

EDITORIAL COMMENT

Cardiac Magnetic Resonance and Cardio-Oncology



Does T₂ Signal the End of Anthracycline Cardiotoxicity?*

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Anthracycline-based chemotherapy has played an important role in cancer care since the 1960s, either as a single agent or in combination with other chemotherapeutics, to treat a broad range of hematological and solid tumor malignancies in children and adults. Anthracyclines, however, are associated with an increased risk of cardiotoxicity, manifest by left ventricular dysfunction and/or heart failure (1). Anthracycline cardiotoxicity is at least in part mediated through the formation of reactive oxygen species, leading to oxidative stress and mitochondrial dysfunction (2). Anthracyclines bind to cardiomyocyte-specific topoisomerase-II β and cause DNA double strand breaks and transcriptome changes that are responsible for regulation of mitochondrial bioenergetics, generation of reactive oxygen species, and oxidative phosphorylation (3).

Risk stratification and early detection of anthracycline cardiotoxicity are 2 important aspects of cardio-oncology care, as they provide an opportunity to initiate cardioprotective strategies and ultimately mitigate the risk of myocardial injury and heart failure. Major risk factors for anthracycline cardiotoxicity include high cumulative anthracycline dose, age, radiation exposure to the heart, and concomitant treatment with other cardiotoxic therapies, such

as targeted anti-HER2 agents. Current strategies to prevent anthracycline cardiotoxicity remain limited, and include avoidance of high cumulative anthracycline doses, use of less cardiotoxic anthracycline preparations such as liposomal doxorubicin, and prophylaxis with cardioprotective medications such as dexrazoxane (4). Data on the prophylactic role of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in this treatment setting remains mixed (5-7). Although measurement of left ventricular ejection fraction (LVEF) remains the most common method to monitor for anthracycline cardiotoxicity, declines in LVEF are thought to represent a late and too often irreversible stage of myocardial injury, with up to 45% of patients failing to respond to standard heart failure therapy, in part depending on how early in the course of disease these therapies are started (8). What remains lacking is a well validated early-stage marker of anthracycline-induced myocardial injury (i.e., prior to the development of heart failure or an overt LVEF decline), which when intervened upon, can prevent the development of adverse cardiac events.

Cardiac magnetic resonance (CMR) has played an increasingly prominent role in the multimodality imaging approach to diagnose cardiotoxicity and better understand the underlying mechanism of cancer therapy-induced cardiac injury. CMR T₁ and T₂ mapping techniques represent a promising noninvasive tool for earlier identification of cardiotoxicity through the quantification of myocardial tissue alterations via changes in longitudinal and transverse relaxation (9). Native T₁ detects myocardial changes due to focal and/or diffuse cardiomyopathic processes, and post-contrast T₁ mapping offers the additive benefit of quantifying extracellular volume as a marker of myocardial fibrosis. Conventional T₂-weighted imaging can detect myocardial edema

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but has several technical limitations, including variability of signal intensity caused by phased array coils, motion artifacts, signal loss in higher heart rates/arrhythmias, and incomplete blood suppression in areas of slow moving blood (10). In contrast, T₂ mapping overcomes these problems encountered with conventional T₂-weighted imaging. T₂ mapping is typically performed using a balanced steady-state free precession (SSFP) sequence sampled at several different echocardiography times and fitted to an exponential decay curve to determine myocardial T₂ relaxation time. T₂ mapping has been shown to be a highly reproducible technique to quantify intracellular and/or extracellular myocardial edema (11,12).

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With this background in mind, the study by Galán-Arriola et al. (13) in this issue of the *Journal* is an interesting exploration of the potential utility of T₂ mapping in the early diagnosis of anthracycline cardiotoxicity. The authors present data from a large animal model of doxorubicin-induced cardiotoxicity utilizing an elegant approach of serial multiparametric CMR combined with histopathological correlation to characterize doxorubicin-induced myocardial injury. This study included 20 pigs divided into 4 groups: group 1 received 5 biweekly intracoronary injections of doxorubicin via the left anterior descending artery and was followed until sacrifice at 16 weeks; group 2 received 3 doxorubicin doses and was followed to 16 weeks; group 3 received 3 doxorubicin doses and was sacrificed after the third dose; and a control group was sacrificed after the initial CMR. That the authors designed the experiments in groups 2 and 3 to explain the findings from group 1 is a particularly impressive strength of this scientific exploration. CMR was performed weekly prior to, during, and after anthracycline treatment.

