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Noninvasive Imaging of Cardiovascular Injury Related to the Treatment of Cancer

CME

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CME Objective for This Article: After reading this article the reader should be able to: 1) review the categories of potentially cardiotoxic agents associated with treatment for breast cancer; 2) understand the relationship between cancer-related therapies, associated measures of left ventricular ejection fraction, and the future occurrence of cardiovascular events; and 3) review the current information pertaining to global longitudinal strain assessments with transthoracic echocardiography and T1 and T2 related mapping results obtained from cardiovascular magnetic resonance and coronary artery calcium scores obtained from computed tomography for identifying those individuals that may be at risk of cardiovascular dysfunction upon receipt of treatment for cancer.

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ABSTRACT

The introduction of multiple treatments for cancer, including chemotherapeutic agents and radiation therapy, has significantly reduced cancer-related morbidity and mortality. However, these therapies can promote a variety of toxicities, among the most severe being the ones involving the cardiovascular system. Currently, for many surviving cancer patients, cardiovascular (CV) events represent the primary cause of morbidity and mortality. Recent data suggest that CV injury occurs early during cancer treatment, creating a substrate for subsequent cardiovascular events. Researchers have investigated the utility of noninvasive imaging strategies to detect the presence of CV injury during and after completion of cancer treatment because it starts early during cancer therapy, often preceding the development of chemotherapy or cancer therapeutics related cardiac dysfunction. In this State-of-the-Art Paper, we review the utility of current clinical and investigative CV noninvasive modalities for the identification and characterization of cancer treatment-related CV toxicity. (J Am Coll Cardiol Img 2014;7:824–38) © 2014 by the American College of Cardiology Foundation.

Advancements in the treatment of cancer occurring over the past 3 decades have resulted in decreased cancer-related morbidity and mortality, and increased long-term survivorship. Today, data from billing codes related to cancer patients indicate that cardiovascular (CV) disease (CVD) is the leading cause of death among breast cancer survivors, replacing recurrent cancer or development of a new cancer (1). In childhood cancer survivors (2,3), the risk of CV death is now higher than the actual risk of tumor recurrence (with a reported 7-fold increase in cardiac mortality rate relative to siblings without cancer).

In this paper, we review the cancer therapies and their associated CV events, existing noninvasive imaging study results highlighting methods to detect early evidence of CV injury upon receipt of treatment for cancer, and emerging noninvasive imaging technologies that may further enhance the detection of CV injury. Results of several studies raise the possibility that noninvasive imaging may be useful for identifying CV injury after receipt of cancer treatment.

CARDIOVASCULAR INJURY FROM CANCER TREATMENT

The type and duration of cancer treatment still plays an important role in determining CV injury or toxicity. Cardiovascular toxicity can be caused by: 1) direct injury to or death of cardiac myocytes; 2) stimulation of myocardial fibrosis; 3) provocation of stress induced myocardial ischemia via endothelial dysfunction; 4) vascular injury; 5) myocardial and/or pericardial inflammation; 6) arrhythmogenic or conduction abnormalities; 7) autonomic dysfunction; 8) valvular disease; or 9) exacerbation of known CV risk factors (e.g., hypertension, accelerated atherosclerosis, or Raynaud's syndrome, etc.) (4,5). In addition to traditional cardiotoxic agents, such as anthracyclines or radiation-related heart disease, newer therapies including tyrosine kinase inhibitors (6–11) and even therapies that are not necessarily classified as "chemotherapy" may also promote CV disease or events. For example, the administration of hormone deprivation therapies, which have dramatically reduced cancer recurrence and improved survival in women with breast cancer or men with prostate cancer, are now increasingly associated with CV events (12–16). Online Table 1 in the Online Appendix presents a summary of the types of cardiac injuries, the agents that commonly cause these injuries, and noninvasive investigations to determine the extent of these injuries.

CURRENT CLINICAL NONINVASIVE IMAGING STRATEGIES FOR SCREENING CANCER TREATMENT-RELATED CARDIOTOXICITY

A literature review from the American Society of Clinical Oncology has recently noted that there are no available systematic evaluations published regarding the role of routine noninvasive testing for cardiac dysfunction in patients treated for cancer. Moreover, the effectiveness of screening techniques for detecting subclinical CV injury in asymptomatic survivors of cancer is not established. Yet, there are recent research initiatives suggesting the possible utility of noninvasive imaging technologies for identifying subclinical CV injury in those receiving treatment for

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

CMR = cardiovascular magnetic resonance

CV = cardiovascular

CVD = cardiovascular disease

ERNA = equilibrium radionuclide angiography

ERNV = equilibrium radionuclide ventriculography

FDG = ^{18}F-fluorodeoxyglucose

GLS = global longitudinal strain

IVRT = isovolumic relaxation time

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

LVMi = left ventricular mass index

MIBG = metaiodobenzylguanidine

MRS = magnetic resonance spectroscopy

PFR = peak filling rate

SPECT = single-photon emission computed tomography

and surviving cancer. In the following sections, we provide an overview of the data accumulated to date that address the utility of noninvasive imaging strategies for assessing cancer therapy related to CV disease.

NUCLEAR MEDICINE IMAGING. The first studies of cancer therapy-related cardiac toxicity relied on equilibrium radionuclide angiography (ERNA) to measure left ventricular (LV) function through determination of LV ejection fraction (LVEF). Established in the 1970s, reductions in LVEF identified those with anthracycline-related cardiotoxicity; in the single largest study using serial ERNA, 19% of patients who dropped their LVEF by >10% from baseline, or to a value <50% went on to develop heart failure (17). Today, ERNA is used to identify LV dysfunction from other cardiotoxic agents (17,18).

In addition to resting measures of LVEF, investigators have also assessed the utility of ERNA stress-induced changes in LVEF as markers of early anthracycline induced cardiomyopathy. McKillop et al. (19) found that the sensitivity for detecting patients that may develop heart failure increased from 58% to 100%, but this occurred with a concomitant decrease in specificity from 75% to 41%. Thus, to date, stress nuclear assessments of LVEF to identify cardiac injury after receipt of anthracycline are not widely performed.

