Non-invasive cardiac imaging for evaluation of cardiotoxicity in cancer patients - early detection and follow-up

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ABSTRACT

Cardiotoxicity is an increasingly important clinical entity that occurs as a result of untoward, and incompletely understood, effects on cardiac function. It is primarily caused by the anthracycline agents (doxorubicin, daunorubicin) but has also been observed with monoclonal antibody agents such as trastuzumab and small molecule tyrosine kinase inhibitors. The most feared net result of these agents is left ventricular (LV) dysfunction resulting in symptomatic congestive heart failure (CHF). Other manifestations can include arrhythmias, pericardial constriction, valvulopathy and hypertension. Standard cardiac imaging techniques have largely focused on LV ejection fraction (LVEF) quantification. Contemporary cardiac imaging technologies now exist that are capable of evaluating for and detecting earlier stages of cardiotoxicity, including those which occur prior to changes in LVEF. Therapeutic algorithms have been devised to tailor chemotherapeutic regimens based on these results and have resulted in a dramatically reduced incidence of overt CHF.
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BACKGROUND

Cardiotoxicity of chemotherapeutic agents has become an important clinical entity faced by oncologists and cardiologists when treating patients with cancer. It is most commonly caused by anthracycline-based therapies (doxorubicin, daunorubicin) as well as the newer monoclonocal antibodies or small molecule tyrosine kinase inhibitors, most notably trastuzumab (Herceptin). Although the mechanism of cardiotoxicity differs considerably between anthracyclines and trastuzumab, the net result is generally ventricular dysfunction and heart failure. Other manifestations of cardiotoxicity include myocardial ischaemia, arrhythmias, hypertension, pericardial disease, and thromboembolic disease.

The anthracycline agents, such as doxorubicin, are effective agents used in the treatment of breast cancer, ovarian cancer, leukaemia, lymphoma, neuroblastoma, sarcoma and gastric cancer. The mechanism of anthracycline cardiotoxicity is complex but a primary mediator is thought to be oxidative damage to myocytes through free radical formation. This may lead to membrane disruption, extensive cellular dysfunction and ultimately myocyte death. There is a dose-response relationship between dose of doxorubicin and cardiotoxicity with rates of congestive heart failure rising rapidly at mean cumulative doses above 550mg/m$^{2(1)}$. Nevertheless, there is considerable variability among patients receiving doxorubicin, which highlights the need for reliable imaging techniques for monitoring and early identification of cardiac toxicity during and after treatment. Non-invasive cardiac imaging techniques have been widely used for identification of patients with pre-clinical and clinical cardiotoxicity as well as for follow-up. Until recently, these modalities were predominantly limited to echocardiography and radioisotope-based nuclear imaging, but cardiac magnetic resonance has emerged and appears to may have unique advantages over traditional techniques. Coronary computed tomography, likely due to its relative lack of physiologic information, need for ionising radiation and nephrotoxic contrast, has thus far not been widely investigated in this patient population.

NUCLEAR CARDIOLOGY

Identifying patients at risk for the development of cardiotoxicity is paramount to the identification, early treatment and prevention of clinical forms of cardiomyopathy. Radionuclide-based techniques, through equilibrium radionuclide angiocardiography (ERNA), gained favour in the late 1970s as a reliable method to quantify left ventricular ejection fraction (LVEF). More recently, interest has grown in the use of molecular based imaging with targeted agents such as Iodine-123 MIBG for neuronal imaging, Indium-111 anti-miosin for myocardial necrosis and Tc-99m–labelled annexin V for

imaging cell death or apoptosis.[2] Lastly, targeted cardiac imaging with Positron Emission Tomography (PET) may be able to detect early cell death due to doxorubicin.

Equilibrium Radionuclide Angiocardiography (ERNA)

ERNA, also known as a MUGA scan (multi-gated acquisition), involves tagging a patient's red blood cells with a radionuclide agent, technetium-99m, using an in-vivo or in-vitro technique. The tagged red blood cells are typically re-injected followed by image acquisition 15-30 minutes later depending on technique. Importantly, image acquisition is gated to the patient's cardiac rhythm at rest via an ECG monitor and 300-600 heartbeats are obtained on average over 5-10 minutes. A minimum of 16 frames should be acquired per cardiac cycle, but 24 to 32 frames provide better temporal resolution and are preferred for LVEF calculation. The patient is imaged in 3 standardised views: left anterior oblique (LAO), anterior and left lateral (Figure 1). By drawing regions of interest (ROI) around the left ventricle in the LAO view, absolute ventricular volumes can be computed by a count-based algorithm at end-systole and end-diastole from which background counts are subtracted (arbitrarily placed ROI lateral to the left ventricle) (Figure 2) to derive a volumetric-time curve (Figure 3). Additional parameters including diastolic function, peak and mean filling and emptying rates can also be derived, most of which appear to be equally accurate in predicting early cardiotoxicity.[3] The inherent advantages of this technique are its non-invasive nature, high reproducibility and the fact that measurements of LV volume and function do not rely on geometric assumptions regarding LV shape but rather on total LV counts. Limitations include the need to weigh the individual's risk of total effective radiation dose versus net clinical benefit, difficulty ensuring optimal image acquisition angles and problematic ECG gating in the setting of baseline arrhythmias such as atrial fibrillation.

