REVIEW

Special Focus Issue: Cardio-oncology

Current and emerging modalities for detection of cardiotoxicity in cardio-oncology

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Advancements in diagnostic tools and curative-intent therapies have improved cancer-specific survival. With prolonged survival, patients are now subject to increased aging and development of cardiovascular risk factors such that further improvements in cancer-specific mortality are at risk of being offset by increased cardiovascular mortality. Moreover, established and novel adjuvant therapies used in cancer treatment are associated with unique and varying degrees of direct as well as indirect myocardial and cardiovascular injury (i.e., cardiotoxicity). Current approaches for evaluating anticancer therapy-induced injury have limitations, particularly lack of sensitivity for early detection of subclinical cardiac and cardiovascular dysfunction. With emerging evidence suggesting early prevention and treatment can mitigate the degree of cardiotoxicity and limit interruption of life-saving cancer therapy, the importance of early detection is increasingly paramount. Newer imaging modalities, functional capacity testing and blood biomarkers have the potential to improve early detection of cardiotoxicity and reduce cardiovascular morbidity and mortality.

Mortality rates from cancer have declined over the past 30 years as more effective methods of early detection, pharmacologic treatments and surgical approaches have resulted in significant cancer-related survival gains [1–3]. Long-term survivors with cancer are expected to increase by approximately 30% in the next decade to an estimated 18 million by 2022 in the USA alone [4]. With prolonged survival, cancer patients are now subject to the effects of aging and to the development of other risk factors that determine the long-term risk of cardiovascular disease (CVD) [5–7]. In this setting, CVD may limit the survival gains of oncology and is already the predominant cause of mortality in breast cancer patients over 50 years of age [5,6,8] and a more common contributor than cancer to mortality among older survivors [9,10].

The cardiovascular effects of a prolonged survival are also compounded by those of standard modern cancer therapy. Current anticancer therapies are associated with unique and varying degrees of direct (e.g., myocardial toxicity, ischemia, hypertension, arrhythmias) [11–14] as well as indirect (e.g., unfavorable lifestyle changes) sequential and progressive cardiovascular insults [11]. The most well known direct cardiotoxic effects of cancer therapy historically occur with anthracycline-containing regimens (i.e., doxorubicin, epirubicin). Anthracyclines are still widely used in solid tumors (i.e., breast cancer, osteosarcoma etc.) and hematologic malignancies (Hodgkin's/non-Hodgkin's lymphoma, acute lymphoblastic leukemia etc.) and are well recognized to trigger dose-dependent, cumulative, progressive cardiac dysfunction [15,16] manifest as decreased left ventricular ejection fraction (LVEF) [17–19], and ultimately, symptomatic heart failure (HF) in up to 5% of patients [20]. Newer, targeted agents have dramatically improved the antitumor efficacy of therapies

KEYWORDS

- anthracyclines
- biomarkers • cardiotoxicity
- chemotherapy
- echocardiography
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- trastuzumab

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for various cancers but are not without adverse cardiovascular effects [13,21–23]. In fact, many targeted therapies, particularly monoclonal antibodies and tyrosine kinase inhibitors targeting HER-2 (i.e., trastuzumab, pertuzumab etc.), VEGF and VEGF receptors (i.e., bevacizumab, sunitinib, sorafenib etc.), and Abl kinase activity (i.e., imatinib, nilotinib, dasatinib etc.) have been demonstrated to interfere with molecular pathways crucial to cardiovascular health [23,24]. Moreover, cardiac damage inflicted by the newer agents may be additive; specifically, trastuzumab (Herceptin®), a humanized monoclonal antibody used in *HER-2* positive early-stage breast cancer has demonstrated synergistic cardiotoxicity when added to anthracyclines [25,26].

The magnitude of cardiovascular morbidity is likely to increase with continual improvements in cancer-specific survival in the setting of sequential use of targeted therapies [23] and the approval of newer antineoplastic agents for which the long-term cardiovascular safety profile is not yet known [27,28]. Going forward, cardiovascular detection and surveillance needs to sufficiently identify patients susceptible to therapy-related cardiotoxicity early to prevent morbidity and mortality, as well as to avoid unnecessary discontinuation of essential anticancer therapy or overtreatment of individuals not at risk.

