STATE-OF-THE-ART REVIEW ARTICLE

Use of Echocardiography to Evaluate the Cardiac Effects of Therapies Used in Cancer Treatment: What Do We Know?

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Cardiologists and oncologists today face the daunting challenge of identifying patients at risk for late-onset left ventricular (LV) systolic dysfunction from the use of various chemotherapeutic agents. Currently, the most widely used method in clinical practice for monitoring the potential of chemotherapy-induced cardiotoxicity is calculation of LV ejection fraction. The use of LV ejection fraction to determine whether to continue or discontinue the use of chemotherapeutic agents is limited, because decreases in LV ejection fraction frequently occur late and can be irreversible. These limitations have led to the exploration of diastolic function and newer modalities that assess myocardial mechanics to identify sensitive and specific variables that can predict the occurrence of late systolic function. The cancer therapies associated with cardiotoxicity are reviewed in this report. Additionally, the authors evaluate the role of present-day echocardiographic parameters, complementary noninvasive imaging modalities, and biomarkers in the prediction of cardiotoxicity. The authors address the evolving role of cardioprotective agents and potential therapies to prevent or reverse the progression of LV systolic dysfunction. Finally, they provide some ideas regarding future directions to enhance the knowledge of predicting late-onset LV systolic dysfunction secondary to cancer therapy. (J Am Soc Echocardiogr 2012;25:1141-52.)

Keywords: Chemotherapy, Cardiotoxicity, Echocardiography, Longitudinal strain, Diastolic and systolic function

Cancer and cardiovascular diseases are the two leading causes of morbidity and mortality in the world. Annually, worldwide mortalities due to cardiovascular diseases and cancers are 17 million and 7.6 million, respectively. Globally, cancer is diagnosed in 12.7 million people annually, with fewer than one-third in high-income countries. Cancer incidence is projected to increase by 40% in high-income countries from 2008 to 2030.[1] Cancer therapies are used worldwide; yet, although chemotherapy is beneficial by destroying malignant cells, it can simultaneously cause injury or death to myocardial cells or, in other words, cardiotoxicity. The resulting paradox for cancer patients is, frequently, premature death without treatment and, possibly, irreversible myocardial cell dysfunction, potentially leading to heart failure (HF) and death, with treatment, if not recognized early. Presently, chemotherapy-induced cardiotoxicity limits the ability to reduce morbidity and mortality associated with cancers throughout the world.

Chemotherapy-induced cardiotoxicity encompasses a broad spectrum of electrophysiologic and HF abnormalities. In this review, we focus on the HF aspects of chemotherapy-induced cardiotoxicity. Chemotherapy-induced cardiotoxicity is well defined[2] as a spectrum of cardiac dysfunction that ranges from subclinical to manifesting as overt HF. The early identification of changes in myocardial function that predict cardiotoxicity from the use of various chemotherapeutic agents, and its attendant morbidity and mortality, is needed. The capacity to predict future cardiotoxicity would allow cardiologists and oncologists to tailor therapies that yield the greatest benefit with the least risk for HF and adverse outcomes, including death.

In this report, we review the cancer therapies associated with cardiotoxicity. The review does not include the effects of radiotherapy. We evaluate the role of echocardiography to identify and predict cardiotoxicity, using left ventricular (LV) systolic and diastolic function measurements, tissue Doppler techniques, and myocardial deformation analysis. Additionally, we briefly explore other imaging modalities and biomarkers that assist in the prediction of cardiotoxicity. Last, we identify what we know and do not know about echocardiography's potential to predict adverse consequences associated with the use of cancer therapies and provide future directions to enhance our knowledge of predicting late-onset LV systolic dysfunction secondary to cancer therapy.

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Abbreviations

ACE = Angiotensin-converting enzyme

ARB = Angiotensin receptor blocker

DT = Deceleration time of early diastolic filling

DTI = Doppler tissue imaging

HF = Heart failure

IVRT = Isovolumic relaxation time

LV = Left ventricular

LVEF = Left ventricular ejection fraction

CANCER THERAPIES AND CARDIOTOXICITY

Systemic anticancer therapies include different classes of drugs with variable mechanisms and targets of action. Conventional chemotherapy is classically represented by antiproliferative actions and includes alkylating agents (cyclophosphamide), platinum-based drugs (cisplatin), antimetabolites (methotrexate, 5-fluorouracil, capecitabine), microtubule agents (vinca alkaloids, taxanes), antibiotics (anthracycline, actinomycin D, bleomycin). Alternative anticancer strategies are available, including hormone therapy (tamoxifen) and immunotherapy (most commonly monoclonal antibodies). Also, recent molecularly targeted agents, principally protein tyrosine kinase inhibitors, are available.[3] The classification of chemotherapy-induced cardiotoxicity is not defined in a universally accepted schema. The classification of the type 1 and type 2 toxicities has been proposed and is the classification we will define and use.

Many chemotherapeutic agents are associated with cardiotoxicity that manifests as LV systolic dysfunction. In particular, anthracycline and trastuzumab-induced cardiotoxicities are well described.[2,4]

Type 1 Chemotherapy-Mediated Cardiotoxicity

Anthracycline-induced cardiotoxicity, type 1 chemotherapy-related cardiac dysfunction, is typically dose related and irreversible, associated with microscopic ultrastructural changes, and frequently results in myocardial cell death. It is due, at least in part, to oxidative stress on cardiac myocytes resulting in free radical formation and cell death. Chemotherapeutic agents classified as causing type 1 chemotherapy-related LV systolic dysfunction include doxorubicin, epirubicin, idarubicin, liposomal anthracyclines, cyclophosphamide, and docetaxel (see Table 1).[5-8] In patients with cancer who develop asymptomatic or symptomatic anthracycline-induced cardiotoxicity, LV ejection fraction (LVEF) recovery and cardiac event reduction can occur if there is early detection and treatment with modern HF therapy.