In addition to systolic dysfunction, LV diastolic function is often assessed with radioisotope-based techniques. Count-time curves, the peak filling rate (PFR), the PFR normalized to stroke volume, and time-to-peak filling rate detected with planar equilibrium radionuclide ventriculography (ERNV) are associated with anthracycline-induced diastolic dysfunction (20,21). Reductions in these ERNV measures of LV diastolic function correlate with the simultaneous decreases in LVEF, suggesting that anthracyclines impair both systolic and diastolic function (21). Moreover, a recent study by Cochet et al. (22) demonstrates that baseline prolongation of time-to-peak filling rate (which reflects impairment of diastolic function before treatment) is an independent predictor for trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer.

It is important to recognize that although ERNA is widely available for identifying LV dysfunction associated with chemotherapy-related cardiotoxicity (17,20,23,24), there are limitations to the procedure. First, the procedure exposes patients to an ionizing radiation dose (estimated at 7.8 mSv per examination). This is problematic for childhood cancer patients or those who receive repeated exposures by surveillance protocol guidelines. Second, the procedure produces little information regarding other cardiac parameters such as those related to valvular structure or the pericardial space. Finally, the technique is not well suited for detecting small changes in LVEF or direct measures of myocardial injury that may provide important evidence of early injury that predispose one to future CV events.

In patients with heart failure, the single-photon emission computed tomography (SPECT) and positron emission tomography (PET) techniques using radiolabeled neurotransmitters and receptor ligands have been used to evaluate pre-synaptic reuptake, neurotransmitter storage, and also activity of post-synaptic receptors (25–27). Metaiodobenzylguanidine (MIBG) is a quanethidine analog that shares type I adrenergic neuroreceptor uptake storage and release mechanisms throughout the body with norepinephrine (25–27). After being labeled with ^{123}I, uptake of regional ^{123}I-MIBG reflects neuronal integrity, and its release reflects adrenergic function (25–27). Calculation of the heart-to-mediastinum count ratio of ^{123}I-MIBG uptake and delay in the 4-h post-injection washout rates have been observed in patients with heart failure or those receiving anthracycline-based chemotherapy. Also, a decrease in the heart-to-mediastinum count ratio correlated with a higher cumulative dose of anthracycline (27–29). Decreases of MIBG uptake may be seen up to 10 years after development of heart failure in patients with a history of severe anthracycline-induced cardiomyopathy, regardless of recovery of LV function. These findings suggest myocardial cell injury and adrenergic dysfunction from destruction of adrenergic nerve tissue and functional alteration or adrenergic nerves by cytotoxic effect of itself, as in animal or human models, may persist for years after the initial exposure to anthracyclines (30,31).

ECHOCARDIOGRAPHY. Its wide availability and absence of nonionizing radiation render echocardiography a very attractive imaging option for assessing patients with cardiac abnormalities during or after cancer treatment (32–37). In addition to evaluating LV structure, echocardiography provides information on both systolic function (LVEF and fractional shortening in the pediatric population), and diastolic function (E/A ratio, E/e′, e′, isovolumic relaxation

time [IVRT], and pulmonary venous flow) (38–44). Also, recent techniques have become available to measure myocardial deformation, including LV strain, strain rate, or twist and torsion that may provide new understanding regarding the early stages of the pathophysiology of cardiac dysfunction upon receipt of cancer treatment (37,45–50). Moreover, echocardiography provides additional information about valvular function and pericardial fluid/physiology that might occur after cancer treatment (32,51,52).

From a standard 2-dimensional (2D) echocardiogram, LVEF can be estimated visually, or quantified by M-mode (the fractional shortening method), single or biplane area-length methods, or the modified Simpson summation of disks technique as per American Society of Echocardiography chamber quantification guidelines (53). In general, CV medicine consultations should be considered for those patients experiencing reductions in LVEF of ≥5% to <55% with symptoms of heart failure, or an asymptomatic reduction in the LVEF of ≥10% (54,55). It is important to note, however, that although 2D echocardiography can identify relatively large drops in LVEF (e.g., from 60% to 40%), smaller changes such as from 54% to 48% are more difficult to obtain with a high degree of certainty (17,23,56).

To address this limitation, 3-dimensional (3D) methods are now available to improve the detection of small changes in LVEF (40,42). Recently, Thavendiranathan et al. (57) demonstrated that 3D echocardiography was more reproducible and had lower interobserver variability LVEF and volume measurements. This finding correlated well with a previous study by Walker et al. (35) that found the technique to be more accurate when compared with 2D, and not inferior when compared with multigated acquisition scanning and cardiac magnetic resonance. To date, however, researchers have not accomplished the utilization of 3D echocardiographic strategies in measuring LVEF on a large scale in community hospitals or clinically in large numbers of patients treated for cancer for the purpose of detecting CV injury.

Some studies have shown that LV diastolic properties, such as a decrease in the E/A ratio, or prolongation of IVRT or deceleration time of early diastolic filling can predict doxorubicin-induced LV systolic dysfunction (58,59). However, other studies have not observed a relationship between changes in diastolic measures and long-term changes in LVEF (60,61). In fact, increases in the E/A ratio and shortening of IVRT occurring 1 h after administration of the first dose of doxorubicin can return to pre-chemotherapy levels within 3 weeks (60,61). Given the transient nature of these diastolic findings, they have not been widely utilized to direct cardioprotective strategies to prevent chemotherapy-related cardiotoxicity.

