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Novel mechanisms, imaging approaches and management strategies for anthracycline-induced cardiotoxicity

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Editorial: Novel mechanisms, imaging approaches, and management strategies for anthracycline-induced cardiotoxicity

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anthracycline, cardiotoxicity, cardiac imaging, exercise oncology, mechanisms and management of anthracycline associated cardiac injury

Editorial on the Research Topic
Novel mechanisms, imaging approaches, and management strategies for anthracycline-induced cardiotoxicity

1. Introduction

Anthracyclines remain one of the essential chemotherapy class drugs due to their effective antineoplastic properties in multiple adult and pediatric cancers. Decades of observed cardiotoxicity—that predominantly manifest as cardiomyopathy and/or heart failure (1)—have made anthracyclines a "flagship" drug responsible for the rise of cardio-oncology. Much progress has been made in understanding the mechanisms and clinical presentations of anthracycline-induced cardiotoxicity (AIC), with their known risk of acute or delayed-onset cardiac injury ranging from cardiac fibrosis (2) to focal or global ventricular dysfunction (3), compounded by the negligible ability of the mammalian heart to regenerate, contrary to other species (4, 5). Yet, despite these efforts, accurately predicting, and effectively providing cardioprotection to patients who are vulnerable to AIC remain elusive. This has led to intense basic, translational, and clinical research over the past decades in an effort to dissect and deepen our understanding of AIC. As topic editors, we are grateful to the contributing authors for their expertise and manuscripts published in *Frontiers in Cardiovascular Medicine* comprised of the latest state-of-the-art reviews and clinical studies on novel mechanisms, imaging approaches, and management strategies of AIC.

2. Pathobiological mechanisms

Al-Otaibi et al. address the genetics of AIC, including genomic variants associated with AIC, stratified according to presumed pathophysiologic mechanisms. The authors analyze overlapping genes implicated in AIC and other types of cardiomyopathies: truncating variants in the titin gene (TTNtv), BCL2 associated athanogene 3 (BAG3), lamin A/C (LMNA), and Myosin Heavy Chain 7 (MYH7). They further develop 11 identified genes specific for AIC, including retinoic acid receptor-g (RARG), solute carrier family 28 member 3 (SLC28A3), and Rac family small GTPase 2 (RAC2). For translational and clinical applicability, the authors present a framework for interpreting genetic reports and potential applications to patient management.

Antoniak et al. explore less appreciated aspects of AIC: thrombosis, cardiac atrophy, and programmed cell death. In particular, the authors detail pro-thrombotic effects of anthracyclines on vascular cells, blood flow perturbation, platelet activation, release of tissue factor-bearing extracellular vesicles, and thrombus formation. They develop anthracycline induction of p53 expression, necessary for inactivation of mammalian target of rapamycin (mTOR), a serine-threonine kinase essential for protein synthesis. Furthermore, anthracyclines also induce expression of muscle RING finger1 (MuRF1), a striated muscle specific ubiquitin ligase and a key mediator of cardiac atrophy. Finally, the authors scrutinize programmed cardiomyocyte death pathways induced by AIC, including apoptosis, necroptosis, ferroptosis, and pyroptosis, illustrating the complex biology of anthracycline-mediated cardiac injury.

3. Imaging approaches

With the continued developments and improvements in advanced multimodality imaging, our series further explores applications of echocardiography, cardiac computed tomography (CT), cardiac magnetic resonance (CMR) imaging, and nuclear and molecular cardiology in AIC. Piveta et al. prospectively scrutinize echocardiographic metrics associated with subsequent cardiotoxicity in $n = 51$ patients with breast cancer treated with a chemotherapy regimen containing anthracyclines. Echocardiograms were evaluated at baseline, after 120 and 240 mg/m^2 cumulative doses of doxorubicin, and 6- and 12-month after treatment completion. Among multiple 2-D and 3-D strategies analyzed by the authors, only changes in 3-D global area strain (GAS) were associated with a subsequent decrease in left ventricular ejection fraction (LVEF). 3-D GAS is a promising metric which assesses myocardial deformation mainly in the subendocardial layer (6) and will require further large-scale prospective evaluation.

Anthracyclines continue to be used for a variety of hematologic malignancies and certain solid tumors in the pediatric population, and delayed cardiotoxicity remains a topic of concern. This is particularly relevant due to an overall increase in childhood cancer survivors reaching adulthood. Niemelä et al. combined two Finnish cohorts of childhood cancer survivors ($n = 90$) that were exposed to anthracyclines and compared to healthy controls ($n = 86$) to evaluate left ventricular longitudinal strain detection of cardiac dysfunction in a cross-sectional manner. The authors indicate that longitudinal strain may be a more sensitive method than LVEF to detect cardiac dysfunction in pediatric patients.

Feher et al. provide a review of novel cardiac CT methods for the assessment of AIC. Cardiac CT has an increasing number of indications in cardiovascular medicine and cardio-oncology (7). Beyond the evaluation of coronary arteries and cardiac function, the authors develop new CT techniques including myocardial deformation, extracellular volume measurement, coronary vasoreactivity, determination of microvascular dysfunction, and even nanoparticle-based molecular imaging, highlighting their potential applicability in AIC.

Mabudian et al. dissect CMR imaging measures of left ventricular volumes and function applied to AIC. The authors also explore quantitation of left ventricular mass, perfusion imaging, and tissue characterization by T1/T2 mapping and late gadolinium enhancement. In particular, they highlight myocardial fibrosis characterization by methods utilizing gadolinium contrast, as well as those that don't (native T1) such as T1 and T2 mapping which measure longitudinal and transverse relaxation times, respectively.

Jong et al. explore nuclear imaging in AIC, from pathobiology to the identification of molecular targets. Indeed, nuclear imaging can map molecular processes perturbed in AIC in a specific manner using radioactively labeled probes. Targeted pathways that have been studied in nuclear medicine include metabolic dysfunction (glucose uptake, oxidative metabolism, fatty acid metabolism, mitochondrial membrane potential measurement, and determination of reactive oxygen species), cell death, sympathetic innervation, myocardial perfusion and blood flow measurement, and detection of cardiac fibrosis. The authors further provide a clinical framework for potential applications of nuclear molecular imaging in predicting and reclassifying cardiotoxicity in cancer patients undergoing anthracycline treatment, in a role complementary to that of echocardiography.

4. Management strategies

Kang et al. explore a less well-known but an emerging topic of interest of AIC management, namely exercise as a potential therapeutic modality. This strategy is complementary to current approaches seeking to mitigate the risk and consequences of

AIC, including decreasing cumulative anthracycline doses, use of pegylated liposomes for chemotherapy delivery, and concomitant treatment with dexrazoxane. The authors review the potential of exercise therapy to stimulate biochemical and physiological responses leading to cardioprotective effects, including decreased cardiomyocyte apoptosis, improved endothelial and microvascular function, and decreased reactive species production. The authors also provide a valuable comparison of exercise guidelines, applicable to exercise cardio-oncology, between various societies.

Finally, Vuong et al. review current and potential novel therapeutics for AIC. The authors categorize their review of treatment strategies into three categories. First, preventive and early-stage therapies which beyond dexrazoxane include neurohormonal therapies such as b-blockers and aerobic exercise. Second, moderate to end-stage therapies which include cardiac resynchronization therapy, mechanical circulatory support systems for advanced ventricular dysfunction, and also orthotopic heart transplantation. Finally, the authors develop areas of ongoing research with potential future applicability, including mechanism-specific pharmacotherapies targeting apoptosis, oxidative stress, and inflammation, and also stem cell and gene therapy.

5. Conclusions

While the road to understanding the mechanistic underpinnings of AIC has been a long one, there continues to be exciting advances made from the bench to the bedside that improve our ability to identify, protect against, and/or treat AIC. This science has exponentially grown in pace and scale because of the rapidly rising multidisciplinary field of cardio-oncology. Our series hopes to highlight the many advances made in recent years to understand one of the oldest known forms of cancer treatment associated cardiotoxicity. As cancer survival continues to improve with overall advances in therapies, attenuating cardiotoxicity is of the utmost importance in order to ensure that patients do not suffer from the double-edged sword of anthracyclines with short- and long-term cardiac consequences that may lead to increased comorbidity and mortality.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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ORIGINAL RESEARCH
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Cardiac Function After Cardiotoxic Treatments for Childhood Cancer—Left Ventricular Longitudinal Strain in Screening

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Background: The majority of childhood cancer survivors (CCSs) have been exposed to cardiotoxic treatments and often present with modifiable cardiovascular risk factors. Our aim was to evaluate the value of left ventricular (LV) longitudinal strain for increasing the sensitivity of cardiac dysfunction detection among CCSs.

Methods: We combined two national cohorts: neuroblastoma and other childhood cancer survivors treated with anthracyclines. The final data consisted of 90 long-term CCSs exposed to anthracyclines and/or high-dose chemotherapy with autologous stem cell rescue and followed up for > 5 years and their controls ($n = 86$). LV longitudinal strain was assessed with speckle tracking (Qlab) and LV ejection fraction (EF) by three-dimensional echocardiography (3DE).

Results: Of the CCSs, 11% (10/90) had abnormal LV longitudinal strain (i.e., <-17.5%); of those, 70% (7/10) had normal 3DE LV EF. Multivariable linear model analysis demonstrated that follow-up time ($p = 0.027$), sex ($p = 0.020$), and BMI ($p = 0.002$) were significantly associated with LV longitudinal strain. Conversely, cardiac risk group, hypertension, age, cumulative anthracycline dose or exposure to chest radiation were not.

Conclusion: LV longitudinal strain is a more sensitive method than LV EF for the detection of cardiac dysfunction among CCSs. Therefore, LV longitudinal strain should be added to the screening panel, especially for those with modifiable cardiovascular risk factors.

Keywords: cardiotoxicity, childhood cancer, longitudinal strain, speckle tracking, cardiovascular risk (CV risk)

INTRODUCTION

The number of childhood cancer survivors (CCSs) reaching adulthood is increasing rapidly (1). In contrast, the doses of anthracyclines and chest irradiation have decreased in modern treatment protocols due their dose-dependent cardiotoxicity (2, 3). Some novel drugs, mainly used in adult oncology, also have cardiovascular side effects (4). Although cardiovascular damage coincides with exposure to the toxic treatment, clinical heart failure may not manifest until decades later. Modifiable cardiovascular risk factors, e.g., obesity, hypertension and dyslipidemia (5), are also common among CCSs and potentiate therapy-related adverse events (6, 7). As a result, a frequency of clinical heart failure ranging between 0 and 16% among CCSs has been reported post-treatment (8), and subclinical toxicity is even more prevalent (9). Thus, meticulous, long-term follow-up is of key importance for identifying patients at risk and for offering adequate treatment (3, 10). Consequently, a consensus recommendation on cardiomyopathy surveillance of CCSs has recently been put forth (1). However, the most commonly used echocardiographic methods, including ejection fraction (EF) and fractional shortening for the evaluation of systolic function, have some limitations with regard to sensitivity and accuracy (9, 11).

Speckle tracking-based LV longitudinal strain is a sensitive method for detecting decreased systolic function, even when the LV EF is still within normal limits (12). The subendocardial longitudinal fibers are prone to subtle injury because of their location; however, the LV EF comprises of radial, circumferential and longitudinal functions and thus deteriorates later than does longitudinal strain (13, 14). Left atrial (LA) strain is a promising tool for the detection of LV diastolic dysfunction (15). Guidelines recommend the use of global longitudinal LV strain together with LV EF for screening among adults during and after cancer treatment (4, 16). However, the inclusion of global longitudinal LV strain measurements has not yet been applied to children or adolescent protocols. Indeed, the best echocardiographic methods for the detection of asymptomatic cardiotoxicity remain to be determined.

The purpose of this study was to evaluate the additive value of strain imaging with regard to the sensitivity of cardiac dysfunction detection after childhood cancer.

MATERIALS AND METHODS

Participants

For this study, we combined data from two previously published cohorts of CCSs, firstly childhood cancer patients treated with anthracyclines, and secondly, a national cohort of neuroblastoma patients (**Figure 1**) (17, 18). The study group consisted of 95 long-term CCSs treated between 1980 and 2006 at the five university hospitals in Finland. The study patients were exposed to cardiotoxic treatments, e.g., anthracyclines and/or high-dose therapy with autologous stem cell rescue, and followed up for >5 years. None of the patients were given dexrazoxane during the survey. Six patients (6%) had heart failure treatment at the time of evaluation: 4 were treated with enalapril and two with enalapril combined with a beta-blocker. Stratification for long-term cardiac risk (i.e., cardiac risk groups) was performed according to the International Late Effects of Childhood Cancer Guideline Harmonization Group based on cumulative anthracycline and chest radiation doses (1). Healthy, age- and sex-matched controls were included for both study groups. The details of the clinical characteristics are shown in **Table 1**.

The Research Ethics Committees of Helsinki and Tampere University Hospitals approved the study carried out in accordance with the Declaration of Helsinki. All the study subjects and their legal guardian(s) provided a written, informed consent.

Blood Pressure

Right arm blood pressure was measured at rest according to guidelines. Stage one hypertension was defined as blood pressure ≥95th percentile or ≥130/80 mmHg (whichever was lower) for children under 13 years and ≥130/80 mmHg for those ≥13 years (19).

Echocardiography

Echocardiographic examinations were performed by iE33 ultrasound (Philips, Andover, MA, USA) (17, 18) according to the American Society of Echocardiography (20, 21). The acquisition of the echocardiographic images was performed as described previously (17, 18).

Age-dependent reference values of the LV transmitral to septal mitral annular early diastolic velocity ratio (E/E') and peak septal myocardial systolic velocity (S') were used for subjects up to 18 years of age (22). LV E/E' >10.0 and S' <6.1 were considered abnormal for those over 19 years of age (23).

Three-Dimensional Echocardiography

Analyses of three-dimensional echocardiographs were performed using commercial software (Qlab v9, Philips Medical Systems, Andover, MA, USA), as previously described (24). Briefly, the three-dimensional echocardiography (3DE) LV EF was calculated, and end-diastolic, end-systolic and stroke volumes were indexed to the body surface area (BSA). The LV end-systolic mass (LVMS) was normalized to height (meters) to a power of 2.7 (LVMSi), and the result expressed as $g/m^{2.7}$.

Qlab Peak Systolic Strain Analysis

LV longitudinal peak systolic strain from the four-chamber view was analyzed with Qlab (Philips Qlab, version 10.5, CMQ; Philips Healthcare, Bothell, WA, USA) and designated LV longitudinal strain. In the analysis, the points were placed at the edge of the mitral valve annulus on the septal and lateral sides and apex at end-diastole. The frame chosen by the program also automatically performed the rest of the tracing, which was manually checked and corrected if needed; the case was excluded if correction was not feasible. All systolic strain measurements were analyzed by one investigator blinded to all clinical and

Abbreviations: BSA, body surface area; CCS, childhood cancer survivors; E/E', transmitral to septal mitral annular early diastolic velocity ratio; EF, ejection fraction; LA, left atrial/atrium; LV, left ventricular; LVMSi, indexed left ventricular mass at end-systole; S', peak myocardial systolic velocity; VVI, velocity vector imaging; 3DE, three-dimensional echocardiography.

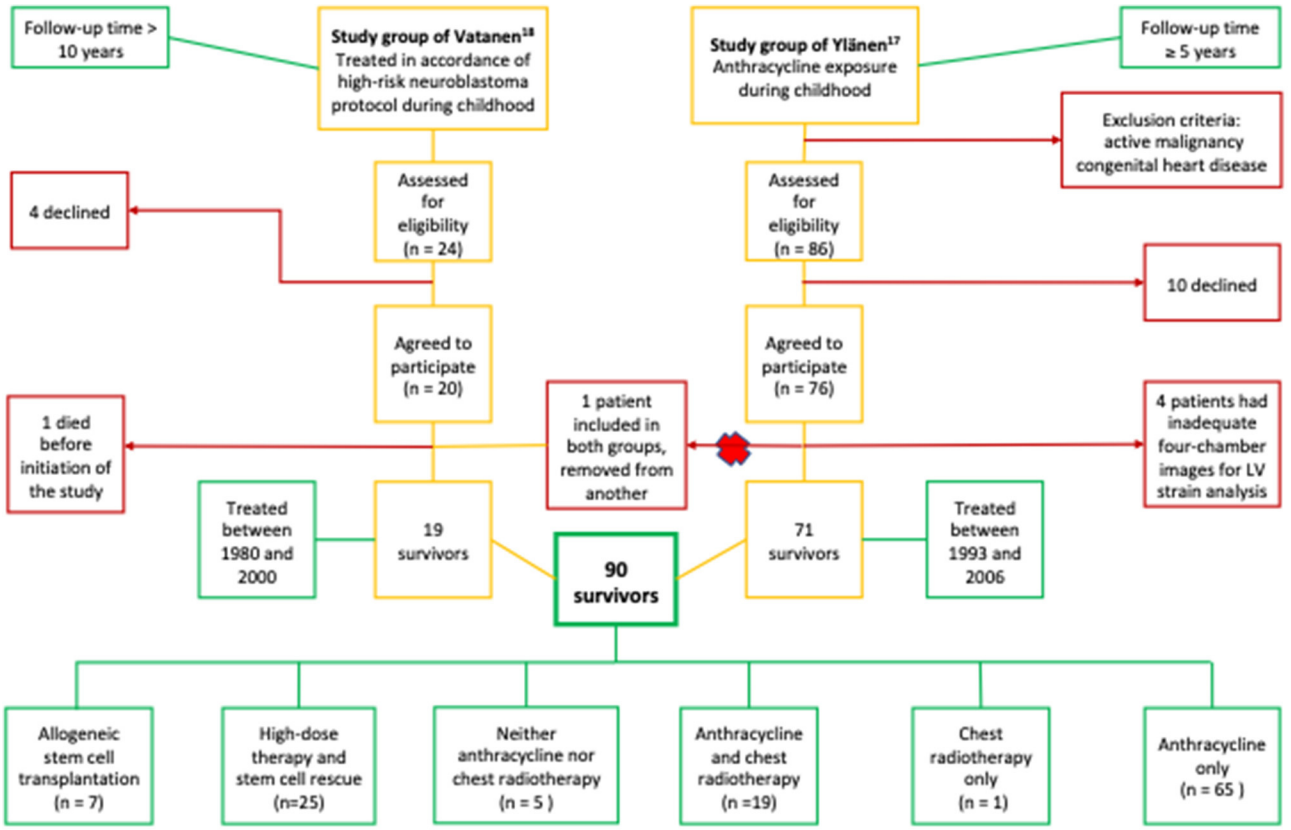

FIGURE 1 | Study recruitment and combination flow chart. The number of study patients and their cancer therapy. The majority of the patients, 94% (85/90), were treated with anthracyclines and/or chest radiotherapy. The rest (5/90, 6%) were not exposed but had received high-dose therapy and stem cell rescue. Altogether, 28% (25/90) of the patients had received high-dose therapy and stem cell rescue, and 80% (20/25) of them were also exposed to anthracyclines and/or chest radiotherapy.

outcome data. Intraobserver analysis, performed using the Bland-Altman analysis ($n = 10$), showed mean of difference of 0.12 with limits of agreement between −1.08 and 1.32.

