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POSITION PAPER

Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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I. Cancer therapeutics–related cardiac dysfunction

A. Definition, classification, and mechanisms of toxicity

Cardiac dysfunction resulting from exposure to cancer therapeutics was first recognized in the 1960s, with the widespread introduction of anthracyclines into the oncological therapeutic armamentarium.[1] Heart failure (HF) associated with anthracyclines was then recognized as an important side effect. As a result, physicians learned to limit their doses to avoid cardiac dysfunction.[2] Several strategies have been used over the past decades to detect it. Two of them evolved over time to be very useful: endomyocardial biopsies and monitoring of left ventricular (LV) ejection fraction (LVEF) by cardiac imaging. Examination of endomyocardial biopsies proved to be the most sensitive and specific parameter for the identification of anthracycline-induced LV dysfunction and became the gold standard in the 1970s. However, the interest in endomyocardial biopsy has diminished over time because of the reduction in the cumulative dosages used to treat malignancies, the invasive nature of the procedure, and the remarkable progress made in non-invasive cardiac imaging. The non-invasive evaluation of LVEF has gained importance, and notwithstanding the limitations of the techniques used for its calculation, has emerged as the most widely used strategy for monitoring the changes in cardiac function, both during and after the administration of potentially cardiotoxic cancer treatment.[3–5]

The timing of LV dysfunction can vary among agents. In the case of anthracyclines, the damage occurs immediately after the exposure;[6] for others, the time frame between drug administration and detectable cardiac dysfunction appears to be more variable. Nevertheless, the heart has significant cardiac reserve, and the expression of

Table 1 Characteristics of type I and II cancer therapeutics-related cardiac dysfunction

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose-related	Not dose-related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

ACE, Angiotensin-converting enzyme.

damage in the form of alterations in systolic or diastolic parameters may not be overt until a substantial amount of cardiac reserve has been exhausted. Thus, cardiac damage may not become apparent until years or even decades after receiving the cardiotoxic treatment. This is particularly applicable to adult survivors of childhood cancers.

Not all cancer treatments affect the heart in the same way. Therefore these agents cannot be viewed as a single class of drugs.

1. Definition of cancer therapeutics–related cardiac dysfunction

Different definitions of CTRCD have been used historically.[7] It is the consensus of this committee to define CTRCD as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE) (see Section II). This decrease should be confirmed by repeated cardiac imaging. The repeat study should be performed 2 to 3 weeks after the baseline diagnostic study showing the initial decrease in LVEF. LVEF decrease may be further categorized as symptomatic or asymptomatic, or with regard to reversibility:

- Reversible: to within 5 percentage points of baseline
- Partially reversible: improved by ≥10 percentage points from the nadir but remaining >5 percentage points below baseline
- Irreversible: improved by <10 percentage points from the nadir and remaining >5 percentage points below baseline
- Indeterminate: patient not available for re-evaluation

In this expert consensus document, a classification of CTRCD on the basis of the mechanisms of toxicity of the agents is used (*Table 1*).

2. Classification by mechanism of toxicity

a. Type I CTRCD

Doxorubicin is believed to cause dose-dependent cardiac dysfunction through the generation of reactive oxygen species. Recently, investigators using an animal model proposed that doxorubicin-induced CTRCD is mediated by topoisomerase-IIβ in cardiomyocytes through the formation of ternary complexes (topoisomerase-IIβ–anthracycline–deoxyribonucleic acid). These complexes induce deoxyribonucleic acid double-strand breaks and transcriptome changes responsible for defective mitochondrial biogenesis, and reactive oxygen species formation.[8] The damage caused by the anthracyclines occurs in a cumulative dose-dependent fashion. The expression of damage is related to pre-existing disease, the state of cardiac reserve at the time of administration, co-existing damage, and individual variability (including genetic variability). Electron microscopy of myocardial biopsies shows varying degrees of myocyte damage: vacuolar swelling progressing to myofibrillar disarray and ultimately cell death.[9] Once myocytes undergo cell death, they have minimal potential for replacement via regeneration. In this regard, cardiac damage at the cellular level may be deemed irreversible, although cardiac function may be preserved and compensation optimized through antiremodelling pharmacologic therapy, and/or less frequently, mechanical intervention. Agents that are associated with Type I CTRCD include all of the anthracyclines (doxorubicin, epirubicin, and idarubicin) as well as mitoxantrone. These agents are now considered to have increased potential for long-term cardiac dysfunction, increased morbidity, and mortality.[10,11]

b. Type II CTRCD

A number of agents do not directly cause cell damage in a cumulative dose-dependent fashion. There is considerable evidence for this: first, the typical anthracycline-induced cell damage by electron microscopy is not seen with these agents, and second, in many instances, these agents have been continued for decades, without the progressive cardiac dysfunction that would be expected with type I agents. Finally, functional recovery of myocardial function is frequently (albeit not invariably) seen after their interruption, assuming a type I agent was not given before or at the time of therapy.[10] This document uses trastuzumab as the classical example of Type II CTRCD and presents evidence and consensus recommendations for cardiac evaluation of patients receiving this targeted therapy, primarily indicated for *HER2*-positive breast cancer (summarized in Section V of this document). The role of cardiac assessment and imaging in patients receiving this regimen is further complicated by the fact that type I (doxorubicin) and type II agents (trastuzumab), are often given sequentially or concurrently. Such sequential or concurrent use may increase cell death indirectly by compromising the environment of marginally compensated cells, contributing to the

concern that type II agents can still result in cell death at the time of administration. We recognize that in the setting of a variety of predisposing factors, varying cumulative dosages of recognized cardiotoxic agents, and use of other agents that are known to increase oxidative stress and compromise myocyte stability, the algorithm proposed in this document cannot be based on strong clinical data.

Since the approval of trastuzumab, numerous agents have entered the therapeutic armamentarium, including the small-molecule tyrosine kinase inhibitors. It is difficult to make broad generalizations about these agents, because they often have different kinase targets. However, it appears that the most problematic are the agents that target vascular endothelial growth factor (VEGF) and VEGF receptors. These agents typically are associated with severe systemic arterial hypertension and ischaemic events. The development of CTRCD in these patients may be related to transient impairment of the contractile elements within the cell or to the increased afterload on a compromised ventricle. The most concerning of this group are the non-selective agents, including sunitinib and sorafenib, because these drugs can target up to 50 different kinases, in addition to the intended target.[12] Because those "off-target" kinases play important roles in the heart and vasculature, the risk of toxicity is increased. As a result of the unspecific nature and predictability of myocardial damage, it is difficult to provide general recommendations regarding how to monitor patients receiving these agents. A number of attempts have been made to unify approaches to manage these patients, all stopping short of proposing guidelines; one attempt focused on arterial hypertension[13] and the other on CTRCD.[14] Careful management of comorbidities was urged in these documents.

Key points

- Highly effective chemotherapeutic agents may cause CTRCD.
- CTRCD has been classified as follows:
  (1) Type I CTRCD is characterized by anthracyclines. It is dose-dependent, leads to cell apoptosis, and is therefore irreversible at the cell level. Early detection and prompt treatment may prevent LV remodelling and the progression to the HF syndrome.
  (2) Type II CTRCD is characterized by trastuzumab. It is not dose dependent, does not lead to apoptosis by itself, and is often reversible.

II. Echocardiographical evaluation of cardiac structure and function in cancer patients

Echocardiography is the cornerstone in the cardiac imaging evaluation of patients in preparation for, during, and after cancer therapy, because of its wide availability, easy repeatability, versatility, lack of radiation exposure, and safety in patients with concomitant renal disease. In addition to the evaluation of LV and right ventricular (RV) dimensions, systolic and diastolic function at rest and during stress, echocardiography also allows a comprehensive evaluation of cardiac valves, the aorta, and the pericardium.[15] *Table 2* summarizes the recommended cardio-oncology-echocardiogram protocol.

Table 2 Recommended cardio-oncology echocardiogram protocol

Standard transthoracic echocardiography
• In accordance with ASE/EAE guidelines and IAC-Echo
2D strain imaging acquisition
• Apical three-, four-, and two-chamber views ☐ Acquire ≥3 cardiac cycles
• Images obtained simultaneously maintaining the same 2D frame rate and imaging depth ☐ Frame rate between 40 and 90 frames/sec or ≥40% of HR
• Aortic VTI (aortic ejection time)
2D strain imaging analysis
• Quantify segmental and global strain (GLS)
• Display the segmental strain curves from apical views in a quad format
• Display the global strain in a bull's-eye plot
2D strain imaging pitfalls
• Ectopy
• Breathing translation
3D imaging acquisition
• Apical four-chamber full volume to assess LV volumes and LVEF calculation
• Single and multiple beats optimizing spatial and temporal resolution
Reporting
• Timing of echocardiography with respect to the i.v. infusion (number of days before or after)
• Vital signs (BP, HR)
• 3D LVEF/2D biplane Simpson's method
• GLS (echocardiography machine, software, and version used)
• In the absence of GLS, measurement of medial and lateral s′ and MAPSE
• RV: TAPSE, s′, FAC

BP, Blood pressure; FAC, fractional area change; HR, heart rate; IAC-Echo, Intersocietal Accreditation Commission Echocardiography; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; VTI, velocity-time integral.

A. Left ventricular systolic function

Exposure to potentially cardiotoxic chemotherapeutic agents is a well-recognized indication for baseline and longitudinal evaluation of LV function.[16,17] The most commonly used parameter for monitoring LV function with echocardiography is LVEF. Accurate calculation of LVEF should be done with the best method available in a given echocardiography lab. Consistency with regard to the method used to determine LVEF should be maintained whenever possible during treatment and surveillance after treatment. Importantly, the digital images obtained to calculate LVEF on follow-up echocardiography should be visually compared with the previous ones to minimize reader variability. As previously reported,[18,19] imaging at baseline has been particularly helpful in patients with a history or clinical findings suggestive of LV systolic dysfunction (known cardiac ischaemic or non-ischaemic insult) and those at high risk for cardiac events on the basis of traditional risk factors (age, gender, hypertension, hyperlipidaemia, and family history of premature coronary artery disease [CAD]). Other imaging modalities, such as multi-gated blood pool imaging (MUGA) and cardiac magnetic resonance

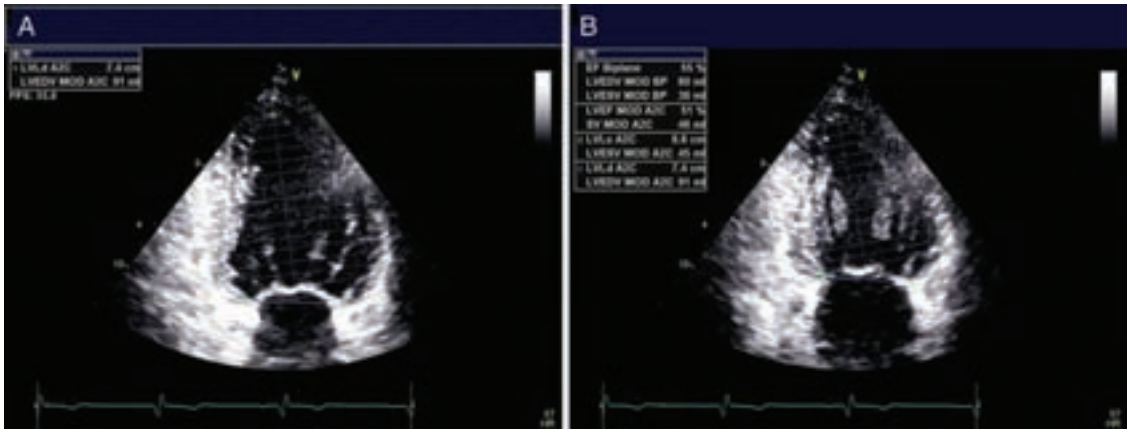

Figure 1 Calculation of LVEF using the biplane Simpson's method. (A) Apical two-chamber view obtained at end-diastole. (B) Apical two-chamber view obtained at end-systole.

(CMR) imaging, have been used in the evaluation of LVEF. CMR is considered the reference standard for the calculation of LV volumes and LVEF. However, echocardiography is suitable for serial evaluation of LV structure and function. The incorporation of modern techniques such as myocardial contrast echocardiography, three-dimensional (3D) echocardiography (3DE), Doppler tissue imaging (DTI), and speckle-tracking echocardiography (STE), offer a prudent compromise between cost-effectiveness and clinical predictive value (discussed in detail in Sections II and III of this document). According to joint recommendations from the American Society of Echocardiography (ASE), and the European Association of Echocardiography (EAE), the method of choice for LV volumes quantitation and LVEF calculation is the modified biplane Simpson's technique (method of disks) by 2DE (*Figures 1A* and *1B*).[20] Historically, fractional shortening using linear measurements from M-mode echocardiography or 2DE was used as a surrogate of LVEF in the evaluation of oncological (especially paediatric) patients. However, this approach should be discouraged, as it takes into consideration only two LV walls (the anterior septum and inferolateral wall) for the calculation of LVEF. The common occurrence of CAD in patients with cancer, along with the observation that CTRCD due to some chemotherapeutic agents may be regional, and not necessarily global, makes necessary a calculation of LVEF using a volumetric assessment.[21] The recommendations for chamber quantification from the ASE and EAE established LVEF $\geq$ 55% as a normal reference range.[20] New data extracted from six databases, including Asklepios, FLEMENGHO, CARDIA5 and CARDIA25, Padua 3D Echo Normal, and the Normal Reference Ranges for Echocardiography (NORRE) study, indicate that the normal LVEF using the biplane method of disks is 63 $\pm$ 5%. LVEF in the range of 53–73% should be classified as normal.[22–26] A revision of the current guideline incorporating these new data is being completed as of this writing. Changes in LVEF indicative of LV damage can be more appropriately identified when comparisons are made between baseline and follow-up studies. In addition, the calculation of LVEF should be combined with assessment of the wall motion score index.[20] Resting wall motion score index based on a 16-segment model of the left ventricle has been demonstrated to be a more sensitive marker of anthracycline-induced CTRCD than relying on the LVEF alone.[27]

Several studies have been published on cardiac monitoring to assess CTRCD, particularly with anthracyclines, the most frequently implicated agents.[28–35] There has been controversy as to the definition of CTRCD by using changes in resting LVEF, occurring during or after chemotherapy. The use of different LVEF cut-offs and methods of measurement (Teichholz, Simpson's biplane, or area-length method) have compromised the ability to compare results from different studies and collect evidence-based data.[36,37] Although monitoring guidelines have been proposed for several potentially cardiotoxic treatments,[33,38–40] limited data are available to formulate evidence-based screening and follow-up recommendations for CTRCD.[41]

Although LVEF is a robust predictor of cardiac outcomes in the general population, it has low sensitivity for the detection of small changes in LV function. LVEF calculated by conventional 2DE often fails to detect small changes in LV contractility because of several factors. These factors include LV geometric assumptions, inadequate visualization of the true LV apex, lack of consideration of subtle regional wall motion abnormalities, and inherent variability of the measurement.[42] It is also important to bear in mind the load dependency of this measurement. Changes in loading conditions are frequent during chemotherapy and may affect the LVEF value (volume expansion due to the intravenous administration of chemotherapy or volume contraction due to vomiting or diarrhoea).