One newer measure that may be helpful to identify cardiac injury includes the assessment of global longitudinal strain (GLS) (**Fig. 1**) (39,41). In general, longitudinal LV mechanics are the most vulnerable and highly reproducible component of LV mechanics that can be assessed with well-performed transthoracic echocardiography (39–41). Stoodley et al. (50) demonstrated that anthracycline chemotherapy can reduce global and regional longitudinal and radial strain by more than 10% as early as 1 week after receipt of treatment. This corresponds well with results by Sawaya et al. (37) in which reduced global longitudinal and radial strain after 3 months of cancer treatment with an anthracycline and trastuzumab predicted the later development of a reduction of LVEF 6 months after initiation of these therapies. In this same study, reductions in longitudinal strain of >10% from baseline predicted future declines in LVEF with a sensitivity of 78% and specificity of 79%, and a negative predictive value of 93%. Abnormalities of global measures of longitudinal strain evaluated in combination with determinations of ultrasensitive troponin I measured at the completion of treatment may prognosticate subsequent development of LV dysfunction 12 and 15 months after completion of chemotherapy treatment ($p = 0.0003$ and $p = 0.04$, respectively) (62,63). In a recent systematic review, a 10% to 15% early reduction in GLS by speckle tracking echocardiography during therapy appears to be the most useful parameter for the prediction of cardiotoxicity defined as a drop in LVEF or heart failure (64).

Myocardial twist, untwist, and torsion of the LV apex have been studied with transthoracic echocardiography. Myofilament disorganization and cardiomyocyte necrosis impact the passive and restoring forces of the ventricle in in vitro animal model studies (43,65). To this end, Motoki et al. (48) identified deterioration in LV apical and torsion, twisting rates, and untwisting rates 1 month after chemotherapy that correlated with prolongation of IVRT 3 months after chemotherapy. However, this finding did not forecast future reductions in LVEF or CV events. Cheung et al. (45) demonstrated that 1 year after treating children with acute lymphoblastic leukemia, LV apical torsion and twisting and untwisting velocities were reduced. Future studies are required to determine the prognostic utility of echocardiographic measures of twist and torsion in those treated for cancer.

The role of microbubble contrast in assessing cardiac function after treatment for cancer is not well

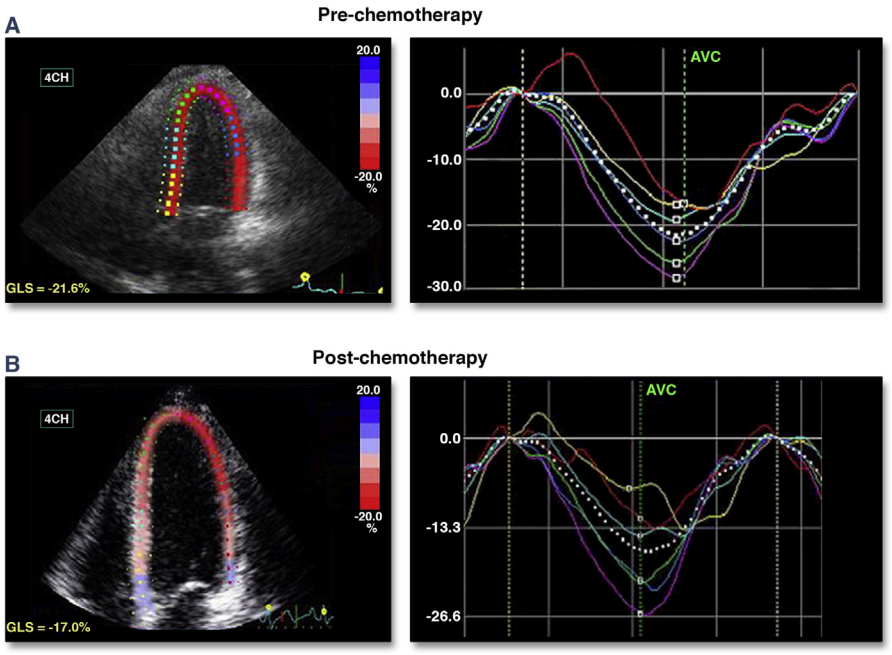

FIGURE 1 2D Speckle-Tracking Echocardiogram-Based Strain in a Patient With Invasive Ductal Carcinoma

A patient with invasive ductal carcinoma (estrogen receptor negative, progesterone receptor negative, human epidermal growth factor receptor 2/neu positive), treated with the TCH regimen (docetaxel, carboplatinum, and trastuzumab), had a baseline ejection fraction (EF) of 65%. The EF after 3 months of therapy was 58%. **(A and B)** utilize color to illustrate the global longitudinal strain (GLS) and regional strain values obtained at baseline (pre-chemotherapy) and 3 months after the initiation of trastuzumab-based regimen. The septal and anteroseptal segments exhibit abnormal regional strain after treatment. (Courtesy of Dr. Juan Carlos Plana, MD, FACC, Co-Director Cardio-Oncology Center, Cleveland Clinic, Cleveland, Ohio). 2D = 2-dimensional; AVC = aortic valve closure.

studied and has produced conflicting results related to its overall utility. In those patients with poor LV endocardial visualization, the American Society of Echocardiography suggests the intravenous administration of microbubble contrast may improve assessment of LV wall motion and LVEF post-cancer treatment, especially in those undergoing mastectomy or breast implants (66). However, recently, Thavendiranathan et al. (57) demonstrated that in breast cancer patients post-chemotherapy with stable measures of GLS, noncontrast 3D assessments of LVEF exhibited lower temporal variability in comparison with contrast-based methods.

CARDIOVASCULAR COMPUTED TOMOGRAPHY. The use of cardiovascular computed tomography to assess the CV system after treatment for cancer and to forecast future CV events has not been well studied. This technology may be useful in 2 respects: first, for evaluating the pericardium of patients that received radiation or surgical treatments to identify abnormal thickening and calcification of the pericardium, and second, to measure coronary artery calcium or directly visualize the coronary arteries (67). Although coronary artery calcium scores are elevated when mediastinal radiation is administered at doses >20 Gy (68,69), and anthracycline chemotherapy has been associated with accelerated atherosclerosis (69–72), in the absence of symptomatic coronary artery disease, there is currently insufficient data to recommend the routine use of coronary CT angiography or calcium scoring in patients who underwent high-dose radiation therapy. In addition, the presence of coronary artery calcification before treatment for cancer has not been shown to predict future CV risk upon receipt of chemotherapy, tyrosine kinase inhibitors, or radiation therapy. For these reasons, cardiovascular computed tomography has not been widely used to screen for adverse subclinical CV disease after cancer treatment or predict CV risk pre-cancer treatment. Whether existing planning or surveillance images acquired as components of clinical exams used to stage cancer could be used for these purposes requires further study (68–73). At present, information related to the CV system is often not reported on

these relatively routinely acquired cancer surveillance studies.

