Cardio-Oncology

38

Juan Carlos Plana

Introduction

Cardiac toxicity by chemotherapeutic agents was first described more than 50 years ago, after the introduction of Daunomycin as an antimitotic agent [1]. The early recognition of heart failure as a side effect of anthracyclines, led the oncologists to limit its cumulative dose, and prompted them to serially monitor heart function looking for left ventricular dysfunction [2]. Initial tools included voltage reduction in electrocardiograms and measurement of systolic ejection time assessed by "sphygmo-recording" [3]. Nevertheless, endomyocardial biopsy and the echocardiographic evaluation of the left ventricular ejection fraction (LVEF) evolved as the methods more commonly used for the identification of anthracycline-induced cardiomyopathy [4, 5]. The importance of endomyocardial biopsy decreased over time due to cost, risks inherent to its invasive nature and more importantly the important advances made in noninvasive cardiac imaging. As a result, noninvasive calculation of LVEF became the most widely used tool for monitoring cardiac function during and after cancer therapy [6].

Side Effects of Chemotheraputic Agents and Cardiac Complications Following Chemotherapy

Chemotherapeutic agents may affect the cardiovascular system in different ways. Table 38.1 summarizes the most common side effects.

Historically, the term cardio-toxicity was used indistinctly to refer to all types of cardiotoxicity, although more commonly referring to left ventricular dysfunction.

The expert consensus on the multi-modality imaging of the adult patient during and after cancer therapy coined the new term of

Table 38.1 Most common side of effects of different chemotherapeutic agents in the cardiovascular system

Agent	Most frequent toxicity
Anthracyclines	Heart failure, myopericarditis, arrhythmias
Trastuzumab	Heart failure
Cyclophosphamide	Heart failure, myopericarditis, arrhythmias
Taxanes	Heart failure, ischemia, arrhythmias
Fluoracil	Myocardial ischemia and infarction
Cisplatin	Hypertension
Methotrexate	Ischemia, arrhythmias
Tamoxifen	Venous thrombosis
Radiotherapy	Restrictive heart disease, accelerated atherosclerosis, pericardial effusion

J. C. Plana
Baylor St. Luke's Medical Center,
Baylor College of Medicine, Houston, TX, USA
e-mail: Juan.PlanaGomez@bcm.edu

P. Nihoyannopoulos, J. Kisslo (eds.), *Echocardiography*,
https://doi.org/10.1007/978-3-319-71617-6_38

cancer therapeutics related cardiac dysfunction (CTRCD) to specifically refer to left ventricular dysfunction caused by chemotherapeutic agents. CTRCD was defined as a confirmed drop (by repeated cardiac imaging performed 2–3 weeks following the study showing the initial drop) of greater than 10 absolute points of LVEF to a value less than 53%. Drops may be further categorized as symptomatic or asymptomatic, or with regard to reversibility, i.e., reversible (to within 5% points of baseline) partially reversible (improved by at least 10% points, but remaining more than 5% points below baseline) irreversible (remaining within 10% points of the nadir) or indeterminate (patient not available for re-evaluation due to death or refusal to undergo further imaging [7].

Classification of Cardio-Toxic Drugs

Although there are more than 200 chemotherapeutic agents with different mechanisms of action and toxicity, for the sake of day to day clinical practice the expert consensus breaks CTRCD down in two types: Type I and II. Table 38.2 summarizes the differences using anthracyclines and trastuzumab as the prototypes for type I and II CTRCD. The understanding of the mechanisms of toxicity is essential, as it will give the clinicians the knowledge needed to know what to look for during surveillance of toxicity.

Mechanisms of Toxicity

Anthracyclines

Anthracycline cardiac toxicity has been for long attributed to the production of reactive oxygen species. Nevertheless, in the last decade the role of the enzyme topoisomerase 2 has gained significant relevance [8]. There are two topoisomerase 2 iso-enzymes in mammal species: Top2α and Top2β. It has been demonstrated that the anti-tumoral effect of doxorubicin is mediated by the formation of a ternary complex between Top2α, doxorubicin and the DNA double helix [9]. Top2α is only expressed in cells with a high mitotic rate like neoplastic cells, which explains the high efficacy of anthracyclines. In contrast, Top2β is only expressed in normal tissue like cardiac cells. It was recently demonstrated in a Top2β knockout animal model that dexrazoxane, a known cardio-protectant against doxorubicin cardiotoxicity, is active through the inhibition of Top2β, which supports the role of Top2β in anthracycline-induced CTRCD [10].

The incidence of heart failure fluctuates between 2.2 and 5.1% depending on the series [11]. The curves elaborated by Von Hoff and Swain showed that heart failure incidence is relatively low until a cumulative dose of 450 mg/m^2 is achieved [12]. This finding promoted the common belief that CTRCD was unlikely with doxorubicin doses lower than 450 mg/m^2.

Table 38.2 Characteristics of type I and type II CTRCD

	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)

Adapted with permission from Plana JC, Galderisi M, Barac A. Expert consensus for the multi-modality imaging of the adult patient during and after cancer therapy. J Am Soc Echocardiogr : 2014;27:911–39

Nevertheless, animal data reported by Neilan et al. showed that CTRCD is produced with doses as low as 20 mg/kg of doxorubicin, after detecting a 75-fold increase in cardiac cell apoptosis only 24 h after exposure [13]. The actual theory of anthracycline-induced CTRCD, supports the concept of an early and cumulative-dose dependent myocyte apoptosis. The later drop in LVEF follows the heart failure bio-mechanic model associated with negative left ventricular remodeling with subsequent secondary neuro-hormonal activation [14]. Anthracycline-induced CTRCD has been linked to a very poor prognosis, with 2-year mortality as high as 60% [15].

Trastuzumab

The amplification of the HER2/neu (ErbB2) gene identifies a group of breast cancer patients with very poor prognosis. Trastuzumab (Herceptin®) is a humanized monoclonal antibody that targets the tyrosine kinase receptor encoded by ErbB2 gene [16]. The development of this monoclonal antibody has been one of the most significant breakthroughs in the history of translational research after its approval in 1998. Multiple large-scale studies have proven that trastuzumab significantly reduces the risks of recurrence and early death in patients with HER2-positive breast cancers. However, symptomatic heart failure has been reported in 4% of treated patients and subclinical LV dysfunction in up to 10% of treated patients [17].