Otterstad *et al.*[43] reported in 1997 that 2DE is capable of recognizing differences in sequential measurements of LVEF of 8.9%. In a more recent study of cancer patients undergoing chemotherapy but free of HF symptoms, the upper limit of the 95% confidence interval for longitudinal variability of 2D LVEF measurement was 9.8% (range, 9.0%–10.8%). In this study, Thavendiranathan *et al.*[44] followed the ASE recommendations for the biplane calculation of LVEF (using apical four- and two-chamber views), in contrast to the apical four- and three-chamber views used by Otterstad *et al.*, and adjusted for intraobserver variability in their calculation of interobserver variability. They concluded that 2DE appears to be reliable in the detection of differences close to 10% in LVEF. Because this is the same magnitude

of change used to adjudicate CTRCD, the sensitivity of 2DE has been questioned. Accordingly, strategies using newer echocardiographical technology, such as STE-derived strain imaging for the early detection of sub-clinical LV systolic dysfunction, have been actively investigated (see Section III). When this technology is not available, the quantitation of LV longitudinal function by simple ultrasound tools such as mitral annular plane systolic excursion by M-mode echocardiography, and/or the peak systolic velocity (s′) of the mitral annulus by pulsed-wave DTI, could be useful adjunct information to LVEF in the evaluation of LV systolic function.[45–49] Mitral annular plane systolic excursion is less dependent on image quality. Although there are no cut-off values that allow the prediction of CTRCD, a progressive decline should raise concern for sub-clinical LV dysfunction.

Key points

- Echocardiography is the method of choice for the evaluation of patients before, during, and after cancer therapy. Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3DE).
- When using 2DE, the modified biplane Simpson's technique is the method of choice.
- LVEF should be combined with the calculation of wall motion score index.
- In the absence of global longitudinal strain (GLS) by STE, quantification of LV longitudinal function using mitral annular displacement by M-mode echocardiography and/or peak systolic velocity (s′) of the mitral annulus by pulsed-wave DTI is recommended.
- LVEF assessed by 2DE often fails to detect small changes in LV contractility.

B. Left ventricular diastolic function

A comprehensive assessment of LV diastolic function should be performed, including grading of diastolic function, and providing an estimate of LV filling pressure (by using the E/e′ ratio) according to the joint ASE and EAE recommendations on LV diastolic function.[50] Use of the E/e′ ratio remains questionable in the oncological setting, as E and e′ velocities fluctuation in these patients could be the consequence of changes in loading conditions as a result of side effects associated with the chemotherapy (nausea, vomiting, and diarrhoea) more than the result of a real change in LV diastolic performance. Diastolic parameters have not yet demonstrated value in predicting subsequent CTRCD (please see full discussion in Section III.A).

Key point

- Although diastolic parameters have not been found to be prognostic of CTRCD, a conventional assessment of LV diastolic function, including grading of diastolic function and non-invasive estimation of LV filling pressures, should be added to the assessment of LV systolic function, per ASE and EAE recommendations for the evaluation of LV diastolic function with echocardiography.

C. Right ventricular function

RV abnormalities may occur in oncological patients for a number of reasons: pre-existing RV dysfunction, neoplastic involvement (primary or metastatic), or as a result of the cardiotoxic effects of chemotherapy. It may be implied that the right ventricle is affected by chemotherapy, as early studies of CTRCD often included RV biopsies.[51] However, the frequency of RV involvement or its prognostic value has not been adequately studied. There is only one study reporting sub-clinical decrease in RV systolic and diastolic echocardiographical indices, although mostly in the normal range in 37 patients in a relatively short time interval after onset of chemotherapy with anthracyclines.[52]

Evaluation of the right ventricle should include qualitative and quantitative assessments of chamber size (at least RV basal diameter) and right atrial size (area), as well as quantitative assessment of RV longitudinal M-mode-derived tricuspid annular plane systolic excursion (*Figure 2A*) and pulsed DTI–derived systolic peak velocity of the tricuspid annulus (s′) (*Figure 2B*) and RV radial function (fractional area shortening).[53]

It is recommended when technically possible to provide an estimate of RV systolic pressure. This is particularly important in patients

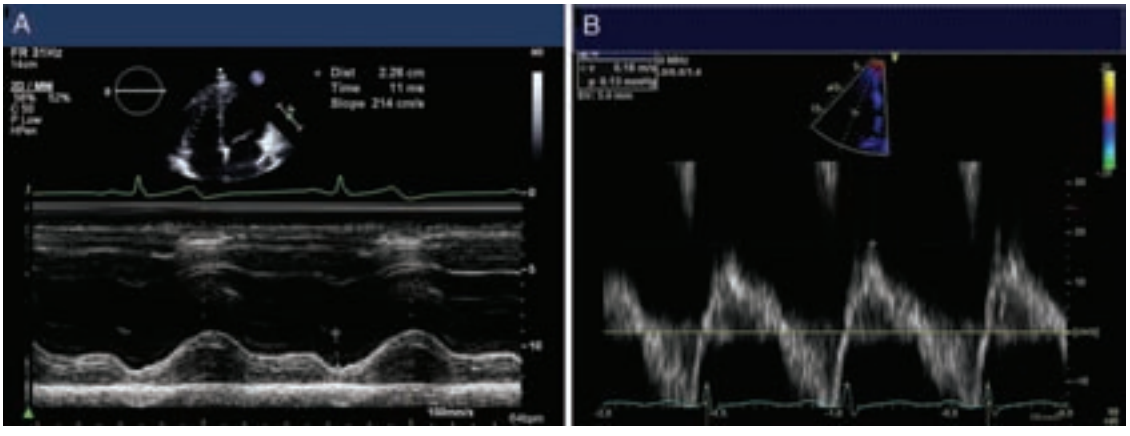

Figure 2 (A) Tricuspid annular plane systolic excursion (TAPSE) obtained from an apical chamber view in patient receiving anthracycline-based therapy. The TAPSE is normal, measuring 2.26 cm (abnormal <1.6 cm). (B) Pulse Doppler peak systolic velocity at the tricuspid valve annulus in a patient 6 months after completion of trastuzumab-based therapy. The measurement is normal at 18 cm/sec (abnormal <10 cm/sec).

treated with dasatinib, a tyrosine kinase inhibitor, as pulmonary arterial hypertension may be a specific complication.[54]

Key point

- Although the prognostic value of RV dysfunction has not been demonstrated in patients undergoing chemotherapy, a quantitative assessment of RV chamber and function should be performed because of possible RV involvement.

D. Valvular heart disease

Chemotherapeutic agents do not appear to directly affect cardiac valves. However, valvular heart disease may manifest in oncological patients for a number of reasons, including pre-existing valve lesions,[55–57] concomitant radiation therapy,[58] severe infection as a complication of chemotherapy, or CTRCD.

Primary or secondary cardiac tumours may rarely affect valve function by their local effects. In patients with advanced malignant tumours, non-bacterial thrombotic, or marantic endocarditis (*Figures 3A* and *3B*) may occur.[59,60] This is more common with left-sided valves. Valve lesions may vary in size from microscopic to large bulky lesions, leading to impaired valve coaptation and regurgitation, which is occasionally severe. Significant valve stenosis is infrequent. However, it is thromboembolism from these lesions that is most consequential to the patient rather than haemodynamic impact.

Valve disease may occur because of concomitant or previous radiation therapy.[61–63] The effect of radiotherapy on the valvular apparatus was described thoroughly in the recent joint ASE and European Association of Cardiovascular Imaging (EACVI) recommendations,[58] and cardiac imaging evaluation of patients undergoing radiotherapy should be performed according to that document.

Chemotherapy may lead to pancytopenia and result in bacteraemia and sepsis, which in turn may lead to increased risk for endocarditis, with vegetations and valve regurgitation. This is more likely in those with predisposing valve lesions (i.e. mitral valve prolapse[55] and bicuspid aortic valve) or with indwelling central venous catheters placed for vascular access.[64]

Valve disease may occur as a consequence of CTRCD. This usually manifests as mitral regurgitation caused by annular dilation or apical tethering in the setting of LV dysfunction and secondary LV remodelling. Secondary tricuspid regurgitation may also occur because of RV dysfunction or pulmonary arterial hypertension in the setting of CTRCD. Both secondary mitral and tricuspid regurgitation occur late in the course of CTRCD, after significant ventricular dysfunction and geometric remodelling have occurred.

Echocardiography is the technique of choice for the evaluation of valvular heart disease in patients with cancer. Assessment of the severity of valvular stenosis or regurgitation should be performed on the basis of the current ASE and EAE recommendations.[65–68] Although a complete transthoracic echocardiographical Doppler evaluation is often sufficient to evaluate the valve pathology and the haemodynamic consequences of valve dysfunction, transoesophageal echocardiography may be of incremental value in the setting of suspected endocarditis.[69] Both computed tomographic scanning and CMR are not typically required in the routine evaluation of valve disease in oncological patients, but may have a role in assessing tumour infiltration of valvular structures or when radiation-induced constriction or restrictive cardiomyopathy is suspected.[70] CMR may be valuable in following ventricular volumes and function in patients with significant valve regurgitation.

Patients with significant baseline or changing valvular findings during chemotherapy require more frequent serial echocardiographical examinations. The indications for follow-up and interventions for specific valve lesions should be based on guidelines published by the American Heart Association and American College of Cardiology, and the European Society of Cardiology,[71,72] though follow-up should be adjusted to the clinical situation and individual prognosis of each patient.

Key points

- Cardiac valves should be carefully evaluated in patients undergoing chemotherapy.
- Patients with baseline or changing valvular findings during chemotherapy should undergo careful re-evaluation of valve structure and function on serial echocardiography during and after the course of their treatment.

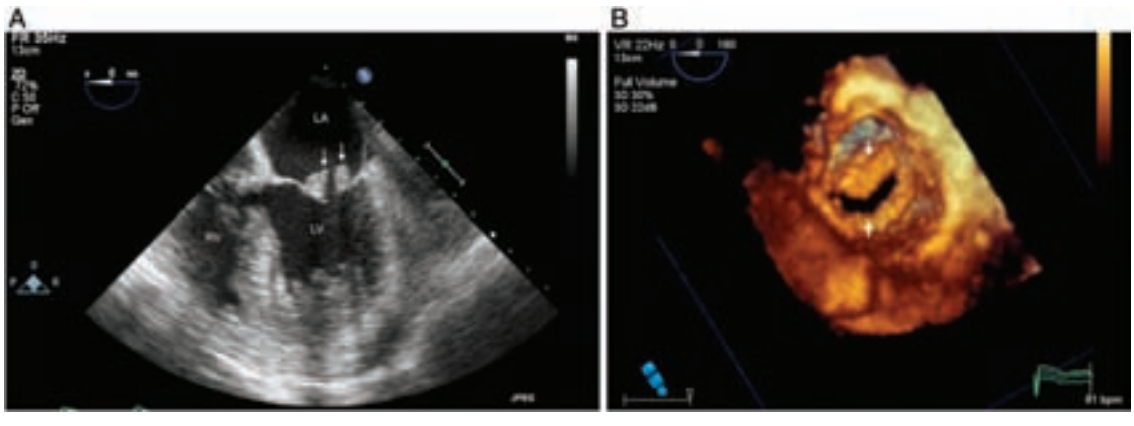

Figure 3 Transoesophageal apical four-chamber and 3D reconstruction in an 86-year-old woman with marantic endocarditis, in the setting of metastatic pancreatic cancer. Please note the diffuse involvement of the edge of the anterior and posterior leaflets.

E. Pericardial disease

Pericardial disease in oncological patients is relatively common. It may be secondary to cardiac metastasis, or may be a consequence of radiotherapy[73,74] and/or chemotherapy.[75]

Pericardial disease induced by chemotherapy usually manifests as pericarditis, with or without associated myocarditis. The pericarditis may be associated with pericardial effusion with varying degrees of haemodynamic impairment.

Several chemotherapy agents are associated with pericardial disease. Anthracyclines,[75–78] cyclophosphamide,[79–84] and cytarabine[85–89] are associated with acute or subacute development of pericarditis and pericardial effusion, which may or may not be accompanied by myocarditis. Imatinib mesylate[90,91] and dasatinib,[92,93] both tyrosine-kinase inhibitors, are associated with the development of pleural and pericardial effusions, which may progress to cardiac tamponade. Interferon-α,[94–98] used in the treatment of melanoma, can cause pericarditis and pericardial effusion. Retinoic acid syndrome occurs in approximately 26% of patients treated with this drug and is characterized by fever, arterial hypotension, acute renal failure, and pleural and pericardial effusions.[99,100] The occurrence of pericardial and endomyocardial fibrosis years after administration of busulfan has also been described.[101] Other agents associated with pericardial disease are methotrexate,[102–105] arsenic trioxide,[106,107] and less frequently, 5-fluorouracil[108] and docetaxel.[109]

Transthoracic echocardiography is the method of choice for the initial evaluation of patients with suspected pericardial disease. In most cases, it allows not only diagnosis but also guidance of pericardiocentesis. The echocardiographical findings in patients with pericarditis can be entirely normal or show evidence of a pericardial effusion. The pericardial effusion should be quantified and graded according to recognized methods, to allow comparison in subsequent evaluations (*Figure 4*).[110] Evaluation of cardiac tamponade (particularly frequent in the case of malignant effusions) should be performed according to published guidelines.[70,111–113]

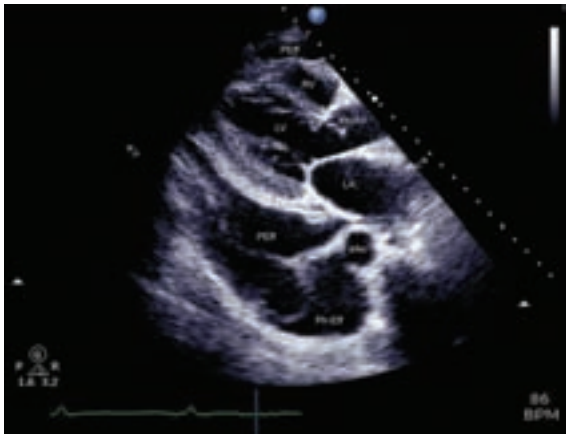

Figure 4 Parasternal long-axis view of a patient with metastatic lung cancer. Echo-lucent spaces are seen anterior (pericardial effusion [PEff]) and posterior to the descending aorta (pleural effusion [Plr-Eff]). Echo-lucent space is also seen anterior to the free wall of the right ventricle (pericardial effusion). Findings are consistent with a circumferential pericardial effusion.

When pericardial thickening is evident, especially if there are clinical signs of RV failure and low cardiac output in the presence of normal ventricular dimension and function, evaluation of constrictive physiology should be made. Constrictive pericarditis is more often associated with radiation-induced cardiotoxicity,[58,114,115] but there are reports of occurrence after high-dose chemotherapy administration.[116] Echocardiographical signs of constriction should be explored according to published guidelines.[70,110,117–119]

Differentiating constrictive pericarditis from restrictive cardiomyopathy in oncological patients may be a challenge because the two conditions can overlap.[70]

In some instances, the use of other imaging modalities, such as computed tomography or CMR, can be a useful complement to the echocardiographical evaluation. They should especially be considered in the evaluation of primary tumours of the heart, with or without compromise of the pericardium, or when the diagnosis of constrictive pericarditis remains uncertain after a careful echocardiographical evaluation.[70] CMR is particularly useful in determining the presence of late gadolinium enhancement (LGE) for the identification of patients with transient constriction, who will benefit from aggressive anti-inflammatory regimens rather than pericardiectomy.

Key points

- Pericardial disease in oncological patients can be associated with cardiac metastasis or be a consequence of chemotherapy and/or radiotherapy.
- Pericardial effusion should be quantified and graded according to standard methods.
- Echocardiographical and Doppler signs of cardiac tamponade should be investigated, particularly in patients with malignant effusions.
- CMR should be considered in evaluation of primary tumours of the heart with or without compromise of the pericardium or when the diagnosis of constrictive pericarditis remains uncertain after a careful echocardiographical evaluation.