CARDIOVASCULAR MAGNETIC RESONANCE. Cardiovascular magnetic resonance (CMR) is a versatile imaging modality in that with a single examination, one can gather information pertaining to cardiac and vascular anatomy, tissue characteristics (presence of fibrosis, inflammation, injury, etc.), left and right ventricular systolic or diastolic function, blood flow, and myocardial perfusion or metabolism (35,42,57,74). These assessments are accurate and reproducible, exhibit high spatial and temporal resolution, and do not expose individuals to ionizing electromagnetic radiation. For this reason, the American College of Cardiology/American Heart Association recognizes CMR as a method to identify CV dysfunction after treatment for cancer and has incorporated it across research studies to define the pathophysiology of cancer treatment-related CV toxicity (75). In addition, CMR can detect myocardial masses associated with metastases, or evaluate the pericardium and pericardial space, and when necessary, assess valuable function (76).

Researchers and clinicians have used LV myocardial mass, volume, and systolic and diastolic function assessments measured from cine white blood imaging sequences to identify evidence of cardiomyopathy among adult cancer survivors (77). Neilan et al. (78) demonstrated an inverse correlation between anthracycline dosage and CMR-derived LV mass index (LVMi) ($r = 0.67$; $p < 0.001$), and an association of LVMi with major adverse CV events (hazard ratio: 0.89, $p < 0.001$). These results indicated a sensitivity of 100% and specificity of 85% to predict major adverse CV events if the LVMi was ≤ 57 g/m^2 after treatment with anthracycline chemotherapy.

In addition to reductions in LV mass, an increase in LV cavity end-systolic volume is associated with the subsequent reduction in LVEF after treatment with trastuzumab or anthracycline-based chemotherapy (35,79,80). Drafts et al. (80) followed 51 subjects treated with anthracycline-based chemotherapy and identified early increases in LV end-systolic volume commensurate with deteriorations in LVEF, myocardial strain, and ability to perform activities of daily living. In addition, these cardiac and of quality-of-life metrics occurred commensurate with increases in serum troponin levels (35,76,77).

A unique feature of CMR is the ability to characterize myocardial tissue by the use of relaxation times (T1, T2, and T2*) in order to identify myocardial injury and fibrosis. Specifically, T2-weighted images are sensitive to regional or global increases of myocardial water content that accumulates in the setting of myocellular or microvascular injury or inflammation (81). A previous small study by Oberholzer et al. (82) identified myocardial edema from a T2-weighted study post-anthracycline treatment. Further research is ongoing regarding the utility of T2 mapping techniques of the LV myocardium in patients receiving treatment for cancer (83).

In addition to assessing myocardial T2 relaxation, properties related to T1 relaxation may also provide insight regarding myocardial injury and fibrosis related to the administration of chemotherapy. In rodent models, Lightfoot et al. (84) demonstrated that an increase in gadolinium-enhanced signal intensity on T1-weighted images after treatment with doxorubicin was associated with histopathological evidence of intracellular vacuolization (consistent with doxorubicin-induced cardiotoxicity) and forecasted a subsequent reduction in LVEF. In a clinical study by Wassmuth et al. (85), an increase of gadolinium signal intensity on post-contrast T1-weighted images within 3 days of the receipt of anthracycline infusions predicted a significant decline in LVEF at 28 days ($p < 0.05$). Tham et al. (86) demonstrated that changes in myocardial T1 values occurred in children post-exposure to anthracycline without correlation to anthracycline levels. Long-term clinical outcome studies are needed to determine whether T1/T2 mapping findings are associated the adverse clinical CV outcomes in patients treated for cancer.

Myocardial fibrosis by late gadolinium enhancement (LGE) is associated with an adverse CV prognosis in patients with coronary artery disease, hypertrophic cardiomyopathy, or infiltrative diseases such as amyloidosis and sarcoidosis (86). For those treated for cancer, data pertaining to the association of LGE with cancer treatment are mostly anecdotal or observational, and somewhat conflicting in regard to reported results. In a chemotoxic cardiomyopathy study by Catalano et al. (87), mid-myocardial LGE is shown in the mid-basal septum and anterior, basal anterolateral, and mid-inferior walls after treatment with anthracycline/cyclophosphamide, and a study by Fallah-Rad et al. (79,88) demonstrates mid-myocardial LGE patterns in the lateral wall after treatment with trastuzumab for 12 months. By contrast, Neilan et al. (78) determined that LGE is an infrequent finding occurring in only 6% (5 cases/91 cases) of patients treated with anthracycline-base chemotherapy despite a reduced LVEF. In addition, a study by Bittner et al. (89) demonstrated that LGE occurs only in 8% (2 cases/25 cases) of patients treated with adjuvant trastuzumab without any change in systolic function or routine diastolic filling parameters.

In addition to functional and structural abnormalities pertaining to the heart, treatment for cancer with hormonal deprivation agents, tyrosine kinase inhibitors, or anthracyclines may impact the vasculature and thereby contribute to other CV events such as stroke and myocardial infarction. Recently, Chaosuwannakit et al. (90) demonstrated that proximal aortic wall stiffness increased 3 months after receipt of anthracycline-based chemotherapy after controlling for factors such as age, sex, diabetes, hyperlipidemia, and hypertension. The increase in stiffening occurred soon after administration of chemotherapy, was not dose dependent, and was equivalent to that associated with aging the CV system by 10 to 20 years (Fig. 2). In other patient populations, such as those with diabetes, hypertension, renal failure, and advanced age, abnormal increases in proximal aortic stiffness have been associated with LV hypertrophy, exercise intolerance, and future CV events (91).

It is important to note that although CMR is accurate and reproducible, it does not expose one to ionizing radiation, and assesses multiple aspects of the CV system in a single exam, its availability is relatively low and is not well suited for use in those with cardiac pacemakers, cardiac resynchronization therapy devices, internal cardiac defibrillators, or intracranial metal. Moreover, in patients with renal insufficiency (estimated glomerular filtration rates ≤30 ml/min), precaution is needed when gadolinium contrast is considered because of an increased incidence of nephrogenic systemic fibrosis (92).