Type 2 Chemotherapy-Mediated Cardiotoxicity

Alternatively, trastuzumab-induced cardiotoxicity, type 2 chemotherapy-related cardiac dysfunction, typically is not dose related and can be associated with reversible myocardial dysfunction rather than structural damage. Reversibility is defined as recovery of LVEF to the normal range. A small study revealed that 60% of patients (25 of 42) who developed trastuzumab-induced cardiotoxicity recovered to normal LVEFs after discontinuation of trastuzumab and initiation of HF therapy.[9] Chemotherapeutic agents classified as causing type 2 chemotherapy-related LV systolic dysfunction include trastuzumab, lapatinib, sunitinib, imatinib, and bevacizumab (see Table 2).[10-14] These differences are fundamental to the dilemma the medical community faces of whether the benefits of chemotherapies outweigh the associated risks for the treatment of life-threatening cancers. However, type 1 and 2 cardiac dysfunctions can coexist in the same patient.

Anthracyclines and Trastuzumab: Two Widely Used Chemotherapeutic Agents

Anthracycline-induced cardiotoxicity is classified on the basis of clinical findings as (1) acute, (2) early-onset chronic progressive, or (3) late-onset chronic progressive. Acute anthracycline-induced cardiotoxicity represents 1% of cases; it can occur hours or days after infusion of the drug, is not dose related, and is usually reversible. Acute anthracycline-induced cardiotoxicity is not a predictor of the future development of HF. Early-onset chronic progressive anthracycline-induced cardiotoxicity occurs during therapy or within 1 year after therapy and, generally, is not reversible. Late-onset chronic progressive anthracycline-induced cardiotoxicity manifests $\geq$1 year after therapy. The two chronic forms of anthracycline-induced cardiotoxicity are dose related and present as dilated cardiomyopathy and, frequently, HF.[2] The limiting dose of anthracycline for each patient is determined by age, cardiovascular risk factors, prior radiation dose, coexisting drug therapy, type of drug, drug schedule, and, most importantly, cumulative dose (see Table 3).[15,16]

Trastuzumab is a widely used chemotherapeutic agent that causes cardiotoxicity. It is a monoclonal antibody binding erythroblastic leukemia viral oncogene homolog 2 gene and human epidermal growth factor receptors 2, and widely used in erythroblastic leukemia viral oncogene homolog 2–positive breast cancer. This agent, in contrast to anthracyclines, does not provoke myocardial necrosis but causes myocardial cell dysfunction that is frequently reversible.[10] The incidence of trastuzumab-induced cardiac dysfunction varies from 2% to 10% but can be up to 27% when used in combination with anthracycline and cyclophosphamide.[2,17] The cumulative effect of these chemotherapeutic agents on cardiac function is critical to treatment decisions.

The challenge the cardiology community faces is the development of parameters to identify early changes in myocardial function that will predict future cardiotoxicity. One of the most important tools for defining myocardial function is echocardiography.

ROLE OF ECHOCARDIOGRAPHY

The role of echocardiography in the detection and prediction of chemotherapy-induced cardiotoxicity is evolving. References to standard measures of ventricular systolic and diastolic functions as well as newer modalities of assessing myocardial mechanics are summarized in Table 4 and discussed in detail below.

LV Systolic Function and Cancer Therapy

The primary goal for the interdisciplinary team of cardiologists and oncologists is the early identification of patients at risk for cardiotoxicity as antineoplastic treatment regimens are introduced into clinical practice. Currently, the most widely used method in clinical practice for monitoring the potential of cardiotoxicity is calculation of LVEF.[18] The use of serial echocardiography to calculate LVEF in patients who could be affected by cardiotoxicity has not been validated, because there is no present gold standard for calculating LVEF to validate it against. The methods available to measure LVEF are prone to variability, particularly in the evaluation of serial echocardiographic studies. It has been observed that LVEF obtained using echocardiographic methods has a 95% confidence interval of $\pm$11%; thus, subtle changes in LV systolic function are frequently not detected because of measurement variability.[19]

Although LVEF has been validated as a measure of LV systolic function,[10,18] there are many limitations that must be recognized when it is

Table 1 Additional type 1 chemotherapeutic agents

Drug	Cardiotoxicity
Mitoxantrone[6]	Increased risk if current or prior heart disease
	Increased risk if prior treatment with anthracycline
	Increased risk if prior treatment with radiation therapy
	Contraindication to use if LVEF < 50%
Cyclophosphamide (>150 mg/kg)	7%–28% risk for HF 1–10 days after first dose
Ifosfamide	10%–30% risk for HF
Mitomycin[7]	Risk for hemorrhagic pericarditis, tamponade, myocarditis, myocardial infarction, and cardiomyopathy
Docetaxel	2%–8% risk for HF[3]
Paclitaxel[8]	Risk for hypotension, bradycardia
	Synergistic effect with anthracycline metabolites yielding HF

Table 2 Additional type 2 chemotherapeutic agents

Drug	Cardiotoxicity
Lapatinib[11]	1% risk for asymptomatic cardiac events
	Reversible decrease in LVEF
	Cardiac events not influenced by prior treatment with anthracycline or trastuzumab
Sunitanib[12,13]	Risk for hypotension
	10%–30% LVEF decrease
	Increased risk if history of CAD or CV risk factors
Bevacizumap[14]	2%–3% risk for LV systolic dysfunction, especially in elderly with CV risk factors

CAD, Coronary artery disease; *CV*, cardiovascular.