Combined Chemotherapy

The addition of trastuzumab to anthracyclines therapy increases the toxicity risk. Slamon et al. compared three chemotherapy regimens in patients with metastatic HER2 positive breast cancer, reporting a rate of 27% drop in LVEF in the group of combined trastuzumab-anthracycline, 13% in the trastuzumab-paclitaxel protocol and 8% in the trastuzumab free group. The incidence of severe cardiac dysfunction with New York Heart Association (NYHA) class III or IV was the highest with 16%, in the patients who received trastuzumab and anthracycline, compared to 3% in patients who received anthracyclines without trastuzumab and 2% of those who received trastuzumab and paclitaxel [18].

Animal studies done using a cardiac stress model mediated by hemodynamic overload (aorta ligation), showed that ErbB2 knockout mice were significantly more susceptible to cardiac toxicity and heart failure. These findings support the crucial role of the ErbB2 as a cardio-protective pathway, that permits myocyte survival during acute stress signaling activation [19]. A blockade in this cardio-protective pathway after anthracycline exposure, creates the substrate for apoptosis during subsequent exposure to trastuzumab. This premise is consistent with clinical findings showing evidence of increased CTRCD after exposure to trastuzumab in patients with underlying myocardial disease in which the cardiac stress signals are presumably already activated [17].

Methods for Early Detection

LVEF is a major predictor of outcome in CTRCD, and the most common method used to evaluate cardiac function at baseline and during cancer treatment [6]. Although different imaging modalities have been used, LVEF is most commonly evaluated with echocardiography [20].

2D Echocardiography

Echocardiography has been established as the cornerstone in the imaging evaluation of patients in preparation for, during, and after cancer therapy. This is due to its wide availability, versatility, lack of radiation exposure, and low cost when compared to other modalities (nuclear medicine, magnetic resonance imaging). In addition to the evaluation of left and right ventricular dimensions, systolic and diastolic function at rest and during stress, it also allows a comprehensive evaluation of cardiac valves, aorta and pericardium, making it the imaging modality

of choice in the evaluation of the cancer patient [21–25]. However, the technique is affected by the quality of the acoustic window, the use of geometric assumptions in the calculation of left ventricular (LV) volumes, load dependency and operator expertise [26]. Thavendiranathan et al., reported that the 95% upper confidence interval for 2D LVEF is 10% when sequentially following cardio-oncology patients. This is problematic as this is the magnitude of change in LVEF that is looked for to adjudicate CTRCD [7, 27]. Additionally, the reported intra and inter-observer variability is significantly high, with ranges that fluctuate between 6–11% and 8–16% respectively, depending on the series [28].

Contrast Enhanced Echocardiography

The use of contrast agents is crucial for the assessment of LV volumes and function when the endocardium is not well defined, as it opacifies the LV and enhances the endocardial border definition [29]. This is particularly important as endocardial border dropout is frequently encountered in the imaging of patients with breast cancer due to prior mastectomy, chest radiation, insertion of breast expanders and breast reconstruction surgery. The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend the use of ultrasonic contrast agents when ≥2 contiguous LV segments are not seen on non-contrast images [7, 30, 31]. Nahar et al. compared LVEF quantification by radionuclide angiography with four different 2D echocardiography techniques (fundamental, fundamental with contrast, harmonic, and harmonic with contrast), reporting incremental correlation with each method. However, harmonic imaging with contrast provided the closest correlation [32]. Also, when compared with standard 2D imaging, contrast enhancement increased the feasibility of biplane volume analysis from 79 to 95%, and narrowed the limits of LVEF agreement between echo and CMR from −18.1 to 8.3% to −7.7 to 4.1% [33]. Intra and inter-observer reproducibility also benefited from contrast use, achieving correlation indices (r) of >0.9 [29].

To obtain the best enhancement echocardiographic contrast, it is crucial to optimize the 2D images in the 4-chamber view; bringing the mechanical index to 0.15–0.3 to decrease the amount of bubble destruction and adjust the probe frequency for best penetration. Once the injection of contrast starts, the rate of injection needs to be decreased if attenuation is present or increased swirling is observed.

3D Echocardiography

The main pitfalls of 2D echocardiography in the calculation of ventricular volumes and LVEF quantification are the geometrical assumptions made, and the common foreshortening of the left ventricle. Real time 3D echocardiography emerged as an alternative because of its ability to capture full ventricular volumes with ho geometrical assumptions and allowing easy identification of the true apex of the heart [34]. Jacobs et al. compared the accuracy of 2D and 3D imaging against CMR for measuring end diastolic volume, end systolic volume, and LVEF. 3D measurements had a higher correlation with CMR (r = 0.96, 0.97 and 0.93 for EDV, ESV and EF respectively) [35].

Real time 3D has also proven to be a reproducible tool, making it the ideal method for the sequential calculation of LVEF required in chemotherapy patients. A comparison of four techniques (2D bi-plane, 2D tri-plane and 3D echocardiogram with and without contrast) in patients undergoing chemotherapy and stable LV function showed that non-contrast 3D volume and LVEF had the best intra and inter-observer as well as the lower test-retest variability giving the operator the possibility of identifying changes of 6 absolute point of LVEF (below the 10 point threshold that would adjudicate CTRCD). 3D LVEF provided an upper CI limit of 4.9 [27] (Fig. 38.1).