Analysis of Diastolic Function and Atrial Parameters

Velocity vector imaging (VVI) of the left atrium (LA) was used to analyze LA indices and diastolic cardiac function. VVI analysis from the four-chamber view was performed with the VVI analysis program (Syngo USWP 3.0, Siemens Healthineers, Erlangen, Germany) as described (25). In short, manual tracing of the LA was performed using a single still frame in end-systole. Endocardial tracing began at the edge of the mitral valve annulus, extended to the base of the atrium and returned to the other edge of the annulus. The VVI algorithm calculated the velocity vectors for each frame of the cardiac cycle, displaying them for the complete loop. If the endocardial border was not traceable throughout the whole cardiac cycle, it was corrected manually. The parameters calculated were the LA area, LA fractional area change and VVI peak longitudinal strain for LA. The LA area was normalized to BSA, and the result expressed as cm^2/m^2.

Statistical Methods

IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA) was used in this study. Categorical data are presented as frequencies and percentages, normally distributed continuous variables as the mean ± SD, and as median and interquartile ranges (IQR) in cases of non-normality. Categorical variables were compared with the chi-square or Fisher's exact-test. Means between two groups were compared using the independent samples *t*-test and medians with independent-samples using the Mann-Whitney *U*-test. Means were compared using one-way analysis of variance (ANOVA), and further pairwise comparisons between groups were performed with the Bonferroni method. When the homogeneity of variance was not met, Welch's ANOVA with Tamhane's-test was used for pairwise comparisons. Univariate associations of continuous variables associated with strain were analyzed with linear regression. A multivariable linear model was used to examine associations of multiple variables with strain. The cut-off value for the follow-up time to detect pathological strain was determined by a receiver operating characteristic (ROC) curve. The optimal cut-off value for follow-up time was chosen by using the Youden Index. A p-value < 0.05 was considered significant.

TABLE 1 | Baseline characteristics of the study subjects.

Variable	Survivors	Healthy controls	*P*
N	90	86	
Age, years	16.0 ± 5.0	15.9 ± 4.9	0.898
Sex, *n* (%)			0.763
Female	49 (54)	49 (57)	
Male	41 (46)	37 (43)	
Height, (cm)	159 ± 15	164 ± 16	0.042*
Weight, (kg)	54 ± 17	57 ± 17	0.329
Body surface area (m^2)	1.54 ± 0.31	1.60 ± 0.31	0.163
Body mass index[a] (kg/m^2)	22.5 ± 4.1	22.3 ± 3.2	0.735
Systolic blood pressure, mmHg (all age groups)	119 ± 14	111 ± 11	<0.001*
Diastolic blood pressure, mmHg (all age groups)	66 ± 9	63 ± 7	0.030*
Malignancy diagnosis, *n* (%)			
ALL	31 (34)		
Neuroblastoma	26 (29)		
AML	9 (10)		
Hodgkin disease	8 (9)		
Non-Hodgkin lymphoma	7 (8)		
Rhabdomyosarcoma	2 (2)		
Ewing	1 (1)		
Osteosarcoma	1 (1)		
Retinoblastoma	1 (1)		
Wilms' tumor	1 (1)		
Other	3 (3)		
Follow-up time post-treatment, years	8.1 (6.0–13.3)		
Anthracycline exposure, *n* (%)	84 (93)		
Cumulative anthracycline dose[b] mg/m^2	185 (120–292)		
Chest radiotherapy, *n* (%)	20 (22)		
TBI only	15		
Local radiotherapy	3		
TBI + local radiotherapy	2		
Cumulative chest radiotherapy doses (among 20 survivors exposed to chest radiotherapy), Gy	11 (10.0–18.3)		
Allogeneic SCT, *n* (%)	7 (8)		
Autologous SCT, *n* (%)	25 (28)		

*Statistically significant.
[a]Body mass index (BMI) in adults, BMI according to age in children.
[b]Doxorubicin isotoxic equivalents.
SCT, stem cell transplantation; TBI, total body irradiation.

RESULTS

A total of 90 CCSs and 86 controls were included (**Figure 1**). Four survivors (4%) and 9 controls (9%) were excluded due to non-analyzable four-chamber views. The demographics of the subjects are listed in **Table 1**. The mean age of the CCSs at the time of the study was 16.0 ± 5.0 (range 7.2–30.1) years, and the median follow-up time post-treatment 8.1 (6.0–13.3) years. Of the survivors, 93% (84/90) were treated with anthracyclines, 28% (25/90) with high-dose therapy with autologous stem cell rescue, 8% (7/90) with allogeneic stem cell transplantation, and 22% (20/90) with radiation involving the heart [15 total body irradiation (TBI) only, 3 local radiotherapy and 2 both] (**Figure 1**). The normal strain value used for the Qlab was >-17.5% corresponding with the lower normal limits (mean –1.96 SD) of our controls. The survivors had higher systolic and diastolic blood pressure than the controls, but BSA and body mass index (BMI) for children according to age (26) did not differ between the two groups (**Table 1**).

LV Study Group Demographics

The baseline characteristics are presented in **Table 2**. Two groups were formed for the analyses: group S1 consisted of survivors with abnormal Qlab LV longitudinal strain (≤-17.5%) ($n = 10$), and S2 of those with normal Qlab LV longitudinal strain (>-17.5%) ($n = 80$). Group C3 included all the controls ($n = 86$). The age and cardiac risk group did not differ between the groups. Group S1 contained more females (90 vs. 50%, $p = 0.019$) and had a longer follow-up (median 14.4 vs. 8.0 years, $p = 0.007$) than group S2. More survivors in S1 underwent chest radiotherapy (60 vs. 18%, $p = 0.007$). Hypertension was more common among the survivors (S1: 30%; S2: 29%) than the controls (C3: 7%, $p = 0.05$ and <0.001, respectively). Blood pressure among those of adult age was evaluated as a continuous parameter between the groups: adult survivors in S2 (n =17) had a higher systolic (128 ± 13 vs. 117 ± 10, $p = 0.010$) but not diastolic blood pressure (73 ± 9 vs. 67 ± 6, $p = 0.088$) than adult controls ($n = 23$). For the adult survivors in S1, the systolic (125 ± 15) and diastolic (75 ± 10) blood pressure was slightly higher than for controls, but the differences were not statistically significant ($p = 0.444$ and 0.132).

Cardiac Analysis

Echocardiographic characteristics are shown in **Table 2**. Of the CCSs, 11% (10/90) had abnormal Qlab LV longitudinal strain. Seven of the 10 S1 survivors had normal LV EF (>55%) despite decreased LV longitudinal systolic function. Nine percent of all the CCS with normal LV EF had abnormal Qlab LV longitudinal strain. Moreover, LV EF was lower in S1 and S2 than in the controls (57.7 ± 6.9, 60.5 ± 4.7 vs. 63.0 ± 4.9%, $p = 0.005$ and 0.004, respectively). Although LV end-diastolic and -systolic volume indexes did not differ between the groups, the LV stroke volume index was lower in S2 than in controls (33.2 ± 5.5 vs. 35.6 ± 7.3 ml/m^2, $p = 0.049$). The LVMSi was also higher in S1 (38.0 ± 8.3 vs. 30.9 ± 7.0 $g/m^{2.7}$, $p = 0.012$).

There was more diastolic dysfunction (an abnormally high LV E/E') in S1 (60%) than in S2 (20%, $p = 0.012$) and controls (5%, $p < 0.001$). The LA area index did not differ between the groups. The LA fractional area change was lower in S1 than in S2 (48.6 ± 7.7 vs. 55.9 ± 9.2%, $p = 0.041$). Despite a trend for lower LA longitudinal strain in S1 than in S2 and C3 (34.5 ± 12.5 vs. 45.5 ± 14.4 and 44.4 ± 13.7%), the difference was not statistically significant ($p = 0.066$).

TABLE 2 | Baseline characteristics and echocardiographic parameters of the study subjects according to group.

Variable	S1: Survivors with abnormal Qlab LV longitudinal strain (≤-17.5%)	S2: Survivors with normal Qlab LV longitudinal strain (>-17.5%)	C3: Healthy controls	*P*
Baseline characteristics				
N	10	80	86	
Age, years	18.1 ± 5.5	15.7 ± 4.9	15.9 ± 4.9	0.343
Sex, *n* (%)				S1-S2: 0.019*
Female	9 (90)	40 (50)	49 (57)	
Male	1 (10)	40 (50)	37 (43)	
Follow-up time, years	14.4 (10.0–20.1)	8.0 (6.0–12.1)		0.007*
Cardiac risk group[a], *n* (%)				0.654
No	0 (0)	5 (6)		
Low	1 (10)	3 (4)		
Moderate	5 (50)	42 (53)		
High	4 (40)	30 (38)		
Cumulative anthracycline dose[b], mg/m^2	120 (118–210)	209 (123–295)		0.101
Chest radiotherapy, *n* (%)	6 (60)	14 (18)		0.007*
TBI only	4	11		
Local	0	3		
TBI + local	2	0		
Cumulative chest radiotherapy doses (among survivors exposed), Gy	12 (10–24.4)	10 (10–14.1)		0.328
Body surface area (m^2)	1.51 ± 0.14	1.54 ± 0.32	1.60 ± 0.31	0.214
Body mass index[c] (kg/m^2)	23.5 ± 3.6	22.4 ± 4.1	22.3 ± 3.2	0.627
Stage 1 hypertension, *n* (%)	3 (30)	23 (29)	6 (7)	S1-C3: 0.050* S2-C3: <0.001*
LV systolic function				
3DE LV EF, %	57.7 ± 6.9	60.5 ± 4.7	63.0 ± 4.9	<0.001* S1-C3: 0.005* S2-C3: 0.004*
3DE LV EDV index, ml/m^2	49.7 ± 13.4	55.0 ± 8.7	56.6 ± 11.0	0.112
3DE LV ESV index, ml/m^2	21.0 ± 6.0	21.7 ± 4.6	21.0 ± 5.0	0.577
3DE LV SV index, ml/m^2	28.8 ± 8.6	33.2 ± 5.5	35.6 ± 7.3	0.019* S2-C3: 0.049*
3DE LV systolic mass index, g/m$^{2.7}$	38.0 ± 8.3	32.3 ± 7.4	30.9 ± 7.0	0.013* S1-C3: 0.012*
Qlab LV longitudinal strain, %	16.5 ± 0.7	21.3 ± 2.4	22.4 ± 2.3	<0.001* S1-C3: <0.001* S2-C3: 0.008* S1-S2: <0.001*
TDI S′, cm/s	7.1 ± 0.9	7.4 ± 1.1	8.2 ± 1.3	<0.001* S1-C3: 0.019* S2-C3: <0.001*
TDI S′ < −2 SD, *n* (%)	1 (10)	7 (9)	0 (0)	S2-C3: 0.005*
LV diastolic function				
LV E/E'	10.5 ± 3.2	8.1 ± 2.3	7.2 ± 1.4	0.001* S1-C3: 0.029* S2-C3: 0.008*
LV E/E′ > +2 SD, *n* (%)	6 (60)	16 (20)	4 (5)	S1-C3: <0.001* S2-C3: 0.003* S1-S2: 0.012*
Left atrium				
LA area index, cm^2/m^2	9.7 ± 1.5	9.9 ± 1.9	10.4 ± 1.9	0.098

(Continued)

TABLE 2 | Continued

Variable	S1: Survivors with abnormal Qlab LV longitudinal strain (≤-17.5%)	S2: Survivors with normal Qlab LV longitudinal strain (>-17.5%)	C3: Healthy controls	*P*
LA FAC, %	48.6 ± 7.7	55.9 ± 9.2	55.5 ± 8.4	0.046* S1-S2: 0.041*
LA longitudinal strain, %	34.5 ± 12.5	45.5 ± 14.4	44.4 ± 13.7	0.066

**Statistically significant.*

[a]Cardiac risk group according to International Late Effects of Childhood Cancer guideline Harmonization Group. High risk: anthracycline dose ≥250 mg/m^2, chest radiation dose ≥35 Gy or combined anthracycline dose ≥100 mg/m^2 together with chest radiation dose ≥15 Gy. Moderate risk: anthracycline doses 100 to <250 mg/m^2 or chest radiation dose ≥15 to <35 Gy. Low risk anthracycline doses below 100 mg/m^2.

[b]Doxorubicin isotoxic equivalents.

[c]Body mass index (BMI) in adults, BMI according to age in children.

E/E' = transmitral to septal mitral annular early diastolic velocity ratio; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; FAC, fractional area change; LA, left atrium; LV, left ventricle; S', peak myocardial sustained systolic velocity; SV, stroke volume; TDI, tissue Doppler imaging; 3DE, three-dimensional echocardiography.

TABLE 3 | Variables associated with strain in the patient group; univariate and multivariable analyses.

		Univariate analysis[b]		Multivariable analysis[c]	
Variable	***N***	**Mean ± SD or β (SE)**	***P***	**Adjusted mean (SE) or β (SE)**	***P***
Age (years)	90	−0.086 (0.058)	0.143	0.043 (0.094)	0.646
Sex (m/f)			0.031*		0.020*
Male	41	21.46 ± 2.59		21.89 (0.75)	
Female	49	20.21 ± 2.78		20.56 (0.72)	
BMI, kg/m^2	90	−0.151 (0.071)	0.036*	−0.215 (0.068)	0.002*
Follow-up time (years)	90	−0.106 (0.048)	0.029*	−0.199 (0.088)	0.027*
Cardiac risk group			0.491		0.222
No risk	5	21.68 ± 2.48		23.83 (1.83)	
Low	4	19.70 ± 3.39		20.48 (1.41)	
Intermediate	47	21.08 ± 2.94		20.94 (0.51)	
High	34	20.37 ± 2.46		19.64 (0.64)	
Cumulative anthracycline dose,[a] mg/m^2	90	−0.001 (0.003)	0.727	0.002 (0.005)	0.619
Chest radiotherapy			0.004*		0.370
No	70	21.22 ± 2.50		21.57 (0.59)	
Yes	20	19.26 ± 3.11		20.87 (0.93)	
Hypertension			0.291		0.527
Normal	63	20.96 ± 2.91		21.43 (0.70)	
High	26	20.27 ± 2.33		21.03 (0.78)	

** Indicates statistically significant.*

β indicates regression coefficient for one-unit increase in continuous variables.

[a]Doxorubicin isotoxic equivalents.

[b]The means between two groups were compared with the independent samples t-test and between cardiac risk groups with the one-way ANOVA. Linear regression was used to evaluate the association of continuous variable with strain.

[c]Multivariable linear model.

Variables Associated With LV Longitudinal Strain

Variables associated with LV longitudinal strain were also evaluated (**Table 3**). According to the univariate analysis, a long follow-up time ($p = 0.029$), female sex ($p = 0.031$), high BMI ($p = 0.036$) and chest radiotherapy ($p = 0.004$) were significantly associated with low strain. Furthermore, follow-up time ($p = 0.027$), female sex ($p = 0.020$) and BMI ($p = 0.002$) remained significant variables in the multivariable linear model, whereas cardiac risk group, high blood pressure, age, cumulative anthracycline dose or exposure to chest radiation did not (**Table 3**).

There was a significant difference in the median follow-up time (14.4 years among the CCS with an abnormal strain vs. 8.0 years for those with a normal strain, $p = 0.007$). Females (9 of 49, 18.4%) had more abnormal strain (i.e., ≤-17.5%) than males (1 of 41, 2.4%, $p = 0.019$). Patients exposed to chest radiotherapy (6 of 20, 30.0%) also had more abnormal strain than those not exposed (4 of 70, 5.7%, $p = 0.007$).

The area under the curve (AUC) for the follow-up time to detect pathological strain (i.e., ≤-17.5%) was 0.76 (95% CI 0.63–0.89). The critical cut-off value for the follow-up time to increase the risk of abnormal strain was ≥ 9.24 years (sensitivity 0.90 and specificity 0.60).

DISCUSSION

Our study demonstrates that among CCSs with abnormal LV longitudinal strain, 70% had normal LV EF, suggesting that decreased LV longitudinal strain may emerge as a more sensitive marker of cardiotoxicity than LV EF following treatment for childhood cancer.

Our results are in line with recent data on adults showing abnormal LV longitudinal strain in 28% of CCSs despite normal LV EF (27). For adults, speckle tracking–based strain imaging has been well-validated for the measurement of LV deformation and recommended for echocardiographic, functional follow-up (1, 4, 16). However, the role of myocardial strain imaging among children is less well-established. In agreement with our results, several studies have found that the global systolic function and LV longitudinal strain are reduced among CCSs (2, 28–31), though these factors have yet to be proven to be more sensitive than LV EF in the early follow-up.

In this study, we report a decrease in strain in a subgroup of patients with preserved EF. This finding could not be explained by the patient age as a confounding variable, as it did not show a significant correlation with reduced longitudinal strain, either in univariate or multivariable analysis. In addition, although some level of decrease in the strain values has recently been shown to occur due to aging, in a recent study (32), any significant decrease in LV global longitudinal strain did not occur until the 8th decade of life and thus did not potentially affect the patients of our young study groups. This underlines the fact that the observed reduction in LV longitudinal strain among the CCSs is not based on increased age alone but instead on accumulated follow-up time after the original cancer treatment. Similarly, and importantly, male sex is known to be associated with lower longitudinal, circumferential, and radial strain (33), whereas in our study, the S1 patients with reduced strain with preserved EF were predominantly females. This further reduces the possibility of sex explaining the observed phenomenon of strain reduction in this population. Instead, females appear to be at higher risk of deleterious cardiotoxic effects of cytotoxic drugs.

