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# Is myocardial fibrosis a new frontier for discovery in cardiotoxicity related to the administration of anthracyclines?

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The success of therapeutic advancements during the last decade have resulted in an increase in the number of cancer survivors with now >14.5 million cases in the United States in 2016.[1] However, this success has created a paradigm: cardiotoxicity and left ventricular (LV) dysfunction have become the most frequent adverse effects of cancer treatment regimens–especially anthracyclines–offsetting the benefits of these life-saving therapies. Navigating patients through cancer treatment whilst mitigating the development of LV dysfunction, has become increasingly important.

Traditionally, the most widely used strategies to detect cardiotoxicity included monitoring of LV ejection fraction (LVEF) by cardiac imaging or directly visualizing myocellular injury from right heart endomyocardial biopsies.[2] While histopathologic examinations are often revealing, their invasive nature and consequent associated risks favor the development of more suitable alternatives. Notably, the rapid evolution of noninvasive cardiac imaging strategies to monitor cardiac function is providing new opportunities for the early detection of LV dysfunction.

Cardiovascular magnetic resonance (CMR) imaging is rapidly becoming a central diagnostic tool in cardiovascular medicine, not only due to its ability to provide accurate volumetric and functional systolic and diastolic function measurements of the ventricles, but also because of its unique ability to characterize myocardial tissue and thereby determine the etiology of myocardial dysfunction.[3] These features are particularly important in the cardio-oncology arena when trying to determine the etiology of an LVEF decline in a patient treated for cancer that also exhibits several other cardiovascular (CV) co-morbidities.

CMR utilizes the tissue response of exposure to non-ionizing electromagnetic radiation within magnetic fields to generate within the body contrast between different structures and tissues and thereby allowing the identification of abnormal pathology.[4] Novel mapping

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techniques capture the evolution of T1-recovery within a single breath-hold, and if measured before and after the administration of intravenous gadolinium chelates, processes involving the myocytes and the extracellular space or volume (ECV) surrounding them can be assessed and quantified.[5] T1-mapping and derived measures of ECV can identify interstitial myocardial fibrosis. The left ventricular (LV) myocardial extracellular matrix (ECM) consists of an intricate fibrillar collagen network that provides support to cardiomyocyte function including contractility (systolic function) and relaxation (diastolic function).[6] Abnormal increases of the ECM (cardiac fibrosis) impairs LV diastolic or systolic function[7] and independently predicts future mortality and heart failure.[8] Additionally, quantification of T2-myocardial relaxation times and mapping techniques can detect myocardial edema and thereby identify processes such as inflammation or injury that promote this edema.[9]

In this issue of *Circulation: Cardiovascular Imaging*, Farhad, et al., report on the use of CMR tissue characterization techniques to better understand the mechanisms responsible for the initiation and progression of anthracycline-induced LV dysfunction. In an effort to mimic clinical chemotherapy regimens for breast cancer and lymphoma, the study employed a mouse model of cardiotoxicity where animals received 5 mg/kg/week of doxorubicin by continuous infusion for 5 weeks and were followed up for 5, 10 and 20 week after completion of doxorubicin therapy. CMR T1 map-derived measures of LV myocardial ECV as well as T2 measurements were acquired at baseline and 5, 10, and 20 weeks after the first administration of doxorubicin. CMR imaging studies were acquired during the same timeframe as the histopathology endpoints.[10]

Using these methods, the investigators report a baseline ECV fraction of 25%, consistent with cancer-free human subjects ECV values,[11] which increased to 34% after 10 weeks post-initiation of doxorubicin treatment and further increased by 7 percentage points to 41% at 20 weeks post-initiation of chemotherapy. The sub-acute increase in ECV at the 10-week time-point corresponded with a decrease in LVEF and an increase in LV end diastolic volume. In addition, myocardial fibrosis (both ECV increase and histopathological fibrosis) was preceded by increases in LV myocardial T2 with measurements advancing from 22 to 32 milliseconds at 5 weeks post-initiation of treatment. The assessments of myocardial T2 correlated with post-necropsy measurements of cardiac water content. LVEF was unchanged at this time-point. Furthermore, they found that both edema (CMR T2) and fibrosis (CMR ECV) predicted the late doxorubicin-induced mortality in the mice. These observations underscore the complexity of the pathophysiology of myocardial and extracellular matrix (ECM) remodeling process induced by anthracyclines and the importance of the utilizing the unique tissue characterization techniques by CMR in the comprehensive assessment of cardiotoxicity.