Table 3 Incidence of cardiotoxicity on the basis of cumulative doxorubicin dose

Cumulative dose (mg/m^2)	Incidence
300	<3%
400	3%–5%
550	7%–26%
700	18%–48%

used to identify the development of cardiotoxicity. Image quality can reduce the precision of endocardial border definition and limit measurement accuracy. The use of contrast often has the potential to overcome this limitation. Contrast allows enhanced accuracy, reduced interobserver variability, and improved correlation with magnetic resonance imaging measurement of LVEF.[20-22] Another major limitation of using LVEF is its dependence on loading conditions that can vary among studies, resulting in changes in the calculated LVEF and, therefore, the perceived LV systolic function. The use of LV systolic function to determine whether to continue or discontinue the use of chemotherapeutic agents also is limited as decrease in LVEF frequently occurs late and can be irreversible.[23]

Despite all these identified limitations of LVEF, it is time tested and the measure most used in clinical practice today. Several studies have shown fractional shortening of the left ventricle to significantly decline soon after low to moderate doses of anthracyclines.[24-26] Regional dysfunction limits this type of linear analysis; therefore, volumetric analysis is essential to systolic function evaluation. The most reliable method to calculate LVEF is the biplane Simpson's method. It requires manual or semiautomated tracing of the endocardial border in four- and two-chamber views at end-diastole and end-systole, and volumetric calculation is based on the geometric assumption of stacked elliptical disks characterizing the LV shape. The complexity of geometric assumptions used in calculating biplane LV volumes has been overcome by three-dimensional imaging. Three-dimensional echocardiographic volume calculation is reliable, lowers the probability of chamber foreshortening, and has proved to be an accurate modality for serial measurements of systolic function.[22] One working definition of cardiotoxicity, and the one we use in our echocardiography laboratory, is when LVEF decreases by ≥10% to <55% in asymptomatic patients or by ≥5% to <55% in symptomatic patients (see Figures 1 and 2).[27-29] The definition of cardiac dysfunction has been defined by the independent Cardiac Review and Evaluation Committee.[28] The following criteria were developed to establish or confirm a diagnosis of cardiac dysfunction: (1) cardiomyopathy established by a decrease in LVEF that is global or more severe in the septum; (2) symptoms of HF; (3) signs of HF, including but not limited to third heart sound, tachycardia, or both; and (4) a decline in LVEF of ≥5% to <55% with accompanying signs and symptoms of HF or a decline in LVEF of ≥10% to <55% without signs or symptoms of HF.[28] However, LVEF evaluation is neither sensitive nor specific enough to allow the early prediction of late cardiotoxicity after the initiation of cancer therapy.[30,31] Despite the present limitations of LVEF, it is the recommended measure to monitor cardiotoxicity. There is a guideline report for pediatric patients recommending the evaluation of LVEF before the initiation of antineoplastic therapy, after the administration of half the total anthracycline cumulative dose, and before every subsequent dose.[32] Additional literature supports the use of LVEF before the initiation of chemotherapy[33,34] and after the cessation of cancer therapy.[30,35]

Stress Echocardiography and Cardiotoxicity

Exercise and pharmacologic stress testing have been evaluated as methods to detect subclinical LV systolic dysfunction. Early detection of cardiotoxicity was not identified in 31 patients with cancer evaluated before, during, and after chemotherapy with low-dose dobutamine stress testing.[36,37] However, in 26 asymptomatic patients treated with high-dose anthracycline therapy, high-dose dobutamine stress testing revealed an alteration of fractional shortening.[38] Exercise echocardiography was demonstrated to detect subclinical cardiac dysfunction in a small study of 23 patients. These patients were survivors of acute lymphoblastic leukemia. They had received anthracyclines

Table 4 Echocardiographic findings on cardiotoxicity reported by several recent studies

Study	Patients*	Drug	Follow-up echocardiography	Parameters	Early/late change	LVEF ↓	Predictive value
Stoddard *et al.* (1992)[44]	26	Dox > 200 mg (+ others)	Pre; each dose (3 wk) up to 3 mo after last dose	Volumes, IVRT, E, E/A, DT	Early: 3 mo ↑ IVRT and DT	9/26 (35%)	IVRT (↑37%); sens, 78%; spec, 88%
Tassan-Mangina *et al.* (2006)[46]	20	Dox 211 mg/m^2	Pre; 1–3 mo; 3, 5 y	E, A, E/A, DT, IVRT, DTI S′, e′, a′, IVRT	Early: 3 mo ↓ DTI IVRT, E, e', E/A Late: 3, 5 y both systolic and diastolic parameters (↓S′, LVEF)	4/16 (25%)	IVRT (↓); sens, 100%; spec, 91%
Ganame *et al.* (2007)[55]	13 children	Dox, dauno, ida; 3 doses, 30–75 mg/m^2 (low to moderate)	Pre; <2 h after each dose	LV mass, FS, LVEF, MAPSE, MPI, E, A, E/A, DT, IVRT, E/e′, IVA, S, D, A pulm, A dur, DTI S′, e′, a′, DTI long and rad strain, SR, global, regional	Early: after 1st dose, ↑MPI, E, A, E/A, IVRT, ↓e′ rad and long, ↓rad and long strain, SR After 2nd and 3rd doses, ↓S′ rad and long; ↓↓rad strain, SR; ↓FS, LVEF (still normal)	—	—
Ganame *et al.* (2007)[24]	56 children	Dox, dauno, ida 240 mg/m^2	5 y after last dose	LV mass, FS, LVEF, MAPSE, TAPSE, MPI, E, A, E/A, IVRT, S, D, A dur, DTI S′, e′, a′, e′/a′, IVRT, IVA, strain, SR each wall segment	Late: ↑MPI; ↓MAPSE, IVA basal lateral ↓S, D; ↑IVRT; ↓rad and long strain, SR	—	—
Dodos *et al.* (2008)[25]	100	Dox, dauno, ida, epi, mitoxantrone 226 mg/m^2 mean dose	Pre; 24–72 h; 1, 6, 12 mo after last dose	FS, LVEF, MPI, E, A, E/A, A dur, DT, IVRT, IVCT, S, D, A, A dur	Early: 24–72 h after, ↓FS, LVEF (still normal) 1 mo after, ↑MPI (67% of pts) Late: 6 mo, ↓E/A; 12 mo after, ↓↓FS, LVEF	15/100 (15%)	—
Stapleton *et al.* (2007)[26]	151	Anthra 200 ± 100 mg/m^2	8 mo after therapy	FS, MPI, IVRT, IVCT, E, A, S′, e′, a′, e′/a′, E/e′	Late: 8 mo ↓E/A, e′/a′, ↑a′, ↓e′ (only septal) For doses >200 mg/m^2, ↓FS		
Jurcut *et al.* (2008)[54]	16	PL-dox (30 mg/m^2) + cyclophosp every 3 wk	Pre; after 3 and 6 cycles	LVEF, E, A, IVRT, DT, MAPSE; S, D, A pulm, DTI strain, SR, long and rad V	Early: 3 cycles ↓S rad Late: 6 cycles ↓S long, SR long, SR rad (not V)	—	—