Anthracycline toxicity and secondary cardiovascular risk factors mainly affect the subendocardial fibers (13, 14, 32), contributing negatively to longitudinal shortening prior to the reduction in LV EF. For example, patients with heart failure and preserved EF compensate for the reduction in longitudinal shortening by increasing twist to maintain normal EF (34). Thus, strain imaging has been proposed as a more sensitive technique to detect myocardial damage than LV EF. Early detection of cardiac failure development may be valuable for treatment with early interventions being considered more efficient than measures taken after abnormal EF is detected or clinical symptoms of dysfunction manifest (3, 16, 31, 35).

The value of LV longitudinal strain in detecting early myocardial dysfunction in cohort studies depends on how many events are assumed to occur simultaneously in the general population. The proportion of abnormal LV functional findings appears to depend on the length of follow-up (2, 6, 27, 31). In our cohort (median follow-up time 8.1; IQR 6.0–13.3 years), the proportion of survivors with preserved LV EF but with abnormal strain was 9%, lower than that reported by two adult studies [28% among those with normal LV EF after a mean follow-up time of 21.6 ± 7.9 years (27) or a median time from diagnosis of 23 years (range 10–48 years) (2)].

However, our results are comparable, albeit clearer, than those reported by others. For example, Slieker et al. (31) recently found reduced longitudinal strain in 7.7% of their 546 CCSs [median time since last anthracycline treatment, 7.9 (IQR, 5.6–10.6) years]. Similarly, three other studies reported significant decreases in the longitudinal function but did not report the prevalence of abnormal strain (median follow-up time, 5.2–13.2 years) (30, 34, 36).

The risk of cardiac dysfunction has been shown to increase with time (3), in line with our results. Similarly, the recent differing report (31) on the role of LV longitudinal strain in the follow-up of CCSs seems to be impacted by a shorter follow-up time than in our study demonstrating cardiac dysfunction more likely to be detectable by pathological strain when the follow-up time exceeds 9 years (sensitivity 0.90, specificity 0.60). Our results thus indicate that the longitudinal strain putatively offers a potent tool for risk assessment among the CCSs, especially early on and beyond the first decade of follow-up.

Our data are in line with those of Christiansen et al. (27) showing exposure to chest radiotherapy to be more common among the CCSs with abnormal LV longitudinal strain than others. However, in our study, the anthracycline dose did not correlate with the reduced longitudinal strain, again in line with the data of Slieker et al. (31), most likely indicating the absence of a safe dose of anthracyclines among the CCSs.

Both of our CCS groups (S1 with abnormal strain and S2 with normal strain) had a lower LV EF than controls (C3). A similar trend was also observed for the TDI S', an additional sensitive marker of systolic function. The most common and best-established form of anthracycline cardiomyopathy indeed resembles dilated cardiomyopathy, with a thin-walled, large LV and low EF (3).

Our data further show and support those of others that the CCSs are at increased risk of modifiable cardiovascular risk factors such as hypertension and obesity (7). Hypertension induces LV hypertrophy and thus increases LV EF but possibly decreases stroke volume. Consequently, as an early marker of systolic dysfunction, the CCSs may have decreased LV longitudinal function with preserved EF. In our study, those with abnormal LV longitudinal strain (S1) had a higher LV systolic mass index and more hypertension than controls, illustrating this phenomenon. A large study on adult CCSs has shown that survivors with metabolic syndrome are twice as likely to have abnormal global longitudinal strain. Each individual component of the metabolic syndrome increases the risk, but without a higher risk for abnormal LV EF (2). Therefore, cancer

treatment-related cardiomyopathy should no longer be solely defined as dilated but rather as mixed and further associated with an increased burden of treatment-related, modifiable risk factors, including hypertension-related LV hypertrophy with abnormal longitudinal strain, as early markers of LV dysfunction with preserved EF. Indeed, cardiomyopathy risk groups based on the anthracycline and chest radiation doses consist of high-risk survivors at an early stage of follow-up (1), but with further follow-up, the risks become less well-delineated due to the impact of modifiable cardiovascular risk factors. The inclusion of LV longitudinal strain in the screening armamentarium might thus improve detection for survivors in the low and moderate cardiomyopathy risk groups but with increased risk of LV dysfunction.

Diastolic LV dysfunction often precedes the systolic. In our study, LV E/E′ as a marker of diastolic dysfunction was higher among survivors than controls and peaked in group S1. However, there was no difference in the LA area index between the groups, most likely reflecting the fact that atrial restriction prevents enlargement despite diastolic dysfunction. In addition, we observed a trend toward lower LA longitudinal strain in our group S1 compared with the others, even though the difference was not statistically significant. A lower LA fractional area change in S1 compared with S2 demonstrated the same. These results are in line with the study of Morris et al. (15), showing LA strain to be more sensitive than the volume index for detecting LV diastolic dysfunction among adult patients at risk. Nevertheless, LA strain is mostly a research tool, with analysis of the thin atrial wall sometimes being technically challenging.

An earlier study comparing the different systems showed small but statistically significant intervendor variation in the assessment of LV longitudinal strain (37). Thus, ideally, an ultrasound device from the same vendor should be used during the follow-up whenever possible. We studied LV longitudinal strain using the more readily employable Qlab system. Importantly, the lower normal limit for Qlab LV longitudinal strain for our controls was in line with the −2 SD value (i.e., −17.5%) derived from recently published pediatric reference values (38).

Limitations

The most important limitation of this study was its cross-sectional nature, rendering future prospective studies important to confirm an increase in the risk of pathological longitudinal strain during and after the first decade of follow-up. Because we used previously acquired echocardiographs from our earlier studies, LV longitudinal strain from the four-chamber views was employed, as opposed to global longitudinal strain. Nonetheless, optimal four-chamber views are easy to obtain, and in addition, four-chamber longitudinal strain has good intra- and interobserver correlation (38) and thus is usually sufficient for daily use in practice. Our division of patients into subgroups may also be considered somewhat arbitrary. Yet, the limits chosen (i.e., EF > 55% and strain > −17.5%) to define clinical normal values were adapted from those, already-published and generally accepted publications, and remained well in line with our own defined −1,96 SD lower limit of values from the age- and sex-matched control population (20, 33, 38). Important to note, none of the patients were given the cardioprotectant dexrazoxane during the survey, eliminating its possible effect on the measured strain rate among the CCS.

CONCLUSIONS

Healthcare providers should pay special attention to the modifiable cardiovascular risk factors among the CCSs, as they play a pivotal role in developing heart failure long-term.

To date, the CCSs at risk for developing cardiac problems may not be identified early enough when using LV EF alone. Indeed, our results indicate that longitudinal strain putatively offers a potent tool for the long-term risk assessment among CCSs beyond the first decade of follow-up. Especially for those with modifiable cardiovascular risk factors and LV hypertrophy with normal EF, LV longitudinal strain would beneficially contribute to the final decision-making already in the pediatric population and among young adults.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Helsinki University Hospital, Helsinki, Finland; Tampere University Hospital, Tampere, Finland. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JN, KY, and TO designed the study, collected and analyzed the data, and wrote the manuscript. KV and TP participated in designing the study, analyzing the data, and writing the manuscript. AS, KP, SM, TS, KJ, and AE participated in analyzing the data and writing the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Exercise Cardio-Oncology: Exercise as a Potential Therapeutic Modality in the Management of Anthracycline-Induced Cardiotoxicity

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Anthracyclines are one of the most effective chemotherapy agents and have revolutionized cancer therapy. However, anthracyclines can induce cardiac injuries through 'multiple-hits', a series of cardiovascular insults coupled with lifestyle risk factors, which increase the risk of developing short- and long-term cardiac dysfunction and cardiovascular disease that potentially lead to premature mortality following cancer remission. Therefore, the management of anthracycline-induced cardiotoxicity is a serious unmet clinical need. Exercise therapy, as a non-pharmacological intervention, stimulates numerous biochemical and physiologic adaptations, including cardioprotective effects, through the cardiovascular system and cardiac muscles, where exercise has been proposed to be an effective clinical approach that can protect or reverse the cardiotoxicity from anthracyclines. Many preclinical and clinical trials demonstrate the potential impacts of exercise on cardiotoxicity; however, the underlying mechanisms as well as how to implement exercise in clinical settings to improve or protect against long-term cardiovascular disease outcomes are not clearly defined. In this review, we summarize the current evidence in the field of "exercise cardio-oncology" and emphasize the utilization of exercise to prevent and manage anthracycline-induced cardiotoxicities across high-risk and vulnerable populations diagnosed with cancer.

Keywords: cardio-oncology, exercise, cardiotoxicity, anthracyclines, cancer survivors, exercise cardio-oncology

INTRODUCTION

Developed in the 1960s, anthracyclines are one of the most effective chemotherapies, including doxorubicin, daunorubicin, epirubicin, and idarubicin (1, 2). In particular, doxorubicin and daunorubicin have been placed on the World Health Organization's model list of essential medicines since 1977 and 1999, respectively (3, 4). Anthracyclines are used across a broad spectrum of cancers and stages including non-Hodgkin's lymphoma, bladder, and breast cancers (5). However, despite the effectiveness of anthracyclines on eliminating cancer cells, they also have

a negative effect on healthy cells leading to acute and long-term side effects such as cardiotoxicities (6–8). The definitions of cardiotoxicity may vary; within this review, we used "toxicity of the heart" or a "decrease in left ventricular ejection fraction" (9). Anthracyclines "attack" the cancer cells by penetrating the nuclear DNA and disrupting the protein synthesis, produce reactive oxygen species, and inhibit topoisomerase II to prevent the repair of DNA (10). However, anthracyclines can also attack healthy cardiac cells, causing the development of toxicities and leading to disabling or fatal cardiac events. Cardiotoxicities may present at any time during the cancer care continuum and are categorized into three stages: acute onset (within the first 2 weeks of treatment), early onset (between the first 2 weeks and 1 year), or late onset (>1 year after treatment) (11). Acute cardiotoxicities, such as tachycardia and arrhythmias, are typically reversible, occur in < 1% of cases, and are often eliminated upon cessation of treatment (9, 12); consequently, it is the long-term cardiotoxicities that are of greatest concern, which are often not detected until they are clinically present, and therefore, likely irreversible (9). Preventative strategies for development of long-term cardiotoxicities are a critical unmet need.

Many strategies have been utilized by clinicians to reduce the risk of anthracycline-induced cardiotoxicities. These include: (a) the restriction of the cumulative dose of anthracyclines, particularly to those with cardiovascular disease (CVD) risk factors, (b) use of pegylated liposomes to deliver the therapy, (c) concurrent prescription of dexrazoxane, the only Food and Drug Association approved drug to prevent cardiotoxicities in survivors receiving anthracyclines (9, 13), and (d) long-term monitoring throughout cancer remission for changes in cardiac function and health. Such strategies have reduced the incidence of cardiotoxicities, however, the risk of anthracycline-induced cardiotoxicities is still high (up to 48%) (9, 14). Exercise delivered before, during, and/or after anthracycline treatment is emerging within the cardio-oncology field as a promising strategy to reduce the risk of developing cardiotoxicities (7, 15–17). Exercise improves cardiac strength, function, and capacity and as a result is a well-established component of non-cancer cardiology prevention, prehabilitation, and rehabilitation since 1975 at which time the American Heart Association presented its first exercise guidelines for cardiac exercise rehabilitation (18). While the mechanisms, progression, and cause of cardiotoxicities are likely different in survivors receiving anthracyclines compared to non-cancer cardiac-related conditions, much can be learned from the use of exercise within cardiology and applied to cancer survivors with cardiovascular-related symptoms and conditions.

Various tailored exercise prescriptions have been consistently demonstrated as safe and feasible for many different types of cancers and stages (19). Most commonly, exercise interventions for cancer survivors have been shown to improve cardiorespiratory fitness, physical function, quality of life, fatigue, and body composition, with emerging evidence for improved treatment tolerance and effectiveness (20, 21) as well as reduced long-term cardiac events (22–24). "Exercise cardio-oncology," a term to our knowledge that is inaugurally coined here, is defined as the application of exercise as a non-pharmacological strategy to prevent, manage, and improve cancer- and treatment-induced cardiotoxicities. This is an underdeveloped field with few longitudinal clinical trials examining the effect of long-term interventions as potentially beneficial strategies for cardio-protection in anthracycline-treated cancer survivors. Therefore, in this review, we summarize the mechanisms of anthracycline-induced cardiotoxicities and present the current pre-clinical and clinical exercise cardio-oncology literature to describe and emphasize the utilization of exercise to prevent, improve, and manage anthracycline-induced cardiotoxicities in individuals diagnosed with cancer.

PubMed, Google Scholar, Web of Science, ClinicalTrials.gov, and NIH RePORTER databases were respectively searched for published studies and ongoing trials which were included until September 2021. Search terms included various combinations of: anthracyclines; cardiotoxicities; cardio-oncology; cardiology; exercise. Secondary searches involved reference lists of eligible articles. The key criterion was to identify studies and ongoing trials that examined cancer survivors, as defined by a person with a cancer diagnosis regardless of treatment status, or animals who were receiving or had received anthracyclines and were undertaking a single bout or long-term exercise intervention and were assessing cardiovascular-related outcomes.

MECHANISMS OF ANTHRACYCLINE-INDUCED CARDIOTOXICITIES

Anthracyclines are an anti-neoplastic treatment that inhibits the reproduction of cancer cells mainly by blocking DNA synthesis during the cell cycle. Specifically, anthracyclines bind to topoisomerase II (Top2), which plays an important role in adjusting the tension of the DNA pairs for cell replication and transcription (25). Additionally, the increased levels of reactive oxygen species (ROS) induced by anthracyclines can impair mitochondrial biogenesis leading to apoptosis (26). However, the mechanisms of anthracyclines as cancer treatments have been identified as cardiotoxic: Top2 inhibition and ROS accumulation can occur in cardiomyocytes, which impairs mitochondrial biogenesis and results in cardiac dysfunctions such as a decline in left ventricular ejection fraction (LVEF) (**Figure 1**) (27).

Cardiotoxicities induced by anthracyclines have been extensively reported in epidemiological studies (14, 27). Overall, 6% of survivors who receive anthracyclines experience clinical cardiac events within ∼10 years of treatment completion (28); however, the incidence rates can substantially vary depending on cumulative treatment doses, ranging from 3% up to 48% with 400 mg/m^2 and 700 mg/m^2 of doxorubicin (DOX), respectively (29–31). Furthermore, the incidence rates increase to 65%

Abbreviations: ACS, American Cancer Society; ACSM, American College of Sports Medicine; AHA, American Heart Association; baFMD, brachial artery flow-mediated dilation; CORE, Cardio-Oncology Rehabilitation; VO_{2peak}, cardiorespiratory fitness; CVD, cardiovascular disease; cIMT, carotid intima media thickness; DOX, doxorubicin; HR, heart rate; HIIT, high intensity interval training; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; RCT, randomized control trial; ROS, reactive oxygen species; Top2, topoisomerase II.

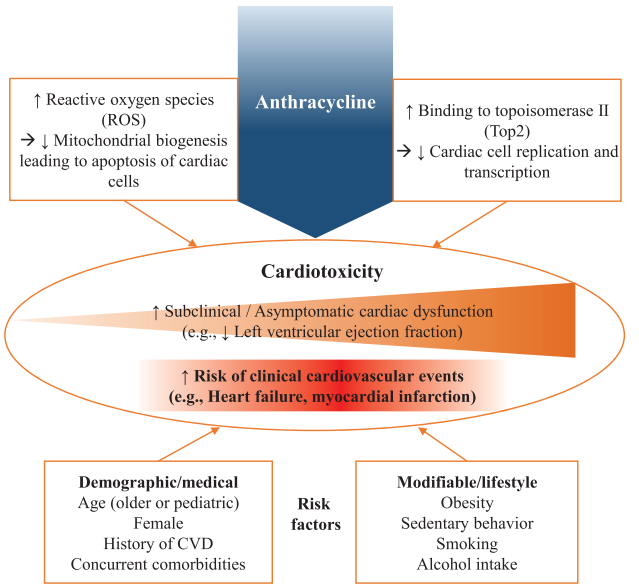

FIGURE 1 | Mechanisms of anthracycline-induced cardiotoxicity.

when including asymptomatic or subclinical cardiovascular events such as left ventricular dysfunction (LVD) (32). In addition, subsets of survivors who receive anthracyclines are more vulnerable due to several known risk factors that substantially increase the chance of developing CVD (14). They include female sex, older age (>65 years) or pediatric population (<4 years), prior or concomitant chest radiation, concomitant chemotherapy (e.g., trastuzumab), pre-existing cardiac conditions (e.g., hypertension), and other comorbidities (e.g., diabetes and hypercholesterolemia) (6, 33). Lifestyle risk factors are also important contributors to cardiotoxicity such as smoking, high alcohol consumption, obesity, and sedentary behavior (6, 33). Notably, pediatric survivors treated with anthracyclines are at exceedingly high risk and have been shown to have an 8.2 times higher risk of cardiac-related death when compared to their siblings (34).

Subclinical cardiotoxicity, such as LVD, has been an emerging interest in cardio-oncology due to its potential to induce long-term cardiac events. While the definitions for LVD are varied (35), the American Society of Echocardiography and the European Association of Cardiovascular Imaging define it as a reduction in LVEF greater than 10% up to 53% (36). The anthracycline-induced decline in LVEF is classified by the severity of the symptoms (e.g., <53% of LVEF as an abnormality cutoff) and time of appearance (e.g., acute onset (<2 weeks), early-onset (<1 year), or late-onset (>1 year); it is also possible that any onset of cardiotoxicity is a result of a gradual decline of the same disease since the time of first chemotherapeutic treatment (11). Nonetheless, there is consensus that such cardiotoxicities may manifest as early as one week after treatment initiation, although this tends to occur in only 1% of survivors and is typically reversible, or as late as several decades after, in which case the damage in cardiac cells could be irreversible (6, 35). Most anthracycline-induced cardiotoxicities present themselves within 1 year from treatment and are associated with 50% of non-cancer-related mortalities (35). In childhood cancer survivors, the development of clinical cardiac events occurs several decades post-treatment with increasing risks overtime; however, while subclinical disorders such as a reduction in LVEF are common among survivors of childhood cancer, the presenting symptoms are often not detected early enough and lead to clinical CVD (8, 37).

