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The Role of Cardiac Magnetic Resonance Imaging to Detect Cardiac Toxicity From Cancer Therapeutics

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Abstract

Purpose of review The emerging complexity of cardiac toxicity caused by cancer therapies has created demand for more advanced non-invasive methods to better evaluate cardiac structure, function, and myocardial tissue characteristics. Cardiac magnetic resonance imaging meets these needs without exposure to ionizing radiation, and with superior spatial resolution.

Recent findings Special applications of cardiac magnetic resonance (CMR) to assess for cancer therapy–induced cardiac toxicity include the detection of subclinical LV dysfunction through novel methods of measuring myocardial strain, detection of microcirculatory dysfunction, identification of LV and LA fibrosis, and more sensitive detection of inflammation caused by immune checkpoint inhibitors.

Summary CMR plays a significant role in the non-invasive workup of cardiac toxicity from cancer therapies, with recent advancements in the field that have opened avenues for further research and development.

Introduction

Although the cardiotoxic effects of chemotherapy and external beam radiation therapy (EBRT) have been known for decades [1], the complexity of these toxicities is expanding in proportion to the rapid growth of oncologic treatments [2]. Echocardiography (echo) and equilibrium radionuclide angiocardiography (ERNA) are routinely used to evaluate for overt and subclinical left ventricular (LV) dysfunction in this setting [3–4]. However, the emerging complexity of cardiac toxicity caused by cancer therapies has created demand for more advanced non-invasive methods to better evaluate cardiac structure, function, and myocardial tissue characteristics. Cardiac magnetic resonance (CMR) imaging meets these needs without exposure to ionizing radiation and with superior spatial resolution. There has been tremendous development in the field of CMR to decrease scan times, improve accessibility of the technology, and to better characterize pathology relating to myocardial blood flow, inflammatory myopathies, myocardial fibrosis, and pericardial disease, all of which can affect patients exposed to potentially cardiotoxic cancer therapies. For this reason, CMR is becoming an integral component in the evaluation of these patients. The following review will discuss both current and emerging technology utilized by CMR to detect both pre-clinical and overt cardiac toxicity inflicted by cancer therapeutics.

Structural and functional analysis

Left ventricular systolic function

Monitoring for decrements in left ventricular ejection fraction (LVEF) has been the cornerstone to detect cancer therapeutics–related cardiac dysfunction (CTRCD) for decades, and has traditionally relied upon ERNA and echo [4]. CTRCD has been defined as a decrease in LVEF by at least 10% from a pre-treatment baseline to a value less than 53% [4]. Although CMR has played a supplementary role in this process due to relative increased cost and reduced availability, it is considered the reference standard to calculate LVEF based on lack of geometric assumptions in asymmetric ventricles [5], and is without limitations from body habitus. Thus, CMR should be considered in any patient where echocardiographic windows preclude accurate calculation of the LVEF. Furthermore, non-contrast 2D Simpson's biplane is only reliable in detecting differences in LVEF of up to 10% in patients exposed to cancer therapies [6], which is insensitive considering the threshold to define CTRCD is 10% [4]. In addition, non-contrast 2D echo has been shown to be inferior when compared with CMR, 3D echocardiography, and ERNA when following serial LVEF in patients exposed to adjuvant trastuzumab after doxorubicin [7]. Thus, CMR should be considered as the first line to monitor for CTRCD whenever 3D TTE is unavailable.

LV structure and function can be evaluated with CMR using gated cine imaging in standard projections including the four-chamber, vertical long axis, and left ventricular outflow tract views. A stack of contiguous short axis slices can be obtained by imaging perpendicular to the interventricular septum and the lateral wall. Post processing algorithms can be applied to this series of short axis images to determine the LVEF by measuring the volume of each short axis slice at end diastole and end systole. The advent of steady-state free precession (SSFP) sequences has allowed for superior signal contrast to noise ratio of gated cine images [8], and has improved the accuracy of LVEF calculations using this method [9]. The same process can be applied to the right ventricle (RV) to define the RVEF, and epicardial borders can be traced to calculate the LV myocardial mass when combined with endocardial tracings.