Hare *et al.* (2009)[56]	35	TZM after others	Pre; 3, 6, 9, 12 mo	2D, 3D LVEF; DTI e′, long strain, SR; STE long and rad strain, SR	3–6 mo ↓DTI long SR ↓DTI rad SR 6–9 mo ↓STE long SR, ↓STE rad SR (long earlier than rad)	9/35 (26%); only 1 LVEF <50%	Long SR (in 51% of pts) identified 3 pts with ↓LVEF after 1 y
Cadeddu *et al.* (2010)[69]	49	Epi 400 mg with placebo vs telmisartan	Pre; 1 wk after each 100-mg dose (T1–T4)	E, A, E/A, DT, DTI S′, e′, a′, long strain, SR	200 mg ↓DTI peak SR in placebo group	—	—
Cheung *et al.* (2010)[57]	45 children	Dox, dauno 240 mg max (off 1 y)	6 y	Volumes, 3D LVEF, E, A, DT, DTI S′, e′, a′, STE strain, SR dyssynchrony	Late: 6 y ↓STE circ SR, ↓↓STE circ strain, ↓↓↓ STE rad strain, ↓STE long strain (16% dyssynchrony)	—	—
Ho *et al.* (2010)[47]	70	Anthra + TZM (after 6 y)	6 y	Volumes, E, A, E/A, IVRT, DT, MPI, DTI S′, e′, a′, e′/a′, E/e′, STE long and rad strain	Late: 6 y ↓S', E, E/A, ↓long strain (26% of pts)	—	—
Appel *et al.* (2011)[50]	80	Epi 270 mg (low dose) + cyclophosp	Pre; after 3 cycles (9 wk each cycle)	E, A, E/A, DT, MPI, DTI S′, e′, a′	Mild ↓E/A	—	—
Fallah-Rad *et al.* (2011)[17]	42	Anthra + TZM	Pre-anthra; pre-TZM; 3, 6, 9, 12 mo during TZM	DTI S′, e′, a′, STE long and rad strain, SR	Early: 3 mo ↓S′, ↓global long, rad strain	10/42 (24%) at 6–9 mo	↓S′: sens, 93%; spec, 99%; long strain 79%–82%; rad strain 86%–81%
Sawaya *et al.* (2011)[58]	43	Dox/epi (240/300 mg/m^2) + TZM	Pre-anthra; 3, 6 mo during TZM	E, A, E/A, DTI e′, a′, e′/a′, E/e′, strain peak systolic long, rad, circ	Early: 3 mo ↓long strain (by 11%) 6 mo ↓circ strain (by 15%)	9/43 (21%) at 6 mo (1 pt at 3 mo)	↓Long strain in 14 pts; sens, 78%; spec, 79%
Stoodley *et al.* (2011)[52]	52	Dox/epi (12–18 wk)	1 wk before; 1wk after	Volumes, STE strain, SR	↓Global long strain (48%), ↓global rad strain (59%)	—	—
Poterucha *et al.* (2012)[59]	19	Anthra 296 ± 103 mg/m^2	Pre, 4, 8 mo	LVEF, long peak systolic strain	↓Long peak systolic strain at 4, 8 mo	↓Long peak systolic strain compared with controls at 4, 8 mo	↓LVEF at 8 mo
Sawaya *et al.* (2012)[60]	81	Anthra + taxanes +TZM	3 mo (15 mo)	LVEF, peak long, rad, circ strain	↓Global long strain	26/81 (32%) at 15 mo	60% symptoms of HF

A dur, Duration of A pulmonary wave; *Anthra*, anthracyclines; *A pulm*, pulmonary vein reversal velocity during atrial contraction; *circ*, circumferential; *cyclophosp*, cyclophosphamide; *dauno*, daunorubicin; *dox*, doxorubicin; *epi*, epirubicin; *FS*, fractional shortening; *ida*, idarubicin; *IVA*, myocardial velocity acceleration during the isovolumic contraction period; *IVCT*, isovolumic contraction time; *long*, longitudinal; *MAPSE*, mitral annular plane systolic excursion; *MPI*, myocardial performance index; *PL-dox*, pegylated doxorubicin; *pre*, before starting therapy; *pt*, patient; *rad*, radial; *sens*, sensitivity; *spec*, specificity; *SR*, strain rate; *STE*, speckle-tracking echocardiographic; *3D*, three-dimensional; *2D*, two-dimensional; *TZM*, trastuzumab; *V*, velocity.
*All studies deal with adult patients, unless "children" is specified.

