Anthraclyne Cardiotoxicity
How Do We Move From Diagnosis to Prediction?

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Antachyclines remain an integral part of chemotherapy regimens in many adult and pediatric cancers but cause myocardial damage that may manifest as either subclinical decrements of left ventricular ejection fraction or overt cardiomyopathy. Anthraclyne-related cardiotoxicity is dose-limiting, and the risks of congestive heart failure increase with higher cumulative doses, particularly above 500 mg/m² in adults and 300 mg/m² in pediatric patients.¹⁻³ The cardiotoxic effects of anthracyclines may be enhanced by other treatments, including radiation or trastuzumab. Anthraclynes may also lower the threshold for developing cardiac damage associated with aging or comorbid conditions, such as hypertension and diabetes mellitus. As the number of cancer survivors continues to grow, the burden of anthracycline-related cardiac damage is higher than previously thought.⁴⁻⁶ Thus, there is a critical need to better define and quantify treatment-related cardiovascular toxicity. Currently, predictors of anthraclyne cardiotoxicity used in standard practice are limited to clinical cardiac risk factors and estimates of left ventricular function by echocardiography or gated radionuclide scans.⁷ This is a limited approach, and there is a need to expand anthraclyne risk assessment in an evidence-based manner, given significant advances in cardiac imaging.

See Article by Jordan et al

Cardiac magnetic resonance (CMR) has become the gold standard for quantifying cardiac function and provides comprehensive tissue characterization of myocardial edema, fibrosis, and other features comparable to direct biopsy examination.⁸ These may serve as early imaging biomarkers and be more predictive of anthraclyne-related cardiac injury. The potential of CMR is to permit earlier, more reliable visualization and assessment of anthraclyne-related cardiac toxicity so that additional cardioprotective therapies or alternative cancer therapies can be considered. Several studies have investigated various parameters using CMR, including delayed gadolinium enhancement, aortic stiffness, strain, and more recently T1 mapping.⁹⁻¹²

Myocardial T1 mapping has become a mainstream sequence at advanced CMR centers for imaging extracellular matrix expansion, given its significant diagnostic and prognostic capabilities. Numerous studies have demonstrated the importance of focusing on the interstitium rather than purely on the structure and function of the myocyte.¹³ Early detection of myocardial fibrosis is key to initiating treatment to halt disease progression and improve patient outcomes. The changes that occur in the myocardial interstitium are a substrate for adverse remodeling because they alter mechanical, electric, and vasomotor function.¹⁴

In this issue of Circulation: Cardiovascular Imaging, Jordan et al⁵ have conducted the first study demonstrating elevations in native myocardial T1 and extracellular cell volume fraction in anthraclyne-treated patients independent of cardiac and oncological comorbidities. The authors conducted an elegant study using well-validated T1 mapping techniques along with volumetric measurements while incorporating anthraclyne and nonanthracyline treated patients, as well as pretreatment cancer patients and cancer-free comparators. The number of patients with and without chemotherapy exposure was 57 and 236, respectively. The number of anthraclyne-treated patients was 37. Most of the participants were women. The authors noted that native myocardial T1 was elevated before and after receipt of anthraclyne chemotherapy, whereas extracellular cell volume fraction was elevated in the anthraclyne-treated patients. T1 mapping elevations noted in anthraclyne-treated patients remained significant even after adjusting for ejection fraction, myocardial mass, radiation, as well as myocardial fibrosis risk factors.

This study offers additional evidence that CMR may be the optimal screening tool for chemotherapy-associated cardiotoxicity, given its comprehensive nature of function, strain, and tissue characterization. One of the main limitations of existing anthraclyne cardiotoxicity research in the oncology literature is the focus on left ventricular changes and myocardial injury, which can miss the early onset of subclinical fibrosis and other tissue-level changes. Although several studies have investigated prevention of myocardial injury using beta blockade or renin–angiotensin aldosterone system blockade, they have not preselected patients at highest risk of needing therapy and may not have chosen antifibrotic therapy.¹⁶

The study has certain limitations. The chemotherapy exposure groups are small, especially the anthraclyne group. It is unclear whether there was a selection bias in patients agreeing to undergo cardiac imaging and how many additional patients underwent chemotherapy but were not included. Serial imaging of the same patient, including an earlier time point of chemotherapy exposure, such as after 1 to 2 cycles, would have been helpful in better understanding the
trajectory of T1 changes that can occur as early as 3 months after anthracycline initiation. The authors acknowledge that a prospective longitudinal study with matched control participants would be helpful in better understanding the time course of myocardial fibrosis development and its association with cardiovascular events.

Native myocardial T1 time was elevated in both chemotherapy-treated groups and the pretreatment cancer patients which raises the question whether the cancer itself alters native T1 signal because of myocardial edema possibly in the earlier pretreatment stages and fibrosis in the latter post-treatment period. Extracellular cell volume fraction, a more robust marker of interstitial expansion, was elevated in both anthracycline- and nonanthracycline-treated patients. A subset analysis demonstrated a trend toward higher extracellular cell volume fraction values in anthracycline-treated patients versus those receiving alternate chemotherapy; however, it was not powered for this supplemental analysis. The presence of myocardial strain and late gadolinium enhancement are not included in the current analysis; however, they have been addressed by these expert investigators in their prior work.

Whether anthracycline-treated patients exhibiting T1 signal changes go on to have significant cardiac events in the future remains to be determined. Additional research with particular attention to cardiovascular outcomes is needed to distinguish patients who are at higher risk for adverse events. Future studies with suitable controls may further illuminate how cancer itself affects the myocardium. Collaboration between oncologists and cardiologists in conducting large multicenter studies is needed. Additionally, future research will need to evaluate whether cardioprotective measures initiated before anthracycline therapy or at time of T1 signal abnormalities can modify the tissue-level changes noted. Most of the existing literature has focused on left ventricular function changes and used drug therapy for prevention. Whether the same drugs would be helpful for prevention or treatment of fibrosis is unclear.

In summary, this study adds additional weight to the mounting evidence that anthracyclines are associated with left ventricular interstitial myocardial fibrosis. Additionally, it highlights the potential for CMR and its ability to characterize subclinical cardiotoxic changes that can develop with our cancer therapies. Cardiac imagers are convinced of this value, and the literature supports this. So what has hindered further progress in this area and why are more oncology researchers and clinicians not aware of this data? Low adoption of CMR due to the ongoing care of adult cancer survivors: cardiac and pulmonary late effects of cancer treatment. Cardiac magnetic resonance imaging in patients treated with anthracycline chemotherapy. Am J Cardiol. 2013;111:717–722. doi: 10.1016/j.amjar.2012.11.022.

As CMR continues to become part of routine clinical practice, evidence that acting on early tissue signal changes modifies the course of treatment and impacts patients’ future cardiac risk is needed. Having an agreed upon CMR imaging protocol for evaluating cardiotoxicity that is done consistently across all centers will permit collection of data that can be brought together to expand our knowledge. Genetic and blood-based biomarkers can be used along with imaging data to develop more accurate risk prediction models of chemotherapy-associated cardiotoxicity. Large multicenter studies in institutions that have state of the art CMR are needed along with carefully designed intervention studies that evaluate whether subclinical cardiac changes can be modified. A close collaboration with cardiology and oncology researchers is critical in developing an evidence-based approach to not just detecting anthracycline injury but predicting and preventing it.

Disclosures
None.

References


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