F. Echocardiography

Although 3DE is more accurate than 2DE for the measurement of LV volumes[120] in normally shaped ventricles, the accuracy of 2D LVEF calculation should be conceptually similar to that of 3DE because the extent of volume underestimation by 2DE should be similar in both diastole and systole. However, improved accuracy of 3DE (sensitivity, 53%; false-negative rate, 47%) over 2DE (25% and 75%, respectively) in detecting LVEF $<50\%$ on CMR has been observed in survivors of childhood cancer.[121] This result may be explained by the fact that 3DE volume measurements are not conditioned by errors induced by geometric assumptions of LV shape, foreshortening of views, or uncontrolled orientation of apical two-chamber and four-chamber views that commonly affect the accuracy of 2DE (*Figure 5*).

Moreover, serial evaluation of patients at risk for CTRCD requires that the imaging technique should be repeatable and provide consistent results when quantitative analysis is performed on images acquired at different time points and also when images are acquired and/or analyzed by different observers. To address this issue, a

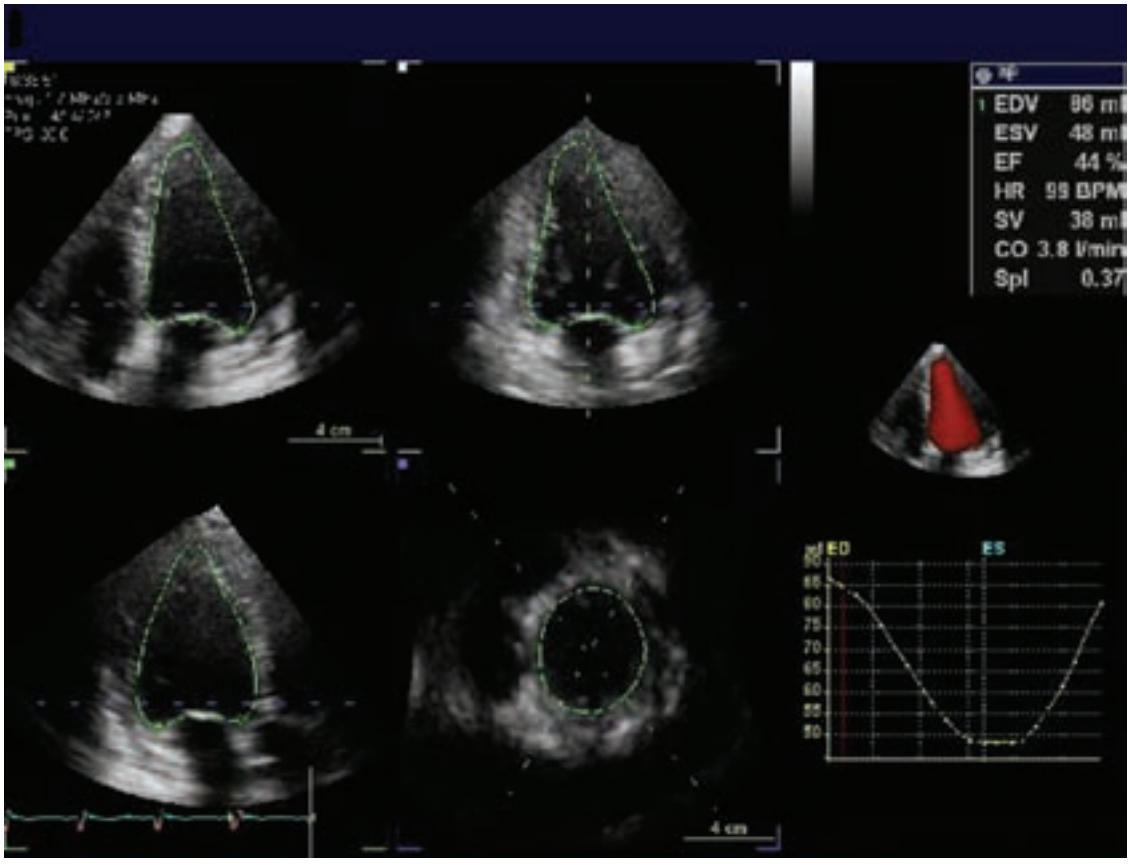

Figure 5 Semiautomated calculation of LVEF using real-time 3DE in a patient with trastuzumab-induced CTRCD. The LVEF is abnormal at 44% (normal >53%).

recent study[44] compared different echocardiographical techniques (2D biplane Simpson's method, 2D triplane, and 3DE with and without contrast) for the serial evaluation of LVEF in patients with cancer undergoing chemotherapy with stable LV function, to identify the technique with the lowest test–retest variability over 1 year of follow-up. Among 56 patients, non-contrast 3DE showed significantly lower temporal variability than all other techniques. Non-contrast 3D echocardiographical measurement of LVEF provided the desired level of longitudinal reproducibility of 5.6% (95% confidence interval, 5.0–6.2%), whereas 2D echocardiographical techniques showed higher temporal variability (9.8%). Non-contrast 3DE also had the best intra- and interobserver and test-retest variability. Low test-retest variability is as important as the actual LVEF measurement and warrants careful adherence to optimal lab techniques aimed at minimizing it. The superiority of 3DE over 2DE may be explained by the fact that the former is less affected by acquisition differences from one scan to the next, as often seen with the latter,[122,123] and by use of an automated or semiautomated method for identifying endocardium, compared with manual tracing of endocardial contour required by 2DE. The improved reproducibility of semiautomated *vs.* manual contouring has been previously reported both with 2DE and 3DE.[124,125] Three-dimensional echocardiography appears to be the technique of choice for monitoring the cardiac effects of chemotherapy.[126] However, it is important to realize that this technology has several limitations as well. It is not widely available because of cost, and it relies heavily on high-quality images and operator expertise to achieve the superior performance mentioned above. A recent study by Tsang *et al.*[127] demonstrated that a quality improvement session dedicated to formally standardizing the analytical approach of the readers in the echocardiography laboratory can eliminate the systematic bias and improve the agreement among readers in the measurement of LV volumes. It is recommended to include in the echocardiographical report the calculation of LVEF by the biplane Simpson's method, allowing comparison with previous studies if this method was used. Where available, serial 3D echocardiographical calculation of LVEF should be encouraged for monitoring CTRCD. It is to be expected that during the years to come, less expensive, more automated, and user-friendly 3DE machines that rely less on operator expertise could allow a wider application of this technique.

Key points

- Three-dimensional echocardiography is the preferred technique for monitoring LV function and detecting CTRCD in patients with cancer. Advantages include better accuracy in detecting LVEF below the lower limit of normal, better reproducibility,

and lower temporal variability than 2DE in patients with cancer treated with chemotherapy.
- Costs, availability, high reliance on image quality, and need for training of operators currently limit the wide application of 3DE in the oncological setting.

G. Contrast echocardiography

Underestimation of volumes may occur when the endocardium is not adequately visualized.[128] Endocardial border dropout can frequently occur in patients undergoing chemotherapy (in particular patients with breast cancer after mastectomy and chest irradiation). According to the ASE consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography and EAE recommendations[129,130] on myocardial contrast echocardiography, a contrast agent should be used when two contiguous LV segments from any apical view are not seen on non-contrast images (*Figure 6*).

There is limited literature to support the use of contrast for 3D assessment of LV volumes in patients with cancer.[122] A recent study performed in patients with cancer undergoing chemotherapy did not demonstrate any advantage of using contrast-enhanced 3DE for the measurement of LV volumes and LVEF (lower reproducibility and higher temporal variability were noted compared with 3DE alone).[44] There are two potential explanations for the findings. First, blooming and attenuation artifacts may hinder the delineation of structures such as the mitral valve, with the resultant variability in contouring of the left ventricle. Second, most of the patients studied had adequate acoustic windows with harmonic imaging and therefore did not meet traditional criteria for contrast administration.

Key points

- The use of myocardial contrast agents could be potentially useful in chemotherapy patients when endocardial dropout occurs.
- According to current recommendations, contrast should be used when two contiguous LV segments are not well visualized on non-contrast apical images.
- Contrast agents are not recommended in conjunction with 3DE in the longitudinal follow-up of patients with cancer.

H. Stress echocardiography

Stress echocardiography, an established technique for the detection and prognostication of stable CAD as recommended by guidelines, may be useful in the evaluation of patients with intermediate or high pre-test probability for CAD (uninterpretable electrocardiogram or unable to exercise),[131] who are undergoing regimens that may be associated with ischemia (fluorouracil, bevacizumab, sorafenib, and sunitinib).[132]

In addition, there are two specific areas in which stress echocardiography may be useful: (i) the evaluation of sub-clinical LV dysfunction and (ii) the evaluation of contractile reserve in patients with CTRCD.

Although both exercise[27] and dobutamine stress echocardiography[27,112,133–140] have been applied to patients with cancer for the identification of anthracycline-induced CTRCD, the results of these studies appear to be inconclusive and contradictory. One of these studies prospectively assessed LV contractile reserve by low-dose dobutamine stress echocardiography in 49 women with breast cancer before each chemotherapy cycle and 1, 4, and 7

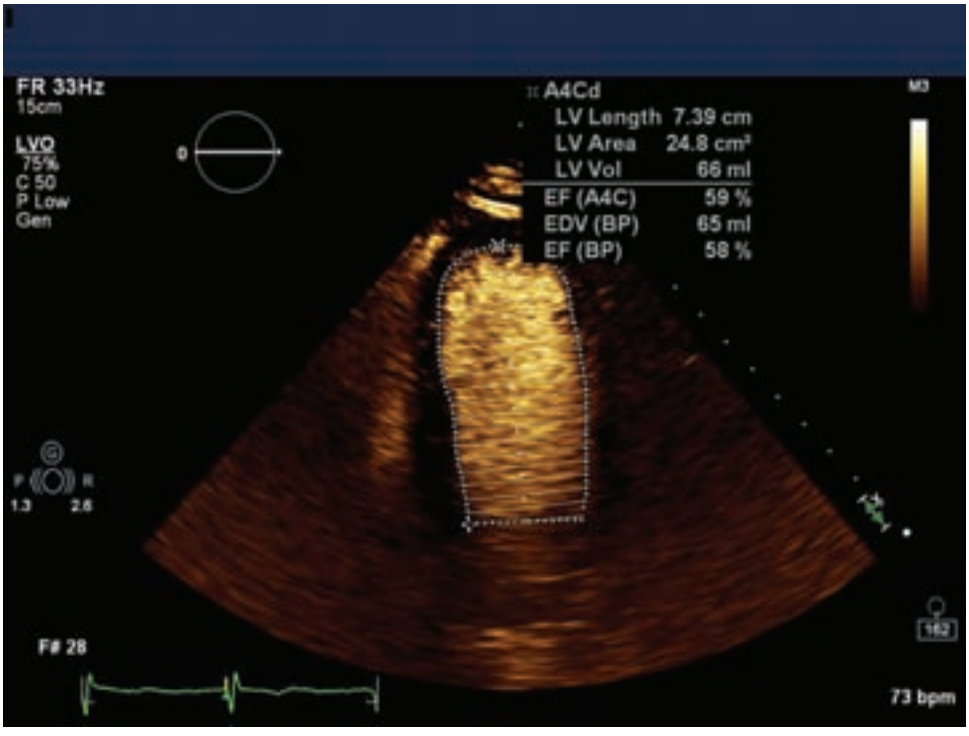

Figure 6 End-diastolic endocardial tracing obtained from the apical four-chamber view after the administration of contrast for the calculation of LVEF using the method of disks in a patient with inadequate 2D echocardiographical images.

months after stopping the treatment. A 5-unit fall in LV contractile reserve was found to be predictive of subsequent LVEF reduction <50%.[140] Dobutamine could potentially allow the earlier identification of disease by recognizing a compromise in cardiac reserve.

In case of the development of CTRCD, the transient recovery of LV function during stress echo may also predict a better outcome.[141]

Key points

- Stress echocardiography may be helpful in the evaluation of patients with intermediate or high pre-test probability for CAD (uninterpretable electrocardiogram or unable to exercise) who will receive regimens (fluorouracil, bevacizumab, sorafenib, and sunitinib) that may cause ischemia.
- Stress echocardiography may be of help in the determination of contractile reserve of patients with evidence of CTRCD.

I. Other

In the presence of implanted ports, tunnelled catheters, or peripherally inserted central lines, it is recommended to report the location of the tip with respect to the superior vena cava–right atrium junction, as well as the presence of thrombus or vegetations.

III. Detection of sub-clinical LV dysfunction

A. Detection of sub-clinical left ventricular dysfunction using imaging

1. LVEF as a tool to detect sub-clinical LV dysfunction

Although the decrease in LVEF during treatment has been associated with symptomatic HF,[31,34,35] the ability of serial LVEF assessment during and after treatment to identify CTRCD and prevent subsequent HF remains controversial.[2,5,30] Recently, the value of baseline LVEF and LVEF measured after anthracyclines in the prediction of subsequent HF was underlined in a large study of women with breast cancer treated with anthracyclines, with or without trastuzumab. In this study, a reduced LVEF (including LVEFs of 50–54%) at baseline or after anthracyclines was associated with higher rates of cardiac events on follow-up,[142] although the percentage of patients with LVEFs <55% after anthracyclines in the study was quite low (10–12%). Unfortunately, detecting a decreased LVEF after anthracyclines may be too late for treatment,[143] suggesting that more sensitive parameters of LV dysfunction would be helpful.

2. Diastolic dysfunction: early signs and prognostic value

In a small prospective study, a prolongation of the isovolumic relaxation time preceded and predicted a drop in LVEF of >10%, occurring up to 3 months later.[144] Larger studies, however, although confirming early changes of LV diastolic parameters after treatment, have not reproduced its predictive value.[145]

Significant increases in the myocardial performance index occur early after anthracycline administration and were reported in two studies to predict later decreases in LVEF.[146,147] The prognostic value of myocardial performance index could not be replicated in subsequent studies.[148]

Two studies have reported LV diastolic abnormalities late after anthracycline administration; these abnormalities were associated with wall motion abnormalities despite a preserved LVEF.[149] Another study reported that a reduced transmitral E/A ratio was associated with a reduction in longitudinal strain by STE in patients with normal LVEFs late after treatment.[150] It is unclear, however, if these findings have any clinical significance.

As a result, it can be concluded that the use of Doppler-derived diastolic indices is not useful in the early detection of CTRCD because of their inability to predict subsequent HF (*Table 3*).

3. Detection of sub-clinical LV dysfunction using DTI velocities

Several investigators have demonstrated an early reduction in e′ velocity of the mitral annulus in patients receiving anthracyclines (*Figures 7C* and *7D*),[48,150–152] which remained reduced during treatment[153] and for several years thereafter.[150] The reductions in e′ velocity appear heterogeneous,[150,151,154] suggesting differences in regional wall stress, apoptosis, or fibrosis.

In a study by Negishi *et al.*,[155] a 10% reduction in e′ velocity was observed in patients who developed CTRCD. Nevertheless, the reduction was not statistically significant ($P = 0.09$) or predictive of subsequent reduction in LVEF ($P = 0.14$).

A reduction in DTI-derived systolic velocity (s′) was reported in animal models of doxorubicin-induced cardiac injury[6] and in the chronic follow-up of patients treated with anthracyclines.[150] A marked early decrease in s′, and its value as a potential predictor of changes of LV systolic function after chemotherapy, was reported in a study of 42 patients with breast cancer treated with trastuzumab in the adjuvant setting.[156] It is to be noted, however, that the rate of symptomatic HF in this study was of 24% at 6 months of treatment, an unusually high rate in chemotherapy-treated populations. Whether these results can be generalized to patients with a lower incidence of HF is unknown.

