Hyperpolarized ^{13}C Magnetic Resonance Imaging and Spectroscopy Uniquely Reveal Early and Late Onset Metabolic Changes in the Failing Heart

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Introduction

While the occurrence of metabolic dysfunction in heart failure (HF) is undisputed, the causal role of altered substrate utilization and myocardial energetics remains controversial. To understand the timing and consequences of metabolic switches occurring during the progression of HF, and to potentially use those switches for disease diagnosis, a non-invasive method capable of serially monitoring metabolism *in vivo* would be required [1]. Hyperpolarized ^{13}C MR, a technique in which the fate of ^{13}C-labelled metabolites can be followed *in vivo* using MR imaging or spectroscopy [2], has enabled non-invasive assessment of cardiac substrate utilization [3]. The aim of this study was to use hyperpolarized ^{13}C MRI and MRS to monitor cardiac carbohydrate metabolism alongside structure and function throughout HF progression.

Materials and Methods

Study overview: Dilated cardiomyopathy (DCM) was induced in pigs (n = 4, ~20 kg at baseline) by rapid ventricular pacing at 188 bpm for 4-5 weeks (instrumentation donated by Medtronic). Pigs were examined at baseline and at weekly time points throughout DCM progression. At each time point: **1)** cine-MRI was used to assess cardiac structure and function; **2)** 0.05 mmol/kg hyperpolarized [2-^{13}C]pyruvate was administered intravenously and ^{13}C MRS was used to assess Krebs cycle-mediated ^{13}C-glutamate production [4], and **3)** 0.05 mmol/kg hyperpolarised [1-^{13}C]pyruvate was administered (a separate bolus, ~1 hr after the [2-^{13}C]pyruvate) to image $H^{13}CO_3^-$ production from pyruvate dehydrogenase (PDH), and thus relative carbohydrate oxidation [3, 5]. Pigs were sacrificed after presentation of clinical symptoms of HF.
MR acquisition: **1)** Cardiac-gated, breath-held SSFP CINE images were acquired in the short-axis view (TR = 4.2 ms, TE = 1.8 ms, FOV 24 cm, slice thickness 5 mm, spacing 5 mm, matrix size 224×224) using a separate ^{1}H transmit/receive surface coil. **2)** Cardiac-gated, dynamic ^{13}C MR spectra were acquired using a pulse-acquire pulse sequence (10° tip angle, TR = 3-4R/R, ~2 s) and a 5" ^{13}C transmit/receive surface coil. **3)** A chemical shift-specific, cardiac and respiratory-gated ^{13}C MRI sequence was used to image [1-^{13}C]pyruvate and $H^{13}CO_3^-$ with 9 mm in-plane spatial resolution in two 1 cm slices, with 2.5 s temporal resolution per set of slices to capture both the time course of the [1-^{13}C]pyruvate bolus and its subsequent metabolism into $H^{13}CO_3^-$.
Data analysis: **1)** EDV and ejection fraction (EF) were calculated from cine ^{1}H images using QMass MR software (Raleigh, NC, USA). **2)** ^{13}C MR spectra were analysed using the SAGE software package (GE-Healthcare). Maximum [5-^{13}C]glutamate / maximum [2-^{13}C]pyruvate was determined for each set of dynamic MRS data. **3)** PDH flux was determined as a $H^{13}CO_3^-$/[1-^{13}C]pyruvate ratio to account for DCM-induced hemodynamic changes affecting [1-^{13}C]pyruvate delivery: total $H^{13}CO_3^-$ signal generated across the anterior wall of the pig heart was normalized to infused [1-^{13}C]pyruvate signal (at the peak of the bolus) in a voxel placed within the left ventricular chamber.

Results

At baseline, pigs had an EDV of 62 ± 5 ml. The maximum ^{13}C-glutamate/[2-^{13}C]pyruvate ratio was 4.9 ± 1.2% (Fig A), whereas the mean $H^{13}CO_3^-$/[1-^{13}C]pyruvate ratio across the anterior myocardium was 2.0 ± 0.3% (Fig B). After 1 week of pacing, the ^{13}C-glutamate/[2-^{13}C]pyruvate decreased significantly by 59% compared with the baseline value, to 2.1 ± 0.8%, and was maintained at this level throughout DCM development. EDV increased linearly with pacing duration, and after 2-3 weeks of pacing was significantly elevated to 84 ± 12 ml. After 4-5 weeks of pacing (at the final time point), the $H^{13}CO_3^-$/[1-^{13}C]pyruvate was decreased by 62% to 0.8±0.2%, and the ejection fraction (EF) was decreased by 30% compared with the baseline value.