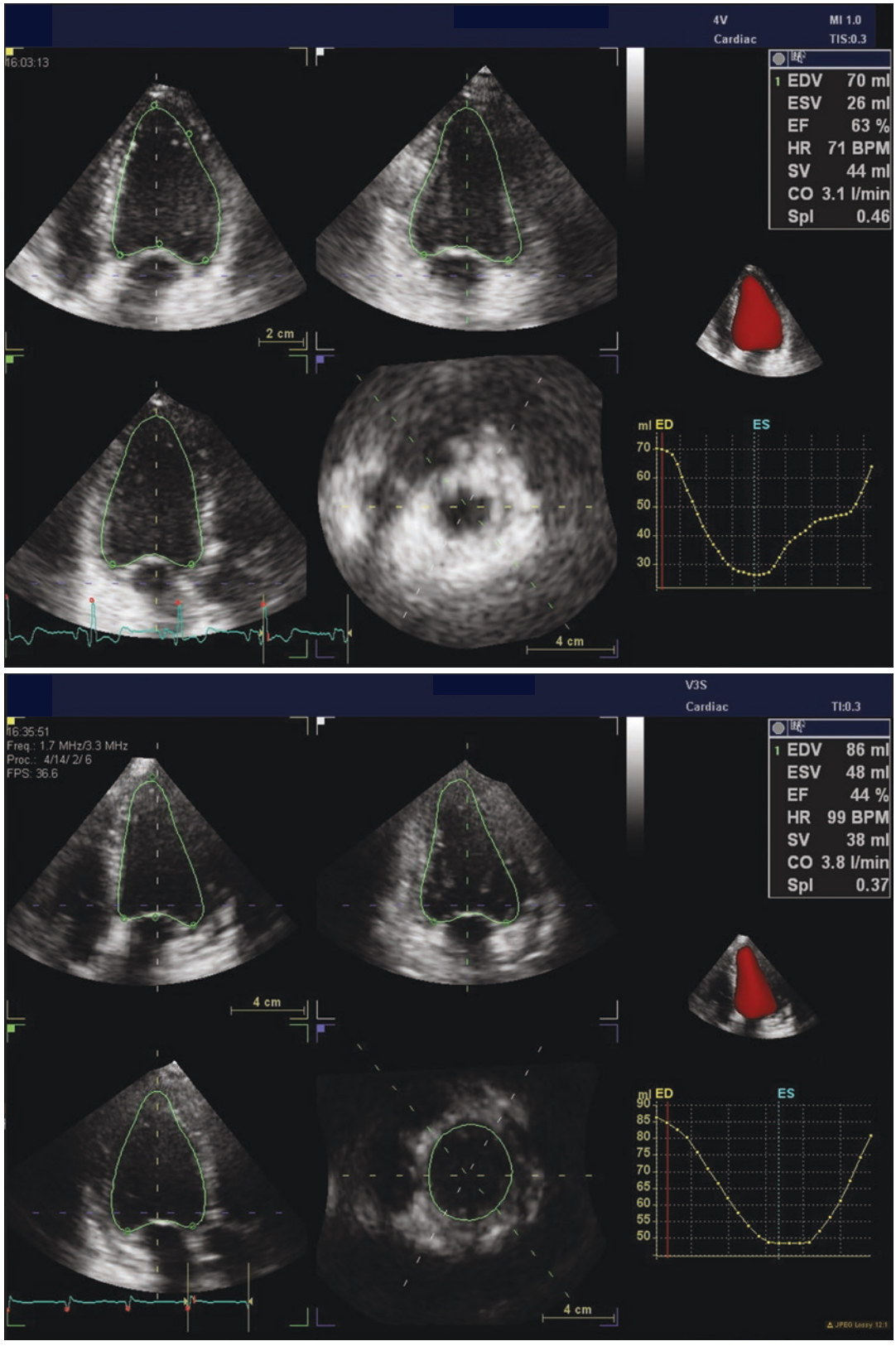

Fig. 38.1 3D LVEF pre and post exposure to anthracyclines

Contrast Enhanced 3D Echocardiography

There is contradictory data regarding the advantages of contrast enhanced 3D echocardiography, currently preventing its use on daily clinical practice.

Corsi et al. compared contrast 3D imaging with CMR, reporting not only an improvement in the accuracy and reproducibility of LV volume measurements in patients with poor image quality, but also an enhancement in the assessment of regional wall motion assessment from 3D datasets [36]. In contrast, Jenkins et al. reported that contrast enhanced 3D echocardiography was not superior to a contrast 2D approach for LVEF measurement when compared to CMR. However contrast 3D was superior to other contrast and non-contrast modalities in patients with previous infarction [37]. Following the same line, a recent study performed in cancer patients undergoing chemotherapy did not show advantage of contrast 3D over standard 3D imaging for determination of LV volumes and LVEF in terms of reproducibility and temporal variability [27] (Fig. 38.2).