The single largest study involving monitoring for cardiotoxicity involved serial ERNA or Single Photon Emission Computed Tomography (SPECT) imaging in 1 487 patients receiving doxorubicin.[4] Using this method of screening, 19% of patients were deemed to be at high risk for developing cardiotoxicity (defined as a baseline LVEF <50%, a drop in LVEF by ≥10% to a value <50% or cumulative doxorubicin doses ≥450 mg/m²). Interestingly, clinical CHF improved in 87% of patients who were given routine therapy with digitalis, diuretics and/or vasodilators. Based on these high risk features, standard criteria were developed to aid in the management of screening for subclinical doxorubicin-associated cardiotoxicity with ERNA (Table 1). The implementation of these guidelines resulted in a reduction in the incidence of heart failure due to cardiotoxicity. This was primarily due to the fact that these guidelines intended purpose was to allow the maximum dose of doxorubicin to be administered based on an individually determined threshold for subclinical cardiotoxicity.
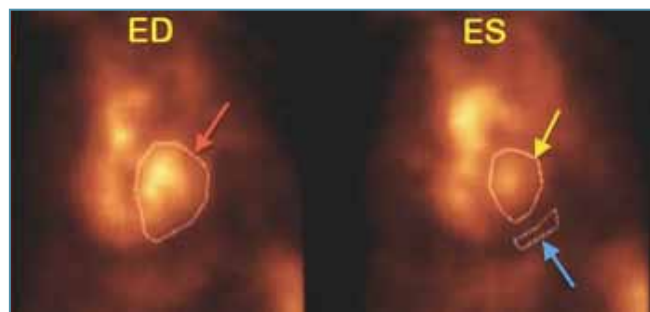

FIGURE 2: Regions of interest drawn around the left ventricular blood pool cavity at end-diastole (ED, red arrow) and end-systole (ES, yellow arrow). The blue arrow represents the region of interest drawn inferior and lateral to the LV for the purposes of correction of background counts.
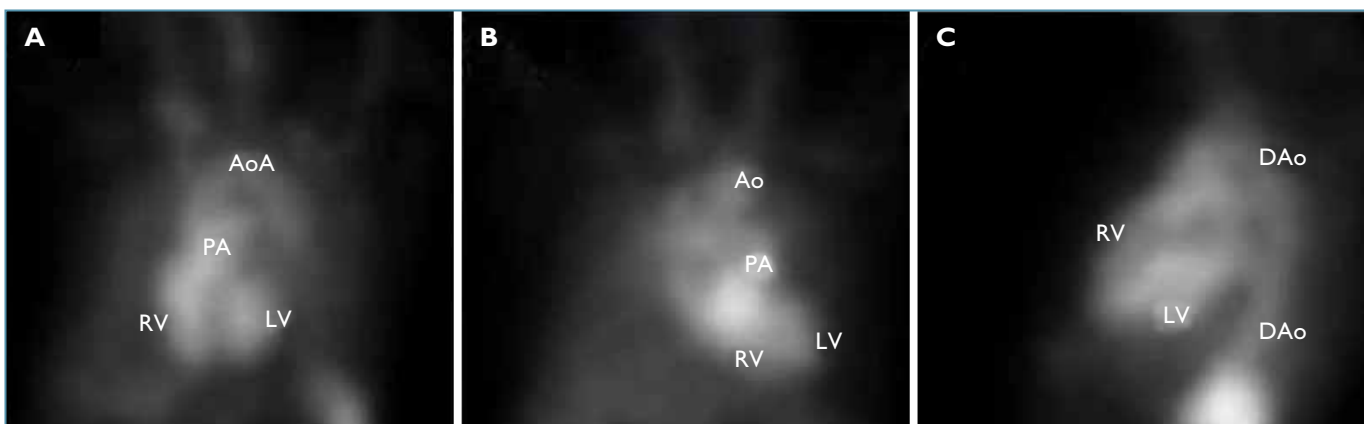

FIGURE 1: Labelled equilibrium radionuclide angiocardiography showing left anterior oblique view (A), anterior view (B) and left lateral view (C).