INVESTIGATIVE NONINVASIVE IMAGING STRATEGIES FOR SCREENING CANCER TREATMENT-RELATED CARDIOTOXICITY

In addition to current clinical applications, there are additional initiatives underway in research venues to image processes involved in cancer therapy-related

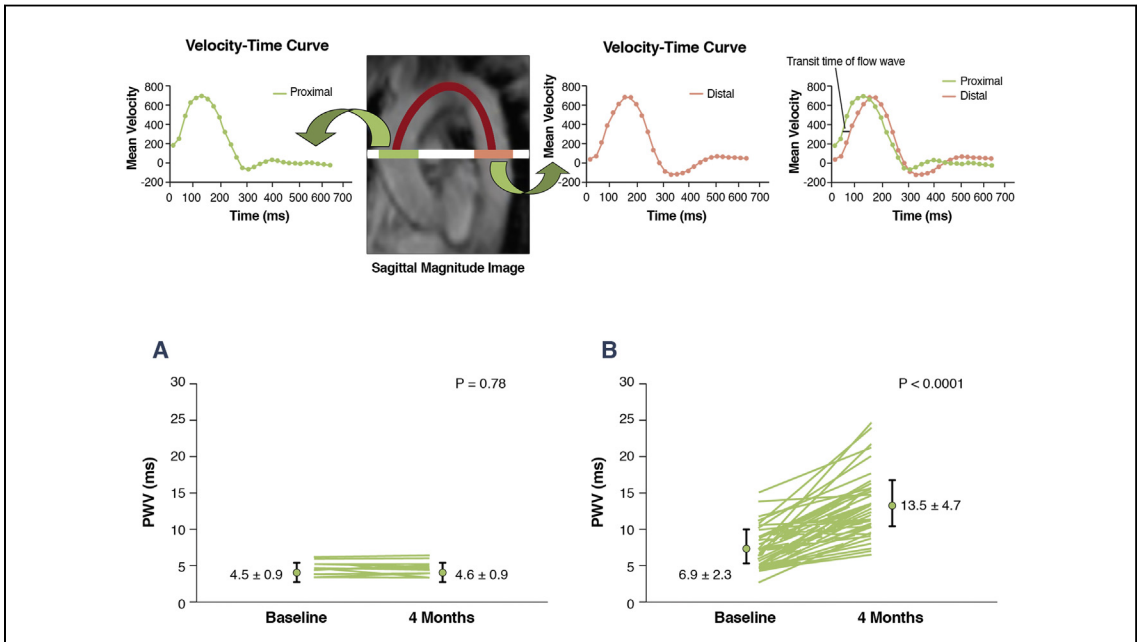

FIGURE 2 PWV Assessments of Aortic Stiffness After Cancer Treatment

Sagittal magnitude image of the thoracic aorta was used to select the axial plane at the level of the pulmonary artery and perpendicular to aortic flow **(solid white line)**. The distance between ascending and descending thoracic aortas was obtained by tracing the centerline of the aortic lumen **(red line)**. The 2 velocity-time curves are shown across the thoracic aorta. The sagittal magnitude image demonstrates the velocity-time curves for the ascending and descending thoracic aortas. Transit time of the flow wave was computed on the basis of the upstroke time difference of the velocity-time curve at 2 different regions **(green line)**. The location of the best cross-correlation of 2 partial upstroke velocity curves was used to estimate the time delay. Pulsed wave velocity (PWV) was calculated by dividing the distance between the ascending and descending thoracic aortas by the transit time of the flow wave. Cardiac magnetic resonance-derived aortic stiffness was determined by the measurement of the PWV between control participants without cancer **(A)** and participants who are receiving cancer therapy **(B)** at baseline and after 4 months of treatment. As shown, the PWV increased in participants receiving anthracycline-based therapy. The magnitude of the increase in PWV is equivalent in other populations to an aortic-stiffness age-associated increase of 15 years. Reprinted with permission from Chaosuwannakit et al. (90).

CV injury. These include molecular and metabolism-targeted imaging. These forms of imaging characterize biological processes at the cellular and molecular level within living organisms, utilizing injectable imaging agents or genetically encoded reporters. Although originating with targeted nuclear imaging, there are now a variety of imaging agents and modalities evolving as methods to detect cardiotoxicity after treatment for cancer (88,93).

IMAGING OF APOPTOSIS AND CELL DEATH. Apoptosis, the physiological adenosine triphosphate (ATP)-dependent, noninflammatory process of programmed cell death resulting in fragmentation and shrinkage of nuclear material, or myocyte death culminates in the activation of a variety of proteins that can serve as imaging biomarkers. Phosphatidylserine (PS), one such protein, is expressed on the cell membrane and serves as a noninvasive imaging biomarker of apoptosis (88,93,94).

Annexin V—a high-affinity calcium-depending PS-binding protein conjugated to radioisotopes (such as ^{99m}Tc) in SPECT imaging, to magnetic iron oxide nanoparticles and gadolinium-containing liposomes in CMR, to positron emitters in PET, and to fluorescence markers in optical imaging—has been used to detect in vivo cell death that is due to myocardial infarction, heart transplant rejection, and end-stage LV dysfunction in human subjects, and cancer-related therapy in animal models. In animal studies of acute and chronic doxorubicin cardiac toxicity, a significant increase in ^{99m}Tc-Annexin V uptake in the myocardium, with dose-dependent cell death confirmed by histopathology and immunohistochemistry, was related to subsequent ventricular dysfunction confirmed by echocardiography (95–97). Recently, Annexin V-based magnetofluorescent superparamagnetic iron oxide nanoparticles in combination with T2*-weighted CMR revealed diffuse myocardial T2* signal loss that correlated with increased caspase activity in an animal receiving anthracyclines (98).