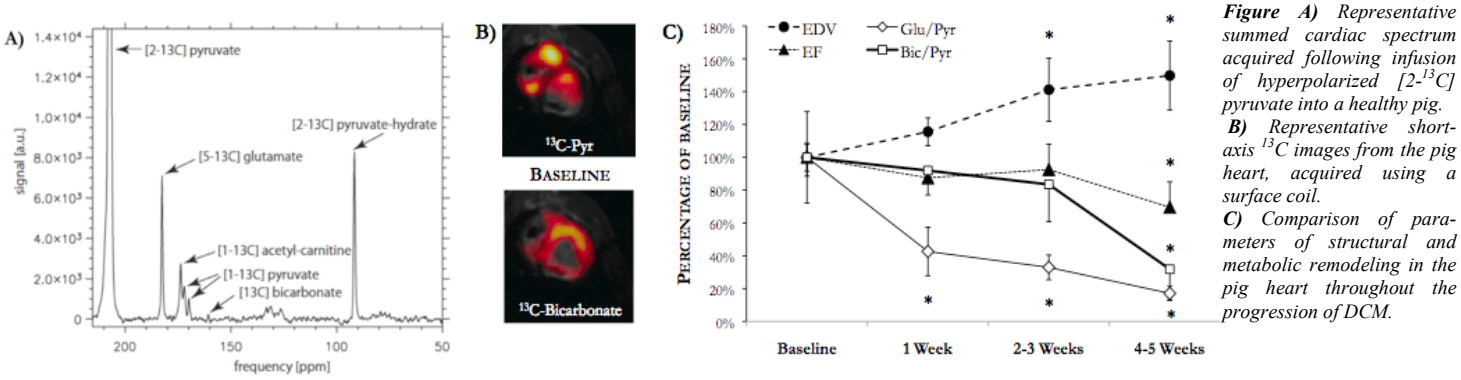

Figure A) *Representative summed cardiac spectrum acquired following infusion of hyperpolarized [2-^{13}C] pyruvate into a healthy pig.* ***B)*** *Representative short-axis ^{13}C images from the pig heart, acquired using a surface coil.* ***C)*** *Comparison of parameters of structural and metabolic remodeling in the pig heart throughout the progression of DCM.*

Discussion

Our hyperpolarized ^{13}C MRI results have shown for the first time that PDH flux was maintained as DCM developed, but was reduced by 62% in late-stage DCM. This result is compatible with previous studies that have shown an increased reliance on glucose oxidation for ATP production, at the expense of fatty acid oxidation, with the development of DCM. The reduced capacity for glucose oxidation via PDH that we observed in end-stage failure occurred concomitantly with decompensation of cardiac function, indicated by a 30% reduction in EF. Further work is warranted to determine why PDH becomes inhibited in late-stage DCM (i.e. due to insulin resistance, elevated plasma FFAs or reduced glucose uptake), and if pharmacological PDH activation could rescue the failing myocardium.
Hyperpolarized ^{13}C MRS revealed a substantial decrease in [5-^{13}C]glutamate production from [2-^{13}C]pyruvate after one week of pacing, observed simultaneously with the first indications of cardiac remodelling, assessed via EDV. This indicates that altered myocardial substrate metabolism may have a role in the initial development of HF, and that the [5-^{13}C]glutamate/$H^{13}CO_3^-$ ratio may be useful for the early detection of DCM.

Conclusions

Metabolism of [2-^{13}C]pyruvate to ^{13}C-glutamate was reduced by 59% at an early stage in DCM, with no change to PDH flux, indicating that ^{13}C-glutamate relative to $H^{13}CO_3^-$ production could be an early marker of disease. Carbohydrate oxidation via PDH was maintained until end-stage DCM, at which point PDH flux was reduced by 62%. With further development, hyperpolarised ^{13}C MR may be useful to characterize HF progression, and to diagnose disease, in patients.

References

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