LV = left ventricle. RV = right ventricle. Ao = ascending aorta. AoA = aortic arch. Dao = descending aort. PA = pulmonary artery.
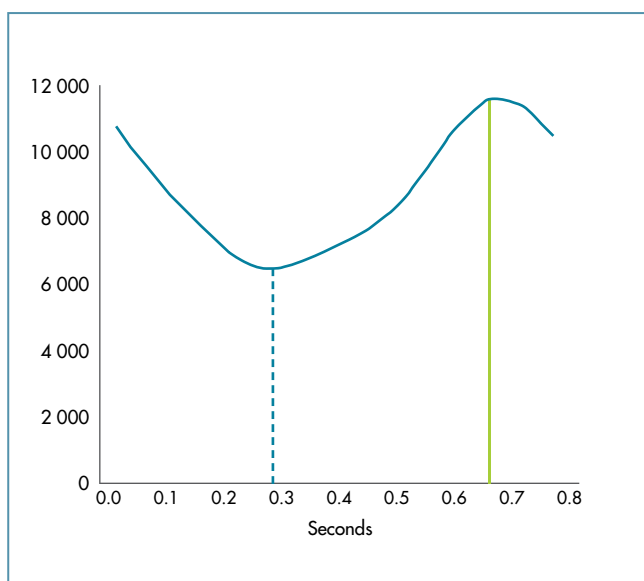
FIGURE 3: Count/volume-time curve derived from obtaining multiple count measurements at distinct points in the cardiac cycle. The solid green line represents the moment of highest counts (end diastole) and the dotted blue line represents end-systole. Due to the directly proportional relationship between counts and volumes, LV ejection fraction can be automatically computed.

TABLE 1: Guidelines for monitoring patients receiving doxorubicin. Adapted from Schwartz RG, et al.[6]

Guidelines for monitoring patients receiving doxorubicin
Perform baseline radionuclide angiocardiography at rest for calculation of left ventricular ejection fraction (LVEF) prior to administration of 100mg/m² of doxorubicin.
Subsequent studies are performed at least 3 weeks after the indicated total cumulative doses have been given, before consideration of the next dose.
Patients with normal baseline LVEF (≥50%)
Perform a second study after 250-350mg/m².
Repeat study after 400mg/m² in patients with known heart disease, radiation exposure, abnormal ECG results, or cyclophosphamide therapy; or after 450mg/m² in the absence of any of these risk factors.
Discontinue doxorubicin therapy once functional criteria for cardiotoxicity develop, e.g. absolute decrease in LVEF ≥10% associated with a decline to a level ≤50%.
Patients with abnormal baseline LVEF (<50%)
Doxorubicin therapy should not be initiated with baseline LVEF ≤30%.
In patients with LVEF >30% and <50% sequential studies should be obtained prior to each dose.
Discontinue doxorubicin with cardiotoxicity: absolute decrease in LVEF ≥10% and/or final LVEF ≤30%.

LVEF = left ventricular ejection fraction. ECG = electrocardiogram.

Based on the guidelines above, a more recent study demonstrated that 15% of patients receiving doxorubicin were deemed at high risk for CHF at some point during their therapy.[5] Furthermore, implementation of ERNA screening led to early discontinuation of treatment in 13% of patients due to criteria for cardiotoxicity, the majority of whom were asymptomatic. The same study found a net cost effectiveness of screening relative to estimated costs for the treatment of symptomatic CHF. This highlights the importance of routine screening, as many patients will demonstrate cardiotoxicity via a reduction in LVEF in the absence of overt heart failure symptoms.

While the accuracy and reproducibility of ERNA-based methods of LVEF quantification are established, the sensitivity and test characteristics for the prediction of CHF is suboptimal.[6] An abnormal LVEF at rest (<=45%) had a sensitivity of 53% and a specificity of 75% for detecting patients at moderate or high risk of developing CHF when compared to the gold standard of endomyocardial biopsy. The addition of exercise LVEF increased the sensitivity of detection of moderate or high-risk patients to 89% but lowered the specificity to 41%. Therefore, single resting LVEF measurements are not likely to possess the sensitivity required for widespread use as screening tests.

Despite certain pitfalls and concerns related to using changes in LVEF for prediction of subsequent cardiac dysfunction, ERNA continues to be a simple, effective and readily available approach for preventing cardiac morbidity and mortality.

Molecular imaging

Iodine-123–labelled metaiodobenzylguanidine (I-123 MIBG) is iodine labelled lab tracer that shares adrenergic neuroreceptor uptake storage and release mechanisms wino epinephrine. Myocardial uptake of I-123 MIBG reflects neuronal integrity and its release reflects adrenergic function.[7] There is animal and human evidence that reduced I-123 MIBG uptake occurs in doxorubicin cardiotoxicity, however this usually parallels changes in LV systolic function.[2]

Indium-111 antimyosin (In-111 antimyosin) is a tracer that was developed for imaging of myocardial necrosis in a diverse set of cardiac pathologies such as myocarditis, transplant rejection and doxorubicin cardiotoxicity. In-111 antimyosin uptake occurs prior to changes in LV systolic function, however no long term studies exist and the specificity of this tracer for the prediction of cardiotoxicity is poor.[9,10] Lastly, tracer availability, expense, and technical challenges limit its widespread clinical and research applicability.

Technetium-99m–labelled annexin V, an exciting radionuclide agent for imaging cell death, has been successfully evaluated in the detection of doxorubicin cardiotoxicity.[11] However, limited human experience means the future role for the precise evaluation, timing and detection of cardiotoxicity by this agent is undetermined.