Although LVEF evaluation is paramount to the detection of CTRCD, it is insensitive to detect subclinical LV dysfunction. This is exemplified by histologic studies showing myocyte damage prior to a decrement in LVEF after exposure to cardiotoxic chemotherapies [10]. Accordingly, assessments of myocardial deformation—or strain—have been developed, and are now broadly applied echocardiographically to detect subclinical LV dysfunction. An increase in global longitudinal strain (GLS) by more than 15% above the pre-treatment baseline is considered as an additional finding to diagnose CTRCD [4], as echocardiographic impairments in GLS have been shown to predict future development of LV systolic dysfunction in patients exposed to anthracycline-based chemotherapies [11].

Although several CMR-based strain detection algorithm methods, such as displacement encoding with simulated echoes (DENSE) [12], have existed in the research space for decades, several additional emerging methods are being developed and applied to the detection of CTRCD. Feature tracking (FT) of myocardial tissue with CMR allows for calculation of myocardial deformation in a similar manner used by speckle tracking echocardiography; however, CMR is able to do so with higher spatial resolution. Abnormalities in both GLS and circumferential strain calculated with FT CMR have be found in breast cancer patients despite a normal LVEF [13], and a decline in CMR-based circumferential strain has been shown to predict decrements in LVEF 3 months after exposure to anthracyclines [14]. Another CMR-based method uses signal encoding to detect myocardial compression with fast-SENC imaging (MyoStrain software, Myocardial Solutions, Morrisville, NC). This method is fast and not reliant on breath hold maneuvers. Furthermore, it has been shown to provide highly reproducible calculations of LV myocardial strain and LVEF [15]. Clinical trials are currently underway to determine if this technology can accurately predict decrements in LVEF in patients exposed to cardiotoxic chemotherapies (https://clinicaltrials.gov/ct2/show/NCT03543228). These methods of CMR-based strain calculation are starting to enter the clinical setting as more data is collected to establish their efficacy and utility.

Right ventricular function

CMR provides accurate assessment of right ventricular (RV) function through volumetric quantification of RV end-diastolic volume and end-systolic volumes using a contiguous stack of RV short axis cine images. The spatial resolution of CMR is also high enough to characterize the RV myocardium. Trastuzumab has been shown to cause subtle declines in RVEF, which seem to recover 6 months after the completion of therapy [16]. This phenomenon has also been reported with anthracyclines [17], with focal RV wall motion abnormalities and RV late gadolinium enhancement (LGE) only described in small case series [18]. Further research is required to determine the clinical significance of these findings.

Left atrial function

The superior spatial resolution of CMR provides a mechanism to define LA structure, function, and tissue characteristics, which is more limited with other imaging modalities given the thin wall of this structure. Imaging the LA with CMR has broad emerging applications to the risk stratification of patients with cardiomyopathies and atrial fibrillation [19]. LA size can be accurately

measured with CMR through biplane area length method, or by a short axis stack to determine more direct volumetric indices [20]. Patients exposed to anthracyclines, such as children, have been shown to have increased LA size when measured by CMR [21]. The superior spatial resolution of CMR provides the additional benefit of LA feature tracking to determine LA strain throughout the cycle of left atrial emptying [22]. Indices of LA strain have been applied in realms outside of cardio-oncology including atrial fibrillation, cardiomyopathies, and valvular disease [19]. Further applications of LA strain indices in the cardio-oncology setting are warranted, and animal models are currently underway investigating the effects of anthracycline-based chemotherapy on LA function as measured by CMR [23].