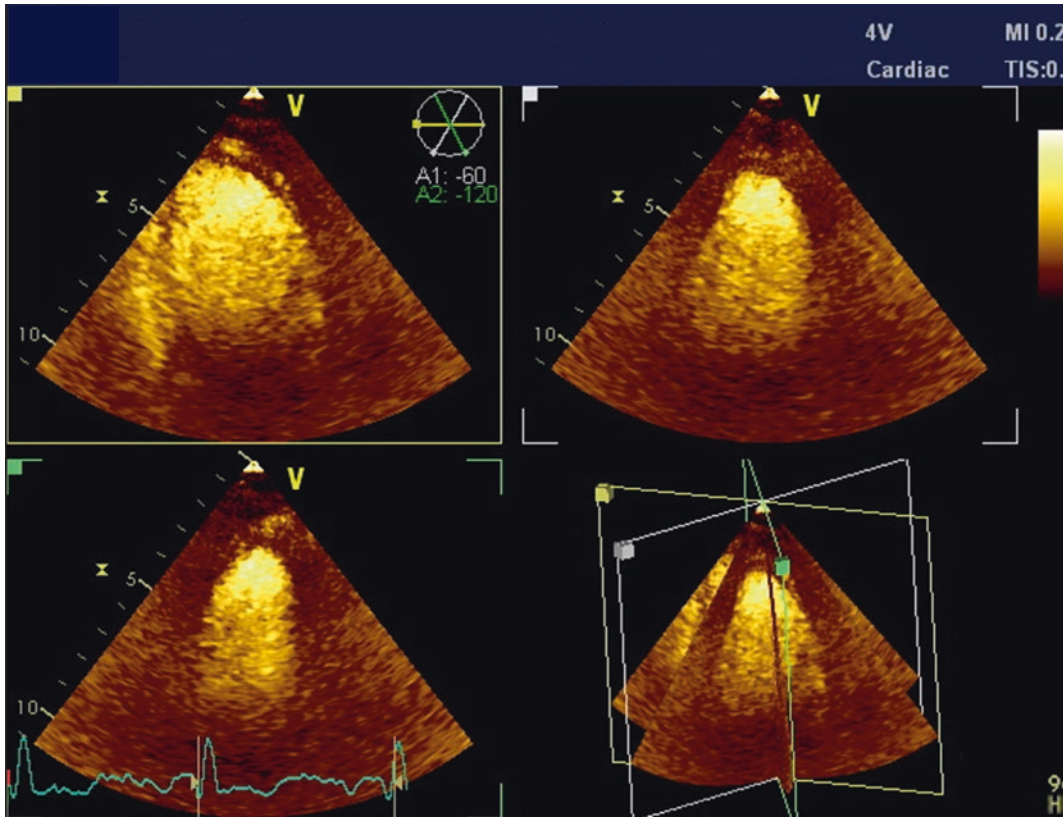

Fig. 38.2 3D LVEF with echocardiographic contrast enhancement

2D Based Left Ventricular Strain

Although LVEF is the most common method of monitoring cardiac function during cancer treatment, it is not optimal due to its inherent variability (>10%) [27], and as a result inability to detect early subtle changes in ventricular function [38]. Evaluation of left ventricular mechanics using 2D speckle-tracking have emerged as a reproducible and more accurate method for evaluation of systolic function [39–41], and the detection of detect subclinical left ventricular dysfunction [42–45].

Global longitudinal strain (GLS) is calculated as the percentage of shortening or lengthening of an individual segment and is reported as a mean of the 18 cardiac segments.

GLS also has a lower inter-observer variability as reported by Marwick et al. [46]. The authors studied the GLS inter-observer variability in 242 normal subjects, reporting a mean difference 0.24% and a 95% CI of −9.6 to +9.7%.

GLS has proven to be an early independent predictor of subsequent reduction in LVEF after exposure to chemotherapeutic drugs. Negishi et al. evaluated the optimal myocardial deformation index to predict CTRCD at 12 months in 100 breast cancer patients that received chemotherapy (46 with simultaneous anthracyclines and trastuzumab). They assessed them at baseline, 6 months and 12 months and found that a 11% drop in GLS (95% CI, 8.3–14.6%) was the strongest predictor of later cardiotoxicity with an area under the curve of 0.87, a sensitivity of 65% and a specificity of 94% [47] (Fig. 38.3).

In clinical practice, GLS should be used in all patients exposed to cardio-toxic regimens where available. When baseline strain measurement is available a GLS reduction ≥15%when compared to baseline is considered of clinical significance. If a baseline strain assessment is not available, the reader is referred to the JUSTICE study defining abnormality as 2 SD below the mean for vendor, gender and age (Table 38.3) [48].

Stress Echocardiography

Exercise and dobutamine stress echocardiography have been used in the identification of anthracycline-induced CTRCD. In 31 cancer patients studied before, during and after 6 months chemotherapy therapy, low dose dobutamine did not provide additional value for the early detection of cardiotoxicity [49, 50]. A prospective study of LV contractile reserve by repeated low-dobutamine stress echocardiograms in 49 women with breast cancer showed that a reduction in LVEF with dobutamine >5%, appeared to be a threshold that discriminate the risk of a future drop in LVEF [51].

It is reasonable to assess the presence of ischemia in patients with risk factors or known history of CAD who will receive regimens associated with ischemia induction (i.e. 5FU and anti-VEGF inhibitors).

Cardiac Complications Following Radiotherapy

Evidence of dose dependent increase in cardiovascular disease after chest radiotherapy has been documented in several studies, especially in the field of breast cancer and lymphoma. Ionizing radiation causes micro and macro-vascular damage in all cardiac tissues (pericardium, valves, heart muscle and coronary arteries). Primary radiation fibrosis is not related to the primary effect of the radiation, but rather to a reparative response of the heart tissue to injury in the micro-vascular system.