The authors report that T₂ relaxation time was prolonged at week 6 after 3 doses of doxorubicin and was the earliest CMR parameter of doxorubicin-induced cardiotoxicity, while T₁ mapping, extracellular volume (ECV), and LVEF were unaffected at this timepoint. Histopathological correlation revealed increased myocardial water content and cardiomyocyte vacuolization without alterations in myocardial tissue structure or an increase in extracellular space, confirming that these early T₂ changes represent intracellular edema of the cardiomyocyte. Continuation of doxorubicin after the development of T₂ prolongation led to overt declines in LVEF accompanied by prolongation of native T₁, increased ECV, and histological changes consistent with the well-described features of anthracycline

cardiotoxicity (i.e., intracardiomyocyte vacuolization, increased extracellular space, and fibrosis). However, when doxorubicin was discontinued right after the detection of T₂ prolongation, LVEF remained stable, T₂ relaxation times normalized, and there was histological resolution of cardiomyocyte vacuolization. Based on these findings, the authors conclude that T₂ prolongation (with normal T₁ and ECV) reflects intracardiomyocyte cellular edema and represents an early imaging marker of reversible anthracycline cardiotoxicity.

Overall, these data represent important contributions to our understanding of how CMR could be used for the risk assessment and surveillance of anthracycline cardiotoxicity. The challenge, however, is to translate these findings from an animal model to the bedside, and this raises several questions that warrant further consideration. Changes in T₂ mapping were observed after direct intracoronary infusion of high-dose doxorubicin, which may not be generalizable to current oncology practice. Whether these findings can be replicated with standard intravenous administration of anthracyclines, in which changes in myocardial tissue properties are likely more diffuse and less severe in nature, is unknown. This may account for the absence of any significant change in T₂ relaxation times reported in a prior study of sarcoma patients who underwent serial CMR before and after anthracycline chemotherapy (14). In the model of acute anthracycline cardiotoxicity utilized by Galán-Arriola et al. (13), the window of opportunity between the detection of a T₂ abnormality and the development of an overt LVEF decline in which one could intervene was short (2 to 3 weeks), although the authors suggest that this time window may be longer in the clinical setting. Given the heterogeneity in patient tolerance to varying doses of anthracyclines as well as differences in treatment schedules and cardiotoxicity monitoring standards, further investigation is needed to establish the diagnostic utility of T₂ mapping in clinical practice, identify the appropriate patients who would benefit from CMR imaging and the optimal timing of these assessments, and demonstrate that incorporation of T₂ mapping will provide incremental benefit to patient outcomes above and beyond the current standard of care. Another tantalizing question not addressed by the current study is whether more accessible and less costly biomarkers, such as global longitudinal strain (GLS) or troponin levels, track with T₂ abnormalities during anthracycline chemotherapy.

A particularly important finding in this study was that anthracycline discontinuation upon detection of T₂ prolongation prevented the development of both

clinical and pathological changes of anthracycline cardiotoxicity. Were this finding to generalize to clinical practice, arbitrary anthracycline dosing limits would not be necessary—therapy could continue as long as the T₂ relaxation time was normal. However, if T₂ prolongation were detected, the complex decision of whether to discontinue lifesaving and/or curative cancer therapy in response to this cardiac imaging abnormality would require the balancing of both cancer-specific and cardiovascular-specific risks and benefits. Recent guidelines from the American Society of Clinical Oncology recognize that there is no high-quality data on the risks and benefits of discontinuing cancer therapy due to cardiac causes, and recommend a careful risk-benefit analysis among the patient, oncologist, and cardiologist (15). If T₂ prolongation is confirmed as an early marker of anthracycline cardiotoxicity, subsequent studies need to evaluate whether initiation of cardio-protective medications (e.g., beta-blockers or dexrazoxane) could allow patients to safely complete the intended course of anthracycline chemotherapy.

With advances in cancer therapeutics and the rapid growth of novel cancer treatments associated with known cardiovascular toxicities, cardiac imaging will

continue to play an important role in ensuring the cardiac safety of patients during cancer treatment. At present, GLS appears to have taken the lead in the race to identify an early marker of cardiotoxicity (16), and a multicenter clinical trial is currently underway to determine whether integration of GLS will lead to improved outcomes (17). Although CMR has several advantages over echocardiography, specifically the ability to perform tissue characterization, as was nicely demonstrated in this issue of the *Journal*, there will remain both economic and logistical roadblocks such as cost and lack of widespread availability that will limit the integration of CMR into cardio-oncology practice. Nonetheless, findings from this study are certain to encourage future investigation into the potential application of T₂ mapping techniques for the surveillance and prevention of cardiotoxicity in cancer patients.

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