

HYPERPOLARIZED ^{13}C MAGNETIC RESONANCE SPECTROSCOPY IDENTIFIES CHANGES TO MYOCARDIAL METABOLIC FLUXES IN A RAT MODEL OF DOXORUBICIN-INDUCED CARDIOTOXICITY

Kerstin N. Timm, J. J. Miller, V. Ball, J. A. Henry, D. Savic, M. S. Dodd, D. J. Tyler

Doxorubicin (DOX) is a widely used anthracycline chemotherapeutic for adult and paediatric patients and its use has greatly improved cancer survival rates. However, DOX can cause serious cardiac side effects leading to congestive heart failure. The mechanisms for this toxicity are not yet fully understood, although mitochondrial oxidative stress and altered cardiac energetics are thought to play a key role in the pathology. In this study, we measured real-time metabolic fluxes in the rat heart following DOX treatment using hyperpolarized ^{13}C magnetic resonance spectroscopy (MRS).

Rats were treated i.v. weekly for 6 weeks 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 $[1-^{13}\text{C}]$ - and $[2-^{13}\text{C}]$ pyruvate MRS were performed at weeks 1, 3 and 6.

DOX treatment lead to 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 models, suggesting altered citric acid cycle flux and reduced acetyl-CoA buffering capacity in the myocardium. Rats showed variability in cardiotoxic severity and the metabolic and functional changes were significantly correlated.

Hyperpolarized ^{13}C MRS is therefore a unique non-invasive method to reveal early metabolic effects of DOX on the heart. Future research will focus on unravelling the relationships between metabolic flux changes and the functional decline observed.