Current state of cardio-oncology

Oncology and cardiology organizations have attempted to classify cardiotoxicity in terms of overt clinical events and subclinical injury. The National Cancer Institute has developed a comprehensive system for cancer adverse events reporting which includes cardiotoxicity, the common terminology criteria for adverse events. This recognizes a broad array of important cardiac and cardiovascular events as well as subclinical laboratory and ejection fraction changes during cytotoxic therapy. Notably, the National Cancer Institute has kept the traditional criteria that define myocardial toxicity (e.g., left ventricular systolic dysfunction, HF and LVEF decline) separate, rather than unifying these parameters under a comprehensive definition of cardiotoxicity [29]. The Cardiac Review and Evaluation Committee criteria were specifically developed in 2002 during an initial extensive safety review of patients treated in trastuzumab trials and defined cardiotoxicity based on physical signs, symptoms and LVEF [30]. The American College of Cardiology/American Heart Association

have developed a staging system (stages A–D) to identify patients during the course of HF development. Asymptomatic patients who receive potential cardiotoxins (stage A) or have asymptomatic left ventricular (LV) dysfunction (stage B) are at risk to develop symptomatic HF (stages C and D) [31]. The transition from American College of Cardiology/American Heart Association stage B asymptomatic to stage C symptomatic HF has been associated with a significant decrease in 5-year survival (96–75%) equivalent to a fivefold increase in mortality risk in a community population [32].

Early detection of cardiotoxicity provides an opportunity to prevent or reverse progression to a more advanced stage (Figure 1); LVEF recovery and cardiac event reduction were more likely with early detection of LV dysfunction and prompt initiation of usual HF therapies in cancer patients with anthracycline-induced cardiomyopathy [33]. In this regard, the evolution of the ‘cardio-oncology’ field, which aims to keep pace with the rapid evolution of cancer therapies and the incidence, magnitude and consequences of their cardiac and cardiovascular side effects, has contributed to improved recognition of the prevalence of treatment-related cardiotoxicity and the importance of early detection [34]. A common pathway for identifying patients at risk for cardiotoxicity, however, remains complicated by the nonspecific nature of treatment-related cardiac and cardiovascular damage, the unpredictability of clinical consequences (e.g., severity, timing etc.), and consequently, uncertainty regarding the optimal strategy for detection.

Current state of detection of cardiotoxicity

In current oncology practice, the cardiotoxic impact of anticancer therapies is primarily evaluated by resting LVEF. Accurate assessment of the frequency and magnitude of cardiotoxicity is challenging, however, given differences in LVEF cut points, monitoring frequency and measurement modalities used in clinical trials that limit direct comparisons. There are currently no consensus criteria for cardiotoxicity [35–37]; trial-based cardiac safety end points have been heterogeneously defined as either an absolute reduction of LVEF >10% or >15%, an LVEF reduction >10% or >15% to a threshold of <55% or <50%, or any LVEF decline to <50% [38]. Echocardiography, multi-gated acquisition (MUGA) or both have been used most frequently for cardiac assessments in clinical trials

Figure 1. Cardiovascular disease and detection of cardiotoxicity in cancer. A schematic representation describing the continuum of cancer treatment, subclinical cardiotoxicity and eventual development of overt cardiovascular disease, in particular, heart failure. Cancer occurs in the setting of the patient's baseline health and risk factors profile. With the administration of potentially cardiotoxic therapies, various surveillance diagnostic strategies may be adopted. Traditional and novel imaging, functional capacity testing and blood-based biomarker strategies have been assessed to detect cardiotoxicity. Once there is evidence of overt cardiac dysfunction (i.e., ACC/AHA stage B heart failure), imaging and blood-based biomarkers may also help to guide treatment.

↓: Decline; ACC/AHA: American College of Cardiology/American Heart Association; CV: Cardiovascular; LVEF: Left ventricular ejection fraction.

Adapted with permission from [36].

and practice, although LVEF measurements by these modalities are not interchangeable [39]. The validity of assumptions common to the spectrum of cardiotoxicity criteria, specifically whether an LVEF decline is always attributable to treatment-related toxicity and whether the absence of an LVEF decline can be interpreted as absence of cardiotoxicity, is also debatable [40]. Moreover, there are currently no adult oncology guidelines in the USA addressing prospective cardiac monitoring in patients treated with potentially cardiotoxic treatment regimens, although clinical practice guidelines have been released in Europe [37]. For certain cardiotoxic agents, such as trastuzumab, serial LVEF measurements are US FDA mandated in the USA [41] and stopping/holding rules (i.e., LVEF decrease of $\geq 16\%$ or 10–15% below institutional lower limits of normal) that were used in the trastuzumab clinical

trials [42–44] during treatment have translated to clinical monitoring practices. However, institutional and provider-based differences remain in approach to long-term cardiac risk surveillance and detection in patients treated with potentially cardiotoxic treatment regimens [45], inconsistency which limits accurate assessment of the incidence of late cardiotoxicity.