Key points

- A decreased LVEF at baseline or after anthracyclines is associated with higher rates of cardiac events on follow-up.
- Although it has been suggested that alterations in LV diastolic function (as evaluated by Doppler indices of mitral inflow and e′ by pulsed DTI) precede alterations in systolic function, the evidence does not support the role of these indices for the prediction of later CTRCD.

4. Early detection of LV dysfunction using strain and strain rate

A recent systematic review shows that as of 2014, 21 peer-reviewed studies have reported the sensitivity of measuring deformation indices (strain, strain rate, and twist) in the detection of sub-clinical LV dysfunction in patients treated for cancer (*Table 4* summarizes these studies).[157] The studies evaluated patients treated with anthracyclines alone, or in association with other therapies, either during treatment or late after completion of the therapy (survivor studies).

The decrease in myocardial systolic function induced by anthracyclines appears to be extremely rapid, as early as 2 hours after the first anthracycline dose.[47] As in most of the other studies, the decrease in

Table 3 Clinical studies assessing diastolic function indices in cancer treatment demonstrating predictive value of subsequent cardiotoxicity

Study	Population	Treatment	Timing of echocardiography	Findings	Decrease in LVEF	Predictive value/correlations
Stoddard *et al.* (1992)[144]	26 adults; mean age, 48 y	Doxorubicin > 200 mg/m^2	Baseline, 3 wk, and 3 mo after treatment	Prolonged IVRT and deceleration time at 3 wk	9/26 (35%)	Prolongation of IVRT > 37% predicted a drop in LVEF > 10% (78% sensitivity, 88% specificity)
Dorup *et al.* (2004)[145]	88 ALL, 66 Wilms' tumour, age not reported	ALL: daunorubicin 90, 180, or 270 mg/m^2; Wilms' tumour. doxorubicin 303 mg/m^2	~1.5 and 6.5 y after treatment	Reduced E wave and reduced E/A ratio, prolonged IVRT and E deceleration time	Not reported	13% of those with reduced E wave at 1.5 y had reduced fractional shortening at FU
Tassan-Mangina *et al.* (2006)[48]	16; mean age, 38 y	Doxorubicin 211 mg/m^2	Before chemotherapy, 1–3 mo and 3.5 y after treatment	Reduced mitral E wave and DTI E velocity at early FU; more pronounced changes at late FU	4/16 (25%)	All those with decreased LVEFs had a short IVRT at early FU

ALL, Acute lymphoblastic leukemia; FU, follow-up; IVRT, isovolumic relaxation time.

deformation indices preceded the decrease in LVEF and persisted during the subsequent cancer treatment. Early decreases in radial and longitudinal strain and strain rate were noted using DTI[158] and STE[153,156,159–161] and have been confirmed in patients treated with anthracyclines (in some studies in association with taxanes and trastuzumab), with or without later decreases in LVEF. In one small study, radial indices decreased earlier than longitudinal indices after three cycles of anthracyclines.[158] Decreases in global[160] and regional[161] circumferential strain have also been reported early after anthracycline treatment. The magnitude of the decrease in longitudinal strain appears to average between 10% and 20% over the length of the treatment, depending on the population, the analysis, and the treatment studied.

The regionality of the impairment of LV systolic function was assessed in 19 children at the midpoint and at the end of their anthracycline treatment. The investigators reported mainly a septal and apical pattern, which was partially improved at the end of the treatment.[159] There does not appear to be preferential impairment of one particular layer (sub-endocardial, mid-myocardial, or sub-epicardial) by anthracyclines, as both longitudinal and radial (and, when studied, circumferential) strain was altered. This result is concordant with experimental models of doxorubicin-induced CTRCD, in which cardiomyocyte apoptosis is present throughout the myocardial layers.[6]

Interestingly, Hare *et al.*[162] did not report any change in longitudinal or radial global systolic strain (but a slight decrease in longitudinal and radial strain rate) in patients treated by anthracyclines and trastuzumab. Strain rate measurements may be more sensitive than strain to subtle changes in cardiac function. However, use of strain rate appears to be more challenging in clinical practice.

The prognostic value of early measurement of systolic deformation indices in the prediction of subsequent LV systolic function has been evaluated in several studies, both in animals[6] and humans.[153,156,159,160] In 81 patients with breast cancer treated with anthracyclines followed by taxanes and trastuzumab who were followed for 15 months with quarterly echocardiography, the average of the basal and midventricular peak systolic longitudinal strain measured in apical four- and two-chamber views using STE after the completion of anthracyclines predicted subsequent CTRCD. CTRCD was defined in this study as a decrease in LVEF of >10% to <55% during the remainder of the treatment (12 months thereafter). Longitudinal strain calculated with EchoPAC software (GE Healthcare, Milwaukee, Wisconsin, USA) was > −19% in all patients who later developed HF (*Figures 8A–8D*). Although reductions were seen in all three layers, neither radial nor circumferential strain was predictive of subsequent CTRCD.[160] A predictive value of regional strain was also reported in smaller studies with shorter follow-up periods.[153,156,159] Importantly, although the decrease in longitudinal strain and LVEF appears to at least partially persist throughout the treatment,[160] it is unknown what their evolution will be in subsequent years, and whether early deformation measurements will predict persistent decreases in LVEF or symptomatic HF.

Negishi *et al.*[155] recently published a study looking for the optimal myocardial deformation index to predict CTRCD at 12 months in 81 women with breast cancer treated with trastuzumab, with or without anthracyclines. The strongest predictor of CTRCD was ΔGLS measured at the 6-month visit. An 11% reduction (95% confidence

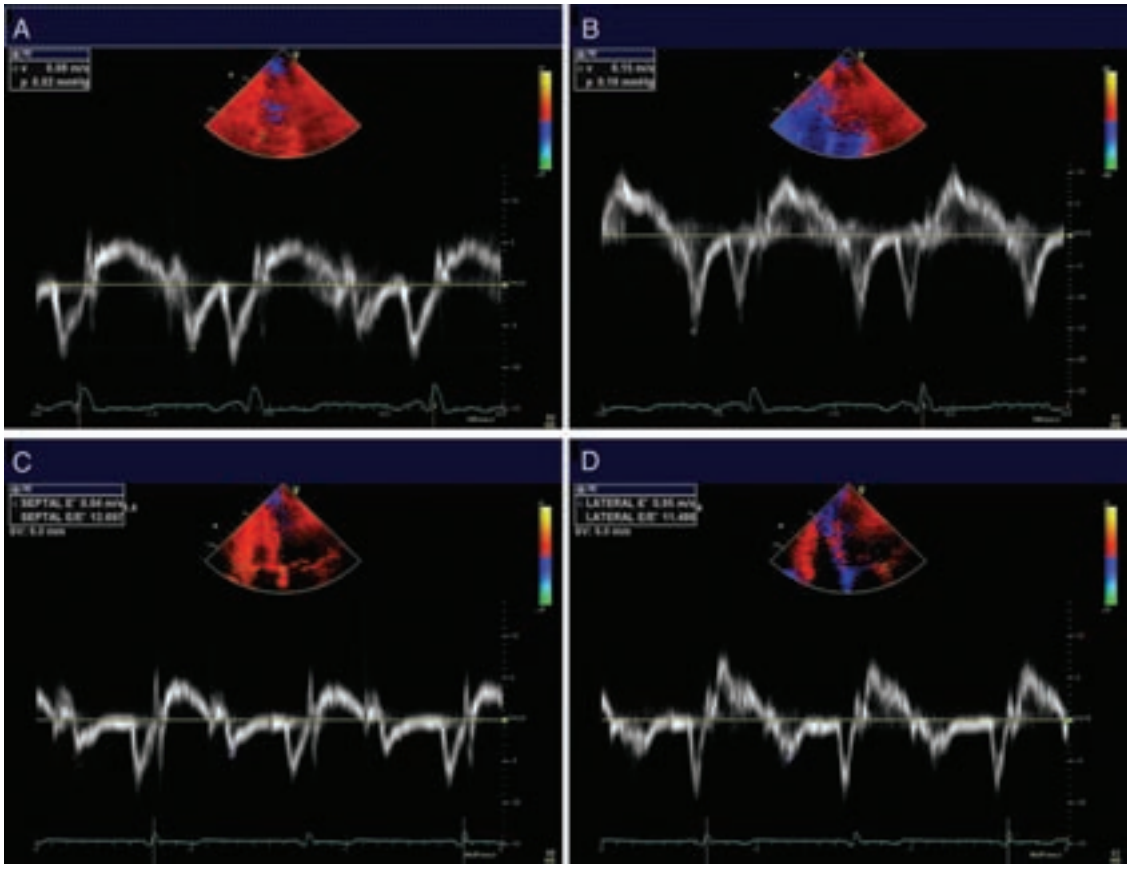

Figure 7 Reductions in pulsed DTI e′ velocities in the setting of anthracycline-induced CTRCD. (A,B) Septal and lateral e′ velocities were 8 and 15 cm/sec, respectively, before the initiation of therapy. (C,D) Septal and lateral velocities decreased to 4 and 5 cm/sec, respectively, during anthracycline therapy.

interval, 8.3–14.6%) was the optimal cut-off, with sensitivity of 65% and specificity of 94%. Of note, ΔGLS was superior to changes in the count of abnormal segments, s′ and e′ velocities. They concluded that in patients with baseline strain measurements, the 95% confidence interval suggests that reductions of GLS of $<8\%$ compared with baseline appear not to be clinically meaningful, whereas those $>15\%$ are very likely to be of clinical significance (see *Figures 9A* and *9B* for example of calculation). They confirmed the findings of Sawaya *et al.*,[160] this time using the conventional calculation of GLS averaging the 18 segments from the three apical views. They showed that in patients without baseline strain measurements, the proposed cut-off of -19% conforms to the confidence interval around -20.5% found in their study. Nevertheless the area under the curve for absolute strain value is less, making the change in strain the preferable approach.

Finally, four studies evaluated the deformation parameters in long-term cancer survivors (range, 2–30 years after treatment).[150,154,163,164] In two of the studies with longer follow-up and/or higher doses of anthracyclines, the LVEF (or fractional shortening) was slightly decreased.[163,164] In contrast, all four studies detected decreases in longitudinal and radial (and circumferential when studied) parameters compared with age-matched control patients, underlining the sensitivity of these parameters in the detection of sub-clinical LV dysfunction. STE appears therefore as the imaging technique of choice for detection of sub-clinical LV dysfunction. Normal values for GLS depend on the measurement position in the myocardium, the vendor, and the version of the analysis software, resulting in considerable heterogeneity in the published literature. Two recently published large studies evaluating the normal ranges of LV 2D strain have shown an effect of gender in LV myocardial deformation.[165,166] The study of Kocabay *et al.*[165] reported a mean normal GLS of -20.7 ± 2 for men and -22.1 ± 1.8 for women. These values are almost identical to the ones reported by the Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study[166] for the same vendor. There is also concern that strain values may decrease with age.[166,167] As a result, it is not possible to recommend universal normal values or lower limits of normal. We refer the reader to *Table 5*, which summarizes the findings of the JUSTICE study, providing mean values for GLS according to vendor, gender, and age. Cheng *et al.*[168] recently evaluated the reproducibility of 2D STE in the Offspring Cohort of the Framingham Heart Study. The interobserver intraclass correlation coefficient was ≥ 0.84 for all global strain measurements, with an average coefficient of variation for GLS of $\leq 4\%$. The intraobserver intraclass correlation coefficient was ≥ 0.91 among time points spanning a total 8-month period, with an average of $\leq 6\%$ for GLS. The authors concluded

Table 4 Clinical studies using STE-derived deformation indices during or early after cancer treatment

Study	Echocardiographical method	Cancer type	n	Age, yrs	Female, %	Treatment	Echocardiography timing	Pre-echo	Post-echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Mornos *et al.* (2013)[234]	STE	Breast lymphoma, ALL, AML, osteosarcoma	74 & 37 controls	51 ± 11	58	Anthracyclines	Pre, post, and 6, 12, 24 and 52 weeks	GLS -21.2 ± 2.5% GRS 47.8 ± 5.3%	GLS -19.0 ± 2.4% GRS 41.1 ± 5.4% (6 weeks)	13	ΔGLS 2.8% (13.1% relative), sensitivity 79% and specificity 73% at 6 weeks for toxicity at 24–52 weeks	GE, intraobserver ICC for GLS 0.95, interobserver 0.91
Negishi *et al.* (2013)[155]	STE	Breast	81	50 ± 11	100	Trastuzumab, doxorubicin 46% RT 62%	Pre-trastuzumab, and 6 and 12 months later	GLS -20.7 ± 2.6% GLSR -1.17 ± 0.24/s GLSR-E 1.36 ± 0.28/s	GLS -18.3 ± 2.1% GLSR -1.00 ± 0.15/s GLSR-E 1.20 ± 0.28/s (at 6 months in patients who later had toxicity)	30	GLS change ≥11% between pre-treatment and 6 months, sensitivity 65%, spec 95% or absolute GLS > −20.5 at 6 months, sensitivity 96%, spec 66% for toxicity at 12 months	GE, intraobserver ICC (95% CI) for GLS 0.85 (0.54%–0.96%), GSLR 0.91 (0.70–0.98/s), GLSR-E 0.90 (0.66–0.97/s), Interobserver 0.71 (0.23%–0.92%), 0.85 (0.28–0.97/s), 0.87 (0.56–0.97/s)
Baratta *et al.* (2013)[235]	STE	Breast	36	47 ± 16	58	Doxorubicin 58% trastuzumab 22%	Pre- and 2,3,4, and 6 months after start of therapy	GLS -20.3 ± 2.7% GRS 53.1 ± 4%	GLS -18.9 ± 2.5% (3 months) GRS 50 ± 3.9% (4 months)	19.4	GLS fall ≥ 15% at 3 months, sensitivity 86%, spec 86%. GRS fall ≥ 10% at 4 months, sensitivity 86% spec 69%	GE, mean (SD) absolute difference inter/intraobserver GLS 0.6 (1.4%)/0.2 (1/1%), GRS 3.4 (7.1%)/3.2 (6.6%)
Sawaya *et al.* (2012)[160]	STE	Breast	81	50 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 60%	Pre-anthracycline and at 3, 6, 9, 12, and 15 months	GLS -21 ± 2% GRS 53 ± 15% GCS -18 ± 4%	GLS -19 ± 2% GRS 50 ± 17% GCS -16 ± 4% at 3 months	32	Absolute GLS < −19% at 3 months, sensitivity 74%, spec 73% for subsequent toxicity	GE, same variability as in previous study (153)
Sawaya *et al.* (2011)[153]	STE	Breast	43	49 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 11.6%	Pre-anthracycline and at 3 and 6 months	GLS -20.5 ± 2.2% GCS 18 ± 4%	GLS -19.3 ± 2.4% GCS 15 ± 4%	21	GLS fall > 10% at 3 months, sensitivity 78%, spec 79% for toxicity at 6 months	GE, intraobserver as absolute mean error (SD) GLS −0.14 (1.1%), interobserver 0.5 (1.5%)
Fallah-Rad *et al.* (2011)[156]	STE	Breast	42	47 ± 9	100	Epirubicin, doxorubicin, trastuzumab, RT 98%	Pre-anthracycline, Pre-trastuzumab and at 3, 6, 9, and 12 months	GLS -19.8 ± 1.8% GLS 41.4 ± 15.2%	GLS -16.4 ± 1.1% GRS 34.5 ± 15.2% (3 months into trastuzumab)	24	Absolute GLS fall of 2.0%, sensitivity 79%, spec 82%. Absolute GRS fall of 0.8%, sensitivity 86%, spec 81% for subsequent toxicity	GE, intraobserver as ICC (COV) GLS 0.94 (3.5%), GRS 0.91 (3.2%). Interobserver 0.90 (5.2%), 0.82 (5.4%)