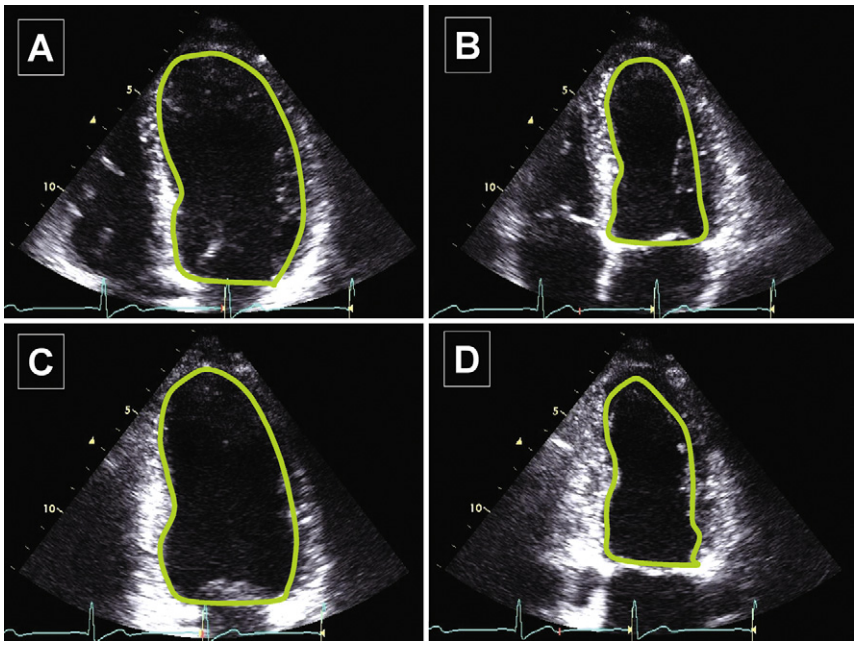

Figure 1 Two-dimensional echocardiographic measurements of end-diastolic (ED) **(A)** and end-systolic (ES) **(B)** volumes in the apical four-chamber view and ED **(C)** and ES **(D)** volumes in the apical two-chamber view. These volume measurements can be used to measure LV systolic function. LVEF can be derived from echocardiographic calculations of LV ED and LV ES volumes, recommended by the American Society of Echocardiography (2005) as a more concise measurement of LVEF compared with the two-dimensional linear approach to LVEF measurement.

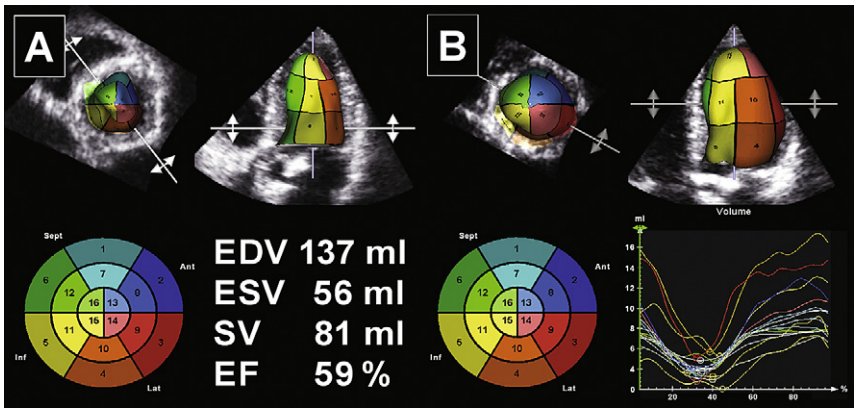

Figure 2 LVEF calculation using three-dimensional (3D) echocardiography. LV volume, or cast, is formed in end-diastole and end-systole and tracked throughout the cardiac cycle. **(A)** A 16-segment model to calculate 3D LVEF. **(B)** Volume contribution per LV segment over time, in this case over a single heart cycle. *Ant*, Anterior; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *Inf*, inferior; *Lat*, lateral; *Sept*, septal; *SV*, stroke volume.

before puberty and were followed after remission for 21 years. Of these 23 patients, 10 had reduced LVEFs on stress echocardiography, while reduction of LVEF at stress testing was not observed in any of the controls.[39] This area needs further investigation to identify if exercise and pharmacologic stress testing used in larger population of patients with cancer could play a role in detection of subclinical cardiotoxicity.

Diastolic Function and Cancer Therapies

Diastolic dysfunction early after chemotherapy occurs frequently and independent of symptoms or changes in systolic function.[40,41] This finding is limited by the observation that abnormal myocardial relaxation is the most common diastolic pattern identified in clinical practice.[42] Myocardial relaxation, the first diastolic event, is an active, energy-dependent process that allows LV pressure to rapidly decrease to a level less than that of left atrial pressure, allowing initial mitral valve opening, followed by early and later diastolic filling of the left ventricle. Abnormal myocardial relaxation is the initial manifestation of diastolic dysfunction.[42]

Different diastolic patterns, classified from normal to grade I to IV diastolic dysfunction, can be distinguished by the comprehensive assessment of isovolumic relaxation time (IVRT), early diastolic velocity (E) and late diastolic velocity (A), early tissue Doppler velocity (e′) and

late tissue Doppler velocity (a′), and deceleration time of early diastolic filling (DT).[42,43] Impaired LV relaxation is characterized by normal LV filling pressures at rest that increase during exercise. IVRT, the interval between aortic valve closure and mitral valve opening, is prolonged (>80–90 m/sec). When impaired myocardial relaxation causes LV pressure to decrease slowly, a longer time is required for that pressure to reach a level less than the left atrial pressure. Concomitantly, DT is prolonged (>240 m/sec) when myocardial relaxation is abnormal. IVRT and DT have been found to be prolonged after 3 months of anthracycline therapy in some patients.[44,45] The prolongation of IVRT and DT predicted doxorubicin-induced systolic dysfunction in some patients at 6 months[44]; alternatively, another study with prolonged IVRT and DT did not reveal any decrease in LVEF.[45] The sensitivity (78%) and specificity (88%) of IVRT in the prediction of systolic dysfunction are similar to the sensitivity and specificity of strain parameters. This study prospectively evaluated 26 patients before beginning chemotherapy (doxorubicin) and 3 weeks after cumulative doses. Observations included prolongation of IVRT preceding a significant decrease in LVEF.[44] Although the number of patients was small, the study highlights the potential predictive value of diastolic indices for the development of subsequent cardiotoxicity. Significant reductions in E, e′, and the E/A ratio were observed in a small population of patients and were associated with a significant reduction in EF after 3 to 5 years.[46]

Chemotherapy-related diastolic dysfunction can occur at any time, acute and transient 1 hour after the administration of doxorubicin. These changes can be paradoxical to expectations, with increasing e′ and E/A ratio and IRVT shortening.[44] Ganame *et al.*[24] observed impaired diastolic and mechanical parameters in conjunction with reduced fractional shortening and LVEF (but still in normal range) 2 hours after the first dose of anthracycline. Additionally, impaired diastolic parameters have been described weeks to months after anthracycline therapy in the absence of reduced LVEF, and the same subtle diastolic abnormalities can be associated with normal LVEF several years after chemotherapy completion.[47] These paradoxical findings associated with cancer therapy reinforce why diastolic parameters currently are not good predictors of future systolic dysfunction. Presently, no early diastolic parameter changes after chemotherapy can predict late-onset systolic dysfunction (see Figure 3).

