruvate (t=0 at the start of infusion, TR=2R-R or ~1.3s). In two of the animals, data was also acquired using only the hard pulse (TR=4R-R, 10°) in separate studies.

Results and Discussion: Representative spectra from hyperpolarized H13CO3 phantom experiments, which were acquired using the interleaved excitation pulse sequence, are shown in Fig. 1. The average pH obtained using the interleaved pulse sequence (using 13CO2 signals from the selective pulse) was 7.42 (n=4, stdev=+0.02), and differed slightly from the pH meter by an average value of 0.07 (pH meter values were lower in all runs, stdev=+0.02). In vivo hyperpolarized H13CO3 and 13CO2 data from the pig heart following infusion of pre-polarized [1,2-13C2] pyruvate are shown in Fig. 2 (left). An increase in the intracellular pH values from 7.1 to 7.5 was observed over the period that 13CO2 was measurable (SNR > 3) in the spectra from ~20 s to 50 s after the start of tracer infusion (Fig. 2 right). The same pattern was observed in all the animals studied. This observation was not likely the result of RF saturation on the 13CO2 resonance as similar trend was observed when only a small tip angle pulse was used, but further investigation is needed to elucidate the mechanism of this increase in H13CO3 /13CO2 ratio over time. It is worth noting that in order to obtain an accurate H13CO3 /13CO2 ratio using the method proposed here, a good knowledge of the B1 is required for tip angle correction. However, in the small tip angle regime, error in the B1 would not influence this correction substantially. For example, for the 10°/40° pulses used here, +/- 3dB in transmit power would change the correction by less than 10%. A 10% error in the H13CO3 /13CO2 ratio would only represent a difference in measured pH of ~0.05 units in the physiological pH range. In conclusion, this study has demonstrated a method that yields higher SNR for the 13CO2 pool when hyperpolarized H13CO3 and 13CO2 are used to estimate pH in vivo.