Continued

Table 4 Continued

Study	Echocardiographical method	Cancer type	n	Age, yrs	Female, %	Treatment	Echocardiography timing	Pre-echo	Post-echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Hare *et al.* (2009)[162]	TDI and STE	Breast	35	51 ± 8	100	Doxorubicin, epirubicin, trastuzumab, RT 77%	Pre- and/or post-anthracycline and at 3-month intervals	STE GLSR -1.30 ± 0.21/s STERSR 2.02 ± 0.61/s	STE GLSR -1.24 ± 0.18/s (by 3 months) STE RSR 1.75 ± 0.41/s (by 6–9 months)	14	A >1 SD drop in GLSR (toxicity at mean follow-up of 22 ± 6 months)	GE, intra/interobserver as ICC for 2D GLS 0.94/0.91, GLSR 0.94/0.91, GRS 0.86/0.50, GRSR 0.83/0.65
Mavinkurve-Groothuis *et al.* (2013)[236]	STE	ALL	60, 60 controls	6 (2.2–15.4)	38	Anthracycline, RT 100%	Pre-anthracycline, 10 weeks, and 12 months	GLS -18.2 ± 3.1% GLSR -1.44 ± 0.3/s GRS 66.8 ± 1% GCS -19.4 ± 4.3	GLS -16.7 ± 5.2% GLSR -1.20 ± 0.4/s GRS 55.2 ± 16% GCS -16.9 ± 3.1% (by 12 months)	0	Strain values were not predictive of decrease in LV fractional shortening	GE, no data

AC, Adriamycin; ALL, acute lymphoblastic leukemia; AML, acute myoblastic leukemia; CHF, congestive heart failure; CREC, Cardiac Review and Evaluation Committee; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; 4CH, four-chamber; FS, fractional shortening; GCS, global circumferential strain; GLSR, global longitudinal strain rate; GLSR-E, global longitudinal early diastolic strain rate; GRS, global radial strain; GRSR, global radial strain rate; LS, longitudinal strain; LSR, longitudinal strain rate; NPV, negative predictive value; PPV, positive predictive value; RSR, radial strain rate; SAX, short-axis; 2CH, two-chamber. Reproduced with permission from the *Journal of the American College of Cardiology*.

that 2D STE is reproducible when performed by trained operators. However, the technique has important limitations (*Table 6*). There are no data currently available as to the reproducibility of GLS at non-academic centres or community hospitals. The presence of a learning curve for sonographers and interpreting physicians makes dedicated training and monitoring of quality (i.e. intra- and interobserver and test-retest variability) essential. When setting a strain program, it is recommended to initially designate one physician and, where available, one technician to perform, interpret, and compare studies over time. As experience is gained with the technique, the effort may be expanded to include other physicians, technicians, and trainees. Nevertheless, the most important limitation is intervendor variability.[166,169] Different echocardigoraphy machines or software packages can in fact produce different results, in particular for circumferential and radial strain, making problematic intraindividual comparisons over time. Recognizing the critical need for standardization in strain imaging, the EACVI and ASE invited technical representatives from all interested vendors to participate in a concerted effort to reduce intervendor variability in strain measurement.[170] Until that is achieved, it is recommended to use the same vendor's machine and software version to compare individual patients with cancer when using 2D STE for the serial evaluation of systolic function.

Individual echocardiographical laboratories following patients with cancer should strive to incorporate strain assessment in their echocardiography laboratory protocols.

Key points

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favoured because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of sub-clinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

B. Detection of sub-clinical left ventricular dysfunction using biomarkers

Biomarkers have the potential to fulfill a critical unmet need as a robust diagnostic tool for the early identification, assessment, and monitoring of CTRCD. A biomarker approach is minimally invasive and can be readily repeated without significant risk. Despite intrinsic assay variability, standardized assays typically have acceptable coefficients of variation of <10%, potentially minimizing intra- and interobserver variability.[171]

1. Troponins

Cardiac troponins are the gold standard biomarkers for the diagnosis of myocardial injury.[172,173] Troponin I (TnI) is a sensitive and specific marker for myocardial injury in adults treated with anthracycline

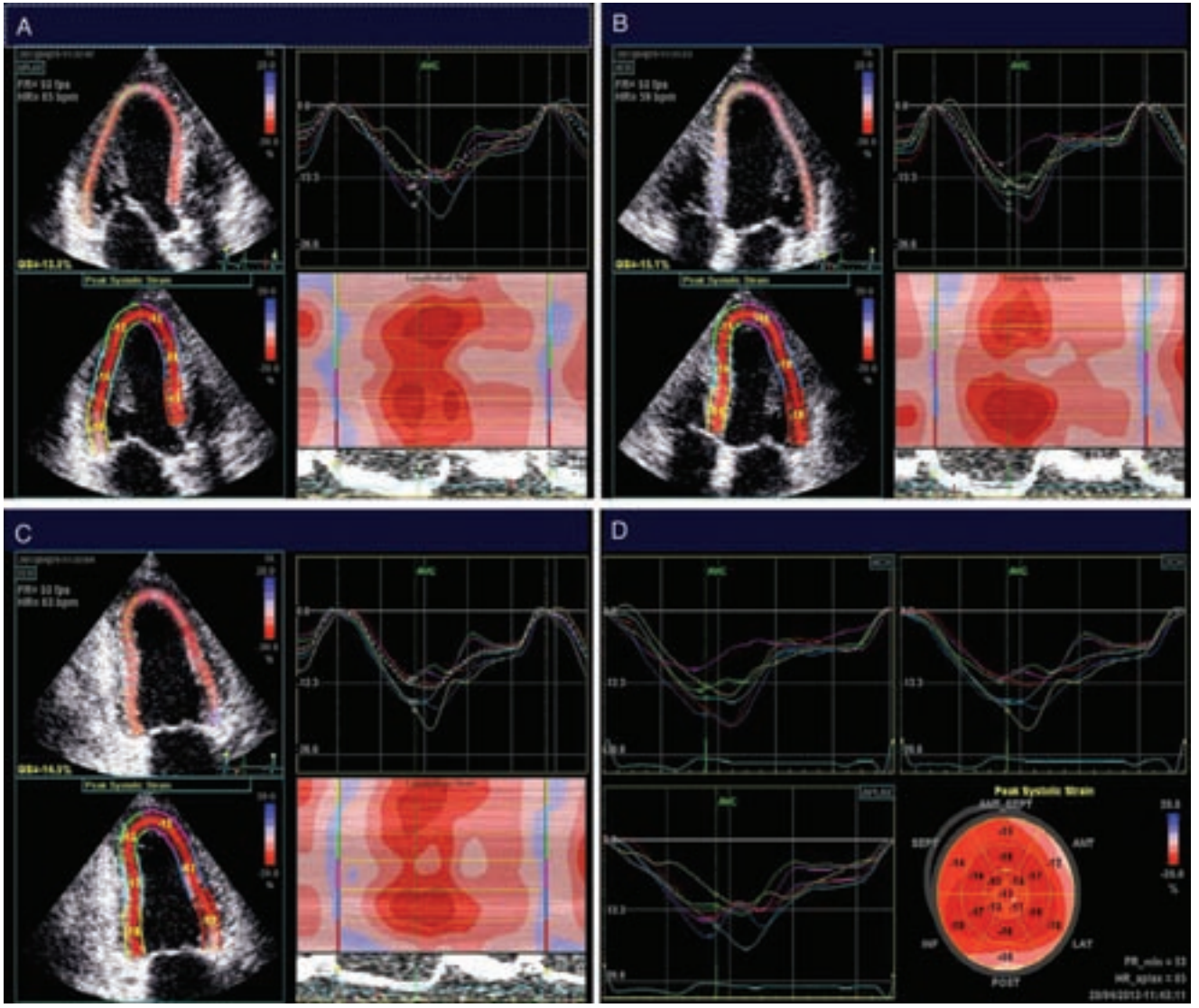

Figure 8 Speckle-tracking echocardiographical images illustrating GLS obtained from the apical long-axis view (A), four-chamber-view (B), and two-chamber-view (C) and strain curves and bullseye plot in a patient with breast cancer who developed CTRCD after receiving doxorubicin followed by trastuzumab. Each segment has a numeric and color-coded strain value. The cardiac dysfunction appears to be regional, with some segments more involved than others.

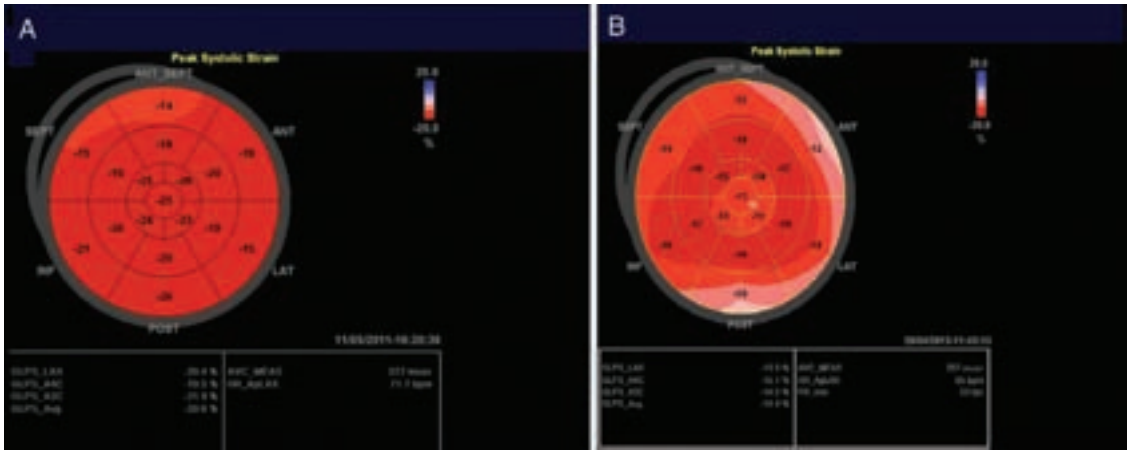

Figure 9 Bullseye plot showing GLS of the patient shown in Figure 8. (A) GLS and regional longitudinal strain at baseline. (B) GLS and regional longitudinal strain 3 months during trastuzumab-based therapy after anthracyclines. GLS has decreased from −20.6% to −14.4% (30% decrease). The decrease in GLS is therefore considered of clinical significance (>15% vs baseline).

chemotherapy, and studies suggest that an elevation of troponin identifies patients at risk for the subsequent development of CTRCD.

The largest of these studies was performed in 703 patients with cancer, in whom TnI was determined with each cycle of high-dose chemotherapy and 1 month after chemotherapy.[174] Patients were classified into three sub-groups on the basis of the combined presence of any detectable TnI either within 72 hours (early) or 1 month after the last administration of chemotherapy (late). In 495 patients, both early (within 72 hours) and late TnI values were <0.08 ng/mL; in 145, there was only an early increase; and in 63 patients, both values increased. These troponin release patterns identified patients at different levels of risk for CTRCD, with the majority of events occurring in TnI-positive patients. Furthermore, a persistent TnI increase was associated with an increase in the severity of CTRCD and a higher incidence or cardiac events compared with transient increases. The correlation between TnI positivity and LVEF maximal reduction ranged from 0.78 to 0.92, with positive and negative predictive values of 84% and 99%, respectively. The advantage of this high negative predictive value is the identification of patients at low risk for CTRCD. However, a persistent TnI increase was associated with an increased severity of CTRCD and a higher incidence of cardiac events compared with transient increases. Additional smaller studies have also demonstrated correlations between troponin elevations and subsequent LVEF decline.[175–177]

Troponins may be also be used to identify early cardiac injury in patients undergoing treatment with newer targeted anti-cancer drugs. The largest of these studies, performed in 251 patients with breast cancer treated with trastuzumab, demonstrated that TnI positivity was associated with an increased incidence of cardiac events and lower likelihood of recovery.[178] Other investigators have also studied the changes in TnI in patients with breast cancer receiving doxorubicin followed by trastuzumab therapy.[160] In women who developed cardiotoxicity at the completion of anthracyclines, the mean ultrasensitive TnI concentration was 32 pg/mL (range, 10–56 pg/mL), compared with 17 pg/ml (range, 5–35 pg/ml) in women who did not. Furthermore, a value >30 pg/mL was associated with specificity of 73% and negative predictive value of 77% for subsequent CTRCD. In contrast, Morris *et al.*[179] demonstrated that TnI increases in patients receiving both trastuzumab and the tyrosine kinase inhibitor lapatinib were common, occurring in 67% of individuals; these elevations were not associated with subsequent CTRCD as detected by serial MUGA scans.

Schmidinger *et al.*[180] also reported an increase in troponin T in 10% of patients with metastatic renal cancer treated with sunitinib or sorafenib. Here, troponin T was used as a surrogate marker for sub-clinical dysfunction. These data suggest that troponins may be a useful tool for assessing CTRCD in patients treated with both conventional and newer anticancer therapies.

The role of TnI has been evaluated in patients with solid metastatic tumours treated with new anti-VEGF monoclonal inhibitors and tyrosine kinase inhibitors.[181] Eleven percent of patients showed increases in TnI during treatment. Normalization of TnI values was obtained with β-blockers and aspirin, allowing patients to be rechallenged with the study drug. No patient experienced any subsequent increase in TnI or cardiac events during the subsequent observation period (mean follow-up period, 3 months).

Currently, there are a number of barriers to the widespread application of troponin as a clinical biomarker in CTRCD. First, the determination of the optimal timing of troponin assessment remains in question, as it is unclear if a single measurement with each cycle of chemotherapy has sufficient predictive value to be of utility or if multiple measurements are needed. Moreover, defining the cut-off point for positivity that maximizes the positive and negative predictive value, determining the optimal assay platform, and minimizing the coefficient of variation at the lower detection limit remain important goals.

2. Other biomarkers

Natriuretic peptides, such as brain-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), have also been measured in adults undergoing chemotherapy, with elevations typically reflective of abnormal filling pressures, but conclusions regarding their utility are conflicting and less consistent.