Left ventricular diastolic function

LA size and function are closely related to chronic perturbations in left ventricular filling dynamics, including elevations in the left ventricular end-diastolic pressure. Accordingly, increases in LA size and indices of diffuse left ventricular fibrosis measured by CMR in patients exposed to anthracyclines have correlated with echocardiographic indices of diastolic dysfunction [24]. Additionally, baseline evidence of diastolic dysfunction, as determined echocardiographically, may be predictive of future decline in LVEF after anthracycline exposure [25]. However, it is unclear how these indices are predictive of future outcomes, and are thus not included in standard parameters to evaluate for CTRCD [4]. Nevertheless, there are several emerging tools to characterize diastolic function with CMR through the measurement of LA size and function, LV peak filling rate, and velocity-encoded phase contrast imaging to assess flow patterns through the pulmonary veins and across the mitral valve [26–27]. CMR-derived flow quantification across the mitral valve and feature tracking–based measurements of e′ have shown good correlation with echocardiographic evaluation of these parameters, and pulmonary capillary wedge pressure measurements in these patients correlate strongly with LA LGE [28]. These CMR-based methods will allow for integration of diastolic parameters with the unique aspects of LV and LA tissue characterization provided by CMR, and may establish future avenues to detect subclinical CTRCD or other novel forms of cardiotoxicity.

Tissue characterization

Left ventricular fibrosis

CMR allows for the detection of both diffuse myocardial fibrosis and discrete scar formation. Gadolinium-based contrast agents (GBCAs) are cleared by normal myocardium, but are deposited in fibrotic or actively inflamed tissue. This appears as the bright white signal of LGE and contrasts the dark signal of normal myocardium through which GBCAs are cleared. On the other hand, diffuse fibrosis is difficult to detect with LGE, but quantitative T1 mapping sequences are able to define both global and regional native T1 values without the administration of GBCA, and have shown promise in detecting diffuse fibrosis in the presence of elevated T1 values. Post contrast T1 mapping can also be used to calculate the extracellular volume fraction (ECV), which is elevated in the setting of diffuse fibrosis.

Although LGE can be found in cardiomyopathy related to trastuzumab [29] (Fig. 1), it is an uncommon finding in anthracycline-induced cardiotoxicity despite reduced LVEF [30–31]. Patients treated with anthracyclines also develop reduced LV mass [30, 32•], suggesting anthracycline-mediated cardiotoxicity may be a diffuse process which is not easily identified with delayed enhancement imaging. Pre-contrast T1 mapping and post contrast ECV calculations have been shown to be elevated in patients receiving anthracycline-based chemotherapy [24, 33]; this phenomenon has been demonstrated to occur only 3 months after the initiation of therapy [34]. Although this suggests diffuse myocardial interstitial fibrosis, alternative hypotheses include the effect of