There are additional limitations with the current paradigm that uses resting LVEF for surveillance of changes in cardiac and cardiovascular function during and after potentially cardiotoxic anticancer therapy. First, resting LVEF provides a snapshot of cardiac performance under optimal circumstances and may not demonstrate subclinical loss of cardiac reserve from early myocyte damage [46]. Second, resting LVEF principally assesses load-dependent changes in LV cavity size. Changes

in loading conditions during chemotherapy are common and, as a result, LVEF may not reflect actual myocardial systolic function [47]. In fact, LVEF may overestimate actual LV health when intrinsic mechanisms are initially compensatory to maintain cardiac output in the face of acute myocardial injury [48]. When such compensation ultimately falters, a drop in LVEF is finally observed that may occur too late to avert irreversible cardiomyopathy [49]. Third, cancer therapy-induced damage often extends beyond the heart and may occur in conjunction with (mal) adaptation in other organ components, which are not evaluated by resting LVEF. Many anticancer therapies cause unique and varying degrees of injury to the cardiovascular system (i.e., pulmonary–vascular/blood–skeletal muscle axis) [50]. For example, radiation and certain forms of systemic therapy (e.g., chemotherapy, molecularly targeted therapies) can cause pulmonary dysfunction, anemia, endothelial dysfunction and pulmonary/systemic arterial stiffness as well as skeletal muscle dysfunction [11,12,51–53]. These direct insults occur in conjunction with ‘indirect’ lifestyle perturbations (e.g., physical inactivity) that synergistically cause marked impairments in cardiovascular reserve capacity [54].

As current detection strategies in the oncology setting focus almost exclusively on LVEF at rest, alternative assessments that provide better measures of cardiac (i.e., myocardial) as well as global cardiovascular function are required to identify those cancer patients at high risk of CVD but who do not experience overt HF or a decline in LVEF. The purpose of this review is to summarize other potential strategies for the early detection of cardiotoxicity, a term used herein to describe cancer therapy-related clinical as well as subclinical cardiac and cardiovascular injury.

Resting left ventricular ejection fraction

In current practice, 2D echocardiography (2DE) and MUGA scanning are most frequently used to evaluate resting LVEF. These techniques have advantages, including portability (for 2DE), ease of use and availability. However, there are also well-described limitations, including limited reproducibility and accuracy for assessment of LV volumes and LVEF by 2DE that limits sensitivity for detection of small changes in LV function and radiation exposure for MUGA [35].

3D echocardiography (3DE) preserves many of the advantages of echocardiography while mitigating some of the limitations that exist with 2DE. In adjuvant breast cancer, 3DE was superior to 2DE, and had similar accuracy to MUGA (with cardiac magnetic resonance [CMR] imaging as the gold standard) for LVEF in early breast cancer [55]. Similarly, 3DE may provide more reliable detection of LVEF changes, which is clinically important given the threshold magnitude of LVEF decline (10%) used to adjudicate subclinical cancer therapy-related cardiac dysfunction by existing criteria [36]. In a prospective comparison of 2DE and 3DE in 56 breast cancer patients, Thavendiranathan *et al.* [56] found that the temporal variability of LVEF by 3DE was 5–6% compared with 10–13% by 2DE. In the same study, noncontrast 3DE measurement of LVEF had the best intra and interobserver as well as test-retest variability. Owing to its excellent spatial resolution and the ability to image the entirety of the heart, CMR imaging is the accepted gold standard in cardiac volumetric analysis and LVEF assessment [57–59] and may be particularly useful in cases where data regarding cardiac function and volume with echocardiography and MUGA are conflicting or unclear. Despite their superiority for LVEF assessments, both 3DE and CMR are less available than 2DE (Table 1).

Among noncancer populations, LVEF has been repeatedly shown to be an important and independent predictor of prognosis and is used frequently in clinical decision making [31,60,61]. In a cancer population, the prognosis of developing LV systolic dysfunction is presumably worse compared with the general population, given the continuous nature of the myocardial insult from cytotoxic therapy. In a clinical trial involving 944 early breast cancer patients with LVEF $\geq 50\%$ by MUGA prior to treatment with doxorubicin-cyclophosphamide-paclitaxel-trastuzumab, LVEF independently predicted cardiac events (HF [36 patients], cardiac death [one patient]) over 7 years follow-up when prechemotherapy LVEF was $<55\%$ (i.e., 50–54%) [42]. The predictive utility of LVEF was less apparent among pediatric cancer patients in a retrospective study of 356 children followed over 5 years for possible anthracycline-induced cardiac damage which found that LVEF assessments by 2DE before and during chemotherapy detected only one patient with symptomatic HF and did not

impact treatment decisions [62]. Data addressing the utility of systematic follow-up LVEF assessments in adult cancer survivors with a history of cytotoxic therapy are lacking [63]. Recent evidence, however, suggests that by the time an LVEF decline is detected after anthracyclines, recovery of LV function and attenuation of cardiac events in response to treatment may be limited [33], reinforcing the need for more sensitive measures of early myocardial damage and LV dysfunction.