Lastly, Herceptin (trastuzumab) labelled with Indium-111 (In-111-TZ) has been used to image metastatic breast cancer expressing the human epidermal growth factor receptor 2 (HER2) receptor.[12] A report of 20 patients with metastatic breast cancer expressing the HER-2 receptor demonstrated that 35% of patients had evidence of myocardial In-111-TZ uptake prior to administration of any chemotherapy and 86% of those patients with tracer uptake developed clinical heart failure, whereas none of the patients without uptake had adverse cardiac event.[13]

These findings demonstrate the unique potential for targeted molecular imaging in providing useful therapeutic and prognostic information in patients being treated with potentially cardiotoxic agents. Larger studies are needed to confirm these findings and determine the effects of trastuzumab on cardiac events.

Cardiac PET imaging

The role of cardiac PET imaging has not been extensively investigated for the detection of cardiotoxicity. C-11 acetoacetate and C-11 acetate, markers of myocardial perfusion and oxidative metabolism, have been used and the former appears to be a more sensitive marker for the detection of cardiotoxicity and may be a promising alternative to ventriculography.[8] Cardiac PET is mostly used with fluorine-18-fluorodeoxyglucose (F-18 FDG) for the evaluation of malignant pericardial involvement, cardiac lymphoma staging and has largely focused on the diagnosis of metastatic lesions and response to chemotherapy in a wide range of malignancies.

ECHOCARDIOGRAPHY

Since the report that demonstrated a benefit of adjustment of doxorubicin therapy based on serial monitoring of LVEF employed ERNA,[6] this modality remains a mainstay of LV function assessment during cancer therapy. Nevertheless, echocardiography is preferred in many centres because of lack of radiation exposure, easier availability as well as the added benefit of assessing valvular dysfunction and pericardial disease which are typical sequelae of radiation therapy that is often used in combination with cardiotoxic chemotherapy.[14]

Two-dimensional (2D) echocardiographic assessment

The Cardiology Committee of the Children's Cancer Study Group reported that, as was demonstrated with ERNA-derived LVEF criteria, a protocol of chemotherapy regimen adjustment according to echocardiographic LVEF criteria does reduce heart failure rates, in this case in a paediatric population.[15] A strategy of anthracyclines discontinuation for reductions in fractional shortening (FS) to <30% resulted in a very low incidence of congestive heart failure of 0.4% (3 of 766 patients). This is in contrast to the 20 patients that would have been expected by historical cardiotoxicity rates in the absence of cardiac monitoring.

Traditionally, however, 2D-based echocardiographic methods have been considered less accurate than ERNA in the assessment of LVEF. The drawback of 2D-echocardiography stems from inherent limitations in how ejection fraction is mathematically extrapolated. Echocardiographic LV volumes are best estimated using the modified Simpson (or disk summation) method. In the modified Simpson method, orthogonal apical four- and two-chamber views are obtained. The endocardial borders are traced either automatically or manually and the LV is divided into disks of equal heights. The volume of each cylinder is calculated from the four- and two-chamber image derived diameters and then the volumes are summed to give the LV volume. This method is highly dependent on reliable visualisation of the endocardial borders and absence of foreshortening. In addition this method extrapolates a volume from two 2-dimensional slices by assuming that the LV is symmetric which is frequently not the case.[16] Only a handful of early studies have directly compared 2D-echocardiography with radionuclide imaging in the detection of cardiotoxicity. The first of these was a study comparing radionuclide imaging to echocardiography in 37 patients receiving doxorubicin or daunorubicin and found that echocardiography was less sensitive and specific.[17] In another study comparing radionuclide based assessment to early echocardiography in those receiving doxorubicin who had received endomyocardial biopsy and right heart catheterisation also found that echocardiography was less sensitive.[6] Both studies, however, were limited to M-mode based fractional shortening assessment, which cannot be extrapolated to modern 2D imaging technology.

More recent studies have demonstrated that despite good correlation between LVEF by echocardiography versus LVEF by ERNA (r = 0.81), intra- and inter-observer reproducibility is better for ERNA.[18] As a result, the authors proposed that ERNA should be the method of choice when precise reproducibility is important in patient management. Since relatively modest falls in EF by 10% or to a level less than 50% may trigger a discontinuation of potentially life-saving cancer therapy, precision should be considered a priority in monitoring for cardiotoxicity. When 2D-echocardiography and ERNA were utilised routinely before and after anthracycline use in a paediatric population, ERNA detected a significantly higher rate of cardiac dysfunction, and only ERNA detected diastolic dysfunction.[19]

Lastly, the most comprehensive study from a multi-modality perspective examined ERNA, 2D-echo, 3D-echo and cardiac magnetic resonance imaging (CMR) for the evaluation of cardiac function during trastuzumab therapy after doxorubicin. All patients received serial imaging using all 4 modalities at baseline, 6 and 12 months after beginning trastuzumab. They found a weak correlation between 2D-echo and CMR ($r = 0.31$ at baseline and $r = 0.42$ at 12mo), whereas the correlation for both 3D-echo and ERNA versus CMR were strong ($r = 0.91$ at baseline; $r = 0.90$ at 12 months', respectively.[20]

A retrospective review of 217 consecutive patients who underwent pre-chemotherapy echocardiograms revealed relevant cardiac abnormalities that would not have been identified by radionuclide imaging such as aortic stenosis or moderate mitral regurgitation in 7.4% of patients, and led to a change of chemotherapy in 2.8%.[21] Based on this finding, this group proposed that echocardiography is more useful than radionuclide imaging; however, studies which demonstrate that the identification of these incidental findings leads to improved outcomes would be needed to support a change in practice.