While the mechanisms underlying the toxic effect of anthracyclines in the heart are not yet fully understood, the plausible explanations include that anthracyclines cause injury to healthy cells including cardiomyocytes (6, 27, 35), which constitute 80% of heart mass (38), along with cells providing support to myocytes such as cardiac progenitor cells, cardiac fibroblasts, and endothelial cells (38, 39). The subsequent death of these healthy cells induces cardiomyopathy that can lead to heart failure with symptoms requiring clinical care or, at best, asymptomatic systolic dysfunction indicated by a decline of LVEF (6, 27). Specifically, the generation of ROS by metabolism of anthracyclines that increases cardiac oxidative stress to directly cause damage to DNA, as well as the induction of DNA-strands cleavage by the formation of Top 2β-DNA-anthracycline complex and the suppression of mitochondrial biogenesis have been suggested to induce anthracycline-induced cardiomyopathy (30, 40–42).

Of importance, the series of cardiovascular insults by anthracyclines are also coupled with multiple risk factors including demographic and medical profiles as well as modifiable lifestyle factors, which is labeled as the "multiple-hit" hypothesis by Jones et al. (43). This hypothesis highlights the complexities of cardiotoxicities that not only include the direct cardiac damages of anthracyclines but also the indirect factors that can exacerbate cardiotoxicities such as the systemic effects of treatments on the overall cardiovascular system as well as survivors' with pre-existing or elevated risks of CVD (43). While various pharmacological and monitoring approaches have been employed to prevent or reverse cardiotoxicities in research and clinical settings, there is a lack of non-pharmacological comprehensive interventions that can effectively prevent, improve, or manage cardiotoxicities. Exercise has thereby been proposed as a therapeutic modality that can address anthracycline-induced cardiotoxicities through directly intervening in the biological mechanisms in cardiac cells and cardiovascular system as well as managing pre-existing medical conditions or modifiable CVD risk factors that can worsen cardiotoxicities (44, 45).

EXERCISE AS MEDICINE TO IMPROVE ANTHRACYCLINE-INDUCED CARDIOTOXICITIES

In order to examine exercise cardio-oncology literature among survivors prescribed anthracyclines, a discussion of the current exercise guidelines is required (**Table 1**). In 2009, the American

TABLE 1 | Comparison of the exercise guidelines recommended by the American College of Sports Medicine (ACSM)/American Cancer Society (ACS), American Heart Association (AHA), and American College of Cardiology (ACC).

Exercise guideline components	ACSM/ACS	AHA (CORE Guidelines)	ACC
Frequency and duration			
Aerobic ≥150 minutes/week over 3–5 days/week	✓	✓	✓
Strength ≥ 2 sessions/week	✓	✓	✓
Intensity			
Aerobic-moderate (50–70% peak HR)	✓	Variable	Variable
Resistance (60–70% 1-RM)	✓	Variable	Variable
Type			
Aerobic	✓	✓	✓
Resistance	✓	✓	✓
Multi-modality	✓	✓	✓
Setting			
Institutional/clinic-based	Nor reported	✓	✓
Home-based	Nor reported	✓	✓
Community-based	Nor reported	✓	✓
Timing			
Pre-treatment (diagnosis)	✓	✓	✓
During treatment	✓	✓	✓
Survivorship	✓	✓	✓

CORE, cardio-oncology rehabilitation; HR, heart rate; RM, repetition maximum.

College of Sports Medicine (ACSM) held the Roundtable on Exercise Guidelines for Cancer Survivors (46), providing an initial framework for the use of exercise in cancer prevention and management. In 2019, a subsequent meeting reflected the exponential rise in interest in the benefits of exercise in oncology, and drew attention to the underlying mechanisms (47). The ACSM and the American Cancer Society (ACS) recommend that cancer survivors should avoid inactivity and undertake regular exercise with the general aim to progress to an accumulation of 150 min of moderate-intensity, or 75 min of vigorous-intensity, per week of aerobic exercise and two strength training sessions, though exercise must be individually tailored to the survivor (47); said guidelines are additionally supported by the American College of Cardiology. Whilst there is strong evidence that exercise improves psychosocial and physical function outcomes, evidence for preventing, managing, and improving cancer- and treatment-related cardiotoxicities is insufficient leading to national recognition of the need for what we have coined here for the first time, exercise cardio-oncology.

In 2019, the American Heart Association (AHA) proposed Cardio-Oncology Rehabilitation (CORE), a multidisciplinary approach to the cardiovascular rehabilitation of cancer survivors based on the well-established cardiac rehabilitation programs for non-cancer cardiology patients (48). CORE integrates structured exercise training with a comprehensive infrastructure of nutritional counseling, weight and blood pressure control, diabetes management, assistance with smoking cessation, and psychosocial support. Specifically, CORE recommends individualized aerobic and resistance-based exercise, based on the aforementioned guidelines from ACSM, for survivors with cancer who are identified as being at increased risk of cardiotoxicity development e.g., those receiving anthracyclines. The implementation of exercise cardio-oncology programs should be considered at all stages of the cancer care continuum e.g., pre, during, and post-treatment, and not only target survivors exposed to high risk cancer-related therapies e.g., anthracyclines, which is the focus of the present review, but also survivors with pre-existing CVD risk factors such as obesity and smoking (32). For example, targeted aerobic and resistance exercise therapy for overweight/obese survivors with early-stage breast cancer can significantly reduce their Framingham risk score and therefore reduce their risk of cardiotoxicity development (49). Based on the evolution of these approaches in support of exercise, the subsequent sections acknowledge the probable mechanisms of action exercise elicits on anthracycline-induced cardiotoxicities.

Mechanistic Actions of Exercise

The cardioprotective mechanisms of exercise are illustrated in **Figure 2**. Cardiac muscle does not act in isolation but functions alongside the lungs, diaphragm, peripheral vasculature, nervous system, and metabolism. By improving the function of these other systems, exercise can decrease strain on the heart (50). For example, exercise training may have direct effects on the improvements of cardiac muscle adaptation and growth through enhancing cardiomyocyte proliferation (50). Also, exercise has been shown to decrease oxidative stress or ROS (51) and improve the cardiometabolic risk profiles, in part by challenging the sarcopenic effects of cancer treatments (52). Specifically, exercise has been shown to increase cardiovascular reserve (50, 53, 54), such as by increasing peak oxygen consumption (VO_{2peak}) through improved endothelial and autonomic function (55), as

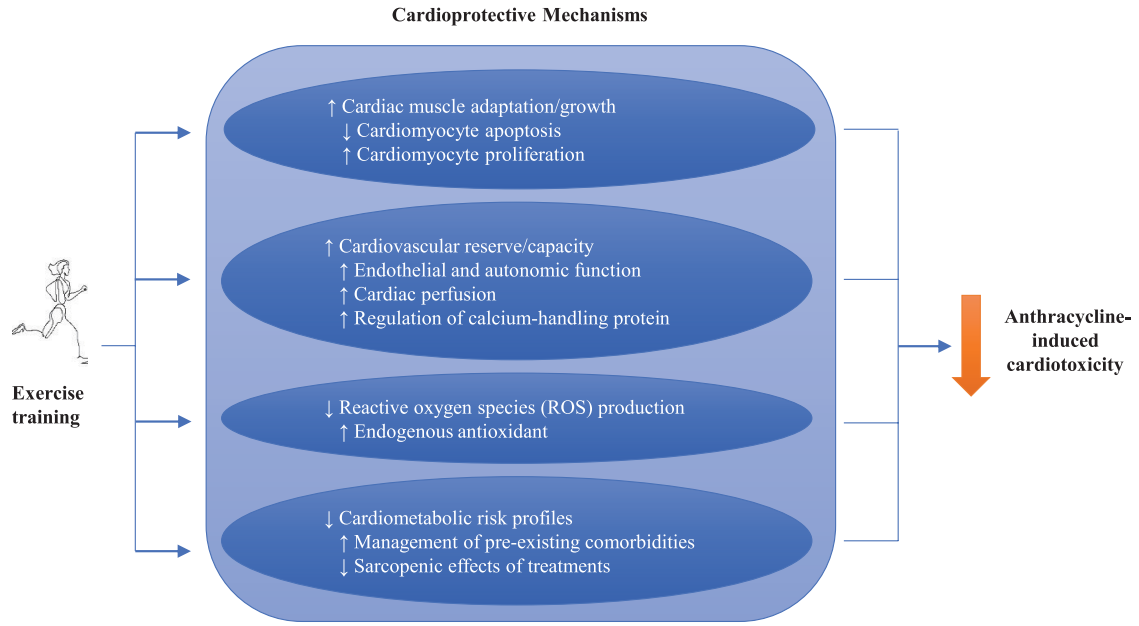

FIGURE 2 | Potential mechanisms of exercise training on anthracycline-induced cardiotoxicities.

well as improved cardiac perfusion (56). Importantly, exercise has been shown to counteract the fall in VO_{2peak} that typically occurs with anthracycline treatment (57). Targeted exercise may also increase cardiovascular reserve by training the diaphragm and decreasing the blood pressure against which the cardiac muscle pumps (58, 59), and additionally has been shown to normalize calcium-handling proteins in cardiac rehabilitation for heart failure (60).

As our understanding grows of the mechanisms by which anthracyclines damage the heart (6, 27, 61), we are able to decipher how exercise can protect myocardial tissue. Owing to the nascence of the exercise cardio-oncology field and the need for non-invasive testing, the mechanistic evidence from human studies is sparse. Nevertheless, several studies have suggested that exercise modulates key biomarkers of cardiac function. Costello, Roberts (62) used cardiac magnetic resonance to show a non-significant but meaningful decrease in longitudinal strain in exercised patients during anthracyclines decreased compared to anthracyclines alone. Also, another study demonstrated that vigorous exercise prior to each DOX treatment can attenuate adverse changes in hemodynamic metrics including cardiac output, resting heart rate (HR) and systemic vascular resistance (63). On a cellular level, the mechanisms by which exercise may protect the myocardium have been studied in murine models. These studies found attenuation of the anthracycline-mediated decreases in end-systolic pressure, left ventricular developed pressure, and maximal rate of left ventricular pressure development (15, 64, 65), through several biomechanisms such as protection against ROS (66–69) by enhancing endogenous antioxidants (70, 71) and heat shock protein action (66, 69).

The cardioprotective mechanisms of exercise training have recently been further investigated by two systematic reviews and meta-analyses. Ghignatti, Nogueira (72) reported a review of 14 preclinical studies and found that trained DOX-treated animals showed significantly better fractional shortening compared to control, with greater benefits from exercise before DOX compared to during or after DOX. The authors highlighted that the most commonly reported cellular mechanism was an exercise-mediated decrease in DOX accumulation in the heart, in addition to the preservation of myosin heavy chain. Similarly, another review by Naaktgeboren, Binyam (73) reported that there is coherent evidence that forced exercise interventions in animals can mitigate DOX-induced cardiotoxicities, where the most commonly reported mechanism of cardioprotection is increased antioxidant production, followed by the enhanced activity of heat shock proteins and the regulation of apoptosis. Other mechanisms include the improved turnover of myocardial tissue by regulating apoptosis (74–76) and increasing the formation of cardiomyocyte progenitors (77), modulation of autophagy and lysosomal signaling (78), and normalization of myocardial calcium activity (79, 80). Although caution must be taken with interpretation because some preclinical models incorporate exercise frequencies and intensities that would not be feasible in humans (81), exercise poses a potential non-pharmacological strategy to protect or even reverse anthracycline-induced cardiac damage in clinical settings.

CURRENT EVIDENCE IN EXERCISE CARDIO-ONCOLOGY

Mechanistically, exercise is a viable non-pharmacological strategy that could be implemented at various stages of the cancer care

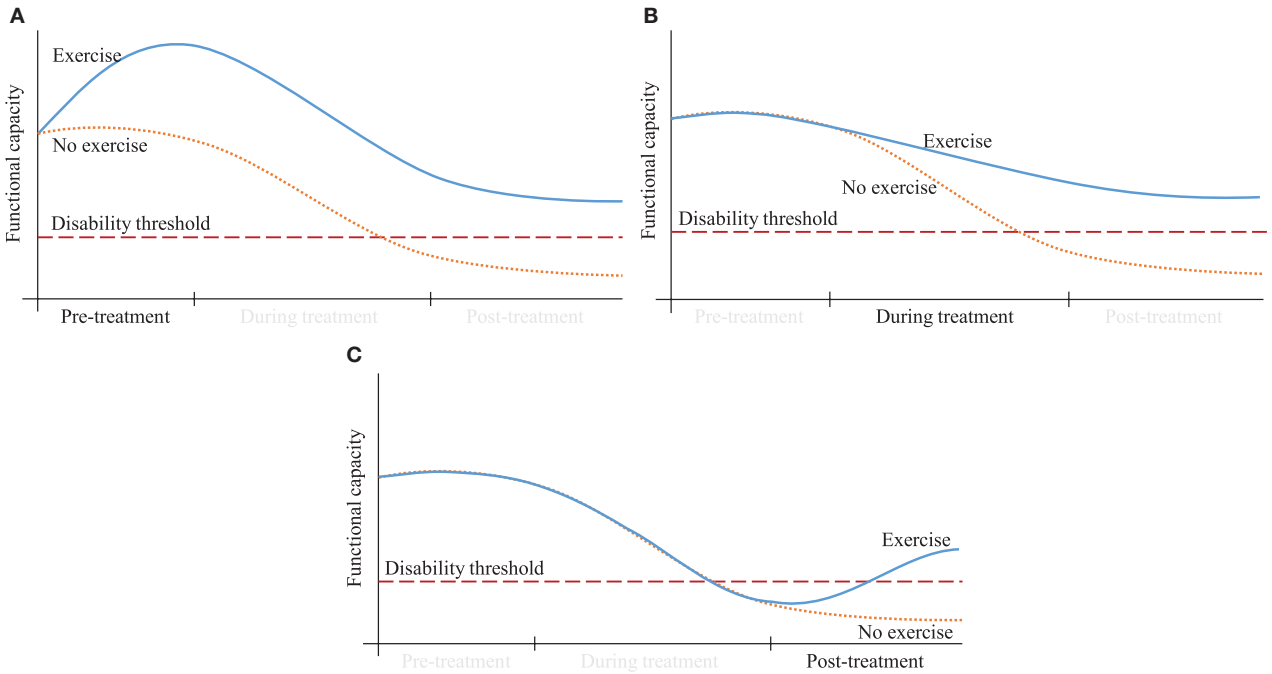

FIGURE 3 | Theoretical representation of how an exercise strategy implemented either at **(A)** pre, **(B)** during, or **(C)** post-treatment could improve a survivor's functional capacity.

continuum to prevent, manage, and improve anthracycline-induced cardiotoxicities, in addition to other detrimental treatment- and cancer-related side effects such as fatigue, reduced physical function, and altered body composition. **Figure 3** provides a theoretical representation of the potential effect of implementing an exercise intervention before, during, or after receiving anthracyclines. Initiated prior to or during anthracycline treatment, exercise may elevate or preserve a survivor's starting point, providing a buffer margin in response to the inevitable treatment-induced decline and preventing a cross into the "disability threshold." Additionally, exercise implemented after treatment may bring the survivor out of the "disability threshold." Here we critically evaluate the existing knowledge to understand the impact of exercise implemented before, during, and after anthracycline treatment, along with identifying specific exercise modalities, and their various combinations, that mitigate cardiotoxic-related side effects. We categorized the evidence into intervention modalities (e.g., aerobic, resistance, and multi-modal) and study settings (e.g., preclinical and clinical) to present the full range of adaptations that result from exercise (**Table 2**).

Aerobic Exercise

Aerobic exercise is traditionally the most common mode prescribed to improve cardiorespiratory fitness and cardiovascular function, both surrogate measures of CVD risk (99). Aerobic exercise is typically well-received given its familiarity with non-exercisers (e.g., walking), ease to implement in both remote and in-person environments with limited or no equipment required, and includes modes that reduce the impact on the joints (e.g., swimming) (100). Here we discuss the effect of aerobic-based exercise interventions on cardiotoxicities and related cardiovascular outcomes in survivors prescribed anthracyclines.

Murine Models

Studies assessing exercise interventions prior to, or concurrent with, anthracycline treatment has been the focus of preclinical trials using aerobic exercise to improve cardiotoxicity outcomes (72, 73). Hydock, Lien (15) examined the effect of a 10-week prehabilitative exercise intervention in preventing the development of DOX-induced cardiotoxicities in rats. Three protocols were compared: treadmill running, voluntary wheel running, and sedentary control, each receiving either saline or DOX. The authors reported that in DOX groups, regardless of modes of activity, exercise was cardioprotective, indicated by the preservation of myosin heavy chain expression and aortic and mitral valve mean and maximal blood flow, which was similar to that in all saline groups and significantly different to the sedentary-DOX control group. Furthermore, the cardioprotective timeline of exercise persisted 4 weeks after completing the 10-day DOX regimen even though the animals remained sedentary during this period. Similarly, studies by Ashraf and Roshan (67) and Ahmadian and Roshan (69) respectively examined cardiovascular-related outcomes in rats using a 3-week aerobic training intervention done prior to anthracycline exposure. Compared to the DOX-sedentary

TABLE 2 | Summary of exercise cardio-oncology trials.