Tissue Doppler–Derived Function and Cancer Therapies

Systolic longitudinal function can be easily assessed with Doppler tissue imaging (DTI), which determines the displacement of the mitral annulus, and is reliably represented by the peak systolic velocity of the mitral annular longitudinal movement (S′). The sample volume is placed on the septal or lateral mitral annulus in a four-chamber view. In normal adults, S′ is typically >15 cm/sec when recorded at the septal mitral annulus and >20 cm/sec at the lateral mitral annulus. These guidelines have some variability on the basis of age and gender.[48,49] Unfortunately, longitudinal tissue Doppler parameters remain insufficient to assign a reliable measure that predicts a future decline in systolic function.[50]

Available DTI findings are often in conflict. A significantly reduced S′ detected as early as 3 months after chemotherapy (anthracycline plus trastuzumab) seems to predict a decline in LVEF after 6 months with high sensitivity (93%) and specificity (99%).[17] However, low S′ has been observed in asymptomatic patients previously treated with chemotherapy several years prior without a decline in LVEF.[47] These contradictory results limit the predictive value of DTI-derived systolic longitudinal dysfunction in identifying future global systolic dysfunction.

In general, longitudinal LV mechanics, which are predominantly governed by the subendocardial region of the myocardium, are the most vulnerable component of LV mechanics and therefore most sensitive to diseases affecting the myocardium. In many disease processes, global longitudinal strain can be abnormal, while midmyocardial and epicardial mechanical functions remain relatively unaffected initially. Therefore, circumferential strain and twist can be normal when longitudinal strain is impaired. Alternatively, a transmural progression of disease results in concomitant midmyocardial and epicardial mechanical dysfunction, leading to a reduction in LV circumferential and twist mechanics and subsequent decrease in LVEF.[51]

The effect of chemotherapeutic agents, however, might not have a differential effect on the layers of the LV myocardium.[23,52,53] In a small pilot study, chemotherapy treatment with postpegylated liposomal doxorubicin resulted in both longitudinal and radial deformation, with radial changes occurring before longitudinal changes. These changes were observed after three cycles of chemotherapy and could suggest a temporally simultaneous damage to myocardial longitudinal and radial fibers.[54] The concept that all myocardial layers are simultaneously affected by chemotherapeutic agents can be inferred from these findings and needs further investgation.[55] This conceptual thinking is further supported by trastuzumab treatment for breast cancer resulting in radial strain and strain rate reduction at the same time as longitudinal strain changes.[17,52,56] The same results have occurred with circumferential and longitudinal strains after anthracycline therapy.[57] These concepts of how chemotherapy affects mechanical function of the myocardial layers need further study and definition.

Global Strain and Chemotherapy

To overcome the intrinsic angle dependency of DTI, speckle-tracking echocardiography has been validated as a more accurate tool for the evaluation of myocardial deformation. Speckle-tracking echocardiography is based on the analysis of discrete areas of the myocardial wall, referred to as "speckles"; any modification of each speckle can be tracked, frame by frame, in any direction of the imaging plane, and parameters of velocity, strain, and strain rate can be evaluated.[51]

Myocardial deformation imaging could have potential to predict future global systolic dysfunction. A significant reduction of longitudinal strain (>10% from baseline) after 3 months is reported to predict a future reduction in LVEF (after 6 months) with sensitivity of 78% to 79% and specificity of 79% to 82%.[17,58] Global longitudinal strain holds promise as a predictor of future global systolic dysfunction. Given the difficulties in tracking radial and circumferential speckles from short-axis views, global longitudinal strain might be a more reproducible measurement of myocardial mechanics (see Figure 4). Global longitudinal strain has been shown in some small studies to have some potential as an early predictor of late LV systolic dysfunction.[58-60]

DETECTION OF CARDIOTOXICITY BEYOND ECHOCARDIOGRAPHY

Planar multigated radionuclide angiography, cardiac magnetic resonance imaging, and cardiospecific biomarkers all have been shown to be valid diagnostic modalities for the identification of cardiotoxicity. Multigated radionuclide angiography is an accepted method to assess LVEF. It is more expensive than echocardiography and has a radiation risk. There are proponents who believe that it has higher specificity and less interobserver variability than

