Hyperpolarized $^{13}$C magnetic resonance spectroscopy reveals real-time metabolic flux changes in a rat model of doxorubicin-induced cardiotoxicity


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Background

Doxorubicin (DOX) is a highly efficient chemotherapeutic for the treatment of a wide range of adult and paediatric cancers. DOX has greatly improved cancer survival rates, however, DOX can cause serious cardiac side effects leading to congestive heart failure. The mechanism for this toxicity is not yet fully understood, though mitochondrial oxidative stress and altered cardiac energetics are thought to play a key role in the pathology. There is currently no clinical non-invasive imaging technique available to assess metabolic fluxes in the heart. Hyperpolarized $^{13}$C magnetic resonance spectroscopy (MRS) can assess real-time metabolic fluxes in vivo and the technique has recently transitioned into clinical trials in oncology and cardiology. We measured real-time metabolic fluxes in the myocardium in a rat-model of DOX-induced cardiotoxicity using hyperpolarized $^{13}$C magnetic resonance spectroscopy (MRS).

Methods

Male Wistar rats were treated weekly for 6 weeks intravenously with either 2 mg/kg DOX (n=12, low-dose) or saline (n=12), or for 5 weeks with 3 mg/kg DOX (n=8, high-dose) or saline (n=8). CINE MR imaging for cardiac functional analysis and hyperpolarized $[^{1-13}]C$- and $[2-^{13}]C$pyruvate MRS were performed at week 1, 3 and 6 and plasma samples were collected for cardiac troponin I measurements.

Results

DOX treatment lead to cardiac troponin I release into blood plasma 6 weeks after the initial dose in both the low- and high-dose model. DOX also induced a progressive and dose-dependent decrease in cardiac ejection fraction and cardiac output. Those functional changes were accompanied by reduced pyruvate dehydrogenase flux in the high-dose model and reduced $^{13}$C label incorporation into the glutamate and acetyl-carnitine pool in both the high- and low-dose models, suggesting altered citric acid cycle flux and reduced acetyl-CoA buffering capacity in the myocardium. Rats showed differences in cardiotoxic severity and the metabolic and functional changes were correlated.

Conclusion

We have shown that hyperpolarized $^{13}$C MRS is a unique and non-invasive method to reveal early metabolic effects of DOX on the heart, opening up the potential to transition the technique to cardio-oncology patients.

References