Table 5 Effect of vendor age and gender on global longitudinal strain

Vendor	Age group (y)						*P*
	0–19	20–29	30–39	40–49	50–59	≥60	
V1							
Overall	−22.1 ± 2.4	−21.2 ± 1.9	−21.1 ± 2.1	−21.4 ± 2.0	−21.0 ± 2.2	−20.3 ± 1.9	0.0218
Male	−21.7 ± 3.1	−20.9 ± 1.9	−20.6 ± 1.9	−20.9 ± 1.8	−21.0 ± 1.9	−19.7 ± 1.4	0.1982
Female	−22.4 ± 1.6	−22.3 ± 1.6	−22.8 ± 1.8	−22.6 ± 2.1	−23.3 ± 1.9	−20.9 ± 2.1	0.0348
P (male *vs.* female)	0.4292	0.0316	<0.0001	0.0178	0.0029	0.1381	
V2							
Overall	−19.9 ± 2.5	−19.0 ± 2.1	−19.5 ± 2.2	−18.2 ± 2.5	−17.6 ± 2.5	−16.7 ± 2.1	<0.0001
Male	−19.4 ± 2.7	−18.8 ± 2.0	−19.1 ± 2.3	−17.9 ± 2.8	−16.9 ± 2.3	−15.8 ± 1.4	0.0019
Female	−20.5 ± 2.2	−20.6 ± 2.3	−20.2 ± 2.0	−19.3 ± 0.9	−20.4 ± 1.5	−17.3 ± 2.3	0.0002
P (male *vs.* female)	0.1349	0.0248	0.1083	0.4316	0.0294	0.0928	
V3							
Overall	−21.4 ± 1.7	−20.2 ± 2.1	−20.4 ± 2.3	−19.4 ± 2.2	−18.5 ± 2.6	−17.8 ± 2.8	<0.0001
Male	−21.6 ± 2.0	−20.2 ± 2.0	−20.4 ± 2.2	−19.8 ± 2.3	−18.7 ± 2.6	−16.3 ± 3.1	<0.0001
Female	−21.2 ± 1.5	−20.2 ± 2.4	−20.4 ± 2.8	−18.7 ± 1.8	−18.3 ± 2.8	−18.6 ± 2.3	0.0141
P (male *vs.* female)	0.6076	0.9787	0.9201	0.1415	0.7374	0.0668	

V1, Vivid 7 or Vivid E9 (GE Healthcare); V2, iE33 (Philips Medical Systems); V3, Artida or Aplio (Toshiba Medical Systems). Reproduced with permisssion from *Circulation Journal*.[166]

Table 6 Strengths and limitations of GLS

	GLS
Strengths	• Superiority in the prediction of all-cause mortality in the general population compared with LVEF[237] • Improved risk stratification in patients with HF[238] • Ability to recognize early LV dysfunction in patients undergoing cardiotoxic therapy and prognosticate subsequent CTRCD[155,160] • Reproducible when performed by trained operators
Limitations	• Heavy dependence on the quality of the 2D echocardiographical images • Influenced by loading conditions • Lack of long-term randomized clinical trials evaluating the ability of GLS to predict persistent decreases in LVEF or symptomatic HF • Lack of data as to the reproducibility of GLS in non-academic centres or community hospitals • Vendor and software specific

In a study using point-of-care testing, serial assessment of natriuretic peptides in 109 patients undergoing anthracycline-based therapy showed that a BNP elevation of >200 pg/mL conferred a significantly increased risk for subsequent CTRCD, as observed in 11 patients.[182] In smaller retrospective studies, patients with persistent BNP elevations 72 hours after high-dose chemotherapy had worsening of LV diastolic and systolic function indices from baseline to 12 months, with the mean LVEF decreasing from 62.8 ± 3.4% to 45.6 ± 11.5%.[183]

In contrast, a study of 100 patients demonstrated transient increases in NT-proBNP in 13 patients treated with anthracycline chemotherapy but no association with LV systolic or diastolic function.[184] Other small studies have also demonstrated a lack of association[113,160,185,186] or only cross-sectional associations between BNP and LV diastolic function.[187]

A larger scale study, the Effectiveness of Using Biomarkers to Detect and Identify Cardiotoxicity and Describe Treatment trial,[188] is currently under way, aiming to comprehensively determine the role of point-of-care biomarker testing in predicting cardiotoxicity in patients being treated with anthracyclines.

Key points

- Elevated troponins in patients receiving cardiotoxic chemotherapy may be a sensitive measurement for the early detection of toxicity.
- In contrast to troponins, serum concentrations of natriuretic peptides, although likely reflective of elevated filling pressures, may be less consistent in the early identification of CTRCD.

C. An integrated approach of imaging and biomarkers

An integrated approach combining echocardiographical data and biomarkers may be of utility and provide incremental value in predicting subsequent CTRCD. It may also provide a strategy for more aggressive surveillance if used in parallel, or reduction in the frequency of imaging when used in series (i.e. alternating imaging with biomarkers). Sawaya *et al.*[160] published findings in the anthracycline and trastuzumab breast cancer population, suggesting that the assessment of ultrasensitive troponin levels at the same time as STE-derived strain imaging obtained after anthracycline exposure has improved specificity of 93%, in comparison with either parameter alone (73%). An elevation in ultrasensitive TnI or a decrease in GLS of > − 19% was associated with sensitivity of 87% compared with 48% or 74% for each parameter alone. Some centres use an integrated approach with the use of echocardiography at standardized,

clinical preselected intervals (e.g. every 3 months during trastuzumab therapy) with biomarker assessment before each cycle of trastuzumab (e.g. every 3 weeks) in patients at high risk for CTRCD. However, there is a critical need for additional research to further strengthen the validity of this approach.

Key point

- An integrated approach may provide incremental value in predicting subsequent CTRCD.

D. Implications of early detection on therapeutic approaches

Although combination regimens for HF therapy have been reported to be effective, HF due to CTRCD is often resistant to therapy if diagnosed late in its course. Therefore, efforts have been directed at prevention of HF. The possible approaches to HF prevention are prophylaxis in all patients or early identification and treatment.

Recognition of the availability of prophylaxis against sub-clinical LV dysfunction is an important step in developing a screening strategy; there would be no purpose in screening if there were no therapeutic implications. Pretreatment with a variety of agents (i.e. iron chelators, angiotensin-converting enzyme inhibitors, β-blockers, or statins) may be helpful in reducing the risk for cardiotoxicity.[189] The most effective agents appear to be dexrazoxane[190,191] and statin therapy.[192,193] The use of vasoactive medications may be limited by the risk for side effects (especially dizziness and hypotension)[194] and is supported by limited evidence for angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and β-blockers.[195–199] Given the frequency of asymptomatic LV dysfunction and the potential side effects associated with the proposed regimens, early identification and treatment may be the optimal path.

Treatment of sub-clinical LV dysfunction is based on a strategy of early detection of myocardial disease with either biomarkers or imaging. The attraction of this approach is that there is potential benefit for any patient, and those without dysfunction are not burdened by the treatment. The disadvantages are that screening has to be sufficiently accurate to identify as closely as possible all at-risk patients and that some patients may have progressed to sufficient damage that treatment may provide only a partial response.

TnI release after high-dose chemotherapy in patients treated by anthracyclines was investigated by Cardinale and Sandri.[171] This team demonstrated the usefulness of enalapril in this population,[178] when given before[178] or early after[143] the LVEF decrease. The initial study in 114 cancer survivors with TnI release demonstrated significant reductions in LVEF but increases in LV volumes only in untreated patients.[178] The study, however, lacked placebo administration, was unblinded, and lacked clinical endpoints. A further study demonstrated the role and limitations of an LVEF decrease initiating cardiac treatment in chemotherapy patients.[143] In 201 consecutive patients with LV dysfunction (LVEF $< 45\%$) due to anthracycline cardiomyopathy,[143] enalapril (and, if possible, carvedilol) were initiated promptly after the detection of reduced LVEF. On the basis of sequential LVEF measurements over the subsequent 36 ± 27 months, 42% of patients were considered responders, 13% were partial responders, and 45% were deemed non-responders. Cardiac events were fewer in responders than partial responders and non-responders. The response rate progressively decreased with increasing time delay between the end of chemotherapy to the start of HF; no complete recovery of LVEF was observed after 6 months.

Similar positive findings have been obtained with β-blockers in patients with sub-clinical LV dysfunction after trastuzumab.[200] Of 42 patients with GLS decreases of $\geq -11\%$, the 19 who were treated showed subsequent significant LVEF increases after 6 months (from $52.6 \pm 5.6\%$ to $57.4 \pm 6.0\%$) but patients not taking β-blockers showed no change (from $56.7 \pm 5.9\%$ to $56.0 \pm 5.2\%$, $P = 0.001$ between groups). Additionally, data from a small number of recent studies indicate that β-blockers have a role as novel therapeutic agents in reducing tumours metastasis, tumours recurrence, and breast cancer-specific mortality.[201]

Key point

- Small studies have suggested that a variety of agents (such as dexrazoxane, β-blockers, angiotensin-receptor blockers, and statins) may be helpful in the prevention or early treatment of CTRCD, but no definitive recommendations can be set with the current available data.

IV. Other imaging modalities

A. Radionuclide approaches for monitoring chemotherapy-induced cardiotoxicity

1. MUGA

Measurement of LV function using either first-pass or equilibrium radionuclide angiography (also known as MUGA) was first used in the late 1970s to identify patients receiving anthracyclines who had declines in LVEF before the development of clinical HF symptoms.[202] When anthracyclines were stopped with a clinically asymptomatic decline in LVEF, there was no further deterioration in function, and in some patients, there was even recovery, especially when aggressively treated with optimal HF medications. Thus, monitoring by MUGA to detect an asymptomatic decline in LVEF was preferable to waiting for the development of symptoms of congestive HF symptoms, by which time CTRCD was irreversible. Serial imaging by MUGA had been reported to allow safe use of anthracyclines even when baseline LVEF was abnormal.[203] On the basis of these results, the following recommendations for the use of MUGA to monitor anthracycline-induced cardiotoxicity were proposed:[33]

(1) LVEF $> 50\%$ at baseline
   (a) Measurement at 250 to 300 mg/m^2
   (b) Measurement at 450 mg/m^2
   (c) Measurement before each dose above 450 mg/m^2
   (d) Discontinue therapy if LVEF decreases by $\geq 10\%$ from baseline and LVEF $\leq 50\%$
(2) LVEF $< 50\%$ at baseline
   (a) Do not treat if LVEF is $< 30\%$
   (b) Serial measurement before each dose
   (c) Discontinue therapy if LVEF decreases by $\geq 10\%$ from baseline or LVEF $\leq 30\%$

These early reports suggested that clinical symptoms of CTRCD develop after irreversible damage has occurred and that asymptomatic declines in LVEF may represent an early sign of permanent damage. Efforts were made for earlier detection using stress testing and detection of fibrosis that preceded decline in LV systolic function. The use of exercise stress to measure LV functional reserve, with normal defined as an increase of $\geq$5 LVEF units, was shown to have a higher sensitivity for early detection of CTRCD.[202,204] Because of relatively low specificity, limited exercise capacity in most patients with cancer, and the requirement for using supine bicycle exercise, this technique is seldom used today. As mentioned with echocardiography, the significant variability in measurements of LV diastolic function by MUGA limits its clinical application.[205]

2. MUGA compared with other modalities

As a 3D imaging technique, MUGA has consistently outperformed standard 2DE with respect to accuracy and reproducibility of LVEF measurements.[206,207] In several studies, the values obtained by MUGA showed much higher correlations with those obtained with other 3D imaging tools, such as CMR and novel 3D echocardiographical techniques, but individual LV volumes and LVEF values still differed significantly across the techniques.[206,208] Together, these findings point out that the LVEF results obtained by different techniques are not interchangeable and suggest that choosing a single technique may provide the best option for serial monitoring of LVEF in patients at risk.

The MUGA technique for monitoring anthracycline-induced CTRCD has been standardized, shown to be highly reproducible, and widely available and effectively applied in academic centres, community hospitals, and physicians' offices.[33] On the basis of these findings, MUGA has been widely used in general clinical practice as well as in the efficacy trials for development of new chemotherapy agents for all tumour types.[209] Advantages of MUGA in evaluation of patients during or after cancer therapy include the following:

(1) Its widespread use in clinical practice with extensive long-term follow up: In the 1980s, there were extensive publications establishing the efficacy of MUGA for all types of adult and pediatric tumours treated with anthracyclines. On the basis of this body of evidence, MUGA was used widely in clinical trials and carried over into clinical practice.
(2) Few technical limitations: ^{99m}Tc red blood cell labeling and planar imaging can be done in all patients without limitations due to obesity, poor acoustic windows, or the presence of cardiac devices such as pacemakers or defibrillators. The technique is widely available, and cost is comparable with that of alternative modalities.
(3) High reproducibility and low variability make it desirable for serial testing. Compared with qualitative estimates of LVEF by 2DE, serial measurements of MUGA have lower intra- and inter-observer variability and a smaller coefficient of variability.[210] This makes measurements highly reproducible, which is critical for serial testing and detecting early deterioration in LVEF.

The main disadvantage of MUGA is radiation exposure. The use of 20 to 30 mCi of ^{99m}Tc pertechnetate exposes patients to approximately 5 to 10 mSv of radiation. Although linkage of such low levels of radiation to increased cancer risk has not been shown, it is good medical practice to keep radiation exposure "as low as reasonably achievable" and assess the risk *vs.* the benefit of MUGA for individual patients.[131] In addition, current gamma cameras may be suboptimal for performing critical measurements of LV volumes and LVEF. Early MUGA studies in the 1970s and 1980s were performed using single-headed, small-field-of-view gamma cameras that allowed optimal positioning of the patient to obtain the best separation between the two ventricles and apply a caudal tilt to avoid overlap with the left atrium. Current gamma cameras are predominately large-field-of-view or two-head systems that do not allow optimal patient positioning. Therefore, the high reproducibility of measurements of LVEF reported in the past may not apply to today's systems. Also, MUGA does not provide comprehensive information about RV function, left and right atrial size, or the presence or absence of valvular or pericardial disease, and it is frequently used as an adjunct and a complementary technique to echocardiography.

B. CMR for monitoring cancer therapeutics-related cardiac dysfunction

CMR imaging has been an important tool for imaging the cardiovascular system since the early 1980s and particularly so over the past decade, with advances in both hardware and software contributing to its increased utility and acceptance.[211] CMR is considered the reference standard in assessing LV and RV volumes and function and has demonstrated at least equivalence, if not superiority, in the detection of myocardial ischemia compared with cardiac nuclear imaging.[212] With the advent of LGE, CMR is now considered the gold standard for myocardial viability imaging accompanied by positron emission tomography.[213] However, only recently have multiple investigators begun to exploit the unique capabilities of CMR in detecting both the acute and chronic complications of cardiotoxic chemotherapeutic agents on cardiac function and to compare CMR's assessment efficacy relative to alternative imaging modalities.[214,215] These initial reports suggest an important and rapidly evolving role for CMR in patients with cancer.

1. CMR in the assessment of cardiac structure and function

CMR is a well-established clinical tool for the structural assessment of congenital and acquired cardiac anomalies and is often preferred to echocardiography and nuclear imaging for its wide field of view, flexible scanning planes, and lack of ionizing radiation.[216] For LV and RV functional determination, CMR offers the advantages of true 3D volumetric coverage, high contrast-to-noise ratios providing excellent discrimination of endocardial and epicardial borders, and lack of reliance on assumed geometric models that may hinder accurate calculation of LV volumes, mass, and function by alternative modalities (*Figure 10*). These features provide a framework for more accurate functional assessment. In a recent study of 91 patients with reduced LVEFs after anthracycline therapy, CMR imaging demonstrated an inverse relationship between anthracycline dose and LV mass, thus illustrating a potential for additive diagnostic and prognostic information provided by CMR in patients with CTRCD. CMR-determined parameters were also predictive of future cardiovascular events; both reduced LV mass and greater anthracycline

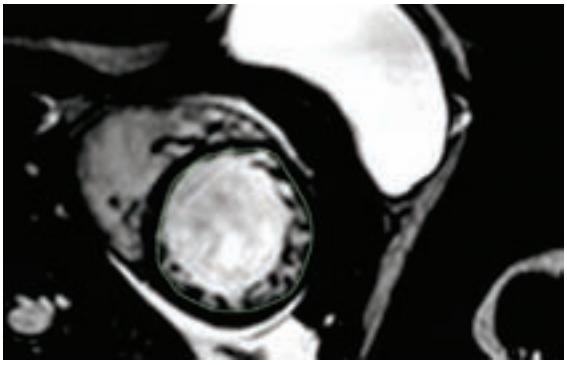

Figure 10 Short-axis, end-diastolic CMR cine image demonstrating quantitative approach to left ventricular volume measurement. Endocardial contour (*green*) is traced in a series of images encompassing the entire ventricle during cardiac cycle. A left breast implant is seen anterior to the chest wall in a patient with a history of left mastectomy and reconstruction.