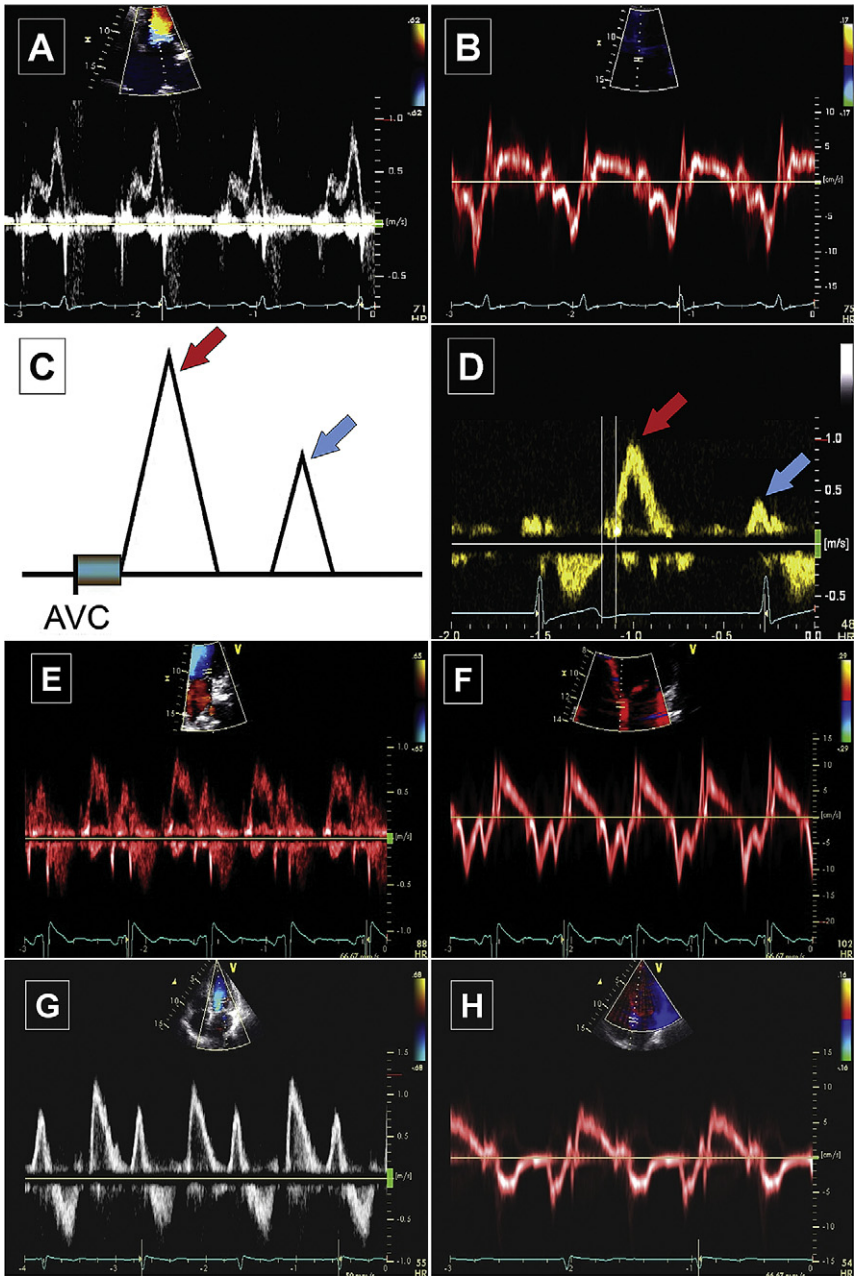

Figure 3 Use of echocardiography to determine variables of diastolic function in patients undergoing chemotherapy. **(A)** By measuring the mitral valve pulsed-wave Doppler pattern at the mitral valve leaflet tips, the echocardiographer can derive early diastolic velocity (E), late diastolic velocity (A), the E/A ratio, and DT. **(B)** Using Doppler tissue imaging, the echocardiographer can derive tissue Doppler early diastolic velocity (e′), tissue Doppler late diastolic velocity (a′), and peak systolic velocity of the mitral annular longitudinal movement (S′). These Doppler-derived variables allow calculation of the E/e′ ratio. **(C,D)** Measurement of IVRT; E is defined by the *red arrow* and A is defined by the *blue arrow*. This timing measurement starts at the cessation of aortic valve systolic outflow to the beginning of mitral valve diastolic inflow. The changes in IVRT are often a harbinger of future diastolic changes. **(E)** Normal mitral inflow pattern. **(F)** Normal Doppler profile before the initiation of trastuzumab for treatment of breast cancer. **(G)** Pseudonormal mitral inflow pattern. **(H)** Tissue Doppler profile consistent with grade II/IV diastolic dysfunction 9 months after chemotherapy. At that time, global longitudinal strain and LVEF, calculated via echocardiography, were normal. These findings emphasize the uncertain nature of changes in diastolic function related to chemotherapy. *AVC*, Aortic valve closure.

echocardiography.[49,61,62] Alternatively, the development of three-dimensional volumetric echocardiography has reduced interobserver variability.[63] Cardiac magnetic resonance imaging is a valuable modality to assess LV systolic function due to higher spatial resolution compared with alternative imaging techniques, and its tissue characterization has prognostic value in chemotherapy patients.[64] Biomarkers are emerging as increasingly important in the detection of cardiotoxicity. Patients with elevated troponin I levels who were treated with anthracyclines had greater reductions in LVEF that persisted over time.[65] Alternatively, patients treated with anthracyclines

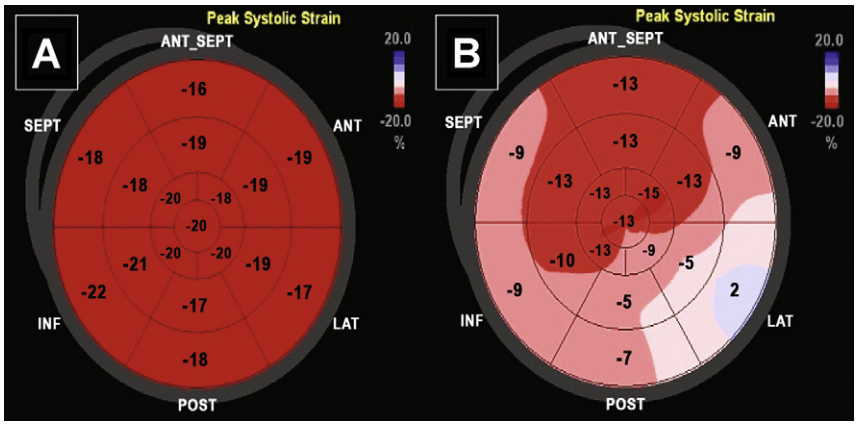

Figure 4 Two-dimensional strain echocardiography. **(A)** Normal global longitudinal strain, measuring −19.5%, in a 22-year-old woman before therapeutic chemotherapy treatment. **(B)** Abnormal global longitudinal strain, measuring −10.1%, captured during routine echocardiography in the same patient 6 months after undergoing chemotherapy treatment. Strain measures the relationship of systolic lengthening or shortening of the myocardium, expressed as a percentage of baseline segment length, whereas lengthening is expressed using positive numbers and shortening is expressed using negative numbers. In this example, a decline in systolic shortening is concerning for myocardial dysfunction related to chemotherapy administration. The patient had the same LVEF at the pretreatment and posttreatment echocardiographic studies. *ANT*, Anterior; *ANT_SEPT*, anteroseptal; *INF*, inferior; *LAT*, lateral; *POST*, posterior; *SEPT*, septal.

who did not have elevations of troponin I levels did not have declines in LVEF and had a 1% cardiac event rate.[66] These various modalities all have an important role in the detection of cardiotoxicity. All the described noninvasive imaging techniques should be used to complement the others.