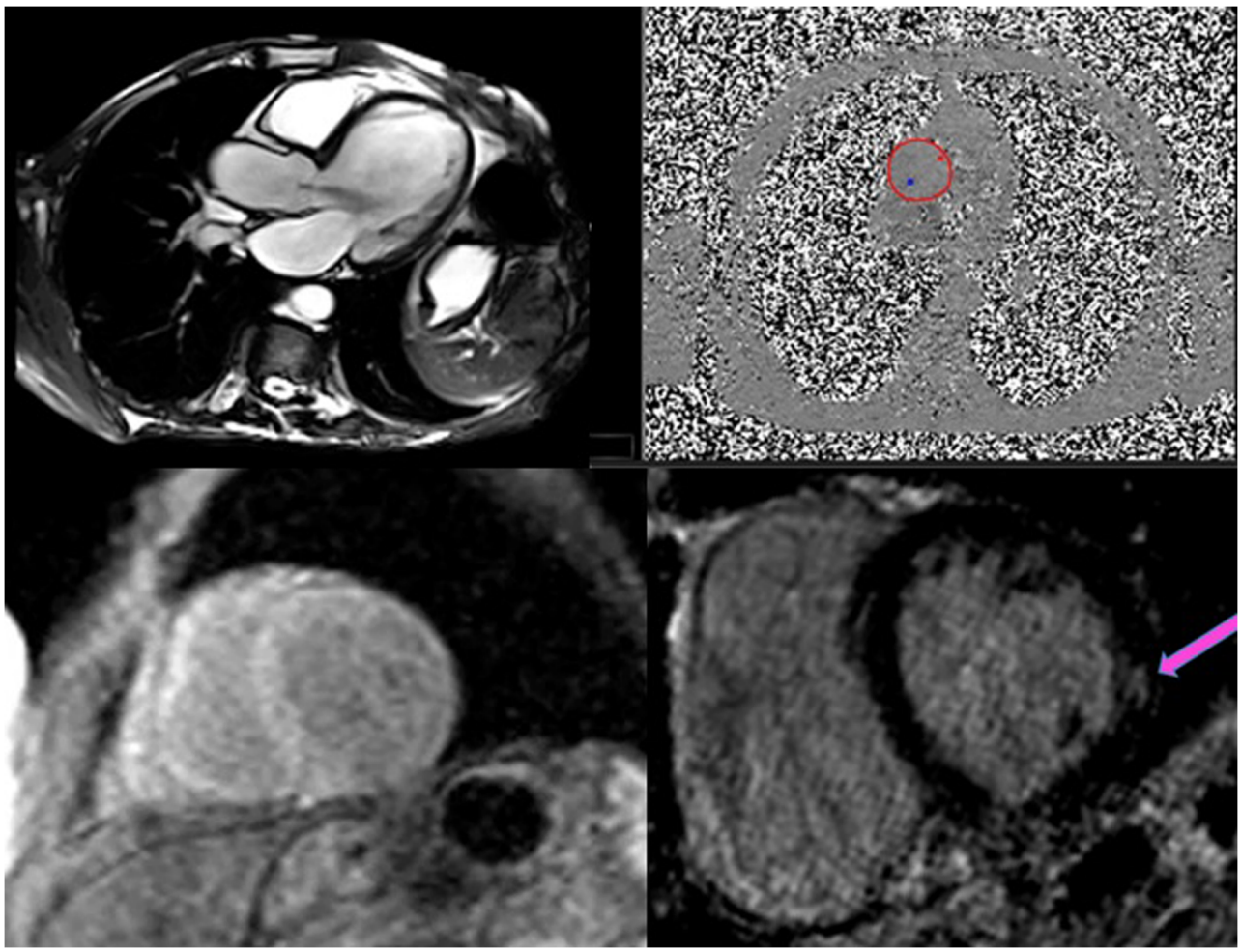

Fig. 1. Complete CMR evaluation of a 44-year-old woman with breast cancer on trastuzumab, with a new drop in LVEF and aortic regurgitation that was difficult to quantify on echo. She was referred for vasodilator stress CMR to assess for ischemic heart disease prior to breast surgery, and to better characterize LVEF and aortic regurgitation. The left ventricle is dilated and there is a dephasing jet indicative of aortic regurgitation (top left). Phase contrast imaging at the level of the aortic valve (top right) allowed for quantification of aortic regurgitation, revealing a regurgitant fraction of 11%. First-pass perfusion during vasodilator stress (bottom left) revealed normal myocardial perfusion with no evidence of ischemia. Delayed enhancement images (bottom right) revealed late gadolinium enhancement in the mid-myocardial portion of the mid-inferolateral wall (purple arrow). This is a non-ischemic scar pattern that has been reported with trastuzumab-induced cardiomyopathy.

cardiomyocyte atrophy causing a relative increase in the ECV [35•]. More recent studies have conversely shown that acute decreases in T1 values 48 h after the receipt of anthracyclines predict subsequent development of cardiomyopathy [32•]. Serial magnetic resonance imaging of porcine models of doxorubicin toxicity has also suggested early increases in native T2 signal despite unchanged T1 values and ECV [36]. The significance of these conflicting findings remains to be clarified, and must be contextualized by other tissue-specific effects on T1 and T2 properties such as myocardial blood volume, fat distribution, and edema.

