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EDITORIAL COMMENT

Anthracycline Cardiotoxicity

Can CT Move Us Further?*

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The primary recognized mechanisms of anthracycline cardiotoxicity include generation of reactive oxygen species and inhibition of topoisomerase 2β (1,2). However, in addition to the cardiomyocyte-specific effects, anthracycline-induced endothelial injury has also been postulated to contribute to the pathogenesis of myocardial damage (3). Doxorubicin induces endothelial cell apoptosis in vitro (4) and causes rapid-onset endothelial dysfunction in the brachial artery of patients undergoing cancer treatment (5). The impact of anthracycline-associated vascular toxicity is highlighted by the evidence that endothelial dysfunction can be detected years after treatment (6), and its persistence may contribute to the increased cardiovascular disease burden seen in cancer survivors (7).

A major obstacle to our understanding of the vascular effects of anthracyclines on the human heart has been the lack of noninvasive techniques with which to investigate endothelial and smooth muscle cell function. In this issue of *JACC: CardioOncology*, Feher et al. (8) propose a novel methodology for assessing vascular reactivity in epicardial coronary arteries using coronary CT angiography (CTA) and report their results using this technique to assess vascular toxicity in a canine model of chronic doxorubicin administration. In a baseline study conducted in 16 dogs, Feher et al. (8) assessed the reproducibility of resting diameter measurements by CTA of the proximal segments of the left anterior descending, left circumflex, and right coronary arteries, as well as the vasodilator responses to intravenous adenosine (ADE) and dobutamine (DOB) infusions. In the treatment study, 8 of the 16 dogs received weekly doxorubicin infusions (1 mg/kg) for 12 to 15 weeks. Vascular reactivity to ADE and DOB was assessed by CTA when the animals had received cumulative doxorubicin doses of 4-mg/kg, 8-mg/kg, and 12-mg/kg, respectively. At the same timepoints, a transthoracic echocardiogram with measurement of left ventricular (LV) ejection fraction, LV volumes, and 2-dimensional strain analysis was also performed. In addition, to assess doxorubicin-induced histopathologic changes, in 4 of the 8 treated dogs, LV endomyocardial biopsy specimens were collected under fluoroscopy at cumulative doxorubicin doses of 4-mg/kg and 8-mg/kg, and pathologic myocardial specimens were harvested after dogs were sacrificed at the end of the study. Feher et al. (8) report that, in the baseline study, the resting diameter measurements by CTA were highly reproducible and that vasodilator responses to ADE and DOB were measurable in all major epicardial vessels, confirming the validity of the technique. In the treatment study, coronary vascular reactivity to ADE, but not to DOB, was significantly reduced at a cumulative doxorubicin dose of 4-mg/kg. However, statistically significant vasodilator impairment was observed after infusion of both agents at a cumulative dose of 8-mg/kg. Among the echocardiographic parameters, global longitudinal strain was significantly reduced starting at a cumulative doxorubicin dose of 4-mg/kg, whereas LVEF showed a significant decline only at

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the highest cumulative dose. Finally, histopathologic examination showed the expected progression of myocardial damage with increasing cumulative dose.

The results of this study address 2 important questions. First, can we use coronary CTA as a novel noninvasive research tool for the assessment of the effects of cancer treatments on coronary endothelial function? The data reported by Feher et al. (8) suggest that, in this dog model, the reproducibility of the measurements is adequate and that appropriate vasodilator responses may be triggered, whether they are primarily endothelium dependent (ADE) or a combination of endothelial and smooth muscle cell stimulation (DOB). The potential applications of this methodology are numerous and may include the assessment of vascular toxicity of traditional and targeted/novel cancer treatments, particularly those associated with the vascular endothelial growth factor pathway and other small molecule tyrosine kinase inhibitors (9), as well as the investigation of the potential interactions between pre-existing cardiovascular risk factors (e.g., hypertension, obesity, and diabetes) and cancer treatments. Furthermore, it may allow more in-depth evaluation of the vascular pathways affected by a specific cancer treatment with the use of selective pharmacologic tools (e.g., L-N-monomethyl arginine for the nitric oxide pathway, aspirin for cyclo-oxygenase-dependent synthesis of vasoactive prostanoids, angiotensin receptor blockers and endothelin-1 receptor antagonists for the detection of vasoconstrictor tone) (10), as well as the investigation of potential vasculoprotective treatments to reduce cardiotoxicity.

The second question addressed by this study is whether endothelial function assessment by coronary CTA can be used clinically to predict cardiotoxicity in patients receiving specific cancer therapies. It is well established that patients with baseline cardiovascular risk factors or cardiovascular disease are at increased risk of developing cardiotoxicity (11). Endothelial dysfunction is associated with almost every risk factor for atherosclerosis and with established cardiovascular disease (12). As such, it is a barometer of total cardiovascular risk and has been shown to predict future cardiovascular events, even after adjustment for traditional risk scores (13). Furthermore, coronary CTA allows calculation of a coronary artery calcium score during the initial noncontrast, low-radiation phase of the study, as well as detection of coronary stenosis severity and plaque morphology with contrast administration. Thus, using the technique described in this study, coronary CTA could theoretically provide both physiologic and morphologic data that could improve baseline risk stratification and guide cardioprotection in patients undergoing specific cancer therapies. Unfortunately, the lack of established normal reference ranges for endothelial function using this technique and the inability to account for the vascular effects of other confounding variables in the real-world setting may limit the clinical utility of this methodology.

Based on the results of this study, Feher et al. (8) suggest that repeated noninvasive measurements of endothelial function could be reliably performed over time in the same individuals and in the same arterial segments to assess progressive changes before the development of overt cardiotoxicity. For this technique to be used clinically, these results would not only have to be reproducible but also have low interoperator variability. Even though coronary CTA has the advantage of being noninvasive, repeated testing would expose patients to significant radiation exposure and the risks associated with iodinated contrast, making it less attractive than other predictive modalities, such as global longitudinal strain measured by echocardiography.

In conclusion, the study by Feher et al. (8) describes a novel noninvasive technique, using coronary CTA, to demonstrate the link between anthracycline-induced endothelial injury and cardiomyopathy in a canine model. This methodology could serve as an important research tool to evaluate the vascular impact of new and emerging cancer therapies and to guide cardioprotective drug development.

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