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Pre-clinical studies								
Aerobic exercise								
Sequeira et al. (82)	RCT	Cardiomyocyte ultrastructure: protein synthesis and oxidative stress reductions	Non-tumor bearing mice	On and post-treatment 1mg/kg DOX hydrochloride 1x/day for 10 days	DOX + exercise ($N = 16$); DOX + sedentary ($N = 16$); Saline + sedentary ($N = 16$)	Aerobic exercise 9 weeks 5x/week 30min/day Treadmill running 50–60% maximal velocity	Not reported	Cardiomyocyte volume density[B] LV oxidative damage[B] Superoxide dismutase[B]
Wang et al. (83)	RCT	Ejection fraction and fractional shortening	Model 1: Juvenile tumor bearing mice	Model 1: Pre-treatment 10mg/kg DOX one dose	DOX + exercise ($N = 8$); DOX + sedentary ($N = 8$)	Model 1: 10 days 5x/week 45 min/day Treadmill walking 12 m/min 0% slo	Not reported	DOX in heart tissue[B]
			Model 2: Juvenile tumor and non-tumor bearing mice	Model 2: On-treatment 2.5 mg/kg DOX 2x/week for 2 weeks	DOX + exercise ($N = 8$); DOX + sedentary ($N = 8$); Exercise ($N = 8$); Sedentary: ($N = 8$)	Model 2: 2 weeks 5x/week 45 min/day Other parameters as above.		Fractional shortening[B] Ejection fraction[B]
			Model 3: Juvenile non-tumor bearing mice	Model 3: Post-treatment Cumulative dose of 25 mg/kg DOX over 5 weeks	DOX + exercise ($N = 8$); DOX + sedentary ($N = 8$); Exercise ($N = 8$); Sedentary: ($N = 8$)	Model 3: 8 weeks 3x/week Other parameters as above.		Not reported
Ahmadian and Roshan, (69)	RCT	Cardiotoxicity	Non-tumor bearing mice	Pre-treatment 20 mg/kg DOX hydrochloride one dose	DOX + exercise ($N = 8$); Doxorubicin ($N = 8$); Saline + exercise ($N = 8$)	3 weeks 5x/week Treadmill running Progressive increase each week 15 to 17 m/min 25 to 39 min	Not reported	Superoxide dismutase[B] C-reactive protein[B] Heat shock protein[B] Malondialdehyde[B]
Hayward et al. (84)	RCT	Cardiac function	Non-tumor bearing mice (juvenile)	On treatment 2 mg/kg DOX 1x/day for 7 days	DOX + sedentary ($N = 22$); DOX + exercise ($N = 22$); Saline + sedentary ($N = 10$); Saline + exercise ($N = 10$)	10-weeks 24-h access to running wheel.	Not reported	HR[B] Blood velocities[B] Isovolumetric relaxation time[B] LV developed pressure[B] endSP[B] endDP[B]

(Continued)

TABLE 2 | Continued

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Pre-clinical studies								
Aerobic exercise								
Ashraf and Roshan (67)	RCT	Cardiac oxidative damage biomarkers	Non-tumor bearing mice	Pre-treatment 10 mg/kg or 20 mg/kg DOX hydrochloride one dose	DOX (10 mg/kg) + exercise ($N = 8$); DOX (20mg/kg) + exercise ($N = 8$); DOX (10mg/kg) + sedentary ($N = 8$); DOX (20mg/kg) + sedentary ($N = 8$); Saline + sedentary ($N = 8$); Saline + exercise ($N = 8$)	See Ahmadian and Roshan (69)	Not reported	Malondialdehyde [B] Apelin[B] Superoxide dismutase[B]
Hydock et al. (15)	RCT	MHC and SERCA2a alterations	Non-tumor bearing mice	Pre-treatment 1mg/kg DOX 1x/day for 10 days	DOX + treadmill ($N = 23$); DOX + voluntary wheel running ($N = 14$); DOX+ sedentary ($N = 17$); Saline + treadmill ($N = 12$); Saline + voluntary wheel running ($N = 17$); Saline + sedentary ($N = 11$)	10 weeks 5x/week Treadmill running Or 24-h access Voluntary wheel running	Not reported	SERCA2a[B] β-isoform MHC[B] LV mass[B] Fractional shortening[B] RWT[B] SWs[B] SWd[B] PWs[B] PWd[B]
Matsuura et al. (85)	RCT	Platelet L-arginine-nitric oxide pathway and vasodilator properties	Non-tumor bearing mice	Post treatment 1mg/kg DOX 1x/day for 10 days	DOX + exercise ($N = 12$); DOX + sedentary ($N = 12$); Saline + sedentary ($N = 12$); Saline + exercise ($N = 12$)	Aerobic exercise 6 weeks 5x/week 60 min Treadmill running 50–60% maximal velocity	Not reported	Vasodilation of mesenteric vascular bed[B]
Resistance exercise								
Feitosa et al. (86)		Cardiac contractility, hemodynamics, baroreflex, cardiac autonomic tonus and oxidative stress	Non-tumor bearing mice	During treatment 2.5 mg/kg DOX 1x/week for 6 weeks	DOX + exercise ($N = 13$); DOX + sedentary ($N = 13$); Control ($N = 13$)	8-week resistance training: 40% 1RM (weighted leg extensions: 3 sets of 10 reps with 60 second rest, 3× per week)	Not reported	HR[B] Oxidative stress[B] Diastolic arterial pressure[B] LV developed pressure[B]

(Continued)

TABLE 2 | Continued

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Pre-clinical studies								
Resistance exercise								
Pfannenstiel and Hayward (87)	RCT	Cardiac function	Non-tumor bearing mice	Pre-treatment 12.5 mg/kg DOX one dose	DOX + exercise (N = 15); DOX + sedentary (N = 15); Saline + sedentary (N = 9); Saline + exercise (N = 9)	Resistance training 12 weeks Bipedal stance (cage lid elevated 1–2.5 cm each week)	Not reported	Fractional shortening^{B} Maximal blood flow through aortic valve^{B} Maximal blood flow through mitral valve^{B} LV developed pressure^{B} MHC isoform distribution^{B}
Clinical studies								
Aerobic exercise								
Lee et al. (88)	RCT	ECM-regulating enzymes: matrix metalloproteinases	Breast cancer (Stage I-III)	On treatment. DOX and cyclophosphamide (every 2 weeks for 4 cycles).	Intervention (N = 15); Usual care (N = 15)	8 weeks 3x/week 30-min sessions Supervised Cycle-based HIIT 10–90% intervals of PPO	HIIT session attendance was 82.3%.	MMP-9^{WI} MMP-2^{WIWC}
Lee et al. (16)	RCT	Vascular endothelial function	See Lee et al. (92)	baFMD ^{B,WI,WC} cIMT ^{WC} Lee et al. (91)	RCT	Cardiorespiratory fitness	See Lee et al. (92)	VO_{2max}^{WC}
Kirkham et al. (63)	RCT	Acute changes in cardiac function	Breast cancer (Stage IIB-IIIC)	Pre-treatment	Intervention (N = 13); Usual care: N = 11	Acute bout aerobic exercise 70% age-predicted HRR	N/A	NT-pro-BNP^{B,WI} Ejection fraction^{WI} Systolic strain rate^{WI}
Hornsby et al. (89)	RCT	Adverse events; cardiopulmonary function, patient-reported outcomes	Breast cancer (Stage IIB-IIIC)	On-treatment Neoadjuvant chemotherapy (4 cycles): 60 mg/m^2 DOX and 600 mg/m^2 cyclophosphamide	Intervention (N = 10); Usual care (N = 10)	12 weeks 3x/week Supervised 15–45 min sessions (progressive design) 60–100% VO_{2peak}	Attendance rate was 82%, adherence to protocol was 66%.	Resting HR^{WC} Peak exercise HR^{WC} Oxygen pulse ^{B,WI,WC} $VO_{2peak}^{B,WI,WC}$
Resistance exercise								
Schmidt et al. (90)	RCT	Fatigue and quality of life	Breast cancer (Stage I-III)	On treatment Adjuvant chemotherapy (89.5% received anthracyclines)	Intervention (N = 49); Muscle relaxation control (N = 46)	12 weeks 2x/week 60 min Supervised Resistance exercise: Eight machine-based progressive exercises 3 sets, 8-12 repetitions	Median attendance in both groups was 17 out of 24 sessions.	Not reported

(Continued)

TABLE 2 | Continued

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Clinical studies								
Multi-modal exercise								
Ansund et al. (91)	RCT	Long-term myocardial damage and physical capacity	Breast cancer (Stage I-III)	On and post treatment Anthracycline, taxane, or combination of the two.	Resistance + HIIT (N = 79); Aerobic + HIIT (N = 80); Usual care (N = 81)	16 weeks 2x/week Supervised Resistance: 8–12 repetitions at 75–80% of 1RM Aerobic: 3 × 3 min bouts of HIIT at RPE of 16–18 Moderate-intensity and high-intensity aerobic training: 20 min of moderate-intensity at 13–15 on Borg scale followed by 3 × 3 min bouts of HIIT at RPE of 16–18	Not reported	Nt-pro-BNP^{B}
Kirkham et al. (92)	Non-RCT	Resting cardiac function and hemodynamics	Breast cancer (Stage I-III)	On treatment 240 mg/m^2 DOX and 2400 mg/m2 cyclophosphamide over four cycles (2-3 weeks apart).	Intervention (N = 26); Usual care (N = 11)	Estimated 8–12 weeks 3x/week Supervised (progressions 1–2 weeks) Aerobic 50–75% age predicted HRR Resistance exercise (moderate intensity, whole body)	Median adherence 3x/week: 63%. Adherence to aerobic protocol was 86% for intensity & 96% for duration.	Diastolic strain rate ^{WI} Hemoglobin^{WIWC} Hematocrit^{WIWC} Cardiac output^{WC} Resting HR^{WC} Systemic vascular resistance^{B,WI,WC} Mean arterial pressure^{WIWC} VO^{WI}_{2peak}
Kirkham et al. (92)	Non-RCT	Resting cardiac function and hemodynamics	Breast cancer (Stage I-III)	On treatment 240 mg/m^2 DOX and 2400 mg/m2 cyclophosphamide over four cycles (2–3 weeks apart).	Intervention (N = 26); Usual care (N = 11)	Estimated 8–12 weeks 3x/week Supervised (progressions 1–2 weeks) Aerobic 50–75% age predicted HRR Resistance exercise (moderate intensity, whole body)	Median adherence 3x/week: 63%. Adherence to aerobic protocol was 86% for intensity & 96% for duration.	Diastolic strain rate ^{WI} Hemoglobin^{WIWC} Hematocrit^{WIWC} Cardiac output^{WC} Resting HR^{WC} Systemic vascular resistance^{B,WI,WC} Mean arterial pressure^{WIWC} VO^{WI}_{2peak}

(Continued)

TABLE 2 | Continued

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Clinical studies								
Multi-modal exercise								
Kirkham et al. (93)	Single group	Cardiovascular autonomic function	Breast cancer (Stage I-IIIA)	On treatment and post treatment. DOX + cyclophosphamide + paclitaxel: *N* = 49 DOX + cyclophosphamide: *N* = 3 Docetaxel + cyclophosphamide: *N* = 21 Anthracycline + another drug: *N* = 73	Intervention (*N* = 73)	Estimated 8–12 weeks 3x/week Supervised Aerobic/Resistance 50–75% HRR/1RM Post treatment 2x/week (week 1–10) 1x/week (week 11–20) Supervised Aerobic intervals 4 × 4 min at 75–85% + 4 min at 40–65% VO_2/HRR	Attendance ranged from 51–71% depending on treatment plan.	Resting HR^{WI} Resting SBP^{WI} Resting DBP^{WI}
Howden et al. (57)	Non-RCT	Cardiovascular fitness	Breast cancer (Stage I-III)	On-treatment DOX, cyclophosphamide (71%) Fluorouracil, epirubicin, cyclophosphamide, docetaxel (11%)	Intervention (*N* = 14); Usual care (*N* = 14)	12 weeks 3x/week 2 supervised sessions per week, 1 home-based session 60 min Aerobic exercise 30min Resistance exercise 30min Periodization plan (2 week loading, 1 week unloading)	Compliance to supervised exercise session: 76%	VO^{B}_{2peak} Arterio-venous Oxygen $difference^{B}$
Foulkes et al. (94)	Non-RCT	Cardiovascular fitness, cardiac function	Breast cancer (Stage I-III)	Off-treatment 12-months post treatment	Intervention (*N* = 7); Usual care (*N* = 8)	See Howden et al. (57)		$VO^{B,WI,\ WC}_{2peak}$
Mijwel et al. (95)	RCT	Cardiorespiratory fitness; Muscle strength			See Ansund et al. (91)			$VO^{B,WI}_{2peak}$

(Continued)

TABLE 2 | Continued

Author, year	Study design	Primary outcome	Subject	Treatment	Intervention groups	Intervention	Intervention adherence	Significant* cardiovascular-related outcomes
Clinical studies								
Multi-modal exercise								
Järvelä et al. (96)	Single group	Myocardial function	Survivors of childhood ALL (>10 years)	Off treatment Cumulative dose of 120–370mg/m^2	Intervention ($N = 21$)	12 weeks 3–4×/week Unsupervised home-based Resistance training 8 exercises – as many repetitions as possible for 3 cycles Aerobic exercise 30min (recommended 3×/week)	Not reported	Early diastolic mitral filling wave (E)^{WI}
Smith et al. (97)	Case series	Peak oxygen consumption and exercise tolerance	Survivors of childhood osteosarcoma or Ewing sarcoma (>10 years)	Off treatment	Intervention ($N = 5$)	12 weeks Unsupervised home-based Aerobic exercise 3–5 days/week Resistance exercise 2–3days/week	Compliance to prescribed exercise: 86%	VO^{WI}_{2peak} Ejection fraction^{WI} Oxygen pulse^{WI}
Järvelä et al. (98)	Single group	Cardiorespiratory fitness	Intervention ($N = 17$)		See Järvelä et al., 2016 (96)			VO^{WI}_{2peak}

**Significance defined as $p < 0.05$ with the following indicating what was significant: B, between group significance; WI, within group significance for the intervention group; WC, within group significance for the control group. RCT, randomized clinical trial; DOX, doxorubicin; LV, left ventricle; MHC, myosin heavy chain; SERCA2a, sarcoendoplasmic reticulum Ca^{2+} ATPase 2a; RWT, relative wall thickness; SWs, septal wall thickness at systole; SWd, septal wall thickness at diastole; PWs, posterior wall thickness at systole; PWd, posterior wall thickness at diastole; HR, heart rate; endSP, end systolic pressure; endDP, end diastolic pressure; 1RM, one-repetition maximum; HIIT, high intensity interval training; PPO, peak power output; MMP, matrix metalloproteinase; baFMD, brachial artery flow mediated dilation; cIMT, carotid intima media thickness; $VO_{2maxorpeak}$, maximal or peak oxygen consumption; HRR, heart rate reserve; N/A, not applicable; NT-pro-BNP, amino terminal of B-type natriuretic peptide; RPE, rate of perceived exertion; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALL, acute lymphocytic leukemia.*

groups, rats in the respective DOX-exercise groups exhibited upregulation in antioxidant markers (e.g., superoxide dismutase, malondialdehyde), further demonstrating the ability for exercise to counteract the increase in oxidative stress of anthracyclines, which has been linked to the development of cardiotoxicities (67, 69). These studies highlight the potential of pre-treatment exercise in preventing DOX-induced cardiotoxicities and the potential in inducing a sustainable effect post-chemotherapy even in an inactive state.

While exercise prior to anthracycline treatment has been shown to have a significant impact on cardiotoxicities, only one study, to date, utilized exercise after treatment and targeted rats with DOX-induced heart failure. Matsuura, Brunini (85) reported survival rate to be significantly improved in those rats with DOX-induced heart failure who undertook 6 weeks of aerobic exercise (67% survived), compared to the DOX-sedentary group (33% survived). Similarly, Sequeira, Martins (82) reported that, the exercised rats during DOX treatment had a 100% survival rate compared to 68.8% in the rats who were sedentary. It should be noted that the above preclinical studies (15, 67, 69, 82, 85) did not utilize rats that were diseased with cancer, as such, the inflammatory and biologic nature of the tumor and how these react with the exercise and anthracycline drug cannot be identified. Wang, Iskra (83) used both tumor and non-tumor bearing juvenile mice and reported: (1) in tumor-bearing mice, 2-weeks of aerobic exercise followed by DOX infusion resulted in less DOX in the heart tissue compared to sedentary controls, (2) in both tumor and non-tumor bearing mice, 2-weeks of aerobic exercise completed concurrently with DOX resulted in preserved fractional shortening and ejection fraction, and (3) in non-tumor bearing mice, 8-weeks of aerobic exercise implemented after DOX resulted in no recovery of fractional shortening or ejection fraction. However, the tumor and non-tumor-bearing juvenile mice were not directly compared, thereby the effect of the tumor is still unclear. While not tumor-bearing, Hayward, Lien (84) also examined a juvenile murine model and reported 10-weeks of voluntary aerobic exercise, performed concurrently with DOX regimen, to preserve HR, blood flow velocities, and isovolumetric relaxation time, all measures of cardiac function, when compared to significant impairments in the DOX-sedentary group. Exercise conducted prior to, or in conjunction with, anthracyclines may be beneficial for pediatric cancer survivors prescribed anthracyclines as demonstrated by the preservation of cardiac-related outcomes in juvenile murine models (83, 84). Overall, the improvement in cardiovascular-related outcomes reported in these preclinical studies offers a promise of aerobic-based exercise as a possible strategy to improve cardiac-related health status and even reduce cardiotoxicity-related mortality, however, further studies with tumor-bearing or human tumor xenograft models are warranted to provide more transferable evidence to human settings.

Clinical Interventions

Aerobic-based clinical studies have predominantly focused on exercise during treatment. Hornsby, Douglas (89) implemented a supervised 12-week progressive aerobic-based intervention in breast cancer survivors receiving anthracyclines ($n = 20$) and found that exercise significantly increased VO_{2peak} from 19.5 to 22.1 ml/kg/min when compared to the usual care group who had a statistically significant decline in VO_{2peak} from 17.5 to 16.0 ml/kg/min, which was approaching the cut off value for independence for women at 15 ml/kg/min (101). No changes were observed in any echocardiography measured cardiac function outcomes for either group. Furthermore, the significant improvement in VO_{2peak} occurred irrespective of a reduction of exercise dose by 23% due to nausea, tiredness, or not feeling well, yet exercise session attendance was high (82%). This suggests that the modification of the exercise prescription when survivors are not feeling up to the prescribed program can still result in clinically meaningful benefits, although low and high adherers were not distinguished within the analysis. Supervised exercise during treatment should be encouraged as exercise physiologists will be able to provide appropriate, tailored, real-time advice that will ensure survivor safety within the exercise environment, yet still provide an adequate exercise stimulus to ensure adaptations occur.

