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Assessment of in vivo metabolism in failing hearts using hyperpolarised 13C magnetic resonance

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Introduction

Increasingly, abnormal metabolic substrate utilisation is considered a cause of heart failure (HF). Hyperpolarised ^{13}C MR, a technique in which the fate of ^{13}C-labelled metabolites can be followed *in vivo* using MR imaging or spectroscopy, has enabled non-invasive assessment of cardiac substrate utilisation.

Purpose

The aim of this study was to monitor carbohydrate metabolism alongside cardiac structure and function, throughout HF progression.

Methods

Dilated cardiomyopathy (DCM) was induced in pigs (n = 4) by rapid ventricular pacing at 188 bpm for 4-5 weeks. Pigs were examined at baseline and at weekly time points throughout DCM progression. At each time point, cine MRI was used to assess cardiac structure and function, 0.05 mmol/kg hyperpolarised $^{13}C_2$-pyruvate was administered intravenously and MRS was used to assess Krebs cycle-mediated ^{13}C-glutamate production, and hyperpolarised $^{13}C_1$-pyruvate was administered to assess $H^{13}CO_3^-$ production from pyruvate dehydrogenase (PDH), and thus relative carbohydrate oxidation. A new cardiac and

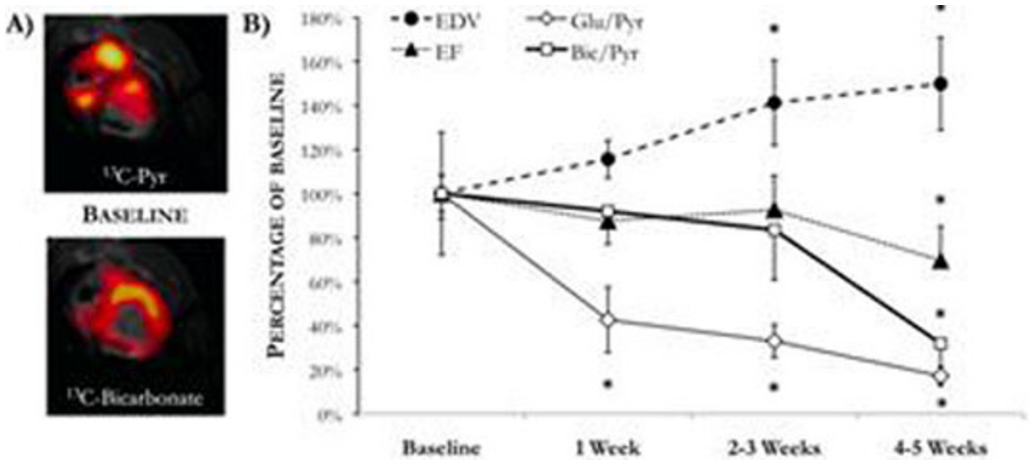

Figure 1 A) Representative short-axis ^{13}C images of the healthy pig heart, acquired with a surface coil. B) Comparison of parameters of structural and metabolic remodeling in the pig heart throughout the progression of DCM. *p<0.05.

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respiratory-gated ^{13}C MRI sequence was used to image $^{13}C_1$-pyruvate and $H^{13}CO_3^-$. The chemical shift-specific pulse sequence used allowed temporally resolved imaging of $^{13}C_1$-pyruvate and $H^{13}CO_3^-$ with 9 mm in-plane spatial resolution in multiple slices (two in these studies), all within a 23 s scan. Pigs were sacrificed after presentation of clinical symptoms or >25% increase in end diastolic volume (EDV).

Results

At baseline, pigs had an EDV of 62 ± 5 ml. The maximum ^{13}C-glutamate/$^{13}C_2$-pyruvate ratio was 4.9 ± 1.2% (Fig 1A), whereas the mean $H^{13}CO_3^-/^{13}C_1$-pyruvate ratio across the anterior myocardium was 2.0 ± 0.3% (Fig 1B). After 1 week of pacing, the ^{13}C-glutamate/$^{13}C_2$-pyruvate decreased significantly 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 ejection fraction (EF) was decreased by 40% compared with the baseline value, and the $H^{13}CO_3^-/^{13}C_1$-pyruvate was decreased to 0.8±0.2%.

Conclusions

In conclusion, metabolism of $^{13}C_2$-pyruvate to ^{13}C-glutamate was reduced by 59% at an early stage in DCM, with no change to PDH flux. Reduced ^{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, metabolic imaging using hyperpolarised ^{13}C MR may similarly characterize HF progression in patients.

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