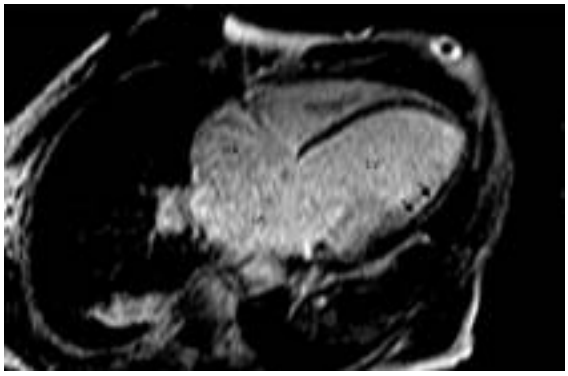

Figure 11 CMR image using LGE in four-chamber projection in a patient with a history of anthracycline-induced cardiomyopathy. The left ventricle is dilated with wall thinning. There is no evidence of LGE.

dose were associated with increased rates of major adverse cardiovascular events in patients followed for a median of 88 months.[214]

2. CMR and echocardiography

The best-documented CMR technique for the assessment of LV volumes, LV mass, and LVEF uses a set of contiguous short-axis slices covering the entire left ventricle from the atrioventricular plane to the apex, acquired from a cine sequence. The short-axis slices can also be used for the assessment of RV volumes and ejection fraction. Cine steady-state free precession is the technique currently used to measure these parameters.[217] Measurements of LVEF and volumes by CMR have been shown to be highly accurate and reproducible[218] and have been demonstrated to be more reproducible than LV volumes and mass by echocardiography.[111,219,220] Therefore, one obvious advantage of using CMR is in clinical research studies using LV volumes as outcome parameters.[221,222]

In most studies, CMR and echocardiographical measurements show high correlation. The absolute values, however, may differ.[223,224] LVEF by CMR, echocardiography, and radionuclide ventriculography were not interchangeable in a study of 52 patients with HF.[219] Recently, Armstrong *et al.*,[221] in a cohort of long-term survivors of chemotherapy, demonstrated similar mean LVEF values by CMR and 3DE, whereas 2DE values were higher by approximately 5%. This largest study with direct comparison of 2DE and 3DE with CMR showed that 3DE was superior to 2DE, but both 3DE and 2DE were suboptimal at identifying patients with LVEFs below a threshold value of 50% defined by CMR. These data suggest that CMR may be the preferred technique for LVEF determination when echocardiography reaches a threshold value of LV dysfunction. It is the recommendation of this committee to consider the use of CMR in situations in which discontinuation of chemotherapeutic regimens secondary to CTRCD is being entertained or when, because of technical limitations or the quality of echocardiographical images, the estimation of the LVEF is thought to be controversial or unreliable. CMR may provide an important advantage in patients in whom extracardiac masses represent a concern.[225] Measurements from CMR, echocardiography and nuclear techniques cannot be regarded as identical or be directly compared from one modality to another. Ideally, a single technique should be chosen for baseline assessment and follow-up studies during and after cancer treatment.

Disadvantages of CMR include its lesser flexibility and availability and higher operational cost than echocardiography.[221] In addition, issues with claustrophobia and hazards associated with ferromagnetic devices need to be considered. Contraindications for CMR imaging that may be particularly relevant in some patients with cancer include the presence of ferromagnetic components within some breast tissue expanders (i.e. Contour Profile Tissue Expander [Mentor, Santa Barbara, CA, USA], which contains a magnetic injection dome) used for breast reconstruction after mastectomy.

3. Beyond the LVEF: advanced CMR assessments

Contrast-enhanced CMR offers a unique capability to assess myocardial tissue characteristics compared with other imaging techniques. This technique has demonstrated excellent ability to outline myocardial fibrosis and is commonly used in detection of myocardial scar and workup of cardiomyopathies.[226] All CMR contrast agents are gadolinium based, and at the present time, contrast-enhanced CMR of the heart represents an off-label use for all US Food and Drug Administration-approved agents. Their main limitation is a potential to cause nephrogenic systemic fibrosis, an exceedingly rare but serious condition.[227] The risk for nephrogenic systemic fibrosis increases in patients with renal insufficiency, and contrast CMR use should be limited to patients without significant kidney dysfunction. Gadolinium accumulates in the normal myocardium a few seconds after contrast injection. LGE can be observed 10–20 min after contrast injection and represents myocardial fibrosis. Lack of LGE is the most common finding in patients who develop anthracycline-induced CTRCD (*Figure 11*).[121,214] LGE has been the most frequently used technique to exclude other causes of cardiomyopathy, such as myocardial infarction, cardiac sarcoidosis, or amyloid heart disease. The recent findings from a single centre of the presence of lateral wall LGE in patients who received *HER2* therapies[156] have not been reproduced. CMR may also have added value

in the evaluation of cardiac metastasis or invasion tumour to the heart.

More recently, gadolinium-based contrast has also been used in T1 mapping, a novel, quantitative CMR technique that identifies subtle myocardial abnormalities such as diffuse fibrosis, not visible on LGE imaging.[228,229] One recent study in a small cohort of 13 patients after anthracycline therapy and with normal LV function demonstrated no correlation between anthracycline dose and myocardial fibrosis, though there was a relationship with increased LV volume.[230] Using this technique, Neilan *et al.*[231] recently reported increased extracellular volume as a surrogate of myocardial fibrosis in 42 patients treated with anthracyclines, compared with age- and gender-matched controls. A positive association was found between the extracellular volume and the left atrial volume, and a negative association was found between the extracellular volume and LV diastolic function. Although this technique suggests promise for future diagnosis and possibly prediction of risk for cardiomyopathies, its current use is limited to research studies.

C. Specific challenges

Patients with breast cancer (the majority of patients to whom this document applies) present specific challenges in their cardiac imaging. The feasibility of 2DE, 3DE, and strain imaging may be limited by the inability to obtain images of diagnostic quality because of mastectomy, radiation, or the presence of breast implants. It is important to adequately document these limitations in the report and to refrain from reporting findings if uncomfortable with the technical quality of the study. In these specific situations, the use of echocardiographical contrast (please see Section II.G) may be useful for an accurate calculation of ejection fraction. If with the administration of contrast the calculation of LVEF is still not feasible using the biplane method of disks, CMR is recommended. It is important to inquire about the presence of ferromagnetic components, if the patient has breast tissue expanders.

Key points

- The calculation of LVEF by MUGA is highly reproducible. The main limitations are radiation exposure and the lack of ability to report on pericardial and valvular heart disease and RV function.
- The newer and most commonly used dual-head gamma cameras were not used in the initial reproducibility studies, and their inter-study reproducibility is not well known.
- CMR is the reference standard in the evaluation of LV and RV volumes and LVEF. Its main limitation is its limited availability. It may be particularly useful in situations in which discontinuation of chemotherapy is being entertained and/or when there is concern regarding echocardiographical or equilibrium radionuclide angiographic calculation of LVEF.
- Standard precautions for CMR safety need to be followed, including consideration of electromagnetic interference. This may be particularly relevant in patients with breast cancer, in whom tissue expanders placed for breast reconstruction may represent a hazard.
- It is important to realize that the different techniques use different normal reference values. Thus, the same technique should be performed for baseline assessment and follow-up studies during and after cancer treatment.

V. Integrated approach

This section represents the consensus of the current clinical practices of the academic institutions represented by the authors of this report. We recognize the limited scientific data available and the lack of class A evidence (derived from randomized clinical trials) supporting the algorithms. The algorithms represent our current knowledge of the field. As new data becomes available, we anticipate that updates will be required.

A. Baseline assessment and monitoring

- Co-operation between cardiologists and oncologists is absolutely essential.
- It would be ideal to perform a baseline cardiac assessment in every patient scheduled to receive a potentially cardiotoxic agent. However, this is often not possible.
- If not possible in all patients, it is recommended to perform a baseline cardiac assessment in those considered to be at high risk for development of CTRCD, such as those patients with established or risk factors for cardiovascular disease, those with LV dysfunction, those >65 years of age, and those scheduled to receive high doses of type I agents (>350 mg/m^2) or combination chemotherapy with both type I and type II agents (*Figure 12*).
- The baseline cardiac assessment, in addition to a thorough medical history and physical examination, should include electrocardiography to evaluate the cardiac rhythm and detect signs of resting ischemia and a cardiac imaging test (usually echocardiography) for the evaluation of cardiac structure and function (see *Table 2* for cardio-oncology echocardiogram protocol).
- A baseline assessment of GLS and/or troponin is desirable. Although GLS has negative values in normal individuals, for the=sake of simplicity in this section, we will refer to it as an absolute value (without the negative sign).
- A pretreatment assessment may help cardiologists advise oncologists as to known or anticipated risks.
- If the LVEF is <53%,[22–26] GLS is below the limit of normal (*Table 5*), and/or troponins are elevated, a cardiology consultation should be considered, with discussion between the cardiologist and oncologist of the risk/benefit ratio, and cancer treatment at the discretion of the oncologist (*Figures 13–15*).
- If the quality of the echocardiogram is sub-optimal, CMR is recommended.
- Follow-up assessment is recommended on the basis of the specific type of anticancer agent received (*Figure 13*).

1. Type I agents

- Historically, there has been concern for cumulative doses of anthracyclines exceeding 400 mg/m^2, because of an associated 5% risk for HF. However, the risk for doxorubicin-related CTRCD is really a continuum that spans from 0.2% to 100%, for cumulative doses of 150 to 850 mg/m^2, respectively. In the study by Swain *et al.*,[30] the earliest step-up in cardiac events occurred from 250 to 350 mg/m^2 (9–18%).[232] New data evaluating patients who have received low doses of anthracyclines (<375 mg/m^2) revealed a rate of sub-clinical LV dysfunction (LVEF < 50%) of

26% at 6 months of follow-up after therapy.[233] As a result, this committee recommends follow-up at the completion of therapy for regimens including doses <240 mg/m^2. After exceeding the dose of 240 mg/m^2, an evaluation before each additional cycle is considered prudent (*Figures 13* and *15*).

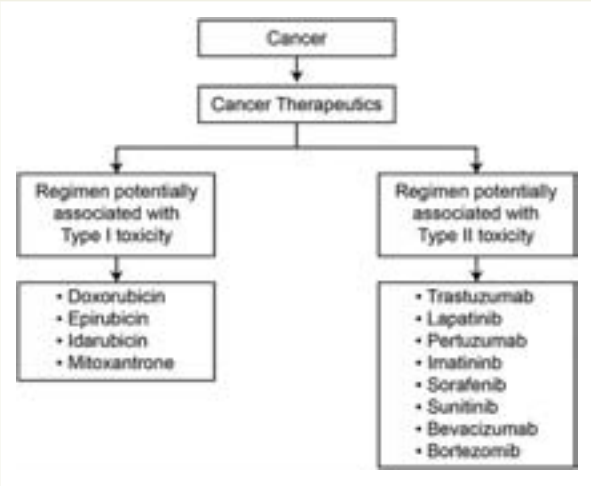

Figure 12 Cancer therapeutics regimens associated with type I and Type II CTRCD.

2. Type II agents

- Patients receiving trastuzumab should undergo follow-up echocardiography every 3 months during therapy (*Figures 14* and *15*).
- The potential haemodynamic burden of other tyrosine kinase inhibitors (sunitinib, sorafenib) should be considered in patients with known CAD and should be assessed according to perceived individual risk with appropriate close monitoring and treatment of blood pressure and symptoms in patients at high cardiovascular risk. In the absence of data, we recommend a baseline echocardiographical evaluation, with follow-up at 1 month and every 3 months while on therapy with VEGF or VEGF receptor inhibitors.

B. Detection of sub-clinical left ventricular dysfunction

- During chemotherapy, patients are longitudinally followed for evidence of CTRCD or sub-clinical LV dysfunction (abnormal GLS [*Figure 16*] or elevated troponins [*Figure 17*]). With these changes, a cardiology consultation should be considered, with discussion between the cardiologist and oncologist as to whether to continue the agent, alter the regimen, and/or consider the initiation of cardioprotective agents.
- The ideal strategy for the detection of sub-clinical LV dysfunction is to compare the measurements of GLS obtained during chemotherapy with the one obtained at baseline, allowing the patient to serve as his or her own control. A relative percentage reduction

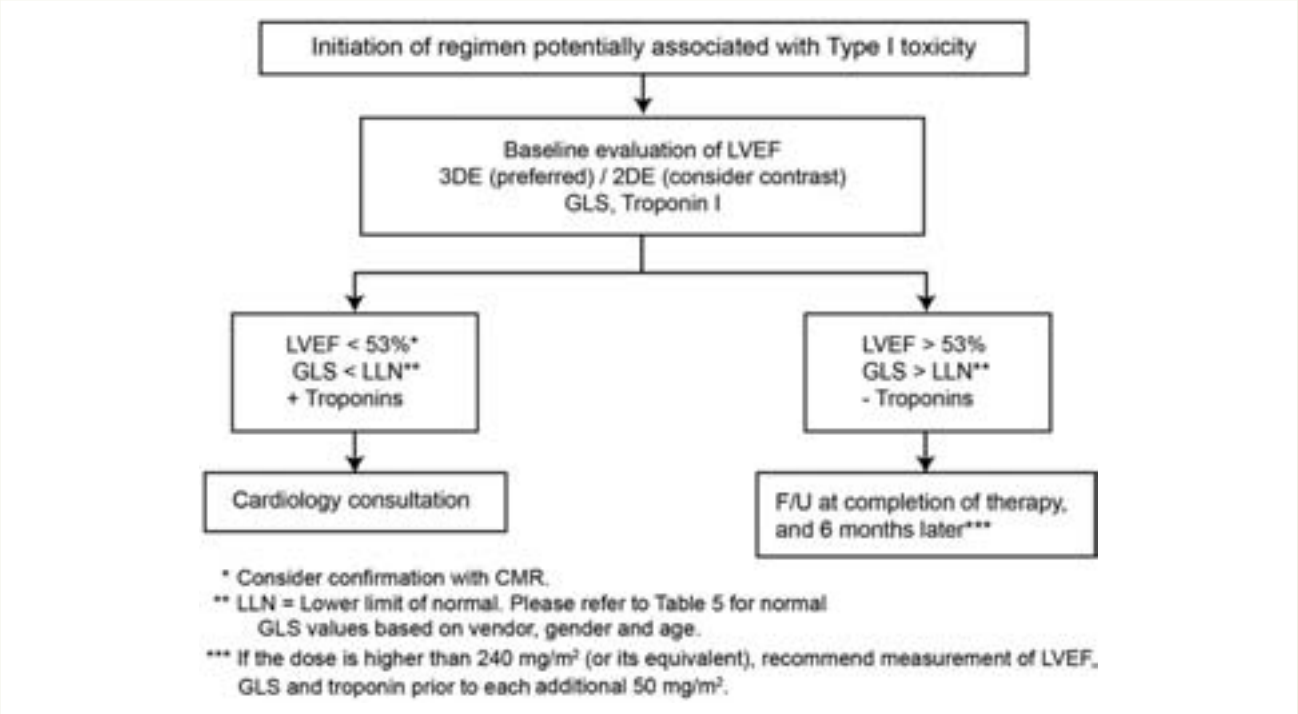

Figure 13 Initiation of a regimen potentially associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Follow-up is recommended at the completion of therapy and 6 months later for doses < 240 mg/m^2 or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m^2.

in GLS of >15% is very likely to be abnormal, whereas a change of <8% appears not to be of clinical significance (*Figures 9A* and *9B*). The abnormal GLS value should be confirmed by a repeat study. The repeat study should be performed 2 to 3 weeks after the initial abnormal study.

