# Spin Labeling Cardiac MR Allows Early Detection of Cardiotoxicity Induced by Doxorubicin

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Doxorubicin (Adriamycin®), a member of anthracyclines family, remains among the most potent and widely prescribed drug for treating breast, blood and pediatric cancer patients. However, following a cumulative dose of 550 mg/m$^2$ body surface area, as many as 20% of patients develop heart failure.[1] Combined therapies (e.g., Herceptin combined with DOX for Her2/neu$^+$ breast cancer) often substantially increases the risk of cardiotoxicity.[2] Unfortunately, currently available methods in the clinic, which focus on cardiomyocyte death or deterioration in global cardiac function (LVEF), cannot predict or discriminate patients who will suffer from cardiomyopathy after exposure to doxorubicin. In this study, we demonstrate myocardial blood flow (MBF) quantified by spin labeling cardiac MR (SL-CMR) method reveals a sharp decline in MBF in response to DOX treatment when LVEF is still normal.

**Materials and Methods** C57/B6 mice were treated with a single ip injection of DOX at 10 mg/kg. CMR (LVEF and MBF) was performed prior to DOX treatment (day 0) and at day 1, 7, 14 and 28 after DOX administration, on a 9.4 T horizontal bore magnet (Varian DirectDrive™) interfaced to a 12 cm gradient insert capable of generating magnetic field gradients of up to 40 G/cm. A 35- mm ID $^1$H quadrature volume coil (M2M, qbir35h1m) was used. MBF was measured from a 1.5mm short axis slice at mid left ventricle. To map T1 corresponding to non-slice-selective ($T1_{ns}$) and slice-selective ($T1_{ss}$) inversion, a modified TOMROP sequence [3,4] was used, which consists of an inversion pulse (followed by crusher gradients) and a gradient echo module that samples the same phase-encoding line multiple times during the inversion recovery. A hyperbolic secant adiabatic pulse [5] lasting 6-7 ms (permitted by RF coil power limit) was used for inversion. Under global inversion, the slice thickness of the inversion pulse was set to a large value ($3\times10^5$ mm), while under slice-selective inversion it was set to 2.5 times of the imaging slice thickness. The parameters were: FOV = 30 × 23 mm$^2$, slice thickness = 1.5 mm, matrix =192 ×100, TE = 2.31 ms, bandwidth =50 kHz, inversion pulses 4 s apart, excitation flip angle = 8°. The respiratory waveform and acquisition timings of k-space lines were simultaneously recorded (SA Instrument, NY) for retrospective gating to eliminate images acquired out of the quiescent phase of expiration. For each pixel, the signal intensities along the delay time array were put in a three-parameter fitting algorithm [6] to generate the $T_1$ value. The pixel-wise MBF was calculated based on equation [1], where $T1_b$ is T1 of blood under global inversion and  is the blood-tissue partition coefficient of water and set to 0.83 mL/g.

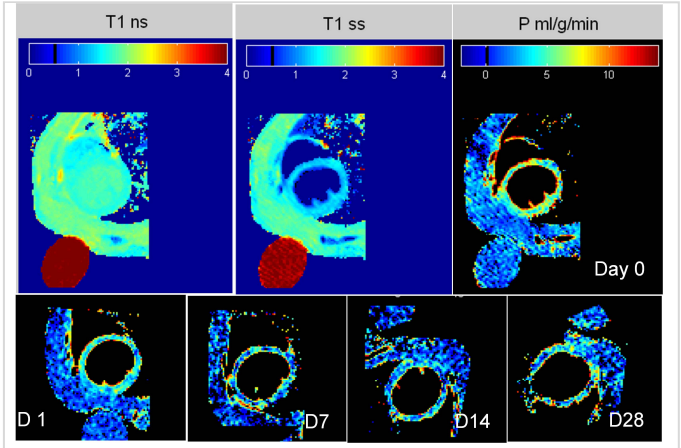


**Fig 1.** T1 maps obtained from non-slice-selective and slice-selective inversion. MBF maps obtained prior to and post DOX treatment.

$$\frac{MBF}{\lambda} = \frac{T1_{ns}}{T1_b}\left(\frac{1}{T1_{ss}} - \frac{1}{T1_{ns}}\right) \quad [1]$$

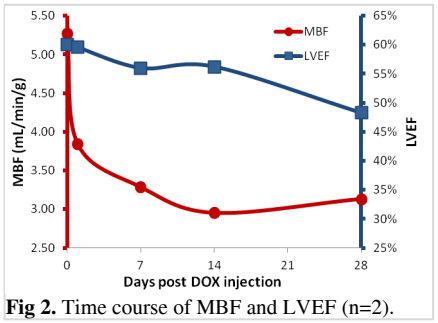


**Fig 2.** Time course of MBF and LVEF (n=2).

**Results** Fig 1A-C shows the maps of $T1_{ns}$, $T1_{ss}$ and MBF of a mouse at prior to DOX treatment (D0). A gel phantom (arrow) was included each time as quality control. MBF measured at day 1, 7, 14 and 28 post DOX treatment are shown (D-G). In response to DOX, MBF appeared to decrease rapidly from 5.3 mLmin$^{-1}$g$^{-1}$ at D1 to 2.95 at D14 whereas global cardiac function (LVEF) remained relatively stable: 60% at D1 and 56% at D14 (n=2). At day 28, LVEF decreased to 48%, a 12-point drop from baseline, which indicates heart failure state, while MBF remained stable at 3.1 mLmin$^{-1}$g$^{-1}$. Consistent with literature, normal mice and rats in response to DOX treatment have heterogeneous degrees of cardiac injury revealed by histological analysis. In contrast, spontaneous hypertensive rats (SHRs) have more consistent cardiac lesion and a chronic cardiotoxicity model induced by multiple infusion of low dose DOX into SHRs is being examined.

**Discussions** These preliminary data demonstrate the ability of SL-CMR to detect the change of MBF in response to DOX treatment, and suggest MBF is an early indicator of cardiomyopathy compared to LVEF, whose deterioration is a reliable index for staging heart failure. These data are consistent with the vasoconstriction we observed previously in Langendorff-perfused hearts exposed to DOX, and suggest abnormal endothelial function might precede the injury to cardiomyocytes. While serum levels of cardiac troponin (cTnT or I) and annexin-V labeled with imaging probes are excellent markers of cell death, indicators of cardiotoxicity prior to extensive cell death might be more useful. The encouraging data presented here justify further investigation of the underlying mechanism, and with validation we expect to develop a sensitive, non-invasive method for assessing the early onset of DOX cardiotoxicity. Such a prognostic tool would allow cardiologists to apply cardiac protective strategies to those vulnerable patients early enough to prevent the onset of congestive heart failure.

**References:**

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