Myocardial deformation imaging

There are several indices available to assess myocardial deformation, including strain, strain rate and torsion. Current echocardiographic assessments of myocardial deformation are based on tissue Doppler imaging (TDI) or speckle-tracking echocardiography (STE), the 2D tracking of unique speckle patterns created by the constructive and destructive interference of ultrasound beams within tissue, which has technical advantages compared with TDI. These speckles are tracked on a frame-by-frame basis and the accuracy of speckle tracking has been validated against sonomicrometry and tagged CMR imaging [64]. Strain reflects the global deformation of ventricular myocardium during the cardiac cycle, is typically measured at peak systole (i.e., at aortic valve closure) and can be determined in the longitudinal (GLS), radial (GRS) and circumferential (GCS) planes [64]. Beyond measuring linear deformations, peak systolic LV torsion by STE can also measure myocardial rotational deformation due to helical orientation of the myocardial fibers, by calculating the maximum instantaneous difference between peak systolic apical rotation relative to basal rotation [65].

These parameters have emerged as more sensitive measures of subclinical LV dysfunction and may be useful approaches for the early detection of cancer therapy-induced cardiotoxicity and for following patients longitudinally [66]. In clinical studies, reduced TDI strain and strain rate revealed impaired myocardial function prior to LVEF decline [67–69] and HF symptoms [70] in patients treated with anthracycline-containing therapy although the predictive value of these parameters was not evaluated. In separate small studies using STE, Sawaya *et al.* [71,72] found that impaired absolute longitudinal strain (>-19%) at 3 months and Negishi *et al.* [73] found that relative GLS decline ($\geq 11\%$) from baseline to

Table 1. Comparison of modalities of detection for cancer therapy-induced cardiotoxicity[†].

Measure(s)	Echocardiography			Radionuclide angiogram	Cardiac magnetic resonance	Blood biomarkers	
	2D	3D	Strain			Troponin	Natriuretic peptides
	LVEF; volumes	LVEF; volumes	Myocardial deformation	LVEF; volumes	LVEF; volumes; myocardial damage/deformation	Myocardial injury	Myocardial stretch/stress
Availability	++++	+++	+++	+++	+	++++	++++
Cost							Low
Reproducibility	++	+++	+++	++++	++++	++++	++++
Cardiac structure [‡]							
Temporal resolution		++++		+	+++	-	-
Spatial resolution		++		+	+++	-	-
Myocardial function [‡]							
Systolic	+++	+++(+)	++++	++++	++++	-	-
Diastolic	++++	+	++++	-	++	-	-
Tissue characterization	+	-	-	-	++++	-	-
Potential to detect subclinical cardiac toxicity	Low	Low	Moderate-high	Low	Moderate	High	Unknown

Increasing ‘+’ corresponds to increasing efficacy. – corresponds to not available.

[†]Cardiac structure includes visualization and quantification of cardiac chambers (dimension), myocardium (thickness) and valves (mobility, regurgitation, stenosis).

[‡]Myocardial function includes visualization and quantification of systolic function (e.g., LVEF, strain, strain rate, stroke volume etc.) and diastolic function (e.g., diastolic grade/pattern). LVEF: Left ventricular ejection fraction.

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6 months predicted LVEF decline in breast cancer patients treated with trastuzumab with or without anthracyclines. GLS also appears to provide superior prognostic information to LVEF in noncancer populations; a recent meta-analysis showed that GLS independently predicted mortality better than LVEF in 5721 patients with underlying HF, acute myocardial infarction, valvular heart disease and cardiac amyloidosis [61]. Impairments in torsion and torsion velocities in the absence of LVEF changes have been observed 1 month after anthracycline therapy in 25 leukemia/lymphoma patients [74] and after 7 years in 35 anthracycline-treated childhood cancer survivors [75]. Finally, 3D STE is a novel modality that can comprehensively assess LV myocardial mechanics, tracking linear myocardial deformation in multiple dimensions simultaneously as well as torsion and mechanical dyssynchrony, and has demonstrated early promise in this context, with sensitive detection of altered LV mechanics in childhood cancer survivors treated with anthracyclines [76].