Another imaging-related biomarker of cellular apoptosis relates to the activation of caspase proteins. Activation of caspases is associated with cellular apoptosis. In animals, a significant increase in caspase-3 activity has been observed within LV myocardium after treatment with doxorubicin (99,100).

INFLAMMATION IMAGING. Inflammatory injury to cardiac myocytes disrupts the cellular membrane promoting the release of a myosin heavy chain. Investigators developed monoclonal antibodies, ^{111}In and ^{99m}Tc, to identify these heavy chains and thereby assess the degree of myocyte damage in response to inflammation. Studies by Valdes Olmos et al. (101) and Maini et al. (102) both show positive correlation between the cumulative dose of anthracycline and the uptake of antimyosin in the myocardium, with later deterioration of LVEF (101,102) (**Fig. 3**). Importantly, however, the specificity of ^{111}In-antimyosin scintigraphy is low (25% to 50%) for predicting decrements in LVEF 12 months after receipt of cancer treatment (78).

MYOCARDIAL METABOLISM IMAGING. Magnetic resonance spectroscopy (MRS) imaging can assess multiple metabolic pathways simultaneously without exposure to ionizing radiation. The principle of MRS is that the chemical shift influences the different resonance frequencies, allowing for the differentiation of nuclei of the same species in different molecules. MRS allows direct measurement of biochemical information about in vivo processes involving phosphorous (^{31}P), hydrogen (^{1}H), carbon (^{13}C), sodium (^{23}Na), nitrogen (^{15}N), and fluorine (^{19}F). Currently, only ^{31}P has been studied in the assessment of doxorubicin-related cardiotoxicity. In animals receiving doxorubicin, phosphocreatine to adenosine triphosphate ratios (103) and phosphocreatine levels (89) differed after stress compared with those not receiving doxorubicin. These pre-clinical data suggest that MRS may be able to detect abnormal mitochondrial ATP production/utilization related anthracycline therapy.

Myocardial fatty acid metabolism assessed with the SPECT radiotracers IPPA [15-(*p*-iodophenyl) pentadecanoic acid] and BMIPP (^{123}I-betamethyl-p-iodophenyl pentadecanoic acid) have been measured in subjects receiving anthracycline and other chemotherapeutic agents. A study by Saito et al. (104,105) demonstrated early decreased uptake of ^{123}I-BMIPP in patients with preserved LV function after treatment with an anthracycline; similar decreases in ^{123}I-BMIPP uptake were observed in patients experiencing a decline in LVEF after receipt of a taxane and carboplatin. Recently, Carboni et al. (106) evaluated mitochondrial metabolism with ^{99m}Tc-sestamibi in patients receiving multiagent chemotherapy. These investigators demonstrated both early and delayed cardiac ^{99m}Tc-sestamibi uptake with rapid washout rates reflective of mitochondrial membrane dysfunction that were associated with an adverse cardiovascular prognosis (106).

PET with its ability to quantify myocardial blood flow, oxygen extraction (using ^{15}O as a tracer), myocardial glucose metabolism, and fatty acid metabolism has been preliminarily investigated regarding the detection of cardiac toxicity after receipt of cancer

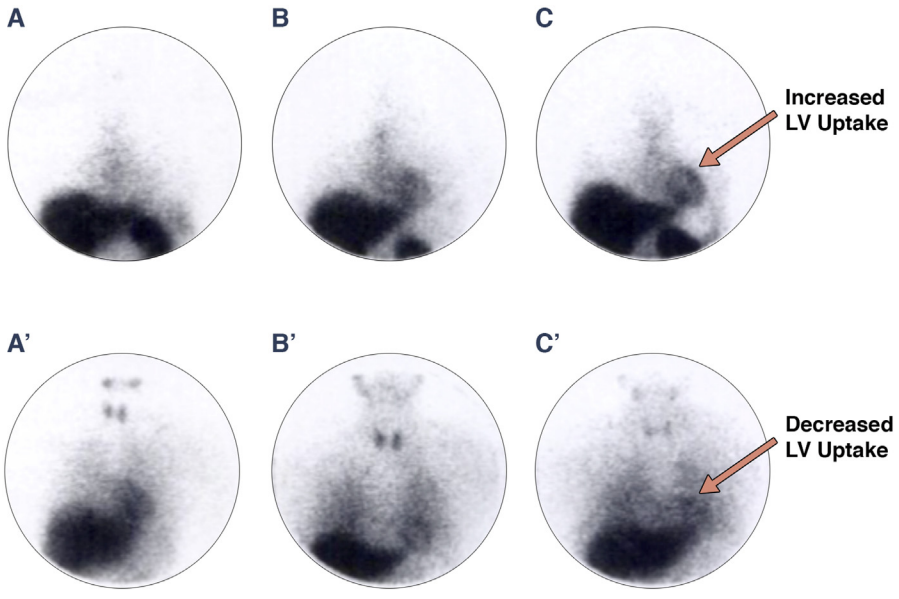

FIGURE 3 Sequential Antimyosin and MIBG Studies Before Chemotherapy

Sequential antimyosin **(A, B, and C)** and MIBG **(A′, B′, and C′)** studies before chemotherapy **(A and A′)** at 240 to 300 mg/m^2 **(B and B′)** and at 420 to 600 mg/m^2 **(C and C′)** of doxorubicin. There is a pattern of increasing myocardial antimyosin uptake with decreasing myocardial metaiodobenzylguanidine (MIBG) uptake, both reflecting ongoing myocellular injury from anthracycline-based chemotherapy. Reprinted with permission from Carrió et al. (28).

treatment. A recent study by Borde et al. (107) demonstrated enhanced myocardial ^{18}F-fluorodeoxyglucose (FDG) uptake in patients treated with anthracyclines. In addition, Toubert et al. (108) demonstrated decreased myocardial uptake of ^{18}F-FDG in patients treated with a combination of tyrosine kinase inhibitors (imatinib and sorafenib) who later developed a cardiac event. It is important to note that FDG uptake is nonspecific and its uptake can change after other disease processes such as diabetes, and thus, fasting status and pre-scan diet must be considered when interpreting the study results.