Current guidelines of practice permit either 2D-echocardiography or radionuclide imaging for the evaluation of cardiotoxicity. One of the only committee-based guidelines came from the Cardiology Committee of the Children's Cancer Study Group. The authors of those guidelines stated that either imaging approach could be selected based on the characteristics of the patient and the availability at the institution. For example, echocardiography works particularly well in children, who have excellent acoustic windows, and who may not be able to tolerate the relative lack of movement during ERNA acquisition and for whom minimisation of excess radiation exposure is a top priority. It should be emphasised, however, that regardless of the modality used, it should be used consistently throughout serial monitoring.[15]

3D-echocardiographic assessment

3D-echocardiography is an emerging ultrasound technology that is not yet universally available in all cardiac ultrasound laboratories. However, it is being rapidly adopted as technology advancements have made routine use more practical in clinical settings. It has not been studied specifically in relation to monitoring cardiotoxicity of cancer therapy, but 3D-echocardiography has been shown to be the most reliable ultrasound based technique for LV function assessment.[22] The main obstacle to accurate assessment of LV function by 2D-echocardiography is the need to make assumptions about 3 dimensional ventricular shapes based on images in 2

dimensions. Through acquisition of pyramidal-shaped volumes, 3D-echocardiography largely avoids this problem. By allowing precise manipulation of imaging planes to the long axis and short axis of the LV, 3D imaging also avoids pitfalls of foreshortening and oblique imaging.[23]

Current real-time 3D technology generally uses matrix phased-array technology, which consists of multiple (>3 000) piezoelectric imaging elements arranged in a grid. LV assessment uses apical wide-angle acquisition with or without ECG gating and breath-holding. Acquired pyramidal data can then be cropped to view cardiac structures including optimised conventional 2D planes. To calculate LV volumes and ejection fraction, the user marks the mitral valve annulus and apex in multiple planes. Semi-automated 3D tracings of the endocardial border enable volumetric and functional calculations. If the LV is particularly asymmetric, a disc summation method using multiple short axis slices can be used instead.[24]

3D-echocardiographic assessment of LVEF has been found to be superior to 2D and comparable to CMR based techniques. A study recently performed 2D-echocardiography, cardiac MR and real time 3D-echocardiography in 50 patients with cardiovascular disease. Real-time 3D measurements of end-diastolic volume, end-systolic volume and ejection fraction correlated highly with measurements by cardiac MR with a correlation coefficient of 0.93 for ejection fraction. 2D-echo measurements correlated less well with cardiac MR with a correlation of 0.86 for ejection fraction. Furthermore, the intra-observer, inter-observer and inter-examination variability of 3D based measurements was small and lower than 2D.[25]

Other groups have compared real-time 3D assessment of LVEF to cardiac MR and have similarly found consistent results.[20,26-29] In most cases, 3D measurements of LV volume have been found to slightly underestimate LV volumes when compared to CMR. This can be explained by the limited spatial resolution of certain 3D-echo datasets (Figure 4), as well as difficulties in differentiating compacted myocardium from non-compacted trabeculae. Recommendations for tracing the endocardial border on 3D-echo to include trabeculae in the LV cavity have been proposed.[27] Since precision is critical to use of any imaging modality for serial assessment to guide therapeutic decisions and limits in the precision of LVEF assessment are the primary drawback of 2D-echo when compared to radionuclide imaging, 3D volumetric assessment of EF holds great promise as a safe, accessible and reliable technique for monitoring cardiotoxicity of cancer therapy.
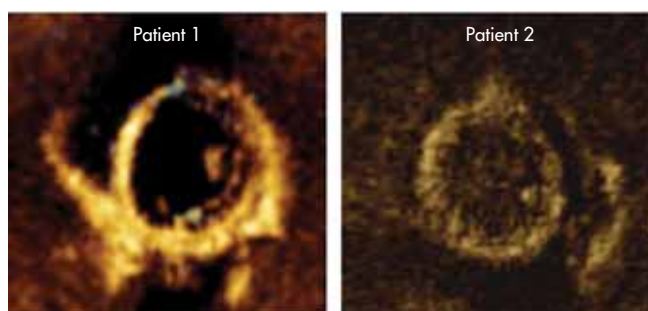
FIGURE 4: Effects of 3D-echo image quality on endocardial visualisation. These examples of short-axis planes extracted from real time 3D-echo datasets demonstrate how spatial resolution may affect the perception of endocardial boundaries. In 1 patient (left), endocardial trabeculae can be well visualized and clearly differentiated from the myocardium and thus appropriately included in the LV cavity. In contrast, in the second patient (right), the spatial resolution of the real time 3D-echo image is not sufficient to provide this kind of detail and is likely to result in erroneous exclusion of the trabeculae from the LV cavity. Reprinted with permission from.[27]

Other echocardiographic parameters

Left ventricular ejection fraction assessment is an unsatisfactory endpoint for monitoring cardiotoxicity because it identifies patients too late to prevent significant morbidity in some. Several alternative markers of pre-clinical cardiac dysfunction have been explored such as diastolic function, stress echocardiography and more recently, myocardial strain imaging.