Despite their potential, echocardiographic myocardial deformation indices have important considerations currently limiting their widespread use in cardio-oncology. The optimal timing for assessments in relation to chemotherapy completion and cut-off values for positive tests remain undetermined. Strain echocardiography is dependent on high quality images, has variability related to different vendor acquisition and analysis platforms, and uncertainty regarding the optimal parameter of myocardial deformation and inter-institutional reproducibility [35]. However, longitudinal strain has been demonstrated to be more reproducible [77] and the emerging evidence suggests myocardial deformation indices have a potential role for early detection of therapy-related cardiotoxicity that merits further investigation and validation in large cohort studies.

Cardiac MRI

Cardiac MRI has an emerging role in the detection and prognosis of chemotherapy-related cardiotoxicity largely due to its unique ability to directly assess tissue characteristics of the myocardium, such as inflammation/edema, fibrosis and extracellular volume. Hyperemia, as assessed by increased myocardial signal early after contrast administration, on T1-weighted imaging may detect acute myocardial inflammation; among 22 patients receiving anthracyclines,

an increase in T1-weighted myocardial signal early after gadolinium administration of ≥ 5 relative to skeletal muscle from baseline to day 3 of chemotherapy predicted LVEF decline from 67.5 to 51.4% at 28 days [78]. Delayed enhancement imaging has been extensively validated for the detection of myocardial fibrosis, a recognized finding from necropsy studies of anthracycline-induced cardiomyopathy [79]. However, findings using this technique have been mixed; a series of studies from one group reported a strong association of late gadolinium enhancement in the subepicardial lateral wall and cardiotoxicity among anthracycline-trastuzumab-treated HER2+ breast cancer patients [80–82] whereas other studies have found minimal or no late gadolinium enhancement in anthracycline-treated patients [83,84]. T1 mapping is a relatively novel technique with the potential to quantify myocardial extracellular volume which is increased in patients after anthracycline-based chemotherapy, compatible with histopathologic findings [79] and associated with LV dysfunction [85] and reduced peak exercise oxygen consumption (i.e., aerobic capacity) (VO_{2peak}) on functional capacity testing [86] in recent small studies.

Imaging with CMR also provides novel insights on cardiovascular structure and function that are incremental to information provided by other detection modalities. Decreases in LV mass, likely due to anthracycline-induced myocyte loss, correlated with cardiovascular death and decompensated HF over more than 7-year median follow-up among 91 patients with reduced LVEF post-anthracycline therapy [83]. A significant increase in aortic stiffness detected by an increase in pulse wave velocity in patients up to 6 months after receipt of anthracyclines may be associated with vascular injury and a higher risk of future cardiovascular events [52,84]. In summary, CMR may be useful to assess cardiovascular function after chemotherapy and offers a variety of techniques potentially well suited to the study of chemotherapy-induced cardiotoxicity; however, data regarding its diagnostic and prognostic utility in this setting remain limited to small studies and consideration of cost, ease of use and availability issues is warranted.

Nuclear cardiology

New radiopharmaceuticals and technical advances in scintigraphy have contributed to

an evolution in nuclear cardiac imaging for cancer patients starting from MUGA, used to quantitate LVEF, to higher order functional techniques capable of visualizing pathophysiologic and neurophysiologic processes at the cardiac tissue level. Molecular imaging techniques including ^{111}In -antimyosin (marker specific for myocardial cell necrosis) and ^{123}I -metaiodobenzylguanidine (imaging the efferent sympathetic nervous innervation) have demonstrated potential as early predictors of chemotherapy-induced cardiotoxicity in anthracycline-treated patients. In one study, ^{111}In -antimyosin uptake was more intense in patients with low LVEF and correlated with LVEF values [87] while increased uptake at intermediate cumulative doses identified patients at risk for cardiotoxicity before LVEF deterioration [88]. The same group showed that patients with more intense ^{111}In -antimyosin uptake at intermediate doses tended to have more severe cardiac functional impairment at maximal cumulative doses [89]. Another small prospective study found that at low doxorubicin and epirubicin dose levels, ^{111}In -antimyosin uptake occurred in the absence of LV systolic and diastolic dysfunction suggesting that ^{111}In -antimyosin is very sensitive in detecting myocyte damage that precedes LV dysfunction [90]. Declines in ^{123}I -metaiodobenzylguanidine uptake have also demonstrated correlation with higher cumulative anthracycline doses and preceded changes in LVEF [89,91]. Nevertheless, despite promising results, these techniques, which were investigated more than a decade ago, have still not been integrated into standard clinical practice.