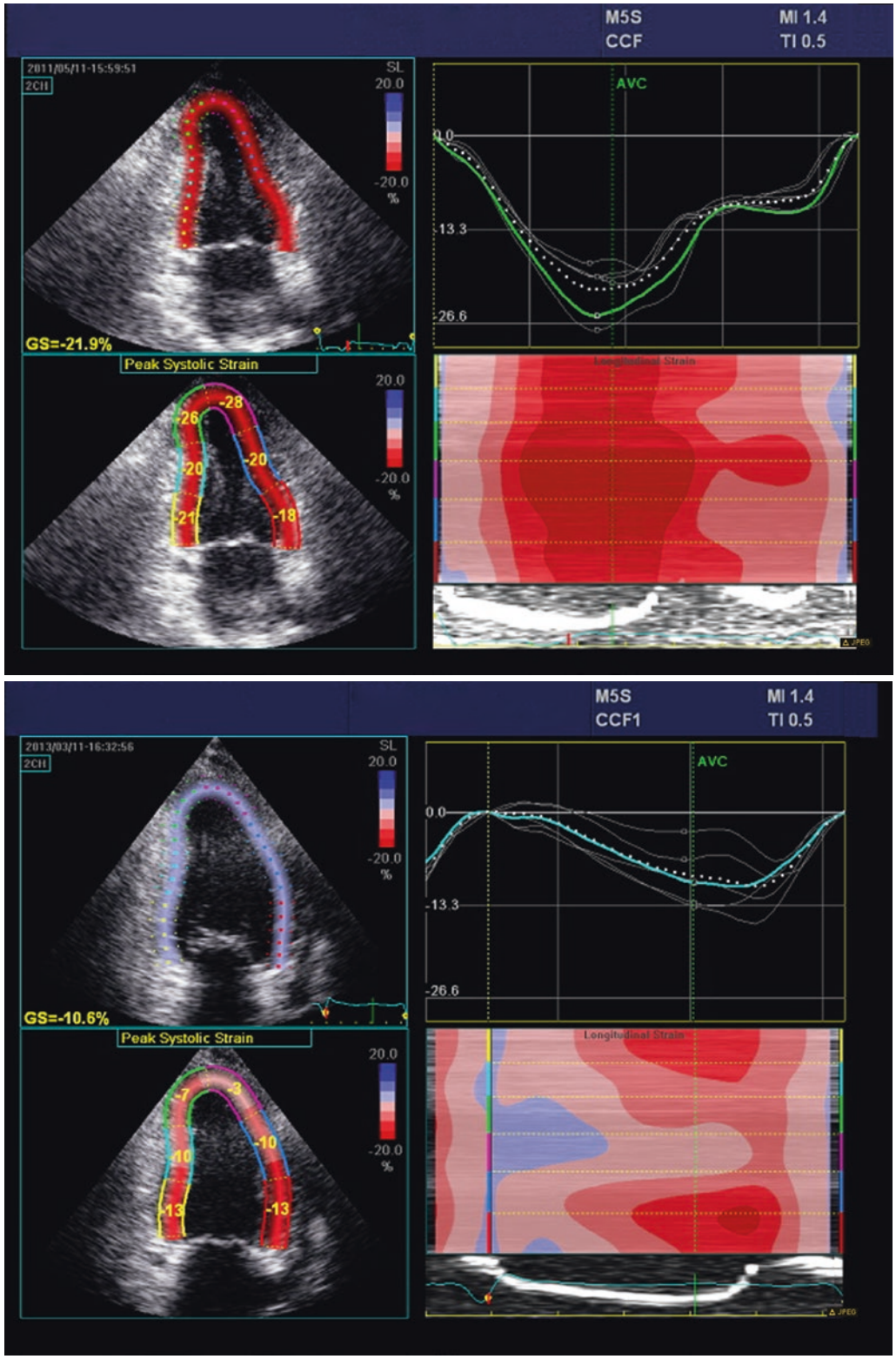

Fig. 38.3 Global longitudinal strain pre and post exposure to anthracyclines. Sub-clinical LV dysfunction is present as GLS has fallen 46%

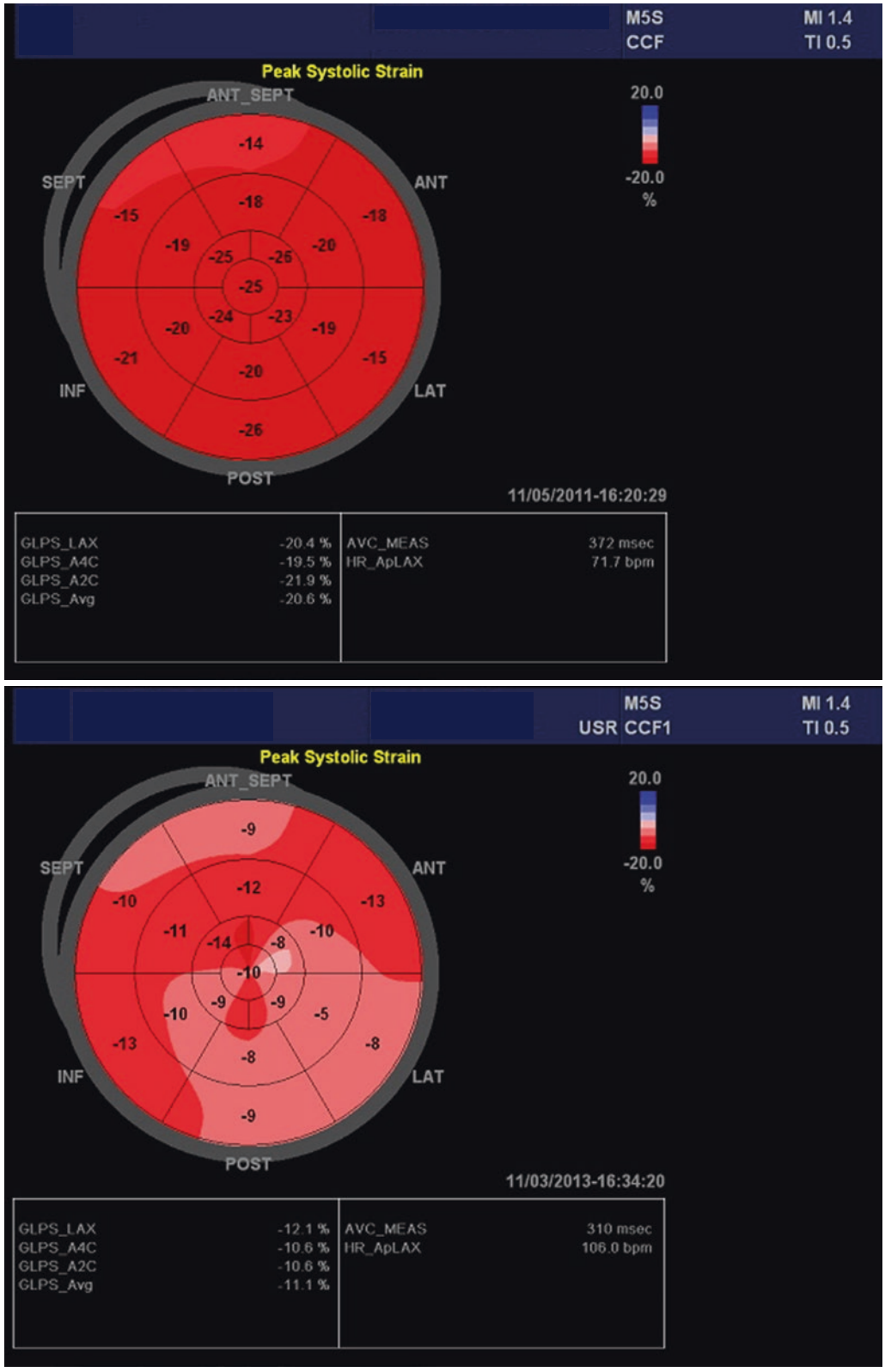

Fig. 38.3 (continued)

Table 38.3 Definition of sub-clinical LV dysfunction by global longitudinal strain measurement

Cardiotoxicity by changes in global longitudinal strain (GLS)	
Change in GLS	Reduction ≥15% from baseline
Absolute number of GLS	Drop below the lower limit of normal for vendor, gender and age when baseline is not available [48]