ANGIOGENESIS IMAGING. Angiogenesis is generally defined as the development of new capillaries from pre-existing microvessels. This complex multistep process involves a variety of cells responding to both stimulatory and inhibitory factors. Several conditions stimulate the angiogenic process, including: ischemia, hypoxia, inflammation, shear stress, and traumatic injury (109). Tumors also modify angiogenesis to enhance their blood supply. For this reason, therapy directed to prevent tumor-associated angiogenesis ("antiangiogenesis therapy") has become one of the cornerstones of many modern chemotherapeutic regimens (109). To assess the efficacy of antiangiogenesis therapy, angiogenesis imaging has been developed utilizing: 1) non-endothelial cell targets (molecules associated with monocytes, macrophages, and stem cells); 2) endothelial cell targets (vascular endothelial growth factor [VEGF], integrins, CD13, and syndecan-4); and 3) extracellular matrix proteins (94,109,110).

Although antiangiogenesis therapy has been found useful for treating cancer, it is now recognized that adverse microcirculatory effects (e.g., hypertension, organ dysfunction) of non-tumor-related host organ tissues occurs after administration of these agents (110). Currently, studies have relied on clinical endpoints to identify and determine the functional importance of injury related to these agents. In animals, investigators have explored the use of isotopes or paramagnetic traces linked directly to VEGF receptors and integrin $\alpha_v\beta_3$ to directly monitor progression of angiogenesis within CV tissues exposed to antiangiogenic cancer therapy (94,109,110).

DIRECT IMAGING OF CHEMOTHERAPEUTICS AGENTS. Directly imaging of chemotherapeutic agents is also an area of active research. Thus far, however, results have been somewhat contradictory. For example, Behr et al. (111) observed reduced uptake of

^{111}In-labeled trastuzumab in the myocardium of patients who developed heart failure and arrhythmia, whereas Perik et al. (112) noticed no myocardial uptake in patients who developed severe symptomatic LV dysfunction during treatment with trastuzumab (111,112). Directly imaging the effects of these agents may also depend on the timing of the image acquisition relative to the administration of the cancer treatment. For example, de Korte et al. (113) identified that myocardial HER2 overexpression was upregulated by cardiac stress induced by the anthracycline administration, but was not present in patients receiving non-anthracycline-based regimens months after receiving their treatment.

CURRENT RECOMMENDATIONS IN CV IMAGING

To date, few, if any, guideline statements exist regarding the implementation of noninvasive imaging techniques for the purpose of monitoring patients receiving treatment for cancer. There has, however, been several suggested management algorithms published over the last 10 years. To date, these algorithms have been created for assessment of those receiving radiation, anthracyclines, or trastuzumab.

In regard to assessments of patients receiving radiation therapy, the European Association of Cardiovascular Imaging and the American Society of Echocardiography recently published an expert consensus statement for multimodality imaging evaluation of cardiovascular complications of radiotherapy in adults (114). This document encompasses assessments of LV function, pericardial diseases, and valvular heart disease. Also, in the case of breast cancer, the document addresses issues associated with irradiation of the right and left breasts.

In regard to receipt of anthracycline-based chemotherapy, there are no evidence-based guidelines for CV monitoring during therapy. The only established guidelines for CV monitoring in children during treatment were published in 1992, by Steinherz et al. (23). This report of the Cardiology Committee of the Children's Cancer Study Group suggested an algorithm for the use of echocardiograms or nuclear medicine scans for assessing children scheduled to receive anthracycline-based chemotherapy (50). This particular statement does not address newer methodologies available (biomarkers, advanced imaging with echocardiography or CMR) that may provide evidence of early cardiac or vascular injury before a decline in LVEF or fractional shortening. More recently, the Cardiology Committee of the Children's Cancer Study Group (23) and Lipshultz et al. (115) indicated that echocardiography with its widespread availability and CMR, when echocardiography is not suitable, could be utilized to identify CV injury upon receipt of chemotherapy in children.

For adults, the European Society for Medical Oncology provided recommendations for assessment of adult patients scheduled to receive anthracycline-based chemotherapy (116). Similar to the recommendations produced in 1992 for children, the current suggestions for assessment of anthracyclines in adults remain primarily based on radioisotope, echocardiographic, or CMR assessments of LVEF. As with assessments in children, these recommendations do not incorporate assessments of subclinical CVD that may portend the future occurrence of advanced CV events. Moreover, these suggestions are developed to prevent the occurrence of marked deteriorations in LVEF. *Following either of the children or adult recommendations for monitoring LVEF upon receipt of anthracycline-based chemotherapy does not guarantee the absence of any future CV events should individuals survive their cancer treatment.*

Raschi et al. (117) published algorithms for monitoring LVEF upon receipt of trastuzumab (Herceptin). Unlike the recommendations pertaining to the administration of anthracyclines, the suggestions provided by Raschi et al. do incorporate measurements of serum biomarkers such as troponin and B-type natriuretic peptide. In addition, suggestions for restarting trastuzumab in the setting of patients that recover their LVEF are provided. *However, as with the suggestions to date regarding the administration of radiation therapy and anthracyclines to children or adults, these current recommendations for trastuzumab do not address the development of subclinical CV injury nor protection against the late occurrence of CV events in cancer survivors.* Similar to the suggestions provided for radiation treatment and anthracyclines, the suggestions for assessments of patients receiving trastuzumab are directed primarily at preventing relatively large declines in LVEF.