Left atrial fibrosis

The thin wall of the LA poses challenges to differentiate the bright appearance of LGE from the blood pool. There have been numerous emerging methods to optimize the detection of LGE in the LA [37]. Patients exposed to EBRT develop increased levels of LA LGE [38–39]. This suggests focal scar in the LA as a result of these therapies, and may place patients at risk for future atrial arrhythmias and stroke [40–41]. Further research is warranted to investigate these clinical correlations. The thin wall of the LA also limits evaluation of diffuse fibrosis, which may be a more predominant pathologic effect of anthracycline toxicity in LV myocardium, as already discussed. There are recently developed sequences to perform T1 mapping of the LA [42]. Although these methods have not yet entered the clinical space, they would be of clinical value in the detection of anthracycline toxicity given its known association with elevated T1 values in the LV [33]. These methods may also be useful in the risk stratification of cancer patients for developing new or recurrent atrial arrhythmias during treatments that are associated with atrial arrhythmias, such as ibrutinib [43].

Detection of myocardial inflammation

The role of CMR is well established in identifying patterns of edema in patients with myocarditis and other inflammatory myopathies [44]. Elevated T2 signal and delayed enhancement provide strong supportive findings of the presence of myocardial inflammation, while pericardial enhancement and depressed LVEF are considered supportive findings [45•]. The increased water content of edematous tissue leads to a longer T2 relaxation time when compared with normal myocardial tissue, which manifests as high signal intensity on T2-weighted imaging. However, the qualitative detection of elevated T2 signal relies on regional differences to compare gradients of different signal intensities, and therefore elevated T2 signal may be missed in the presence of diffuse myocardial inflammation. For this reason, there is a shift in the CMR community to utilize quantitative T2 imaging when available, as this may increase the sensitivity to detect diffuse myocardial inflammation through the quantification of native T2 values [45•].

Vascular assessment

Evaluation of myocardial perfusion

The mechanisms of chemotherapy-mediated vascular toxicities are diverse, and often involve excess reactive oxygen species (ROS) leading to the release of pro-inflammatory cytokines and disrupted cell signaling, causing endothelial

damage and vasoconstriction of both the epicardial and microvascular coronary beds. Several classes of agents are implicated in these vascular sequelae including anthracyclines, antimetabolites, VEGF inhibitors, HER-2 inhibitors, and immune checkpoint inhibitors (CPIs) [2]. EBRT can also induce accelerated onset of epicardial coronary artery disease (CAD) in a dose-dependent manner [46]. Resting perfusion defects have been appreciated in these patients [47], and may be the result of accelerated epicardial CAD, microvascular CAD, or direct myocardial damage. Although there are a myriad of non-invasive means to work up epicardial CAD, the diagnosis of microvascular CAD has remained somewhat of a diagnosis of exclusion in patients with angina, inducible ST depressions, and normal epicardial coronary arteries [48]. The index of microvascular resistance (IMR) has been established as an invasive measure of microvascular dysfunction [49]; however, this procedure carries risks. For this reason, efforts have been made to bolster the non-invasive evaluation of microvascular CAD. This has initially been fulfilled by measuring coronary flow reserve (CFR) with positron emission tomography (PET) imaging [50]. However, similar concepts of myocardial blood flow quantification have been validated with vasodilator stress CMR [51], and may be useful in the evaluation of cardio-oncology patients with suspected epicardial or microvascular CAD.

Vasodilator stress CMR has been shown to be an effective means to diagnose and risk stratify patients with suspected or known epicardial CAD [52–54]. Additionally, various methods have emerged to quantify myocardial blood flow with vasodilator stress CMR, including Fermi function modeling, model-independent analysis, and Patlak plot analysis, all of which have been shown to demonstrate reproducible myocardial blood flow (MBF) quantification [55]. Early studies have shown that coronary flow reserve (CFR) with CMR correlates well with PET-derived values, although absolute quantification of MBF correlates weakly between these two methods, suggesting the need for further refinement of quantitative MBF derived by CMR [56]. Novel methods of automated quantitative analysis of MBF with CMR have been published, and correlate well with both FFR and IMR, suggesting accurate identification of both epicardial and microvascular CAD [57]. T1 mapping with vasodilator stress can also successfully identify both epicardial and microvascular CAD through attenuated augmentation of T1 signal during stress [58•], as hyperemia causes lengthening of the T1 relaxation time. Stress T1 mapping has been shown to be as accurate as first-pass perfusion with gadolinium, and can be done without the administration of contrast [58•]. Other methods of MBF quantification under investigation that circumvent the need for GBCAs include contrast-enhanced CMR with ferumoxytol [59], which is an iron-based MRI contrast agent. Additionally, coronary sinus flow reserve has been validated as a surrogate for CFR, and only requires phase contrast imaging through the plane of the coronary sinus to allow for quantification of coronary sinus flow at rest and with vasodilator stress. The ratio of these values has successfully predicted outcomes after stress CMR [60].

