LETTER TO THE EDITOR

Noncontrast CMR for Detecting Early Myocardial Tissue Injury in a Swine Model of Anthracycline-Induced Cardiotoxicity

Doxorubicin (DOX) chemotherapy maintains a prominent role in treating many forms of cancer and dramatically improves recurrence-free and overall survival. Given that the number of cancer survivors is expected to increase over time, treatment-related cardiotoxicity is a major issue. Left ventricular (LV) ejection fraction (LVEF) is the most commonly used method for assessing anthracycline cardiotoxicity. However, LVEF declines as a late manifestation of cardiotoxic injury. Cellular changes at the myocardial tissue level occur before LV systolic dysfunction and heart failure and can be noninvasively detected by cardiovascular magnetic resonance (CMR) myocardial native T1 and T2 mapping. In this study, we sought to assess the mechanisms and pathophysiology of early potential cardiotoxicity associated with DOX-related chemotherapy in a swine model and establish novel CMR biomarkers of subclinical cardiotoxicity to enable primary prevention of cardiotoxicity and subsequent heart failure through histological confirmation.

Ten female Yorkshire swine (30 to 40 kg) were studied. In the chemotherapy group, 9 swine underwent serial CMR scanning followed by same-day DOX injection (1.6 to 2.4 mg/kg) every 2 to 3 weeks. Six swine completed 4-cycle injections and were then euthanized and submitted for histological assessment, whereas the remaining 3 swine were euthanized and submitted for pathological assessment after their second (n = 1) or third injection (n = 2). One animal served as the control and underwent serial CMR scanning without any DOX injection. The dose of DOX was similar to that of adjuvant chemotherapy regimens of 60 to 75 mg/m² for human breast cancer. After 8 to 12 weeks, explanted heart samples were used for frequency and severity of DOX-induced cardiotoxicity and for quantification of collagen volume fraction with Masson trichrome staining and an extracellular space component with hematoxylin and eosin (Figure 1A). Images were acquired using a 1.5-T scanner. Myocardial native T1 and T2 mapping was performed by slice-interleaved T1 and T2 mapping sequences with balanced steady-state free precession imaging readout. Native T1 and T2 were measured over 16 myocardial segments from 3 short-axis slices.

Of the 9 swine receiving DOX chemotherapy, 8 had histological cardiac abnormalities with increased collagen volume fraction and extracellular space (0.10 ± 0.06, 0.27 ± 0.03 vs. 0.04, 0.24 in the control, respectively). Increased extracellular space with edema or myofibrillar loss was the best documented. Cardiomyocyte vacuolation and myofiber cytoplasmatic vacuolation were also observed, followed by replacement by fibrous and/or fat tissue. Collagen volume fraction tended to be larger with increasing DOX dose (p = 0.08). Figure 1B shows the mean ± SE of myocardial native T1, T2, and extracellular volume fraction (ECV) of baseline and changes with DOX chemotherapy. Myocardial native T1 was elevated immediately after the first dose, and it was significantly more pronounced after the second dose (baseline, 1,085 ± 6 ms; first DOX, 1,103 ± 6 ms; second DOX, 1,113 ± 11 ms; third DOX, 1,107 ± 22 ms; and fourth DOX, 1,142 ± 21 ms). A similar finding was observed in ECV (baseline, 0.25 ± 0.004; first DOX, 0.27 ± 0.006; second DOX, 0.27 ± 0.006; third DOX, 0.27 ± 0.012; and fourth DOX, 0.29 ± 0.003). In contrast, T2 was significantly elevated in all chemotherapy-treated swine immediately after their first dose and tended to decrease after their second dose (baseline, 47 ± 0.7 ms; first DOX, 51 ± 1.4 ms; second DOX, 50 ± 0.9 ms; third DOX, 49 ± 2.2 ms; and fourth DOX, 50 ± 0.4 ms). Myocardial native T1, T2, and ECV in the control did not significantly change (baseline, 1,066 ms, 48 ms, and 0.26; 8 weeks, 1,071 ms, 45 ms, and 0.25, respectively). LV end-diastolic volume and mass increased (baseline, 85.0 ± 8.3 ml, 51.8 ± 7.0 g; fourth DOX, 110.0 ± 11.4 ml, 82.9 ± 10.1 g; p < 0.05, respectively). However, LV end-diastolic volume and mass increased less in the chemotherapy group than in the control animal (baseline, 78.2 ml, 48.7 g; 8 weeks, 144.9 ml, 111.7 g, respectively). LV mass-to-volume ratio did not change significantly (baseline, 0.61 ± 0.07; fourth DOX, 0.75 ± 0.01; p = 0.39). No decline in LVEF (i.e., absolute LVEF <40%) or global longitudinal strain or appearance of late gadolinium enhancement was observed. Histological evaluation was performed at the midventricular level, and the results were compared with CMR findings. CMR ECV and native T1 strongly correlated with histological collagen volume fraction (r = 0.75, 0.79; both p < 0.001,
respectively) and histological extracellular space ($r = 0.81, 0.78$; both $p < 0.001$, respectively). Myocardial $T_2$ moderately correlated with non-collagenous extracellular space calculated as extracellular space minus collagen volume fraction ($r = 0.46; p = 0.004$).

We report a novel swine model of well-characterized subclinical DOX-induced cardiotoxicity in which histological abnormalities of myocardial tissue develop after the second DOX dose and before LV systolic dysfunction and impaired global longitudinal strain. In this model, myocardial $T_2$ increases at the earliest stage and moderately correlates with histological non-collagenous extracellular space expansion. Myocardial native $T_1$ provides comparable ability at assessing histological collagen volume fraction to ECV. We hypothesize that given that $T_2$ is more sensitive to changes in myocardial water content, the increase of histological noncollagenous extracellular space at an early stage is the result of myocardial edema or inflammation. Gadolinium-free, native myocardial $T_1$ and $T_2$ mapping has the potential to assess for early potential cardiotoxicity beyond LVEF assessment.

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