Stress-related functional testing

Cancer therapy is associated with reduced cardiovascular reserve attributed to either the direct effects of therapy or the indirect effects of therapy-associated lifestyle changes [11,92]. Application of 'system stress' (via pharmacologic or exercise) is an established method to detect subclinical impairments in myocardial function and determination of contractile reserve is an independent predictor of prognosis beyond LVEF in patients with coronary artery disease, although these methods have received limited attention in cancer therapy-related cardiotoxicity [54]. Using exercise stress echocardiography in 57 asymptomatic early-stage breast cancer survivors with resting

LVEF $\geq 50\%$, we found that change in LV stroke volume and cardiac index (from rest) were significantly reduced by 12 and 24%, respectively, compared with controls, suggesting that patients have impaired LV contractile reserve (LVCR) [93]. McKillop *et al.* [94] examined radionuclide-determined LVEF at rest and during graded exercise testing in 37 patients receiving doxorubicin; exercise LVEF improved the sensitivity for detection of cardiotoxicity from 58 to 100%. Civelli *et al.* [95] measured LVCR (defined as the difference between peak and resting LVEF) with low-dose dobutamine during and after high-dose chemotherapy in women with advanced breast cancer; an asymptomatic decline in LVCR of ≥ 5 units from baseline predicted LVEF decline to $<50\%$. By comparison, multiple exercise and pharmacologic stress studies have been performed in anthracycline-treated adult survivors of pediatric malignancies with mixed results regarding the incremental sensitivity of exercise [96–99] or pharmacologic [100,101] stress echocardiography to detect subclinical therapy-induced cardiotoxicity over resting echocardiography alone.

Cancer therapy-related cardiac damage also occurs in conjunction with (mal) adaptation in other organ components [11,54,84,86]. Thus, tools with the ability to evaluate integrated crosstalk between cardiovascular organ components, like $\text{VO}_{2\text{peak}}$, may provide a more comprehensive measure of therapy-related global cardiovascular effects in the setting of cancer [54]. As a measure of global cardiovascular function and reserve capacity, $\text{VO}_{2\text{peak}}$ is also inversely correlated with cardiovascular and all-cause mortality in a broad range of adult populations, including lung cancer [102–105]. In breast cancer, Jones *et al.* [106] found that despite preserved resting LVEF $\geq 50\%$, 130 patients, on average 3 years following the completion of adjuvant therapy, had $\text{VO}_{2\text{peak}}$ that was 22% below that of sedentary age-matched women without a history of breast cancer. Studies investigating the prognostic value of $\text{VO}_{2\text{peak}}$ to predict acute and late-occurring cardiac dysfunction and other cardiovascular events in cancer patients are warranted.

Blood-based biomarkers

Blood-based cardiac biomarkers, specifically troponins, have emerged as potentially useful noninvasive markers of cardiotoxicity in cancer

Table 2. Troponin for early detection and prediction of cancer therapy-related cardiotoxicity.