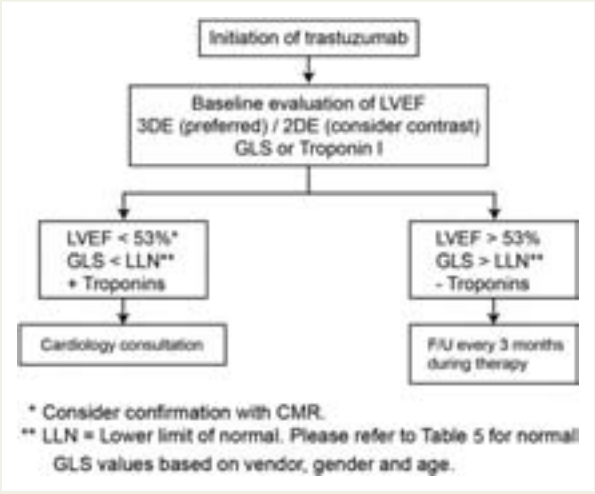

Figure 14 Initiation of trastuzumab. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponins are recommended every 3 months.

- When comparing LVEF and GLS values, it is essential to keep in mind the load dependency of these measurements. This committee recommends reporting the timing of the echocardiographical examination with respect to the intravenous infusion of chemotherapeutic agents (number of days before or after treatment) as well as the vital signs measured during the test (blood pressure and heart rate), recognizing that changes in loading conditions are frequent and may affect the GLS value (volume expansion due to the intravenous administration of chemotherapeutic agents or volume contraction due to vomiting or diarrhoea).
- Troponin levels are measured before and/or 24 hours after each chemotherapy cycle. Patients with troponin elevations during therapy (as defined by the cut-offs specific to the assay platform used in the individual labs) are at a higher risk for subsequent cardiovascular events. As such, it is suggested to obtain a cardiology consultation.
- Troponin levels have added prognostic value to GLS. If both are abnormal, the specificity for the prediction of CTRCD increases from 73% to 93%. If both are normal, the negative predictive value increases to 91%.[160]
- An elevation in NT-proBNP raises concern for increased LV filling pressures in the setting of CTRCD. The negative predictive value of NT-proBNP may be useful, but the variability over time has limited its utility. Further studies in this area are needed.
- It is the recommendation of this committee to consider the use of CMR in situations in which discontinuation of chemotherapeutic regimens secondary to CTRCD is being entertained or when, because of technical limitations or the quality of echocardiographical images, the estimation of the LVEF is thought to be controversial or unreliable.

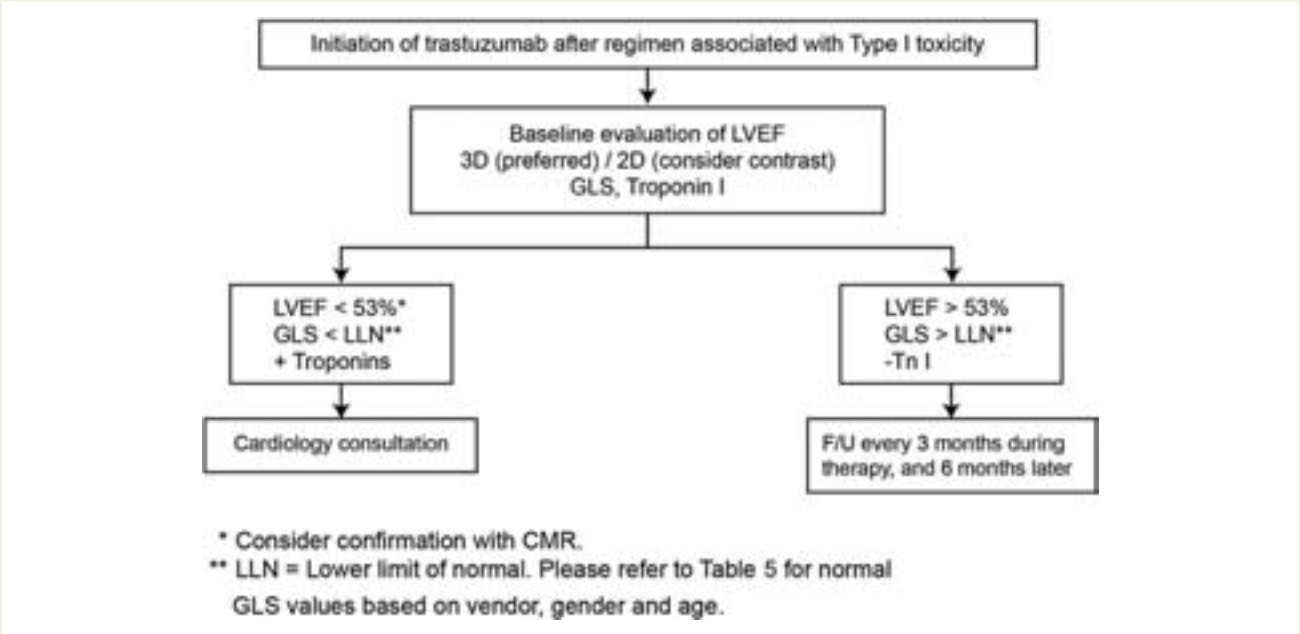

Figure 15 Initiation of trastuzumab after regimen associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponin are recommended every 3 months during therapy and 6 months later.

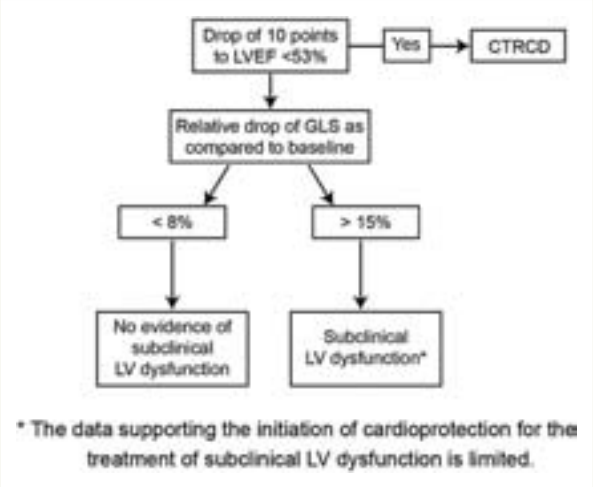

Figure 16 Early detection of sub-clinical LV dysfunction using GLS. In the absence of adjudication of CTRCD, it is recommended to use GLS for the identification of sub-clinical LV dysfunction. If baseline strain is available, a relative percentage decrease of >15% compared with baseline is likely to be of clinical significance, whereas a decrease of <8% is not.

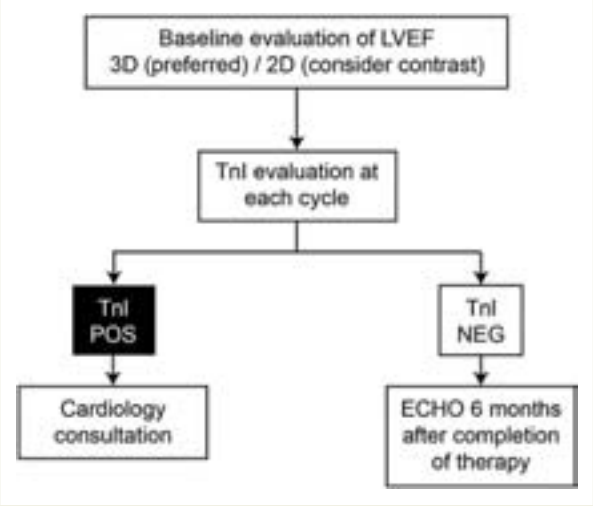

Figure 17 Early detection of sub-clinical LV dysfunction using biomarkers.

- Although small studies suggest the role of the initiation of cardioprotective regimens in the setting of sub-clinical LV dysfunction, there is a lack of conclusive data (randomized clinical trials) supporting this strategy.
- If the agent is continued despite LV functional changes, reassessment should be undertaken by imaging, ideally with GLS and/or troponins before each additional cycle, with the understanding that the risk for cardiac events increases with further exposure. Patients' understanding of the risk-benefit analysis should be adequately documented.
- In the absence of factors that can modify the risk of the patient (concomitant risk factors or radiotherapy), if the GLS has been stable during chemotherapy and is normal at 6 months of follow-up after the completion of therapy with a type I agent, or the troponins have remained negative throughout therapy, additional imaging surveillance for CTRCD is not warranted.
- In the absence of CTRCD or sub-clinical LV dysfunction caused by chemotherapy, patients who have received concomitant radiation need to be followed according to published ASE and EACVI expert consensus.[58]
- After the completion of therapy, and particularly in patients who were not followed using a strategy of early detection of sub-clinical LV dysfunction, this committee suggests a yearly clinical cardiovascular assessment by a health care provider, looking for early signs and symptoms of cardiovascular disease, with further cardiac imaging ordered at the discretion of the provider.

Executive summary

1 Chemotherapy-related cardiac dysfunction

- Highly effective chemotherapeutic agents may cause CTRCD.
- CTRCD is defined as a decrease in the LVEF of greater than 10 percentage points, to a value < 53% (normal reference value for 2DE). This decrease should be confirmed by repeated cardiac imaging. The repeat study should be performed 2 to 3 weeks following the baseline diagnostic study showing the initial decrease in LVEF. Left ventricular ejection fraction decrease may be further categorized as symptomatic or asymptomatic, or with regard to reversibility: reversible (to within 5 percentage points of baseline); partially reversible (improved by at least 10 percentage points, but remaining more than 5 percentage points below baseline); irreversible (remaining within 10 percentage points of the nadir); or indeterminate (patient not available for re-evaluation).
- CTRCD has been classified as:

  (1) CTRCD Type I, characterized by anthracyclines. It is dose-dependent, leads to cell apoptosis, and is therefore irreversible at the cell level. Early detection and prompt treatment may prevent left ventricular remodelling and the progression to the heart failure syndrome.

  (2) CTRCD Type II, characterized by trastuzumab. It is not dose-dependent, does not lead to apoptosis by itself, and is often reversible.

2 Echocardiographical evaluation of cardiac structure and function in the cancer patient

2.1 LV systolic function

- Echocardiography is the method of choice for the evaluation of patients before, during and after cancer therapy.
- Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3DE).
- When using 2DE, the modified biplane Simpson technique is the method of choice.
- LVEF should be combined with the calculation of wall motion score index.

- In the absence of GLS by STE, quantification of LV longitudinal function using mitral-annulus displacement by M-mode echocardiography, and/or peak systolic velocity (s') of the mitral annulus by pulsed-wave DTI is recommended.
- LVEF assessed by 2DE, often fails to detect small changes in LV contractility.

2.2 Diastolic function

- Although diastolic parameters have not been found to be prognostic of CTRCD, a conventional assessment of LV diastolic function, including grading of diastolic function and non-invasive estimation of LV filling pressures, should be added to the assessment of LV systolic function, per ASE/EAE recommendations for the evaluation of LV diastolic function with echocardiography.

2.3 RV function

- Although prognostic value of RV dysfunction has not been demonstrated in patients undergoing chemotherapy, a quantitative assessment of RV chamber and function should be performed due to possible RV involvement.

2.4 Valvular disease

- Cardiac valves should be carefully evaluated in patients undergoing chemotherapy.
- Patients with baseline or changing valvular findings during chemotherapy should have careful re-evaluation of valve structure and function on serial echocardiograms during and after the course of their treatment.

2.5 Pericardial disease

- Pericardial disease in oncological patients can be associated with cardiac metastasis or be a consequence of chemotherapy/radiotherapy.
- Pericardial effusion should be quantified and graded according to standard methods.
- Echocardiographical and Doppler signs of cardiac tamponade should be investigated, particularly in patients with malignant effusions.
- CMR should be considered in evaluation of primary tumours of the heart with or without compromise of the pericardium, or when the diagnosis of constrictive pericarditis remains uncertain after a careful echocardiographical evaluation.

2.6 3DE

- 3DE is the preferred echo technique for monitoring LV function and detection of CTRCD in cancer patients. Advantages include better accuracy in detecting LVEF below the lower limit of normal, better reproducibility, and lower temporal variability, as compared with 2DE in cancer patients treated with chemotherapy.
- Costs, availability, high reliance on image quality, and need of training for operators currently limit wide application of 3DE in the oncological setting.

2.7 Contrast echocardiography

- The use of myocardial contrast agents could be potentially useful in chemotherapy patients when endocardial drop out occurs.
- According to current recommendations, contrast should be used when two contiguous LV segments are not well visualized on non-contrast apical images.
- Contrast agents are not recommended in conjunction with 3DE in the longitudinal follow-up of cancer patients.

2.8 Stress echocardiography

- Stress echocardiography may be helpful in the evaluation of patients with intermediate or high pre-test probability for CAD, (echocardiogram uninterpretable or unable to exercise) who will receive regimens that may cause ischemia (fluorouacil, bevacizumab, sorafenib, and sunitinib).
- Stress echocardiography may be of help in the determination of contractile reserve of patients with evidence of CTRCD.

3 Detection of sub-clinical LV dysfunction

- A decreased LVEF at baseline or after anthracyclines is associated with higher rates of cardiac events on follow-up.
- Although it has been suggested that alterations in LV diastolic function (as evaluated by Doppler indices of mitral inflow and e' by pulsed Doppler tissue imaging) precede alterations in systolic function, the evidence does not support the role of these indices for the prediction of later CTRCD.
- Myocardial deformation (strain) can be measured using Doppler tissue imaging or 2D STE. The latter is favoured due to lack of angle dependency.
- Global longitudinal strain is the optimal parameter of deformation for the early detection of sub-clinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of global longitudinal strain $< 8\%$ from baseline appear not to be meaningful, and those $> 15\%$ from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of cancer patients, the same vendor-specific ultrasound machine should be used.
- The elevation of troponins in patients receiving cardiotoxic chemotherapy may be a sensitive measurement for the early detection of toxicity.
- In contrast to troponins, serum concentrations of natriuretic peptides, although likely reflective of elevated filling pressures, may be less consistent in the early identification of CTRCD.
- An integrated approach may provide incremental value in predicting subsequent CTRCD.
- Small studies have suggested that a variety of agents (such as dexrazoxane, beta-blockers, angiotensin-receptor blockers, and statins) may be helpful in the prevention or early treatment of CTRCD, but no definitive recommendations can be set with the current available data.

4 Other imaging modalities

- The calculation of LVEF by MUGA is highly reproducible. The main limitations are radiation exposure and the lack of ability to report on pericardial and valvular heart disease and RV function.
- The newer and most commonly used dual head gamma cameras were not used in the initial reproducibility studies and their inter-study reproducibility is not well known.
- CMR is the reference standard in the evaluation of LV and RV volumes and LVEF. Its main limitation is its limited availability. It may be particularly useful in situations where discontinuation of chemotherapy is being entertained, and/or when there is concern regarding echocardiographical or equilibrium radionuclide angiocardiography calculation of LVEF.
- Standard precautions for CMR safety need to be followed including consideration of electromagnetic interference. This may be particularly relevant in patients with breast cancer in whom tissue expanders placed for breast reconstruction may represent a hazard.
- It is important to realize that the different techniques use different normal reference values. Thus, the same technique should be performed for baseline assessment and follow-up studies during and after cancer treatment.

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