Timing of exercise during treatment is a widely debated concept with no clear evidence regarding the most effective programming. However, a randomized controlled trial (RCT) by Kirkham, Eves (63) provides insight into the potential benefits of exercise completed 24 h prior to anthracycline infusion. They examined the effect of a single 30-min treadmill walking exercise session completed 24 h prior to anthracycline infusion on cardiac function in breast cancer survivors ($n = 27$). This acute exercise study reported that a single bout of exercise can attenuate the anthracycline-induced increase in NT-pro-BNP ($p < 0.05$), a marker of cardiotoxic effects, and resulted in an increase in systolic strain rate and LVEF, suggesting exercise to improve systolic function compared to usual care ($p < 0.05$). Implementing a single aerobic bout of exercise prior to each chemotherapy infusion is potentially a feasible and more achievable exercise strategy during treatment than multiple weekly sessions. Further research is required to assess the effectiveness of this timing of exercise when completed for all chemotherapy cycles, and gauge if it provides similar or additional benefits to that seen in weekly exercise sessions throughout treatment.

One promising aerobic exercise modality is high intensity interval training (HIIT), which involves alternating bouts of high (e.g., 90% of peak power output) and low (e.g., 10% of peak power output) intensity movement and is considered an effective form of aerobic training to ameliorate CVD risk factors (102). In a RCT by Lee and colleagues among 30 stage I-III breast cancer survivors during anthracycline treatment (103), an 8-week HIIT intervention significantly improved brachial artery flow-mediated dilation (baFMD) and carotid intima media thickness (cIMT) compared to usual care (16), as well as improved levels of matrix metalloproteinases (MMP) within the HIIT group (88), which are implicated in atherosclerosis development (104, 105). Although these findings provide promising insight into the benefits of HIIT in improving vascular endothelial function (88), the study focused on the feasibility of HIIT during anthracyclines and the cardiovascular outcomes were only exploratory, as such, larger trials with the primary focus on anthracycline-induced cardiotoxicities are needed.

Resistance Exercise

Traditionally, resistance exercise is prescribed to improve skeletal muscle strength and hypertrophy (106), yet, improvements in skeletal muscle-related outcomes can also lead to the optimization of cardiac function (107). Resistance training is considered a critical component within exercise oncology given its role in the preservation of lean mass which is positively associated with a number of cancer-related outcomes including prolonged survival, reduced fatigue, and enhanced surgical outcomes (46); however, its use within the exercise cardio-oncology field is limited. Here we describe the current evidence assessing the effect resistance exercise has on anthracycline-induced cardiotoxicities.

Murine Models

Cardioprotective effects have been observed in preclinical resistance training protocols implemented during anthracycline treatment. In a study by Pfannenstiel and Hayward (87) with a 12-week prehabilitation resistance-based intervention in rats receiving either DOX or saline infusion, resistance training was demonstrated to be cardioprotective against DOX-induced cardiac dysfunction. While there was still a drug effect in the DOX compared to the saline groups, the DOX-resistance group had significantly faster mitral and aortic blood flow velocities, higher fractional shortening, and higher systolic and diastolic function compared to the DOX-sedentary group. The authors proposed that this attenuation of cardiac function in the DOX-resistance trained group was a result of preserved myosin heavy chain isoform distribution and decreased oxidative stress (87). Similarly, Feitosa, Carvalho (86) found that 8-weeks of resistance training prevented a DOX-induced increase in diastolic arterial pressure and HR compared to the sedentary group receiving DOX, yet, both DOX groups had a significant treatment-induced reduction in systolic arterial pressure when compared to the placebo-sedentary group. Resistance training also prevented DOX-induced changes in spontaneous baroreflex sensitivity, sympathetic tone, vagal tone, left ventricular developed pressure, and oxidative stress. The authors proposed that the prevention of DOX-induced cardiac-related changes exhibited by the resistance exercise group may be associated with hemodynamic adjustments triggered by baroreflex sensitivity, cardiac autonomic tone, improved contractility, and reduced oxidative stress (86). Although these findings suggest that resistance-based exercise protocols may have cardioprotective effects, more studies are needed to provide further evidence especially using tumor-bearing rats receiving anthracyclines.

Clinical Interventions

To date, only one clinical trial examined the effects of resistance exercise on cardiotoxicity outcomes in cancer patients receiving anthracyclines. In the BEATE RCT, Schmidt et al. assessed a 12-week resistance training intervention in stage I-III breast cancer survivors ($n = 101$), of which 89.5% were receiving adjuvant anthracycline treatment (90). While resistance exercise was deemed feasible during adjuvant chemotherapy with a 71% adherence rate and exerted significant improvements in physical fitness, assessed by isokinetic and isometric muscle strength, role function and social function quality of life outcomes, and fatigue, no improvements in cardiorespiratory fitness were reported (90). Given the desirable effect resistance exercise has on cardiovascular health-related outcomes in the non-cancer population (108), and the previously described cardioprotective benefits identified in preclinical models receiving anthracyclines (86, 87), the unique cardiac-related effects of resistance exercise are worth further exploring within clinical trials among survivors who will, are, or have received anthracyclines.

Multi-modal Exercise Interventions

Both aerobic and resistance exercise have independent, beneficial effects on cardiovascular-related outcomes that potentially lead to different improved effects on anthracycline-induced cardiotoxicities. Within the cancer exercise guidelines recommended by ACSM (46), combined aerobic and resistance exercise are encouraged so that their respective benefits are collectively obtained. Here we discuss the available clinical studies that utilize multi-modal exercise interventions, including combined aerobic and resistance exercise, to target anthracycline-induced cardiotoxicities. Currently, no preclinical studies have examined multi-modal exercise interventions.

Clinical Interventions

Kirkham, Virani (92) completed a non-RCT assessing the effects of an 8–12 week progressive combined aerobic and resistance exercise intervention on cardiac function among breast cancer survivors receiving anthracyclines ($n = 37$). Across the intervention, systemic vascular resistance significantly decreased compared to baseline in both the exercise and control groups, however, the decrease in systemic vascular resistance was significantly attenuated in the exercise group (-264 ± 482 vs. -444 ± 376 dynes·sec·cm^{-5}), where the reduction in systemic vascular resistance in the exercise group was in response to an increase in vessel lumen radius. Cardiac output was also preserved in the exercise group compared to a significant increase from baseline in the control group. In contrast to the preservation of systemic vascular resistance and cardiac output, the exercise group had both a clinically and statistically significant decrease in VO_{2peak} (-2.6 ± 2.2 mL/kg/min), where a >1 mL/kg/min decline has been associated with 9–10% increased cardiac-related mortality risk (109, 110). However, the usual care control group did not have VO_{2peak} data, therefore, it is unclear if exercise attenuated the chemotherapy-induced reduction in VO_{2peak}, or if chemotherapy blunts exercise training adaptations. In spite of this, a secondary analysis identified 61% of the cohort as low-adherers (defined by attendance $\leq$ 67% of sessions), who had a significant within group reduction in VO_{2peak}, but this was only trending as different compared to the high adherers ($p = 0.09$). Of the sessions attended, the program was well adhered to as exhibited by 86% of participants reaching the intended aerobic intensity of 50–75% age-predicted HR reserve, and 96% of participants completed the intended aerobic duration of 20–30 min, therefore, highlighting this prescription as feasible during chemotherapy for breast cancer survivors. However, the results in this study should be interpreted with caution given the potential

selection bias of the assessed cohort. This study compared the exercise group to a concurrent usual care control group from a separate study, previously described (63); survivors were given the choice to participate in the single group intervention exercise study, described here (92), or the RCT examining a single bout of exercise prior to the first anthracycline infusion compared to usual care (63).

During treatment, survivors may experience acute cardiotoxicities such as tachycardia and diastolic hypotension, which can result in dizziness, lightheadedness, and difficulty in changing body position, as such, clinicians should be aware of the pattern in which these cardiotoxicities occur and provide the necessary intervention to ensure improved survivor well-being (93). One such adjuvant strategy is the inclusion of exercise during treatment; Kirkham, Lloyd (93) examined the effect of a combined aerobic and resistance-based exercise intervention during treatment, that continued for 10 weeks post-treatment, on resting HR and blood pressure in breast cancer survivors stage I-III ($n = 73$). Treatment regimens placing survivors at high risk of cardiotoxic side effects, including anthracyclines, which 71% of the cohort were receiving, were significant predictors of a 5–8 beat worsening of resting HR and HR recovery during treatment. However, a high attendance of exercise sessions ($\geq$67%) was associated with a 6-beat improvement in HR and HR recovery suggesting exercise to have a potential counteractive effect. Low aerobic fitness was additionally a strong independent predictor of elevated resting HR and impaired HR recovery both during and after treatment. This study continues to demonstrate the feasibility of exercise during treatment and provides critical insight into the prevalence of acute cardiotoxicities. While exercise is generally safe to complete when these acute cardiotoxicities are present, assessment precautions should be taken before exercise is begun as described within the safety measures of this study, which were taken from the ACSM contraindications to exercise for cancer survivors; if resting HR $>$ 100 bpm, systolic blood pressure $>$ 145 mmHg, or diastolic blood pressure $>$ 95 mmHg, exercise should not be completed (46).

In a non-RCT, both Howden, Bigaran (57) and Foulkes, Howden (94) examined the same cohort primarily assessing the effect of exercise on VO_{2peak} and cardiac function after an 8–12 week intervention. In order to determine if the impact of exercise persists into survivorship, Foulkes, Howden (94) reported on the long-term effects, 12 months following anthracycline cessation, and Howden, Bigaran (57) reported on the effects of exercise during treatment. The exercise intervention consisted of a periodized aerobic interval training and resistance exercise intervention in breast cancer survivors receiving anthracyclines ($n = 28$) (57). As seen in Kirkham, Virani (92), exercise during treatment does not necessarily improve but does attenuate a decline in cardiorespiratory fitness, which is again demonstrated in this study where the usual care control experienced a 15% decline in VO_{2peak} that was significantly different to the 4% decline noted in the exercise group ($p = 0.01$). However, the exercise group had a significantly greater baseline VO_{2peak} and it is unclear if this difference was accounted for in the group x time comparison. Furthermore, anthracyclines induced a significant decline in resting measures of LVEF and hemoglobin, and an increase in troponin I ($p < 0.001$), which were not attenuated by exercise. However, Howden, Bigaran (57) did demonstrate that exercise measures of cardiac function better predicted cardiac impairment than resting measures and proposed the inclusion of exercise tests within the clinical setting. At 12 months following anthracycline cessation, Foulkes, Howden (94) ($n = 17$) reported a continued significant decline in VO_{2peak} for both groups with no between-group differences. Therefore, survivors who undertook exercise during chemotherapy were not protected from the acute or long-term chemotherapy-induced declines in VO_{2peak}. However, exercise was not assessed during the 12 months post-treatment, making it unclear whether this change in functional capacity was treatment-related or if a detraining effect took place. Regardless, continued exercise post-treatment should be incorporated into survivorship care to prevent continued functional decline (**Figure 3**).

Mijwel, Backman (95) and Ansund, Mijwel (91) compared different combinations of multi-modal exercise programs. OptiTrain is a RCT conducted in breast cancer survivors ($n = 206$) receiving adjuvant chemotherapy including taxanes, anthracyclines, or a combination of the two, where survivors were randomized to one of three groups: resistance exercise plus HIIT, aerobic exercise plus HIIT, or usual care control (95). Although cardiovascular outcomes were not a focus of this study, VO_{2peak} (L/min) was measured, and in survivors not receiving taxanes, both the resistance plus HIIT and aerobic plus HIIT groups maintained VO_{2peak}, whereas the usual care group had a significant decline. However, when the groups were compared, only the aerobic plus HIIT group was significantly different from usual care controls among non-taxane survivors. Nevertheless, the within-group maintenance of VO_{2peak} in the resistance plus HIIT in those not receiving taxanes, and the significant difference in VO_{2peak} among those who were receiving taxanes in the resistance plus HIIT group compared to usual care, demonstrates that as little as 9 min of HIIT twice a week in conjunction with resistance training may be a time-efficient way to gain the same preservation of cardiorespiratory fitness compared to high volume aerobic exercise plus HIIT.

Ansund, Mijwel (91) conducted a one-year follow-up of the OptiTrain trial. This study primarily assessed acute and chronic chemotherapy-induced cardiotoxicities monitored by cardiorespiratory fitness, cardiac troponin T, a biomarker used in detecting acute cardiac damage, and NT-pro-BNP, a protein secreted by cardiomyocytes in response to cardiac wall stress a marker of long-term cardiac remodeling (91). This follow-up study examined 88 survivors, of which more than 93% of each group received anthracycline treatment. During the 16-week exercise intervention, where survivors were concurrently receiving chemotherapy, cardiac troponin T significantly increased in all groups, suggesting this was treatment-induced, and values returned to baseline concentration at one-year follow-up. Nt-pro-BNP levels showed no significant difference between groups at baseline or 16 weeks, however, at the one-year follow-up, the usual care group was significantly higher than both exercise groups (91). Survivors who met the biomarker criteria for risk of decreased cardiac function (cardiac troponin T

> 10 ng/ml at post-intervention and Nt-pro-BNP >100 ng/ml at 1 year follow up), most likely in the usual care control group, had significant declines in VO_{2peak} 2-years post-follow up compared to those who did not meet the criteria, suggesting an early change in these biomarkers may indicate compromised cardiovascular function. Further evidence is required into the usefulness of these biomarkers and their potential at identifying the most at-risk survivors which may then allow for the implementation of early intervention strategies.

While supervised in-clinic exercise often induces a superior physiologic benefit, given the face-to-face nature of the intervention and the real-time tactile adjustments that can be made, this form of exercise is not always feasible or desired. Smith, Ness (97) utilized a 12-week home-based combined aerobic and resistance intervention where weekly phone calls were completed to address any concerns and monitor exercise adherence. This study was a case series examining five survivors of childhood cancer (>10 years) diagnosed with subclinical anthracycline-induced cardiomyopathy that primarily assessed their response to exercise. No adverse events were noted, and compliance to exercise prescription was 86%, suggesting the feasibility and safety of home-based exercise in this population. Additionally, survivors showed improvements in VO_{2peak} (10.6%), ejection fraction (12.6%), and oxygen pulse (13.6%), while maximal HR response and respiratory exchange ratio were preserved. Järvelä and colleagues (96, 98) also examined the effect of home-based exercise (16 weeks) implemented post-treatment using a single group study design in childhood survivors of acute lymphoblastic leukemia ($n = 17$, $n = 21$, in the respective studies). Cardiorespiratory fitness and myocardial function were primarily assessed and significant improvements were observed for VO_{2peak}, early diastolic mitral inflow velocity, and lateral early diastolic mitral annulus velocity, which are all useful measures in predicting cardiac events (111). Further studies with a comparison group are needed to confirm the benefits of home-based exercise and the effect it has on acute and long-term anthracycline-induced cardiotoxicities.

ONGOING TRIALS AND CURRENT RESEARCH GAPS

Exercise cardio-oncology is an evolving field, thus, here we describe ongoing trials registered on ClinicalTrials.gov and NIH RePORTER, or published as a protocol paper, that assess survivors receiving anthracyclines, and its accompanying cardiotoxicities, within the context of exercise (**Table 3**). To evaluate research gaps within the field, we discuss the ongoing trials within the following categorizations that require further clarity: prescription of exercise, timing, study size and duration, and participant characteristics.

Prescription of Exercise

Previous anthracycline-based studies have considerable heterogeneity in the modes of exercise, and how they are prescribed e.g., frequency, intensity, duration, which continues to be present among ongoing trials. CORE, as previously described, has provided guidelines for the cardiac rehabilitation infrastructure required to address the unique exposures survivors at high risk of cardiotoxicities experience; however, these guidelines are yet to be evaluated in a clinical setting (48). In an ongoing trial by Thavendiranathan and Adams (119), cardiorespiratory fitness (VO_{2peak}), in addition to other measures of cardiac function and health, is being compared between a CORE-based intervention group and standard of care control group over 24-weeks in survivors of pediatric, adolescent, and young adult cancers (diagnosed $\leq$ 39 years) who had received treatments known to increased CVD risk, including anthracyclines, and are now adults ($\geq$ 18 years old). The results of this trial will provide insight into the effectiveness of the proposed CORE guidelines and how the guidelines may need to be amended to ensure survivors at risk of cardiotoxicities are receiving the most effective exercise prescription.

While heterogeneity of exercise modes and how they are prescribed, may be considered a limitation when trying to compare studies and assess the general effect of exercise on cardiotoxicities, it may also be considered a strength of the study in that it establishes the feasibility of different exercise protocols and their effect on cardiotoxicities for survivors on anthracyclines. For example, Christou (118) is comparing the tolerability of a 12-week novel all-extremity based exercise (mode unspecified) to treadmill walking and usual care to assess the effect on endothelial function in breast cancer survivors receiving chemotherapy, including anthracyclines. However, much of the published literature (57, 63, 92, 94, 96–98) and ongoing trials (113–116) focus on traditional aerobic- and resistance-based exercise prescriptions, as such, there is a lack of understanding as to the effect of other non-traditional modes such as HIIT, yoga, and circuit training. Of the collated list of ongoing trials, only one is prescribing a non-traditional mode of exercise, HIIT (119); however, Monzonís, Peña Gil (117) had to change the environment in which they supervised exercise due to COVID-19 and employed the use of virtually supervised exercise, a non-traditional setting of providing exercise. Further evaluation of the different modes, and the frequencies, intensities, and duration in which they may be prescribed referred to as the FITT (frequency, intensity, time, and type) principle of exercise prescription, will provide further understanding of the most effective prescription and the minimum thresholds in which benefits occur.

Timing

For the majority of cancer survivors, some exercise is preferred over sedentary behavior, and it is never too late to begin participation in exercise; however, the time point that exercise is most effective within the cancer care continuum is an ongoing debate and is likely cancer, treatment, and survivor specific. As described in the previous section, the published literature spans the entire cancer care continuum with exercise interventions being implemented before, during, and after chemotherapy, and have all demonstrated improvement or preservation in one or more cardiac-related outcomes (**Table 2**). Therefore, exercising at any stage of the cancer care continuum for survivors prescribed anthracyclines will likely be beneficial. Nevertheless, the extent of its benefit in the long term may be dictated by

TABLE 3 | Ongoing clinical trials examining the impacts of exercise on anthracycline-induced cardiotoxicities in cancer patients and survivors (as of September 2021).