SUMMARY AND FUTURE DIRECTIONS

As shown in **Figure 4**, there are multiple potential sites and pathways that can be affected by the administration of chemotherapy, and multiple possibilities for clinical (radionuclide, transthoracic echocardiographic, and magnetic resonance) and research developmental (targeted molecular imaging)

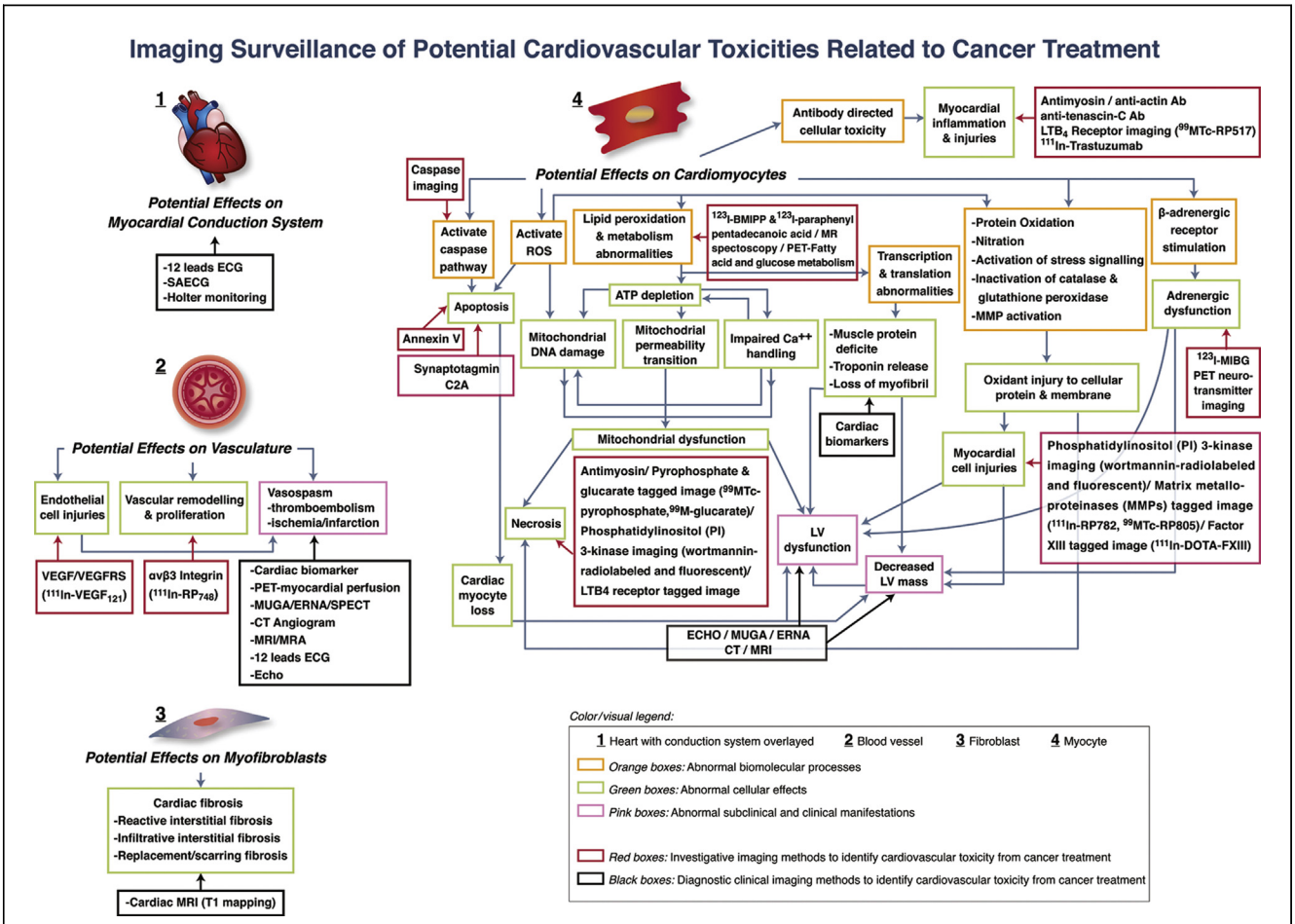

FIGURE 4 Imaging Techniques in Clinical Use and in Development

Opportunities for utilizing existing **(black boxes)** and developmental **(red boxes)** noninvasive imaging technologies for identifying processes associated with myocellular, myofibroblast, myocardial conduction, and vascular injuries associated with the administration of cancer therapies that may adversely impact the cardiovascular (CV) system. As shown, existing technologies identify mainly clinically evident manifestations of CV injury, whereas developmental technologies may facilitate assessment of biomolecular pathways that precede end-organ damage. Ab = antibody; CT = computed tomography; ERNA = equilibrium radionuclide angiography; LV = left ventricular; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography; MUGA = multigated acquisition scanning; PET = positron emission tomography.

methods that may enable detection of the CV effects of cancer treatment.

What then should be the current areas of focus for research in CV imaging as it pertains to the field of cardio-oncology? First, to date, the majority of the management algorithms have focused on the primary use of noninvasive imaging to assess LVEF. Although LVEF is important, it may not reflect the underlying advancements of subclinical CVD that could portend the development of CV events in patients actively treated for or those that survive cancer. Imaging research is necessary to understand the entirety of CV effects after treatment for cancer. This research needs to address therapies beyond the administration of anthracyclines, as shown in Online Table 1.

Second, the array of current and future imaging metrics (Fig. 4) need to be evaluated in terms of predicting future CV events in patients treated for cancer. These imaging-related measures need to be evaluated in the context of existing risk factor prediction models for forecasting risk. Are these imaging markers beneficial and reliable? In which of the patients receiving specific subsets of cancer therapies should the imaging markers be applied? In addition, when should they be utilized, and what are the economic consequences of their use?

Third, does CV imaging have a role in guiding therapy to prevent CV injury after treatment for cancer? If so, how and when should this imaging be implemented, to what extent, and by whom? To date,

CV imaging studies are interpreted primarily by MD or DO physicians with advanced imaging training. Can surveillance imaging programs be designed that utilize this high physician level of expertise in a supervisory rather than a direct interpretive role?

In summary, new advancements related to the treatment of cancer have improved cancer-related survival, but, in many cases, have also increased the risk of CV injury and CV events. To date, noninvasive imaging has been used to assess LVEF before initiation of cancer treatment and in those who develop symptoms after treatment commences. Ongoing and future investigations will help determine the suitability of noninvasive imaging modalities to identify those at risk of developing CV injury upon receipt of cancer treatment and whether noninvasive imaging can be utilized to guide the administration of additional protective therapies to prevent CV injury and events after treatment for cancer. Preventing CV events in patients treated for cancer provides an opportunity to improve overall cancer survivorship and quality of life.

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