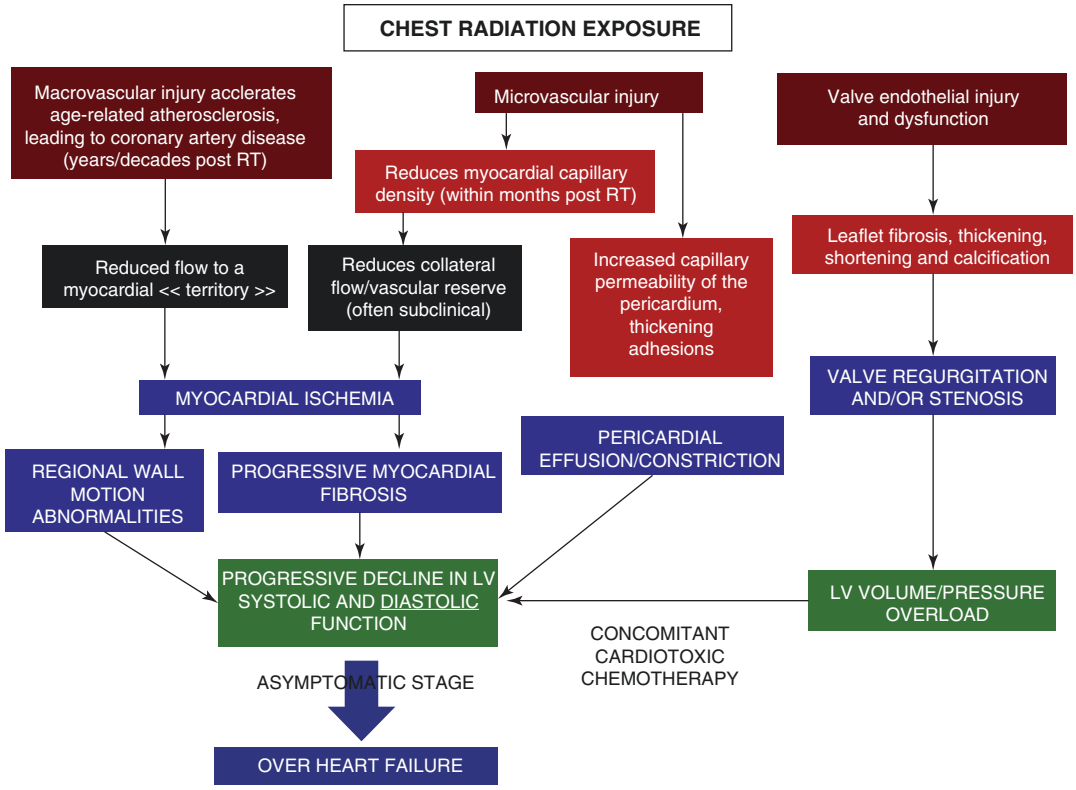

Fig. 38.4 Pathophysiology of radiation-induced heart disease. Reproduced with permission from [53]

Echocardiography continues to be the working horse in the evaluation of pericardial and valvular heart disease in these patients. Strain imaging has emerged as a very useful tool unveiling the presence of myocardial injury not previously recognized with 2D echocardiography [52] (Fig. 38.4). A summary of cardiac changes noted after radiation therapy are noted in Fig. 38.5. Global strain values can also be significantly reduced following radiation (Fig. 38.6).

Acute	Long-term
Pericarditis	Pericarditis
• Acute exudative pericarditis is rare and often occurs during radiotherapy as a reaction to necrosis/inflammation of a tumour located next to the heart.	• Delayed chronic pericarditis appears several weeks to years after radiotherapy. In this type, extensive fibrous thickening, adhesions, chronic constriction, and chronic pericardial effusion can be observed. It is observed in up to 20% of patients within 2 years following irradation.
• Delayed accute pericarditis occurs within weeks after radiotherapy and can be revealed by either and asymptomatic pericardial effusion or a symptomatic pericarditis. Cardiac tamponade is rare. Spontaneous clearance of this effusion may take up to 2 years.	• Constrictive pericarditis can be observed in 4–20% of patients and appears to be dose-dependent and related to the presence of pericardial effusion in the delayed acute phase.
Cardiomyopathy	Cardiomyopathy
• Acute myocarditis related to radiation-induced inflammation with transient repolarization abnormalities and mild myocardial dysfunction.	• Diffuse myocardial fibrosis (often after a > 30-Gy radiation dose) with relevant systolic and diastolic dysfunction, conduction disturbance, and autonomic dysfunction.
	• Restricitive cardiomyopathy represents an advanced stage of myocardial damage due to fibrosis with severe diastolic dysfunction and signs and symptoms of heart failure
Valve disease	Valve disease
• No immdiate apparent effects.	• Valve apparatus and leaflet thickening, fibrosis shortening, and calcification predominant on left-sided valves (related to pressure difference between the left and right side of the heart).
	• Valve regurgiation more commonly encountered than stenosis.
	• Stenotic lesions more commonly involving the aortic valve.
	• Reported incidence of clinically significant valve disease: 1% at 10 years; 5% at 15 years; 6% at 20 years after radiation exposure.
	• Valve disease incidence increases significantly after >20 years following irradiation; mild AR up to 45% ≥moderate AR up to 15%, AS up to 16%, mild MR up to 48%, mid PR up to 12%.
Coronary artery disease	Coronary artery disease
• No immediate apparent effects. (Perfusion defects can be seen in 47% of patients 6 months after radiotherapy and may be accompained by wall-motion abnormalities and chest pain. Their long-term prognosis and significance are unknown.)	• Accelerated CAD appearing in the young age. • Concomitant atherosclerotic risk factors further enhance the development of CAD. • Latent until at least 10 years after exposure. (Patients younger than 50 years tend to develop CAD in the first decade after treatment, while older patients have longer latency periods.)
	• Coronary ostia and proximal segments are typically involved.
	• CAD doubles the risk of death; relative risk of death from fatal myocardial infarction varies from 2.2 to 8.8.
Carotid artery disease	Carotid artery disease
• No immediate apparent effects.	• Radio therapy-induced lesions are more extensive, involving longer segments and atypical areas of carotid segments.
	• Estimated incidence (including sub-clavian artery stenosis) about 7.4% in Hodgkin's lymphoma.
Other vascular disease	Other vascular disease
• No immediate apparent effects.	• Calcification of the ascending aorta and aortic arch (porcelain aorta).
	• Lesions of any other vascular segments present within the radiation field.