Principal investigator	Study design	Outcomes of interest	Population	Intervention groups	Intervention
Hundley (112)	RCT	*Primary*: Attenuate physical inactivity, fatigue, exercise capacity, cardiac and cognitive function, strength, and HRQOL	Lymphoma, anthracycline-based chemotherapy	Individually tailored physical activity intervention	Not specified
Hundley (113)	RCT	*Parent trial aims:* *Primary*: 1. Design an automated MRI hardware/software platform for measuring and reporting LVF. 2. Changes in our MRI platform generated measures of LV volumes, EF, strain, myocardial T1 mapping, and aortic pulse wave velocity to predict pre- to 24-month post-anthracycline chemotherapy treatment differences in these same parameters. *Sub-trial aims:* *Primary*: 1. Feasibility of screening, enrolling, and randomizing patients. 2. Identification of barriers for participating in or adhering to the Physical Activity Intervention and Control Group. *Secondary*: Change in peak exercise cardiac output, A-V O_2, VO_2, LVF, cognitive function, HRQOL, 6MWT, fatigue	21 Non or Hodgkin lymphoma and stage I-IV breast cancer (18–85 years) On-treatment (350 mg/m^2 of anthracycline therapy or combination of anthracycline (250 mg/m^2) and subsequent paclitaxel or herceptin	Physical activity intervention; Healthy living instruction group (Control Group)	6 months Supervised: 1–2 x/week Home-based: 1–2 x/week Combined aerobic and resistance exercise
Grandy (114)	Single group	*Primary*: Feasibility (rate of recruitment) and adverse events associated with exercise program *Secondary*: Program adherence, attrition, cardiac function, cardiac disease risk, aerobic fitness, fatigue, QOL, and other cardiac rehabilitation measures	12 adult cancer patients on anthracycline chemotherapy (minimum dose of 100 mg/m^2 of DOX or 120 mg/m^2 of DAN or 150 mg/m^2 EPI)	Moderate-intensity aerobic exercise	12-week Moderate-intensity aerobic exercise: Supervised group sessions, 2 sessions/week, 45 min/session aerobic with an additional warm-up and cool-down, intensity at 40–60% HRR
Grandy and Keats (115)	RCT	*Primary:* Change in LVF *Secondary:* Change in cardiac electric activity, aerobic fitness, blood biomarkers, QOL, and fatigue	100 breast cancer patients receiving anthracycline (minimum dose of 240 mg/m^2 of DOX or 300 mg/m^2 of DAN)	Exercise + standard care; Standard care	12-week Aerobic exercise: Home based, 2 sessions/week, 20–45 min/session based on intensity; intensity varying between low (35–45% heart rate) low-moderate (46–55%), high-moderate (56–70%), and high (71–85%).
Antunes et al. (116)		*Primary:* Change in cardiac (dsy)function, LV strain, resting LVF *Secondary:* Change in anthropometric measures, physical function, physical activity, HRQOL, fatigue	90 breast cancer stages patients receiving (neo)adjuvant anthracycline	Combined aerobic and resistance; Standard care	2-month Supervised group sessions; 3 sessions/week Aerobic exercise: 70 min/session (60 min of aerobic exercise), progressive volume and intensity based on RPE-scale with goal to reach intensity between 65–80% of heart rate reserve Resistance exercise: Upper body and lower body weight training, progressive volume and intensity using RPE-scale

(Continued)

TABLE 3 | Continued

Principal investigator	Study design	Outcomes of interest	Population	Intervention groups	Intervention
Monzonís et al. (117)	RCT	*Primary:* Improve cardiac remodeling and enhance global cardiovascular risk profile *Secondary:* Change in functional capacity, 6MWT, VO2, HRQOL, chemotherapy tolerance, pain, disability, anthropometrics, biomarkers, dietary pattern, physical activity, lymphedema	122 breast cancer patients; post-treatment; treated with anthracyclines and / or anti-HER-2 antibodies (trastuzumab and / or pertuzumab)	Cardiac rehabilitation; Conventional management	Cardiac rehabilitation: Supervised exercise training (planned to be center-based, shifted to telematic due to COVID-19);
Christou (118)	RCT	*Primary:* 1. The effect all-extremity non-weight bearing exercise intervention, treadmill, and usual care on endothelial cell function and cancer therapy-related cardiac dysfunction. 2. Feasibility, tolerability and safety of all-extremity non-weight bearing exercise intervention compared with TE	68 breast cancer patients receiving (neo)adjuvant anthracycline, alkylating agent and/or taxane	All-extremity non-weight bearing; Treadmill aerobic exercise; Usual care	12-week Supervised; progress to 70% peak heart rate, 50 min/session, 3 days/week
Thavendiranathan and Adams (119)	RCT	*Primary:* Change in cardiorespiratory fitness *Secondary:* Change in cardiovascular disease risk factors, cardiovascular biomarkers, cardiac function, blood biomarkers, insulin sensitivity, BMI, physical activity levels, psychosocial health, QOL	696 young adult cancer survivors (18-39 years); post -treatment	Cardio-oncology rehabilitation (CORE); Standard care	6-month Aerobic exercise: HIIT training 2 times/week (1 supervised session and 1 home-based session), behavioral support

HRQOL, health-related quality of life; RCT, randomized clinical trial; MRI, magnetic resonance imaging; LVF, left ventricular function; EF, ejection fraction; A-V O2, arteriovenous oxygen difference; VO_2, oxygen consumption; 6MWT, 6-minute walk test; QOL, quality of life; DOX, doxorubicin; DAN, daunorubicin; EPI, epirubicin; HRR, heart rate reserve; ROM, range of motion; RPE, rating of perceived exertion; TE, treadmill exercise; UC, usual care; BMI, body mass index; HIIT, high-intensity interval training.

when exercise is initially implemented. This research question is best answered through multi-decade follow-up studies, similar to that being done in the GAP4 (120) and CHALLENGE (121) trials, which assess the long-term impact of exercise on survival outcomes. On a smaller scale, clinical trials are still needed to determine the immediate benefits of exercise at the various stages of the cancer care continuum. Among the ongoing trials described within this review, none are targeting the use of exercise in the prehabilitation stage, six are examining the effect of exercise during chemotherapy (113–116, 118, 122), and two are examining the post-treatment/survivorship stage (117, 119). By understanding the optimal timing of exercise interventions, the cardioprotective benefits of exercise can be maximized and anthracycline-induced cardiotoxicities can be attenuated to a greater degree with integration into clinical practice or survivorship care models. Future studies are warranted to conduct adequately powered RCTs comparing exercise interventions administered prior to, during, and following anthracycline treatment with long-term follow-up for the understanding of sustainability of benefits.

Study Size and Duration

With exercise being consistently demonstrated as a safe and feasible intervention among many cancer types and treatment regimens using small pilot studies and RCTs, larger multi-center trials are now needed to further emphasize the efficacy of exercise. While not an exercise intervention, Hundley (122) is conducting a 2-year prospective study to primarily assess the change in MRI measures of cardiovascular function, exercise tolerance through maximal and submaximal exercise capacity tests, and fatigue in breast cancer survivors on both anthracycline and non-anthracycline chemotherapies with comparison to age-matched non-cancer controls. This observational study has been actively recruiting since 2017 and has reported 403 enrollments as of September 2021. Large prospective cohort studies such as this one, can provide valuable information regarding what outcomes of interest change, the degree to which they change, and when these changes occur. This information can then be used to assess correlations among outcomes, which may assist in identifying who is at increased risk of poor cardiac health in the long term. Additionally, characterization studies like this can help decipher when the appropriate time is to intervene based on the timeline of outcome decline. Moreover, Thavendiranathan and Adams (119), previously described, are conducting a large 2- year exercise intervention trial examining VO_{2peak} with an estimated enrollment of 696 participants. The results of both these studies will be critical in understanding the trajectory of survivor health and the impact of exercise while on anthracycline treatment.

However, both of these studies only follow survivors for 2 years and many of the debilitating cardiotoxicities are likely to develop years, if not decades, beyond treatment cessation. For example, survivors of childhood cancer have been reported to experience cardiotoxicities >40 years post-treatment (123), where those who are more active throughout the years post-treatment are less likely to experience cardiovascular events (22). Large, multi-decade databases such as the Childhood Cancer Survivors Study (124), Nurse's Health Study (125), and Women's Health initiative (126) are valuable resources in assessing the long-term effects of cancer treatment, and as the databases continue to expand, they will become essential in our understanding of anthracyclines and the impact exercise can have on cardiotoxicities.

Participant Characteristics

There is a lack of clinical trials focusing on vulnerable cancer groups undergoing anthracyclines, including cancer types, survivors with a higher risk of cardiotoxicities, and racial minorities. Based on our review of the literature, the majority of studies are preclinical murine models with no specific cancer type or are clinical trials focused on breast cancer populations comprised of non-Hispanic Whites. As such, more studies covering a greater range of cancer types is required e.g., acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphoma, and bladder cancers. In addition to expanding our understanding of the effect of exercise on anthracycline-induced cardiotoxicities across a number of different cancers, it is important to identify who the most vulnerable survivors are that would benefit the most from early intervention. For example, Hundley (113) is assessing the change in cardiovascular MRI measures taken prior to the initiation of anthracycline or other cardiotoxic cancer therapies, and 3 months later, to assess if this predicts cardiovascular-related outcomes at 24 months in Hodgkin's and non-Hodgkin's lymphoma and stage I-IV breast cancer survivors (**Table 3**). A smaller component of this parent trial is to assess the feasibility of combined aerobic and resistance-based exercise compared to a healthy living education group where the cardiac MRIs from the individuals in this pilot study will be compared to the survivors in the parent study. This trial is unique in that it may provide key outcomes worth measuring in the early stages of a cancer diagnosis which could help identify the most vulnerable survivors. Additionally, the same group has proposed a trial to assess how a physical activity intervention attenuates physical inactivity and preserves exercise capacity, cardiovascular and cognitive function, strength, and health-related quality of life for those with lymphoma (112). This trial also has a novel component where they will examine a newly developed magnetic resonance cardiopulmonary exercise treadmill testing method to measure cardiac function and peripheral factors to further understand the mechanics of how physical activity helps preserve exercise capacity and reduce fatigue (112). Vulnerable groups that should be further explored due to the already identified risk of developing anthracycline-induced cardiotoxicities include survivors who receive high doses of anthracyclines, elderly and pediatric cancer populations, and survivors with comorbid disease (e.g., hypertension and diabetes) or with pre-existing CVD. Finally, racial/ethnic minorities are also in need of further study as they are disproportionately underrepresented in exercise oncology, exercise-cardio-oncology, and anthracycline settings, and often have a higher risk of cardiac-related events due to pre-existing conditions and poor lifestyles (127, 128). To establish exercise as a standard of care strategy in reducing anthracycline-induced cardiotoxicities, further clinical trials involving these rarely studied and vulnerable groups are needed to confirm the translation of the benefits of exercise interventions to populations with other cancer types and characteristics.

TABLE 4 | Research questions and considerations for future studies.

Unanswered future research questions	Considerations
What type(s) of exercise is(are) effective to address anthracycline-induced cardiotoxicity?	Modality of exercise (aerobic, resistance, or combined); cancer type; treatments.
What is the ideal time during the cancer continuum to intervene?	Pre-treatment, during treatment, or following treatment.
What is the optimal duration of an exercise intervention?	Timing of intervention, duration of exercise sessions, length of intervention, age of participant, diagnosis, presence of comorbid conditions.
Large, multi-center studies to better understand the feasibility and effectiveness of exercise to address anthracycline-induced cardiotoxicities.	Timing of intervention in treatment timeline, resources, setting of intervention (in-clinic/supervised, home-based/unsupervised, virtual/supervised, hybrid), availability of resources.

Based on the current evidence, exercise is a viable non-pharmacological strategy that can be used to mitigate anthracycline-induced cardiotoxicities among cancer survivors. While the optimal prescription and timing of exercise to elicit the greatest benefit are still unknown, the discussed studies demonstrate exercise induces positive effects on cardiac-related outcomes throughout the cancer care continuum. Within our critical analysis of the published and ongoing studies in exercise cardio-oncology, we established a number of gaps within the field that should be addressed in future studies (**Table 4**). The next section discusses guidelines and considerations for the employment of exercise for cancer survivors on anthracyclines. This information will be useful for researchers and clinicians in developing future research protocols and in-clinic programs to further disseminate the value and clinical application of exercise for this vulnerable population.

EXERCISE CARDIO-ONCOLOGY IN PRACTICE: CONSIDERATIONS FOR IMPLEMENTATION

Should the Current Exercise Guidelines Be Challenged?

Exercise has consistently been deemed safe, feasible, and effective for cancer survivors before, during, and post-treatment, as such, ACSM developed generic exercise guidelines for cancer survivors,

which have been previously described and are summarized in **Table 1**. While these are evidence-based guidelines, and the prescription variables have been identified as the most effective for cancer survivors, exercise should be individualized for each survivor, cancer type, and treatment. Therefore, clinicians and exercise specialists working with survivors with cardiotoxicities or aiming to prevent cardiac-related events, should also consider cardiology and cardio-oncology guidelines to address the unique needs of these survivors, and are also summarized in **Table 1** (48, 129, 130). Before survivors can be referred to or prescribed an exercise program, special considerations must be given to the type of cancer, stage of the disease, survivor health, timing of treatment, treatment tolerance, and what the goal of exercise is (e.g., to improve cardiorespiratory fitness muscle strength) (47, 48, 129, 131). These factors can impact the duration, frequency, intensity, and modalities of exercise that are safe and effective for a survivor. Therefore, to support the integration of safely practiced exercise, the CORE guidelines emphasize the importance of individually tailoring exercise prescriptions, which will be essential for improved adherence to health behaviors and long-term cardiotoxicity outcomes in cancer survivors receiving anthracyclines (47, 48, 129, 131).

Implementation of Exercise Cardio-Oncology in Clinical Practice

The setting in which exercise is performed e.g., supervised, self-directed, home-based, clinic-based, will have critical impacts on the accessibility and longevity for integrating exercise programs into cancer care settings. The CORE guidelines recommend the use of both supervised and self-directed exercise, depending on the needs of the survivor, due to a number of barriers when exclusively using supervised exercise, particularly in a clinic-based environment (48). Supervised, in-clinic settings provide a safe exercise environment for cancer survivors in that exercise physiologists can make real-time, tactile adjustments to ensure the correct execution of exercises. Additionally, survivors can exercise one-on-one with an exercise physiologist or in a supervised group setting that provides social support and accountability in adhering to exercise sessions. However, in-clinic sessions have a number of barriers relating to survivor adherence to the exercise intervention and may deter the development of long-term exercise habits as the burdens of commuting, number of other medical-related appointments, accessibility, cost, and sustainability are more pronounced than exercise interventions offered in a self-directed or virtually supervised home-based setting (48). Additionally, it is important to acknowledge the increased levels of stress and fatigue that a cancer diagnosis and treatment may have on survivors. Therefore, offering a hybrid or choice of in-clinic and home-based supervised exercise sessions may result in greater adherence to exercise programs. Self-directed exercise may be used to complement supervised sessions to increase the volume of exercise without restricting the survivor to specific appointment times. Self-directed exercise may also be prescribed if the barriers identified with supervised exercise are of concern; in this case, survivors may benefit from a one-off supervised exercise session, or a telephone/in-person consultation with an exercise physiologist to establish exercise goals and routine. However, self-directed exercise should only be recommended if the survivor is able to safely perform exercise without assistance and has clinician clearance. To further understand how exercise may be prescribed for survivors receiving anthracyclines to prevent, manage, or improve cardiotoxicities, the CORE guidelines recommend that adherence and feasibility of exercise interventions be incorporated in the design of interventions, which will allow for translation into realistic, clinical care settings (48). In the studies we reviewed, 10 utilized supervised/clinic-based sessions (16, 63, 88–93, 95, 103), three were self-directed and home-based (96–98), and two were combined supervised/clinic-based and self-directed/home-based sessions (57, 94). With the limited research on mitigating anthracycline-induced cardiotoxic outcomes with exercise-based interventions, future studies should prioritize targeted and realistic exercise programs that facilitate survivor adherence across the cancer care continuum, including supervised and self-directed settings and in-clinic, home-based, virtual, and commercial environments, where the latter two are yet to be examined.

Exercise as Prehabilitation

There is a growing interest to utilize exercise in prehabilitation settings early on in the cancer care continuum, as diagnosis provides a "teachable moment" where survivors are often more willing to make healthy changes to their lifestyle (132). Additionally, incorporating exercise between diagnosis and treatment may have protective clinical benefits as demonstrated by a number of interventions described in this review (15, 63, 67, 69, 83, 87), and improve the survivor's "starting point" where they begin treatment with a higher fitness level, improved body composition etc. as depicted in **Figure 3**. Furthermore, survivors may be in a healthier state prior to starting treatment and, therefore, are more likely to be able to complete a greater volume and/or higher intensity of exercise, which may lead to greater benefits and adherence, compared to starting an exercise program during or immediately post-treatment where survivors a likely in a weaker state. The use of exercise prior to anthracycline treatment is in alignment with the recent recommendations from the CORE guidelines for cancer populations at risk of cardiac-related outcomes (48). However, since the timing between cancer diagnosis and the start of chemotherapy treatment is relatively short (i.e. typically 1–12 weeks), future research is needed to understand how acute bouts of exercise immediately prior to anthracycline treatment may impact anthracycline-induced cardiotoxic outcomes (50, 133).