CARDIOPROTECTIVE AGENTS AND CANCER THERAPIES

Aggressive surveillance of chemotherapy patients with early detection and treatment of anthracycline-induced cardiotoxicity with or without HF is essential to cardiotoxicity reversal. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and diuretics all play a role in the treatment of cardiotoxicity in chemotherapy patients. These agents have a role in the treatment of systolic dysfunction due to chemotherapy analogous to their role in systolic dysfunction from other etiologies. The therapeutic approach must be individualized to the patient's clinical condition. ACE inhibitors, β-blockers, and ARBs all can play a role in the medical therapy of patients developing symptoms and/or signs of LV systolic dysfunction. These medical therapies appear to reduce the risk for persistent cardiomyopathy development.

Medical therapy with ACE inhibitors, ARBs, and β-blockers appears to work most favorably in high-risk patients with known cardiovascular disease.[67-69] New York Heart Association functional class and temporal time period to initiate treatment of HF are strong predictors of LV systolic function recovery. Complete recovery of LVEF to the normal range is more likely with rapid time to medical therapy and lower New York Heart Association functional class.[5] The Heart Failure Society of America guidelines set the standard of care for HF, stating that therapy should include a potential treatment strategy including a subset of ACE inhibitors, ARBs, and β-blockers in patients with asymptomatic declines in LVEF of $\geq$10% to <55% and the addition of diuretic therapy when patients have HF symptoms or signs (decline in LVEF of $\geq$5% to <55%).[28,70]

Dexrazoxane is a component of chemotherapy in restrictive settings, its action being a cardioprotective agent against the development of chemotherapy-induced cardiotoxicity. Dexrazoxane is a derivative of ethylenediaminetetraacetic acid that penetrates cell membranes and functions as an intracellular chelating agent. The mechanism of action of this drug as a cardioprotectant is the chelation of intracellular iron; this activity is thought to reduce anthracycline free radical generation. The clinical appeal of dexrazoxane is its cardioprotective effect even when patients have preexisting cardiac disease and that it does not modify the beneficial effect of anthracyclines in treatment of the underlying cancer. Dexrazoxane is approved for use in the United States for cardioprotection in women with advanced and/or metastatic breast cancer undergoing treatment with doxorubicin.[71]

The development of cardioprotective agents to reduce cardiotoxicity is evolving from bench research to clinical applications. These developments are crucial to the prevention of cardiotoxicity. Experimentally, probucol[72] and tannic acid[73] acting as free radical scavengers have demonstrated decreased histologic evidence of cardiomyocyte injury after treatment with doxorubicin. Both of these drugs have a cardioprotective role against anthracycline-induced cardiotoxicity; additionally, probucol has been protective against trastuzumab-induced cardiotoxicity.

Erythropoietin and iloprost[74] have been shown during in vitro experiments to be cardioprotective against doxorubicin-induced cardiotoxicity without affecting the antitumor efficacy of the drug. Vitamin D therapy could reduce the effect of inflammatory cytokines on the cardiovascular system and limit the progression to HF.[75] These evolving therapies hold great promise in the war against chemotherapy-induced cardiotoxicity. Further research and clinical trials should prove promising in the quest to reduce chemotherapy-induced cardiotoxicity.

ECHOCARDIOGRAPHIC FINDINGS AND THERAPEUTIC DECISIONS

Presently, there are no defined, evidenced-based recommendations for alternative cancer treatment stemming from the detection of abnormal echocardiographic findings. Some experts have suggested that when LVEF decreases to <55%, a careful risk/benefit analysis should be performed to determine whether to continue

chemotherapy. There are more questions than answers relating to therapeutic options at this time when considering chemotherapy and cardiotoxicity: (1) What ought to be done if diastolic or mechanical abnormalities are identified? (2) When should chemotherapy be stopped? (3) When should the chemotherapy dosing regimen be altered? (4) When should the chemotherapeutic agent be changed? and (5) When should β-blocker and ACE inhibitor therapy be initiated?

These important questions cannot be addressed with current scientific data and results. Although a significant change in LVEF frequently leads to a change in chemotherapy, the clinical meaning of alterations in diastolic and/or mechanical parameters, without a reduction in LVEF, is, for the moment, open for deliberation. Large-scale studies are needed to address these important, unanswered questions. These studies should attempt to collaboratively evaluate LV systolic function, diastolic function, and mechanical parameters, attempting to identify variables that reliably predict late-onset LV systolic dysfunction.

FUTURE DIRECTIONS

In the past few years, an increasing number of studies of myocardial deformation changes in patients treated with chemotherapy have generated fragmented and heterogeneous data, even more complicated by the use of completely different techniques, such as DTI and speckle-tracking echocardiography. This heterogeneity across variable protocols—types of drugs, doses, timing of follow-up—has resulted in various results across different studies and left us searching for improved methods to predict the potential for cardiotoxicity.

Furthermore, the majority of the studies available do not compare earlier manifestations of subclinical myocardial dysfunction with any real sign or symptom of myocardial damage. A recent study provided evidence of subclinical myocardial dysfunction accompanied by a simultaneous elevation of a cardiac biomarker suggesting the presence of myocardial damage.[58] A group of patients treated for breast cancer with anthracyclines, taxanes, and trastuzumab were found to have abnormal global longitudinal strain, and 11% of these patients had depressed LVEFs at 15 months.[60] Although the number of patients was small and follow-up of short duration, these findings provide a stimulus for continued research attempting to define early echocardiographic parameters that will determine late cardiotoxicity.

Further research of myocardial parameters, such as myocardial mechanics, to determine the early deterioration of myocardial function is required to identify when the risk for chemotherapy outweighs the benefit. This research requires a pooling of available data from institutions dedicated to the identification of early echocardiographic markers to predict late cardiotoxicity manifesting as cardiomyopathy and HF.

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