Fig. 38.5 Acute and chronic manifestations of radiation-induced heart disease. Reproduced with permission from [53]

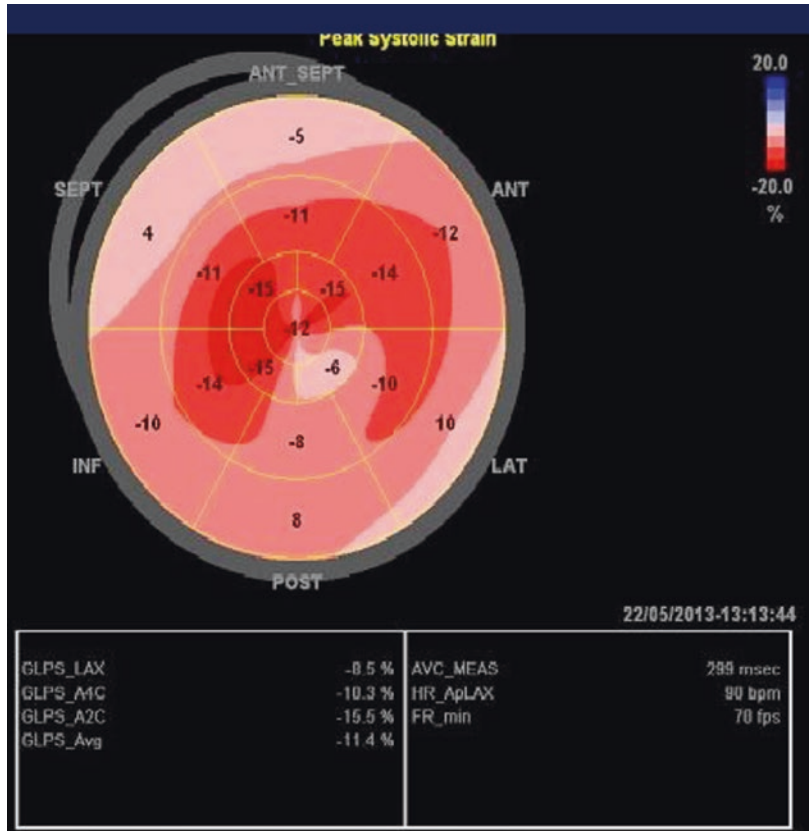

Fig. 38.6 Global longitudinal strain in patient with radiation-induced restrictive heart disease

Conclusions

Echocardiography is the mainstay for the evaluation of the patient during and after cancer therapy (chemo or radiotherapy). Three-dimensional echocardiography is the method choice for the evaluation of LVEF where available, as it has the lowest inherent variability, therefore allowing the adjudication of CTRCD. If the technique is unavailable, the enhancement of 2D echocardiograms with contrast is an acceptable alternative. It is essential to use strain imaging during the surveillance of patients receiving potentially cardiotoxic chemotherapeutic agents due to its ability to recognize subtle changes in cardiac function that prognosticate downstream CTRCD.

References

1. Tan C, Tasaka H, Yu KP, Murphy ML, Karnofsky DA. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer. 1967;20:333–53.
2. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32:302–14.
3. Greco FA, Brereton HD, Rodbard D. Noninvasive monitoring of adriamycin cardiotoxicity by "Sphygmo-Recording" of the pulse wave delay (QKd interval). Cancer Treat Rep. 1976;60:1239–45.
4. Ramos A, Meyer RA, Korfhagen J, Wong KY, Kaplan S. Echocardiographic evaluation of adriamycin cardiotoxicity in children. Cancer Treat Rep. 1976;60:1281–4.

5. Billingham ME, Bristow MR, Glatstein E, Mason JW, Masek MA, Daniels JR. Adriamycin cardiotoxicity: endomyocardial biopsy evidence of enhancement by irradiation. Am J Surg Pathol. 1977;1:17–23.
6. Lenzhofer R, Dudczak R, Gumhold G, Graninger W, Moser K, Spitzy KH. Noninvasive methods for the early detection of doxorubicin-induced cardiomyopathy. J Cancer Res Clin Oncol. 1983;106:136–42.
7. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. 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. Eur Heart J Cardiovasc Imaging. 2014;15:1063–93.
8. De Graff WG, Myers LS Jr, Mitchell JB, Hahn SM. Protection against Adriamycin cytotoxicity and inhibition of DNA topoisomerase II activity by 3,4-dihydroxybenzoic acid. Int J Oncol. 2003;23:159–63.
9. Tewey KM, Rowe TC, Yang L, Halligan BD, Liu LF. Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. Science. 1984;226:466–8.
10. Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, Liu LF. Topoisomerase IIβ-mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Science. 2007;67:8839–46.
11. Von Hoff DL, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91:710–7.
12. Ewer MS, Von Hoff DD, Benjamin RS. A historical perspective of anthracycline cardiotoxicity. Heart Fail Clin. 2011;7:363–72.
13. Neilan TG, Jassal DS, Perez-Sanz TM, Raher MJ, Pradhan AD, Buys ES, Ichinose F, Bayne DB, Halpern EF, Weyman AE, Derumeaux G, Bloch KD, Picard MH, Scherrer-Crosbie M. Tissue doppler imaging predicts left ventricular dysfunction and mortality in a murine model of cardiac injury. Eur Heart J. 2006;27:1868–75.
14. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation. 2005;111:2837–49.
15. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342:1077–84.
16. Baselga J, Norton L, Albanell J, Kim YM, Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. Cancer Res. 1998;58:2825–31.
17. Chien KR. Herceptin and the heart–a molecular modifier of cardiac failure. N Engl J Med. 2006;354:789–90.
18. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
19. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, Peterson KL, Chen J, Kahn R, Condorelli G, Ross J Jr, Chien KR, Lee KF. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002;8:459–65.
20. Jannazzo A, Hoffman J, Lutz M. Monitoring of anthracycline-induced cardiotoxicity. Ann Pharmacother. 2008;42:99–104.
21. Jurcut R, Wildiers H, Ganame J, D'Hooge J, Paridaens R, Voigt JU. Detection and monitoring of cardiotoxicity-what does modern cardiology offer? Support Care Cancer. 2008;16:437–45.
22. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, Schwartz PE, Berger HJ, Setaro J, Surkin L, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987;82:1109–18.
23. Ng R, Better N, Green MD. Anticancer agents and cardiotoxicity. Semin Oncol. 2006;33:2–14.
24. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, Jones SE, Wadler S, Desai A, Vogel C, Speyer J, Mittelman A, Reddy S, Pendergrass K, Velez-Garcia E, Ewer MS, Bianchine JR, Gams RA. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol. 1997;15:1318–32.
25. Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, Shah P, Khojasteh A, Nair MK, Hoelzer K, Tkaczuk K, Park YC, Lee LW. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol. 2001;19:1444–54.

26. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging. 2009;2:356–64.
27. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61:77–84.
28. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. Am Heart J. 2003;146:388–97.
29. Yu EH, Sloggett CE, Iwanochko RM, Rakowski H, Siu SC. Feasibility and accuracy of left ventricular volumes and ejection fraction determination by fundamental, tissue harmonic, and intravenous contrast imaging in difficult-to-image patients. J Am Soc Echocardiogr. 2000;13:216–24.
30. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, Burns PN, Castello R, Coon PD, Hagen ME, Jollis JG, Kimball TR, Kitzman DW, Kronzon I, Labovitz AJ, Lang RM, Mathew J, Moir WS, Nagueh SF, Pearlman AS, Perez JE, Porter TR, Rosenbloom J, Strachan GM, Thanigaraj S, Wei K, Woo A, Yu EH, Zoghbi WA. American Society of Echocardiography consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr. 2008;21:1179–201. quiz 1281.
31. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, Nihoyannopoulos P. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr. 2009;10:194–212.
32. Nahar T, Croft L, Shapiro R, Fruchtman S, Diamond J, Henzlova M, Machac J, Buckley S, Goldman ME. Comparison of four echocardiographic techniques for measuring left ventricular ejection fraction. Am J Cardiol. 2000;86:1358–62.
33. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol. 2004;44:1030–5.
34. Badano LP, Boccalini F, Muraru D, Bianco LD, Peluso D, Bellu R, Zoppellaro G, Iliceto S. Current clinical applications of transthoracic three-dimensional echocardiography. J Cardiovasc Ultrasound. 2012;20:1–22.
35. Jacobs LD, Salgo IS, Goonewardena S, Weinert L, Coon P, Bardo D, Gerard O, Allain P, Zamorano JL, de Isla LP, Mor-Avi V, Lang RM. Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. Eur Heart J. 2006;27:460–8.
36. Corsi C, Coon P, Goonewardena S, Weinert L, Sugeng L, Polonsky TS, Veronesi F, Caiani EG, Lamberti C, Bardo D, Lang RM, Mor-Avi V. Quantification of regional left ventricular wall motion from real-time 3-dimensional echocardiography in patients with poor acoustic windows: effects of contrast enhancement tested against cardiac magnetic resonance. J Am Soc Echocardiogr. 2006;19:886–93.
37. Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. Eur Heart J. 2009;30:98–106.
38. Stapleton GE, Stapleton SL, Martinez A, Ayres NA, Kovalchin JP, Bezold LI, Pignatelli R, Eidem BW. Evaluation of longitudinal ventricular function with tissue Doppler echocardiography in children treated with anthracyclines. J Am Soc Echocardiogr. 2007;20:492–7.
39. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, Abraham TP, Belohlavek M. Two-dimensional strain--a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. J Am Soc Echocardiogr. 2005;18:1247–53.
40. Yeon SB, Reichek N, Tallant BA, Lima JA, Calhoun LP, Clark NR, Hoffman EA, Ho KK, Axel L. Validation of in vivo myocardial strain measurement by magnetic resonance tagging with sonomicrometry. J Am Coll Cardiol. 2001;38:555–61.
41. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation. 2000;102:1158–64.
42. Hare JL, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. Am Heart J. 2009;158:294–301.
43. Ho E, Brown A, Barrett P, Morgan RB, King G, Kennedy MJ, Murphy RT. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: a speckle tracking echocardiographic study. Heart. 2010;96:701–7.
44. Poterucha JT, Kutty S, Lindquist RK, Li L, Eidem BW. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr. 2012;25:733–40.
45. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, Cohen V, Banchs J, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5:596–603.
46. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, Becker M, Thomas JD. Myocardial

strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. JACC Cardiovasc Imaging. 2009;2:80–4.
47. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26:493–8.
48. Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, Tanabe K, Nakatani S, JUSTICE Investigators. Normal range of left ventricular 2-dimensional strain: Japanese ultrasound speckle tracking of the left ventricle (JUSTICE) study. Circ J. 2012;76:2623–32.
49. Bountioukos M, Doorduijn JK, Roelandt JR, Vourvouri EC, Bax JJ, Schinkel AF, Kertai MD, Sonneveld P, Poldermans D. Repetitive dobutamine stress echocardiography for the prediction of anthracycline cardiotoxicity. Eur J Echocardiogr. 2003;4:300–5.
50. Cottin Y, L'Huillier I, Casasnovas O, Geoffroy C, Caillot D, Zeller M, Solary E, Guy H, Wolf JE. Dobutamine stress echocardiography identifies anthracycline cardiotoxicity. Eur J Echocardiogr. 2000;1:180–3.
51. Civelli M, Cardinale D, Martinoni A, Lamantia G, Colombo N, Colombo A, Gandini S, Martinelli G, Fiorentini C, Cipolla CM. Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. Int J Cardiol. 2006;111:120–6.
52. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, Cosyns B, Coucke P, Dulgheru R, Edvardsen T, Gaemperli O, Galderisi M, Griffin B, Heidenreich PA, Nieman K, Plana JC, Port SC, Scherrer-Crosbie M, Schwartz RG, Sebag IA, Voigt JU, Wann S, Yang PC, European Society of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance; American Society of Nuclear Cardiology; Society for Cardiovascular Magnetic Resonance; Society of Cardiovascular Computed Tomography. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2013;14:721–40.
53. Lancellotti P, Nkomo V, Badano L. Expert consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2013;26:1013–32.