Study (year)	Patient population	Treatment	n	Detection	Cut-off	%BM+	LVEF modality	Mean ↓LVEF		Incidence of ↓LVEF >10% or LVEF < 50%		Incidence of HF symptoms		BM predicted (P sig)		Ref.
								BM+	BM-	BM+	BM-	BM+	BM-	↓LVEF	HF	
Sawaya et al. (2011)	Breast	ANT, H	43	hsTnl	0.015 μg/l	28	Echo	-	-	50%	10%	-	-	Yes	-	[71]
Sawaya et al. (2012)	Breast	ANT, H	81	usTnl	30 pg/ml	14	Echo	-	-	42%	27%	8%	5%	Yes	-	[72]
Fallah-Rad et al. (2011)	Breast	FEC, H AC, H	42	cTnl	0.01 ng/ml	0	Echo	-	~4%	-	24%	-	24%	No	No	[81]
Cardinale et al. (2000)	Multiple diagnoses	HDC	204	cTnl	0.4 ng/ml	32	Echo	>10%	~0%	29%	0%	5%	0%	Yes	Yes†	[109]
Cardinale et al. (2004)	Multiple diagnoses	HDC	703	cTnl	0.08 ng/ml	30	Echo	-	-	71%	2%	22%	0.2%	Yes	Yes‡	[110]
Cardinale et al. (2002)	Breast	HDC	211	cTnl	0.5 ng/ml	33	Echo	>15%	~0%	-	-	14%	0%	Yes	-	[111]
Sandri et al. (2003)	Multiple diagnoses	HDC	179	cTnl	0.08 μg/ml	32	Echo	18%	3%	-	-	-	-	Yes	-	[112]
Cardinale et al. (2010)	Breast	H	251	cTnl	0.08 ng/ml	14	Echo	-	72%	7%	19%	0%	Yes	Yes‡	-	[113]
Morris et al. (2011)	Breast	ddAC→THL	95	cTnl	0.04–0.06 ng/ml	67	RNA	-	-	5%	19%	2%	7%	No	No	[114]
<p>All patients (n = 3) developed HF during study were cTnl+.</p> <p>Elevated cTnl predicted composite cardiac events, including heart failure.</p> <p>↓: Decline or impairment; Δ: Change; AC: Doxorubicin and cyclophosphamide; ANT: Anthracyclines; BM: Biomarker; cTnl: Cardiac troponin I; cTnl: Cardiac troponin T; dd: Dose dense; FEC: Fluorouracil, epirubicin, cyclophosphamide; Testuzumab; HDC: High-dose chemotherapy; HF: Heart failure; hsTnl: High-sensitivity troponin I; Lapatinib; LVEF: Left ventricular ejection fraction; RNA: Radionuclide angiography; T: Paclitaxel; usTnl: Ultra-sensitive troponin I.</p>																

based on the findings of numerous small studies. For a comprehensive overview of the utility of blood-based biomarkers for early detection of cardiotoxicity, the reader is referred to prior reviews [107,108]. In brief, a transient rise in cardiac troponin I has been demonstrated to predict the occurrence [109,110] as well as the magnitude of LVEF decline [110–112] in patients with hematologic and solid malignancies receiving high-dose anthracyclines (Table 2). In women receiving anthracycline-trastuzumab-containing therapy, detectable troponin I levels (>0.08 ng/ml) were associated with a 23-fold increased risk of ‘cardiotoxicity’ (LVEF decline >10 to $<50\%$) and an approximately threefold increased risk of LVEF irreversibility following drug discontinuation [113]. Early changes in high- and ultra-sensitive troponin I have shown incremental prognostic power, particularly in combination with STE, to predict HF in early breast cancer patients treated with anthracycline-trastuzumab therapy [71,72]. However, as reported by Sawaya *et al.* [72], the sensitivity and specificity of ultra-sensitive troponin I for predicting anthracycline-trastuzumab cardiotoxicity are not high at 48% (95% CI: 27–69) and 73% (95% CI: 59–84), respectively, and the clinical utility of troponin measurements is not as well established for other chemotherapeutic regimens [114]. The family of natriuretic peptides (e.g., brain natriuretic peptide, N-terminal pro-brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide) appears to be less reliable than troponins in predicting LVEF decline in the oncology setting [107,115].

Overall, the studies of troponins and natriuretic peptides do have notable limitations. The predictive role of these biomarkers has been investigated in small studies with heterogeneous cancer populations receiving a variety of cytotoxic and targeted therapies [107]. Moreover, standardization of timing of assessments, measurement assays and cut-off points remain undetermined, currently limiting translation into clinical practice.

Conclusion

The current state of the art for detection in cardio-oncology with resting LVEF surveillance is insensitive for identification of cardiotoxicity. Many alternative techniques have been proposed including advanced cardiac imaging modalities, functional capacity testing and blood-based

EXECUTIVE SUMMARY

Background

- Mortality rates from cancer have declined over the past 30 years and the number of cancer survivors is projected to increase significantly.
- With increasing survival, patients are increasingly developing cardiovascular risk factors and cardiovascular disease has emerged to rival cancer as the predominant cause of mortality, particularly among older survivors.
- Highly effective conventional and novel anticancer therapeutic agents also have the potential to cause myocardial and cardiovascular injury (i.e., cardiotoxicity) during treatment and may contribute to short- and long-term cardiovascular morbidity and mortality.

Current state of cardio-oncology

- The growing importance of anticancer therapy-related cardiotoxicity and its early detection is recognized by cardiology and oncology societies.
- The cardio-oncology field has emerged to keep pace with the rapid evolution of cancer therapies and their cardiovascular side effects.

Current state of detection of cardiotoxicity

- Surveillance resting left ventricular ejection fraction (LVEF) is the current state of the art for detection of cardiotoxicity.
- LVEF, which may be affected by changes in loading conditions and does not account for therapy-induced cardiovascular damage beyond the heart, has limited sensitivity for early detection of cardiotoxicity.