These new techniques of CMR-based MBF quantification are exciting, and may have value when applied to cancer patients exposed to chemotherapies implicated in vascular toxicities. Preliminary data at our institution show that indices of CMR-based quantitative perfusion correlate with LVEF in breast cancer patients exposed to potentially cardiotoxic chemotherapy, implying that microvascular dysfunction may be related to

CTRCD [61] and could potentially be detected before the onset of overt LV dysfunction. Pilot studies from other institutions have shown that adenosine stress T1 mapping to assess microvascular dysfunction in patients previously exposed to anthracyclines serves as a reasonable alternative to first-pass perfusion with GBCAs [62]. Further studies on larger patient populations are necessary to establish the role of perfusion CMR in characterizing both microcirculatory dysfunction and epicardial CAD in patients exposed to potentially cardiotoxic chemotherapies.

Evaluation of large vessel disease

Aortic pulse wave velocity (PWV) has been applied to measure aortic distensibility, which has been shown to correlate with increased LV afterload, decreased LV function, and increased mortality in the non-oncologic population [63]. These methods have been applied with phase contrast imaging of the ascending and descending aorta to derive flow velocities with velocity-encoded imaging. PWV of the aorta has been shown to increase early after exposure to anthracyclines [31, 64] and trastuzumab, which appears to partially resolve after cessation of treatment [65]. The mechanism of aortic stiffening is unclear, but the resolution of stiffness over time implies endothelial dysfunction rather than a classic mechanism of fibrotic stiffening that is seen with age or hypertension [31]. Further research is required to establish the long-term significance of these findings.

Special conditions

Evaluation of patients exposed to external beam radiation treatment to the chest

Patients exposed to EBRT of the chest are at risk for accelerated onset of CAD, pericardial disease, conduction system abnormalities, valvular heart disease, and heart failure [66]. Accordingly, patients with a history of prior EBRT to the chest presenting with new cardiac symptoms should be approached with these conditions in mind, and CMR can be used as a part of the workup to complement echo and computed tomography (CT). CMR can be protocolled to evaluate specific pathological sequelae of EBRT and should be targeted based on symptoms (Table 1). Cine images provide superior assessment of LV structure and function in patients presenting with heart failure symptoms. CMR can also be used to provide a non-invasive assessment of pericardial constriction in these patients. This can be done with real-time free-breathing short axis cine images to evaluate for septal flattening during inspiration, which is a sign of ventricular interdependence. Additional tagging sequences can be obtained to evaluate for pericardial tethering [67–68]. CMR also allows for characterization of pericardial tissue with both standard T1 and T2 imaging pre-contrast, paired with delayed enhancement imaging to evaluate for pericardial inflammation and thickening [69]. Further distinction can be made between pericardial inflammation and fat with fat-saturation sequences [67]. Vasodilator stress MRI with first-pass perfusion and quantitative analysis of MBF should be considered in these patients who also complain of angina, as the incidence of epicardial and microvascular CAD is high in this patient population [46, 70].

Table 1. Cardiac magnetic resonance imaging–guided evaluation of cancer therapy–induced cardiac toxicity