Diastolic dysfunction

Various studies have explored changes in diastolic function before and after anthracycline exposure[30-34] in an attempt to provide a measure of risk. In patients receiving doxorubicin, the isovolumic relaxation period prolonged, early peak flow (E) was reduced and the ratio of early peak flow velocity to atrial peak flow velocity (E/A) also decreased significantly demonstrating worsening of diastolic indices when compared with age and sex matched controls or when compared with pre-treatment states.[31] It has also been found that a 37% increase in isovolumic relaxation time using Doppler echocardiography after doxorubicin was 78% sensitive and 88% specific for predicting a future drop in systolic function.[30]

Baseline abnormal E/A ratio prior to treatment has also been associated with later development of cardiotoxicity.[32] These findings, however, are inconsistent. Another study found a relationship between anthracycline dose and poorer diastolic function indexes, but failed to find that diastolic dysfunction was helpful in predicting subsequent systolic dysfunction.[33] As a result, monitoring of diastolic function using transmitral flow velocities has failed to become an important component of cardiotoxicity monitoring.

Contractile reserve

Dobutamine stress echocardiography has been used in research settings to assess myocardial reserve in adults treated with anthracyclines, but worsening of systolic augmentation after anthracyclines has not been consistently found.[32,35] One study, however, did note a smaller rise in peak E and fall in E/A ratio during dobutamine administration after anthracycline therapy and concluded that these findings represent the unmasking of early stage anthracycline cardiotoxicity.[36]

Evaluation of contractile reserve by stress testing has also been investigated, specifically in a paediatric population. In children late onset cardiotoxicity is more common and techniques to identify those survivors of childhood cancer at risk for later clinical heart failure are needed.[37,38] Exercise stress testing has been studied repeatedly in those treated with anthracyclines as children and was found to be helpful in identifying subclinical cardiotoxicity.[35,39,40] One study showed that children treated with anthracyclines had lower increases in cardiac index for similar levels of exercise when compared to age match controls.[39] More recently, it was shown that survivors of childhood cancer had lower percent thickening at end systole and reduced end-systolic wall stress after exercise compared to healthy controls.[35] At this time, however, a role for stress echocardiography in the routine clinical evaluation of patients treated with anthracyclines has not been defined.

Myocardial strain imaging

The echocardiographic technique with the greatest potential to improve our ability to identify those with early cardiotoxicity after treatment is strain imaging. Strain imaging previously used tissue-Doppler techniques; however, due to several criticisms, particularly in relation to angle dependency, noise interference and substantial intra- and inter-observer variability, Speckle-tracking Echocardiography (STE) has emerged as an alternative technique in recent years.[41] With speckle tracking, natural acoustic reflectors within the myocardium also known as "speckles" are tracked from frame to frame to determine deformation (strain) and the speed of deformation (strain rate) (Figure 5). For the LV, 3 normal strain components are used to describe normal deformation (longitudinal, circumferential and radial) (Figure 6).