Traditionally, cardiotoxicity has been attributed to myo-cellular DNA damage,[12] and altered cardiac mitochondrial bioenergetics leading to formation of reactive oxygen species and cardiac apoptosis.[13,14] However, the recent evidence by the Farhad, et al., and others[15,16] suggest that cardiac fibrosis represents an additional important mechanism contributing to impaired LV function and adverse outcomes following cancer treatment.

Several mechanisms may promote ECM increases after anthracyclines. Cardiomyocyte death induced by anthracycline associated injury triggers an inflammatory response that ultimately results in fibroblast activation and replacement fibrosis.[17] Also, the formation of reactive oxygen species and mitochondrial dysfunction after anthracyclines activates resident fibroblasts inflammatory cell infiltration into the myocardial extracellular matrix that release cytokines and growth factors that enhance extracellular matrix deposition.[18]

It is interesting that the investigators observed an acute increase of cardiac edema that preceded the deposition of interstitial fibrous tissue. This phenomenon has been described in several other cardiac pathophysiologic conditions (e.g., volume-overload, acute myocardial infarction, and pulmonary hypertension) in which the early appearance of interstitial edema together with a disruption of collagen fibers preceded fibrillar remodeling of the cardiac extracellular matrix. While the mechanisms by which the processes initiating the edema triggers subsequent fibrosis are unclear, it has been hypothesized that the increased in hydrostatic pressure that acts on cardiac fibroblasts promotes the synthesis and secretion of collagen.[19,20]

Taken together, the findings in the current study indicate that inflammation and fibrotic remodeling of the extracellular matrix occur after myocardial edema induced by the administration of doxorubicin. Since myocardial fibrosis and remodeling are essential underlying causes of LV dysfunction and independent predictors of adverse CV events, the results of this study suggest further research should be performed to a) confirm or refute these findings in human subjects, and b) if present, develop strategies to avert fibrotic cardiovascular remodeling during or after receipt of anthracycline based chemotherapy. The results raised from these experiments in mice cause one to question whether the isolated monitoring of LVEF in patients receiving treatment for cancer may create situations in which the onset of irreversible fibrosis was missed and it is thereby “too late” to thwart the inevitable consequences associated with myocardial interstitial fibrosis.

There are several unanswered questions raised by this study. First, from a clinical practice perspective, the interpretation and translation of the results are limited by the relative high doses of doxorubicin (total cumulative dose of 25 mg/kg) used to induce cardiotoxicity in the mice which do not resemble a typical chemotherapeutic regimen in humans. Threshold of fibrosis in women receiving chemotherapy has been previously observed at 3 months post-initiation of anthracycline therapy after receiving a cumulative dose of ~375 mg/m$^2$, equivalent to ~8–10 mg/kg in these animals.[15] Further studies in animals and human subjects are warranted to determine the onset and progression of edema and myocardial fibrosis using weigh-equivalent doses and treatment intervals.

Second, the CMRs were performed on a 9.4-T scanner; thus it is yet to be determined whether identification of these imaging biomarkers is feasible utilizing 1.5-T and 3-T clinical field strengths. Third, the clinical applicability of tissue characterization techniques remain limited by the lack of standardized acquisition sequences and threshold values for different acquisition and analysis hardware-software combinations.

It is important to recognize that the mouse tissue began in a relatively healthy state. It remains uncertain as to whether these CMR mapping techniques can distinguish abnormalities related to cancer treatment in human or animal subjects with pre-existing CV co-morbidites (e.g., hypertension or coronary artery disease). Similarly, it remains unanswered whether measurement of T2, T1, or ECV will be useful to identify myocardial injury or fibrosis if there is an additional active concomitant process that modifies myocardial T1 (e.g. amyloidosis).

Pathophysiologically, it remains to be determined whether anthracyclines induce a direct activation of resident cardiac fibroblasts independent of cardiomyocyte injury and promote their conversion to myofibroblasts (a pro-fibrotic phenotype of fibroblasts). Alternatively, anthracyclines may initiate an inflammatory cascade of events that promotes cardiac fibroblast activation that persists after cessation of treatment.

In summary, mitigation of LV dysfunction induced by cancer therapy is an emerging healthcare concern. Farhad, et al., have demonstrated that CMR imaging incorporating tissue characterization techniques can be used to detect subclinical pathophysiologic processes that influence cardiac function. Further studies are needed to determine if these measurements can be acquired and whether they forecast CV events in human subjects. In addition, given the harmful effects associated with the development of myocardial fibrosis, the results from Farhad, et al, suggest future research should be directed toward the prevention of myocardial fibrosis in those receiving treatment for cancer.

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