Exposure	Questions addressed by CMR	CMR protocol and post processing considerations
Cardiotoxic chemotherapy	-LVEF quantification -Pre-clinical CTRCD -Focal LV fibrosis (LGE) -Diffuse LV fibrosis -Left atrial size, function, and fibrosis -Presence of microvascular CAD	-Short axis cine stack -LV strain -Standard LGE imaging -Native T1 mapping with post-contrast ECV -3D LGE imaging of LA, LA size, and LA strain -Myocardial blood flow quantification with vasodilator stress CMR
EBRT	-LVEF quantification -Pericardial constriction -Pericardial tissue characterization -Diffuse LV fibrosis -Microvascular and epicardial CAD -LA fibrosis	-Short axis cine stack -Free breathing and tagging sequences -Addition of fat saturation to differentiate pericardial LGE -Native T1 mapping with post-contrast ECV -Myocardial blood flow quantification with vasodilator stress CMR -3D LGE imaging of LA
Immunotherapy	-LVEF quantification -Pre-clinical CTRCD -Myocardial edema -Pericardial tissue characterization	-Short axis cine stack -LV strain -T2-weighted imaging, T2 mapping, standard LGE -Addition of fat saturation to differentiate pericardial LGE

EBRT, external beam radiation therapy; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *CTRCD*, cancer therapeutics–related cardiac dysfunction; *ECV*, extracellular volume; *LA*, left atrium; *CMR*, cardiac magnetic resonance imaging; *CAD*, coronary artery disease; *LGE*, late gadolinium enhancement

Patients exposed to checkpoint inhibitors

Immune checkpoint proteins such as cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibit T cells in order to prevent unregulated activation of the immune system [71] and have been targeted by contemporary immune CPIs to upregulate the immune response to malignant tissue [72]. These agents have dramatically improved outcomes in cancer treatment; however, the pro-inflammatory mechanism of these medications has the potential to cause autoimmune sequelae in any organ, including the cardiovascular system. This may manifest either subclinically, or with fulminant myocarditis, pericarditis, and life-threatening arrhythmias [73–74]. CMR can aid in the diagnostic workup of patients with suspected CPI-mediated myocarditis, and provides the most comprehensive non-invasive characterization of myocardial edema with both T2 sequences and delayed enhancement imaging.

Although traditional T2-weighted imaging is effective in identifying regional myocardial inflammation, a global inflammatory process may not be as easily appreciable by qualitative assessment of T2-weighted signal, given a lack of regional variation in signal characteristics. To circumvent this issue, some have proposed using a ratio of T2-weighted signal in the myocardium compared with skeletal muscle, which may signify inflammation when elevated above 2.0 [75]. This approach may be

helpful when evaluating myocarditis from CPI use, as this may manifest itself in a more global manner. Indeed, when we investigated a small case cohort at our institution, 9 of 12 patients with suspected CPI-induced myocarditis had elevated T2-weighted values when taken as a ratio of myocardial to skeletal muscle, despite a relatively normal appearance of qualitative T2-weighted imaging [76]. This suggests a more diffuse nature of myocardial inflammation in patients with CPI-induced myocarditis and highlights the need for quantitative T2 imaging in these patients.

Although LGE patterns in acute myocarditis traditionally affect mid-myocardial tissue with predilection for the inferolateral wall, we have found that more variable patterns have been appreciated ranging from high percentage of myocardial involvement [77] to subtle isolated enhancement at the RV insertion site [78]. Although LGE at the RV insertion has been otherwise interpreted as a non-specific finding seen in cardiomyopathies and pulmonary hypertension [79], further investigation is warranted to determine if this may be a more specific signal of CPI-induced myocarditis in an otherwise structurally normal heart. Future directions in identification of toxicity in this disease state include the incorporation of hybrid PET/CMR imaging and the application of molecular CMR imaging platforms.

Conclusions

CMR provides advanced tools to diagnose and monitor cardiac toxicities related to cancer therapies, given its high spatial resolution for structural and functional assessment, and the unique ability to characterize myocardial tissue with both qualitative and quantitative assessments of myocardial fibrosis and inflammation. Special applications of CMR to assess for cancer therapy–induced cardiac toxicity include the detection of subclinical LV dysfunction through novel methods of measuring myocardial strain, detection of microcirculatory dysfunction, identification of diffuse LV and LA fibrosis, and more sensitive detection of inflammatory myopathy caused by immune CPIs. Further research is warranted in these areas to further establish and expand the role of CMR in the non-invasive workup of cancer therapy–related cardiac toxicity.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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