Several investigations have been published examining myocardial strain imaging after doxorubicin or trastuzumab treatment. In a murine model of cardiotoxicity, while LVEF and FS began to decline around day 5, strain rate imaging fell significantly as early as day 2 indicating the ability to detect earlier stages of dysfunctional myocardial mechanics.[42] In a similar study in humans changes in radial strain appeared earlier and were more pronounced than in
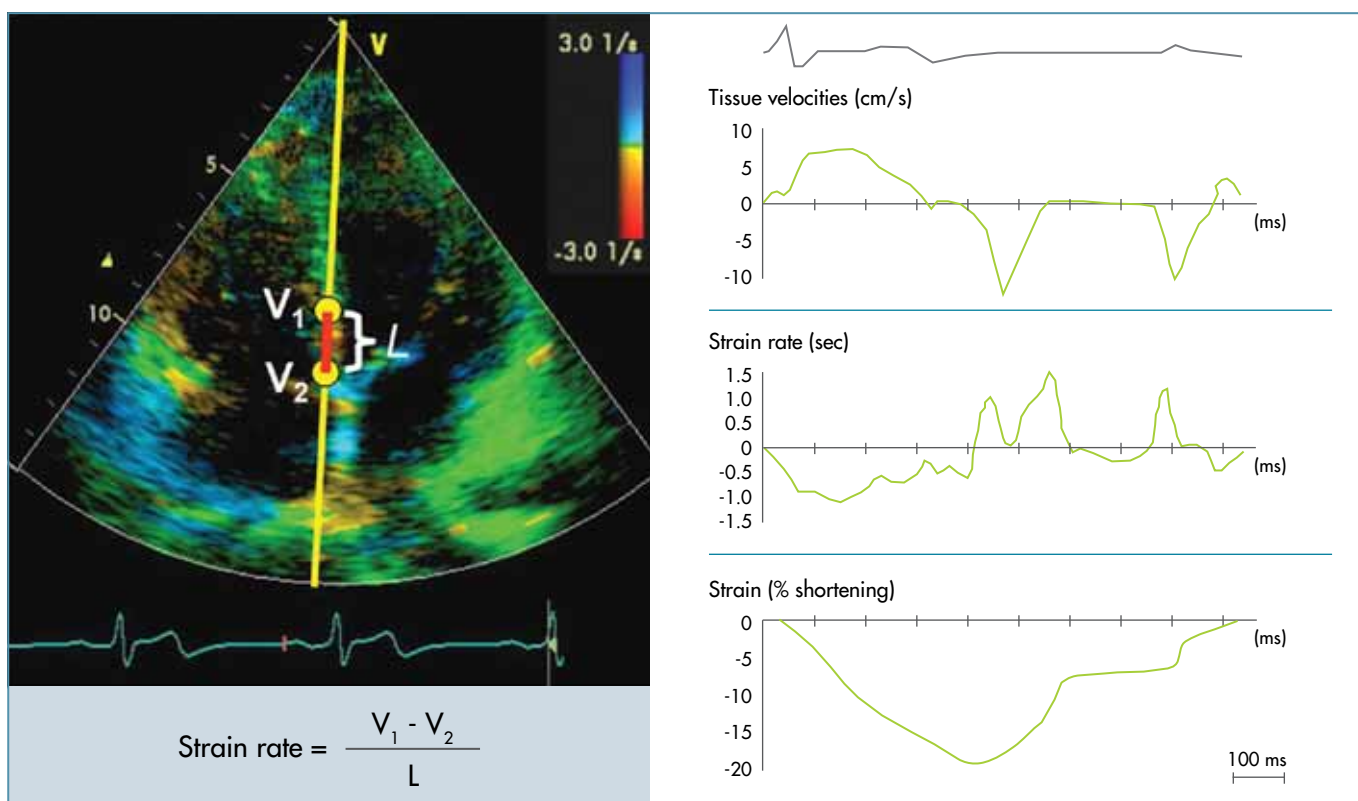
$$\text{Strain rate} = \frac{V_1 - V_2}{L}$$

FIGURE 5: Strain imaging in a normal subject. Examples of tissue Doppler imaging velocity, strain rate and strain curves for a cardiac cycle from a subject with normal cardiac function. L = length. V = velocity. Reprinted with permission from.[27]
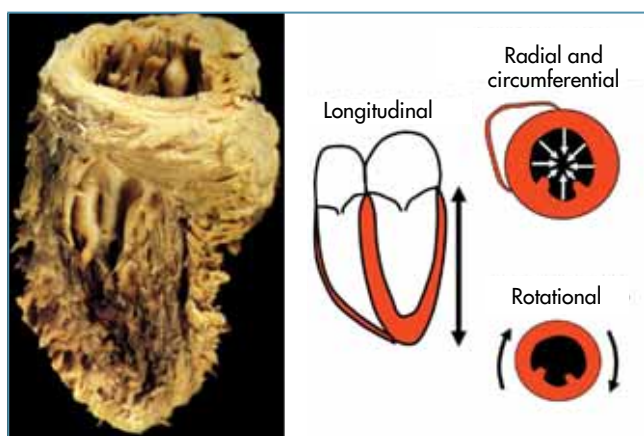

FIGURE 6: Myocardial fibre orientation and principal vectors of left ventricular strain. Echocardiographic application of strain imaging has assessed longitudinal strain from apical windows and radial, circumferential and rotational strain from parasternal windows. Reprinted with permission from.[60]

the longitudinal direction after 6 cycles of pegylated liposomal doxorubicin.[43] Radial deformation, a measure of myocardial wall thickening, may arise as a result of cardiotoxic damage to all 3 layers of the myocardium, unlike in ischaemic heart disease.

Global and regional LV longitudinal and radial strain were significantly reduced in the absence of a significant change in LVEF in the first week after anthracycline therapy.[44] In a paediatric population receiving anthracyclines, early changes in LV longitudinal peak systolic strain occurred and correlated significantly with a subsequent change in EF.[45] Regarding strain imaging after treatment with trastuzumab patients who had received anthracyclines at least 6 months prior to trastuzumab still had a significant difference in mean 2D longitudinal strain rate at 3 to 12 months when compared to 0 to 3 months.[46]

Collectively these data suggest that myocardial strain imaging parameters will be useful adjuncts to echocardiographic assessment of patients treated with cardiotoxic chemotherapy. As 3D speckle tracking becomes more prevalent, 3D strain assessments may further advance our ability to detect subclinical affects of cancer therapy on cardiac function.