Resting left ventricular ejection fraction

- 2D echocardiography and multiple-gated acquisition scanning are the predominant modalities currently used for resting evaluation of ejection fraction.
- 3D echocardiography and cardiac MRI are newer modalities with improved accuracy and reproducibility for LVEF and the potential for detecting small changes in contractility, although availability primarily affects widespread application of these modalities in clinical practice

Myocardial deformation imaging

- Myocardial deformation indices (strain, strain rate, torsion) can be measured (most commonly by speckle-tracking echocardiography) and their utility as more sensitive measures of subclinical left ventricular dysfunction has been assessed in small studies.
- Global longitudinal strain has been studied most extensively but the optimal deformation parameter for early detection and prediction of cardiotoxicity remains uncertain.
- Widespread use of deformation imaging in cardio-oncology has also been limited due to lack of standardization of optimal timing of assessments, cut-off values and variability related to multiple vendor acquisition-analysis platforms.

Cardiac MRI

- Cardiac MRI has an emerging role in the detection of cancer therapy-induced cardiotoxicity due to its accuracy for ventricular volumes and ejection fraction and its unique ability to directly assess tissue characteristics of the myocardium.

Nuclear cardiology

- Multiple-gated acquisition scanning is well established for its reproducibility quantitating LVEF but provides limited further assessment of cardiac structure and function.
- Molecular imaging techniques have demonstrated promising results for early prediction of cardiotoxicity in anthracycline-treated patients but remain outside standard clinical practice.

EXECUTIVE SUMMARY (CONT.)

Exercise-related testing

- Cancer therapy has direct and indirect adverse effects on the cardiovascular system and is associated with (mal) adaptation in other organ components within the cardiovascular–pulmonary–hematologic–musculoskeletal system axis.
- Functional capacity testing aimed at determination of left ventricular contractile reserve capacity and/or cardiorespiratory respiratory fitness (VO_{2peak}) have demonstrated impairments in cancer patients despite normal resting ejection fraction and may provide a more comprehensive assessment of the global effects of cancer therapy.

Blood biomarkers

- Blood-based cardiac biomarkers, specifically troponins, have emerged as potentially useful noninvasive markers of cardiotoxicity in cancer in small studies, although standardization of timing of assessments, measurement assays and cut-off points remain undetermined, limiting translation into clinical practice thus far.

Conclusion

- Current standard detection modalities in cardio-oncology (i.e., resting ejection fraction) are insensitive for cardiotoxicity.
- Emerging imaging modalities that assess myocardial deformation, functional capacity testing and blood-based biomarkers have potential to improve early detection.
- However, evidence with these modalities remains based on small, single-center studies and future investigation with large, prospective studies is required to validate their diagnostic and prognostic utility, determine optimal timing of assessments and standardize cut-off points.
- An ultimate goal for cardio-oncology will be improved detection of cardiotoxicity that informs and facilitates how best to balance cancer and cardiovascular treatments and outcomes.

biomarkers but no best approach or combination of approaches has yet to clearly emerge. Research prospectively evaluating the optimal timing and frequency of alternative detection techniques and their prognostic utility is lacking, limiting translation into routine clinical use. Large prospective, multi-institutional studies are needed to determine whether these techniques can be used practically to improve not only detection of cardiotoxicity but also prediction of cardiovascular and overall survival, thereby, informing oncologic and cardiac treatment decisions and facilitating early interventions that may reduce risk of downstream cardiovascular morbidity without compromising the efficacy of anticancer therapy.

Future perspective

Novel imaging and blood-based biomarkers, likely in combination, will become increasingly prevalent in clinical practice for the monitoring and surveillance of cancer patients on treatment and cancer survivors. Research efforts will evolve from the current evidence base dominated by small, single-center studies to more prospective, multi-institutional studies aimed at: delineating the short- and long-term natural history of

positive blood and imaging biomarkers and their relationship with clinical events, determining the optimal strategy (type of test, timing, frequency and cut-off points) for detection of early subclinical cardiac and cardiovascular dysfunction in patients receiving conventional and/or novel anticancer therapies, and performing adequately-powered multicenter randomized control trials comparing the efficacy of different strategies to individualize anticancer drug therapy and prevent the development of cardiovascular disease. Ultimately, with an evolving understanding and effective use of these modalities, there is the potential to mitigate cardiac and cardiovascular morbidity and mortality, and improve overall survival in cancer.

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