CARDIAC MAGNETIC RESONANCE (CMR)

Cardiac magnetic resonance (CMR) is less frequently used as a non-invasive cardiac imaging tool to detect cardiotoxicity probably

because of the ubiquity of radionuclide and echocardiographic technologies. Nevertheless, due to its good temporal and spatial resolution, CMR is considered the gold standard for the assessment of LV function;[47] is exquisitely sensitive for the detection of unrecognised subendocardial myocardial infarctions by SPECT perfusion imaging;[48] and through T2-weighted imaging, has the unique potential to detect myocardial oedema.[49] Perhaps for these reasons, the American College of Cardiology & American Heart Association Guidelines have recognised CMR as a viable modality for the screening of cardiotoxicity.[50]

The utility of CMR for the assessment of trastuzumab cardiotoxicity was investigated in 10 breast cancer patients with suspected trastuzumab-induced cardiomyopathy.[51] Remarkably, late gadolinium enhancement (LGE), a marker of intramyocardial fibrosis and inflammation, was present in the subepicardial segments of the lateral walls of all 10 patients. Despite the recovery of LV function with appropriate therapy in 6 of these patients, the LGE persisted in all patients up to 6 months suggesting persistent myocardial injury. A follow-up report of 36 patients with trastuzumab-induced cardiomyopathy from the same group demonstrated that 94% of patients had the same subepicardial lateral wall LGE, a potentially pathognomonic sign for trastuzumab cardiotoxicity (Figure 7).

Gadolinium-enhanced T1 mapping is a novel CMR-based technique that allows detection of diffuse myocardial fibrosis that may not be readily visible on LGE images.[52] To date, T1 mapping has been used in 4 studies of doxorubicin cardiotoxicity (3 animal, 1 human) and all have shown correlation to its histopathologic features.[53-56] Collectively, an absence of change of T1 values appears to indicate protection from the development of cardiotoxicity. Conversely, in those subjects with the highest increase in gadolinium-enhanced T1

FIGURE 7: Short-axis mid-ventricular late gadolinium enhancement image in a patient with trastuzumab-induced cardiomyopathy demonstrating mid-myocardial and subepicardial lateral wall delayed enhancement. Reproduced with permission from.[51]

values, an association with the development of congestive heart failure was found. Clearly larger studies with longer patient follow-up are required but for now T1 mapping for the detection of doxorubicin cardiomyopathy appears to hold much promise.

CARDIAC COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA)

Cardiac computed tomography angiography (CCTA) has emerged as a powerful tool for the non-invasive evaluation of the coronary arteries and an alternative to invasive diagnostic angiography. To our knowledge, there are no reports of CCTA for the evaluation of cardiotoxicity-induced subclinical LV systolic dysfunction.

However, there are data emerging on using CCTA for coronary artery evaluation in patients formerly treated for childhood malignancies, such as Hodgkin's lymphoma.[57] In this young asymptomatic patient cohort with a mean age of 20 years (range 6 to 43 years), CCTA detected coronary artery disease in 16% of patients with 2 cases of severe, obstructive coronary artery plaque. In a smaller series of 9 patients formerly treated for Hodgkin's lymphoma, 8 out of 9 had coronary disease and coronary artery calcium scores higher than their aged matched peers. Of these asymptomatic indidivuals 2 out of 9 underwent revascularisation with coronary bypass surgery or angioplasty.[58] Larger prospective studies are required to better define the role of coronary CT angiography and calcium scoring and to ideally establish an algorithm for the evaluation and treatment of such patients.

CONCLUSIONS

Since the initial reports of doxorubicin cardiotoxicity nearly 40 years ago, multi-modality screening cardiovascular imaging techniques have changed dramatically.[59] Since the initial establishment of LV ejection fraction-based techniques such as ERNA, there have been continued advances in the fields of radionuclide imaging, echocardiography, magnetic resonance and computed tomography. Ideally, cardiovascular medicine specialists need to interface in a multi-disciplinary approach to ensure optimal patient outcomes. Much work has been completed, yet further investigation remains for cardiac imaging techniques to provide refinements in screening and ultimately to reduce short and long term cardiovascular morbidity and mortality that patients with cancer are exposed to. Future screening for patients with cardiotoxicity will likely involve a multi-modality approach for improved risk stratification, prognostication and tailoring of individual chemotherapeutic regimens.
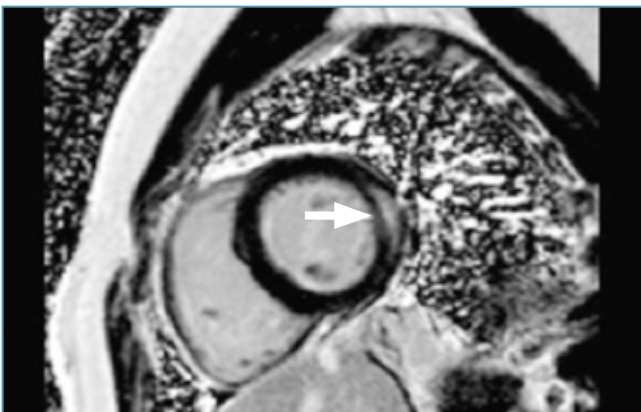
Conflict of interest: none declared.

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