Exercise During Treatment

Exercise during anthracycline treatment has been established as safe and beneficial for cancer survivors (48, 129, 130, 134–136). In the current review, we have addressed how exercise has been shown to be safe and effective for cancer survivors in both the neoadjuvant and adjuvant anthracycline settings, which is associated with improvements in the efficacy of treatment and reduces cardiotoxicity risk in survivors who exercise regularly (**Table 2**). Considerations that may need to be addressed when

prescribing exercise while receiving anthracyclines includes what and when treatment-related side effects are experienced. Understanding the cycle of chemotherapy side effects e.g., which days after infusion survivors feel the best or worst, will assist in developing appropriate individualized exercise protocols. Furthermore, the number of medical-related appointments may also be of concern when prescribing exercise during this period, as it may dictate the preferred setting in which the survivor may prefer to exercise. For example, virtually supervised, as opposed to in-clinic exercise, may be more appealing given survivors will already be attending a number of chemotherapy infusion appointments. On the other hand, exercise bouts conducted at the hospital during an anthracycline infusion, or immediately before or after, may also provide further benefits including chemotherapy tolerance and effectiveness (63). However, exercise during the infusion is a relatively new concept and its feasibility and clinical application is yet to be established. In alignment with the current CORE and non-cancer cardiology guidelines, exercise needs to continue to be integrated into cancer treatment standard of care to support the health of cancer survivors at an increased risk for long-term cardiotoxic outcomes from anthracycline-treatment (48, 129).

Exercise Post-Treatment

Long-term cardiotoxic side effects of anthracyclines can be present anywhere from 1 year to decades after treatment completion, therefore, exercise post-treatment should be considered for long-term health and wellbeing of cancer survivors to improve, manage, or prevent late occurring anthracycline-induced cardiotoxic outcomes. Similar to diagnosis, the period of survivorship is also considered a "teachable moment" as survivors have gone into remission and are often willing to make the necessary lifestyle changes to prevent long-term side effects and cancer recurrence (132, 137). During the survivorship period, cancer care providers should utilize this time to nurture health behavior change and minimize the long-term impacts of cancer and cancer treatment (132, 137–139). There is established research that already supports the use of exercise to reduce the risk of cancer-related co-morbidities and improve health benefits, quality of life, and cardiovascular-related outcomes for survivors of numerous cancers (19, 46–48, 140–142), however, exercise studies during survivorship that exclusively target those receiving anthracyclines are lacking. Given that anthracyclines elevate the risk of cardiotoxicity and cardiovascular morbidity and mortality among cancer survivors, the incorporation of exercise-based interventions into established local and national survivorship programs should be explored, including clinic-based or commercially available group-exercise programs and resources for supervised and self-directed exercise programs. For example, *LIVESTRONG* is an exercise program for cancer survivors available at YMCA facilities in the United States (143, 144). This program offers a 12-week, supervised, individually tailored, small group-based exercise program with two sessions per week at little to no cost to the survivor. In one study assessing the safety and effectiveness of the *LIVESTRONG* program in cancer survivors both on and off-treatment, researchers found improved levels of physical activity, fitness, quality of life, and cancer-related fatigue (144). A similar exercise program by Rajotte, Yi (145) also conducted among cancer survivors of various diagnoses and ages in local YMCA facilities, found significant improvements in blood pressure, strength, fitness, and quality of life (145). Although these programs are not widely available, the expansion of such programs can be utilized to benefit cancer survivors who had anthracyclines. LIVESTRONG, and similar clinic-based and commercially available programs (146), highlight the sustainability and feasibility of these programs in real-world settings. In support of the CORE guidelines, community-based programs may be more realistic and accessible to integrate into everyday life and offer benefits to cancer survivors treated with anthracyclines, while still allowing supervised, tailored exercise prescriptions that can best support vulnerable cancer populations. There is a need for more accessible and affordable exercise programs for cancer survivors to access within their community as part of survivorship to minimize the risk of long-term anthracycline-induced cardiotoxicity.

Multidisciplinary Approaches

In order to have successful integration of exercise-based programs within cancer care, there is a need for multi-disciplinary teams in the prescription, delivery, and promotion of exercise across the cancer care continuum. Oncology is inherently multidisciplinary, as the collaboration across various healthcare professionals, community care resources, insurance companies, and referral pathways is imperative for comprehensive treatment and care (147). Standard of care teams are often cancer-type and treatment specific and may include specialists in medical oncology, radiation oncology, surgical oncology, cancer site specialists, primary care providers, nurses, physical therapists, and nutritionists (148). Exercise programs designed for sustained health benefits should be guided by an exercise physiologist or specialist, yet exercise specialists are not usually a part of the standard of care team (149, 150). The lack of appropriate exercise specialists on the standard of care teams creates a disconnect in the referral pathways for exercise-based programs in critical cancer populations. There is a clear gap between research into the benefits of exercise throughout the cancer care continuum and the incorporation of exercise into the standard of care. Elbourne, Soo (151) reported that fewer than 30% of clinicians working with prostate cancer survivors were aware of referral pathways for a supervised exercise program, and less than 16% of clinicians engaged in conversations with survivors about exercise (151). Though the integration of exercise as adjuvant medicine into the cancer treatment plan was low, nearly 73% of the clinicians in the study agreed that exercise counseling should be incorporated into cancer care (151). In a similar survey by the American Society of Clinical Oncology, 78.9% of oncology clinicians supported recommending physical activity to cancer survivors, yet less than 23% referred survivors to exercise programming (152). To best support the long-term health, wellbeing, and quality of life of cancer survivors prescribed anthracyclines, the standard of care teams should integrate exercise physiologists and rehabilitation specialists into the multidisciplinary teams to ensure that early referrals for

exercise cardio-oncology programs can be incorporated (153–157).

Referral Programs

There are no established best practices regarding referrals for survivors who are at high risk of anthracycline-induced cardiotoxic outcomes, as referrals for exercise are at the discretion of the survivor's physicians and standard of care team (48, 149, 156–158). To ensure referrals in cancer care settings, there needs to be an increased awareness of the importance of exercise as well as appropriate environments to refer to in order to implement exercise as a non-pharmacological strategy to mitigate cardiotoxic outcomes (48, 155–157). In a recent paper by Schmitz, Campbell (157) oncologists and providers within the standard of care team were called to actively "assess, advise, and refer" survivors for physical activity regularly throughout the cancer care continuum. However, one of the prominent barriers to successful utilization of referrals and implementation of exercise programs is the lack of oncologist and provider engagement in the referral process, which hinders the implementation and longevity of exercise programs for cancer survivors (147). For exercise referral to be effective, increased educational opportunities for health care providers and cancer care team members should be integrated into cancer-related conferences, online education modules, and healthcare professional development workshops. These continued education opportunities will aid in expanding awareness and advocacy for exercise in cancer standard of care, which will support the long-term health of at-risk survivors treated with anthracyclines to reduce cardiotoxic outcomes (48, 138, 149, 150, 157, 159).

Referrals for exercise should be unique for each survivor, as cancer type, treatment effects, health/medical status, current activity levels, ability level, and preferences for the type of exercise programming need to be accounted for (48, 157). To support clinicians in the process of assessing, advising, and referring survivors to exercise programs in the standard of care, ACSM developed the *Moving Through Cancer* initiative (160). *Moving Through Cancer* links clinicians with resources to connect survivors with established physical activity guidelines, as well as a directory with exercise professionals and programs in the community (160). Alongside increased education of exercise in the standard of care, the usage of referral programs like *Moving Through Cancer* that connect survivors with community-based exercise professionals and programs will greatly enhance the quality of exercise cardio-oncology care for cancer survivors at risk for anthracycline-induced cardiotoxic effects.

CONCLUSION

The management of anthracycline-induced cardiotoxicities is a serious unmet clinical need. Current scientific evidence suggests that exercise cardio-oncology interventions may be effective non-pharmacological approaches to protect or reverse the cardiotoxicities from anthracyclines. Preclinical studies support the benefits of exercise through various biological mechanisms of anthracyclines in conjunction with physiological effects of exercise, from cellular signaling in cardiac cells to systemic adaptations in the cardiovascular system, while the mechanisms of action in clinical studies need to be elucidated. Furthermore, several clinical studies have focused on the effects of exercise throughout anthracycline trajectories and collectively support the use of exercise as a feasible and safe modality that can prevent treatment-induced changes in cardiorespiratory fitness, biomarkers associated with cardiac damage, and cardiac function. There has been a growing interest in this field, accompanying research funding opportunities specifically targeting cancer treatment-related cardiotoxicities such as the National Cancer Institute and the National Heart, Lung, and Blood Institute (PA-19-112). Further large, multi-center studies with long-term follow-ups are needed to provide comprehensive evidence considering different exercise modalities, timing, intensity, implementations, and dissemination, and more vulnerable and understudied subgroups of cancer survivors before, during, and after anthracyclines.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Novel Mechanisms of Anthracycline-Induced Cardiovascular Toxicity: A Focus on Thrombosis, Cardiac Atrophy, and Programmed Cell Death

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Anthracycline antineoplastic agents such as doxorubicin are widely used and highly effective component of adjuvant chemotherapy for breast cancer and curative regimens for lymphomas, leukemias, and sarcomas. The primary dose-limiting adverse effect of anthracyclines is cardiotoxicity that typically manifests as cardiomyopathy and can progress to the potentially fatal clinical syndrome of heart failure. Decades of pre-clinical research have explicated the complex and multifaceted mechanisms of anthracycline-induced cardiotoxicity. It is well-established that oxidative stress contributes to the pathobiology and recent work has elucidated important central roles for direct mitochondrial injury and iron overload. Here we focus instead on emerging aspects of anthracycline-induced cardiotoxicity that may have received less attention in other recent reviews: thrombosis, myocardial atrophy, and non-apoptotic programmed cell death.

Keywords: anthracycline cardiotoxicity, thrombosis, myocardial atrophy, programmed cell death, protease activated receptor, FOXO1 (forkhead box O1)

INTRODUCTION

Considerable research effort has been invested in understanding the complex and multifactorial mechanisms underlying anthracycline-induced cardiotoxicity. Longstanding evidence has established causative roles for oxidative stress in contributing to cardiomyocyte dysfunction and death (1). Mitochondrial dysfunction generates much of this oxidative stress and the central role of multifaceted mitochondrial injury in anthracycline-induced cardiotoxicity has been comprehensively reviewed recently (2). Here, we will focus on emerging, though less-studied, mechanisms underlying the adverse effects of anthracyclines on both the heart and the vasculature.

ANTHRACYCLINES AND THROMBOSIS

Observational data suggest that some anti-cancer therapies are associated with increased risk for thrombotic events in the venous and arterial vasculature including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (AT) as recently summarized by

Grover et al. (3). Indeed, Weiss et al. reported that 5% of stage II breast cancer patients (22/443) with 2 years of post-mastectomy chemotherapy developed venous thrombosis without signs of metastasis (4). Interestingly, no thrombosis was observed after completion of the chemotherapy (4). In another study of Stage IV breast cancer patients, thrombosis incidence rose to 17.6% in those who received anthracyclines (5). Interestingly, analysis of common risk factors for thrombosis (ambulatory status, obesity, family history, smoking, diabetes mellitus, hypertension, liver dysfunction, thrombocytosis, and previous endocrine therapy) showed no association with the observed thrombotic events (5). With specific regard to anthracyclines, multiple myeloma patients were at an increased risk of DVT (16%) when doxorubicin (DOX) was added to thalidomide and that risk increased with age (6). Importantly, the thrombotic risk for all three of these trials is reported relative to a control group that did not receive an anthracycline. Increased thrombosis incidence (7.5%) was also observed in breast cancer patients undergoing an anthracycline-containing chemotherapy regimen with age-dependent risk increase (27%) in patients over 60 years, though this study did not include a control group that was not exposed to anthracyclines (7).

Patient-specific factors that enhance risk of anthracycline-induced thrombosis are poorly defined, though one intriguing possibility is the metabolic syndrome. Individuals with the metabolic syndrome are at higher risk of both thrombotic events (8), and anthracycline-induced cardiotoxicity (9), possibly as a result of the chronically proinflammatory systemic milieu. Obesity (10) and insulin resistance (11, 12) components of the metabolic syndrome, also independently enhance risk for anthracycline-induced cardiotoxicity, though a direct link to thrombosis has not been established.

PRO-THROMBOTIC EFFECTS ON VASCULAR CELLS

How do anthracyclines, such as DOX, contribute to a prothrombotic phenotype? Multiple studies have shown that anthracyclines increase phosphatidylserine (PS) exposure on the outer cell surface on vascular cells (13–16). Negatively charged PS-rich membranes enhance the coagulation cascade reaction by increasing the activity of gamma carboxyglutamic acid (GLA)-dependent coagulation factors like factor VIIa (FVIIa), FXa, FIXa, and thrombin (17). Liaw's group showed that DOX induces a procoagulant phenotype in human endothelial cells (ECs) by increasing the PS flip to the cell surface which enhances activity of preexisting tissue factor (TF), without increasing its expression level (16). Interestingly, this effect was not seen for methotrexate nor 5-fluorouracil treated ECs (16). Further, the increase in surface PS on the ECs was associated with DOX-induced EC apoptosis (16). Later, Boles et al. (15) confirmed that the anthracycline daunorubicin also increased cellular TF activity without affecting TF protein levels, but rather by enhancing PS surface exposure on the human monocytic cell line THP-1 (**Figure 1**). DOX had a similar effect on platelets, causing increased PS surface exposure due to apoptotic pathway activation in DOX-exposed human platelets and subsequently resulting in enhanced procoagulant activity (14). The authors linked the increased PS exposure to DOX-induced platelet mitochondrial dysfunction at doses of 2.5–7.5 mg/kg in rats (13). Interestingly, at a cardiotoxic DOX dose of 25 mg/kg apoptosis-dependent thrombocytopenia was observed as early as 4 h after DOX injection in rats (13).

Moreover, daunorubicin was shown to increase the release of TF+ extracellular vesicles (EV) from THP-1 cells *in vitro* (**Figure 1**) (15). Increased anthracycline-induced EV release was confirmed by others (18–20). DOX-induced EVs are enriched for 4-hydroxy-2-nonenal (4-HNE), a marker for oxidative stress (19). 4-HNE can directly induce the release of TF+EVs from perivascular cells which can contribute to a prothrombotic state (21, 22). In line with this observation, TF+EVs were shown to enhance thrombus formation in multiple murine models of cancer-associated thrombosis (23, 24). Aside from its procoagulant effects, DOX is known to negatively affect the anticoagulant properties of ECs by downregulating the expression of the endothelial protein C receptor, leading to decreased protein C pathway activation (25).

EFFECTS ON BLOOD FLOW AND THROMBUS FORMATION *IN VIVO*

Injection of DOX (8 mg/kg) leads to occlusive vasoconstriction of smaller vessels ($<15\,\mu m$) and vascular leakage in the murine femoral microvasculature within 4 min (26). Moreover, the same dose of DOX also reduces the blood flow in testicular arteries in mice within 15 min of injection (27). The authors linked these phenomena to DOX-induced vascular toxicity leading to EC-platelet interactions and the formation of EC-bound platelet microthrombi (27). Blood flow was restored by pre-treatment with low molecular weight heparin or the anti-platelet drug eptifibatide, suggesting that anti-platelet/anti-coagulant agents might be effective in reducing the detrimental vascular effects of DOX (27). DOX doses up to 7.5 mg/kg significantly enhanced thrombus sizes in a modified rat $FeCl_3$ vena cava thrombosis model, without causing thrombocytopenia (14). In addition, in a vena cava stasis model DOX (7.5 mg/kg) caused increased thrombus formation that was reduced by administration of clopidogrel, aspirin or an inhibitor of platelet activated factor (28). These findings strongly suggest that DOX-induced venous thrombosis is dependent upon platelet activation (28).

COAGULATION-DEPENDENT SIGNALING IN ANTHRACYCLINE-INDUCED CARDIOTOXICITY

While coagulation activation leads to fibrin deposition, the coagulation proteases that are generated in the process also lead to cleavage of protease-activated receptors (PARs) (29). PAR1 and PAR4 are activated by thrombin and are expressed on human platelets; their cleavage is the strongest platelet-activating stimulus. PAR3 also is activated by thrombin, but PAR3 mostly acts as co-factor for PAR4 and has only limited

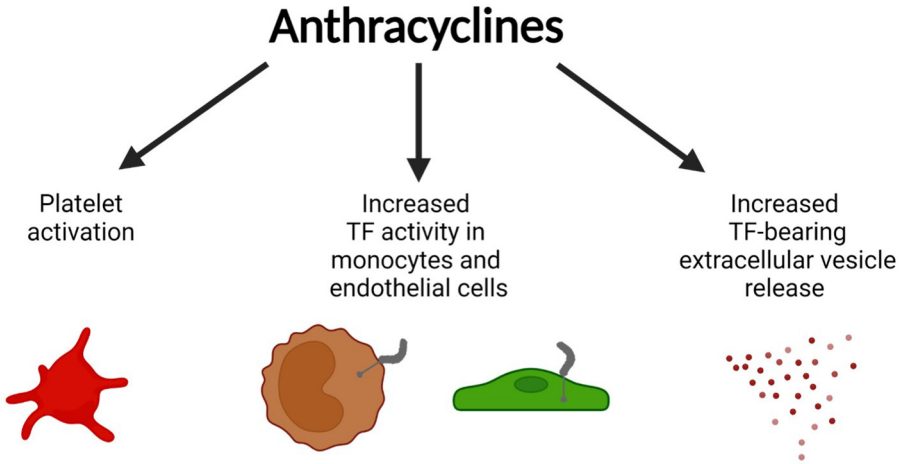

FIGURE 1 | Prothrombotic effects of anthracyclines. Anthracyclines (doxorubicin, daunorubicin) activate vascular cells including platelets, monocytes, and endothelial cells leading to surface phosphatidylserine (PS) exposure, increased activity of pre-existing tissue factor (TF) on monocytes and endothelial cells, and the release of TF-bearing extracellular vesicles (EV). Figure created with BioRender.com.

signaling function in humans (30). PAR2 is rather thrombin-insensitive and is primarily activated by the TF:FVIIa complex or FXa (31). Though PARs frequently are considered for their roles in platelets, they also are expressed on cardiomyocytes, where they contribute to the cardiac response to multiple injury models (29, 31, 32). The absence of PAR1 and PAR2 reduced infarct size and adverse cardiac remodeling in experimental heart failure (29, 31, 32). PAR4 activation can be cardioprotective or detrimental dependent on the chosen injury model and time point analyzed (31, 33–36).

With regard to chemotherapy-induced toxicity, PAR1 deficiency and PAR1 inhibition with the FDA-approved drug vorapaxar protected against DOX cardiotoxicity in mice (37). PAR1 activation exacerbated mitochondrial dysfunction and apoptosis in cardiac cells exposed to DOX *in vitro* (37). PAR1 deficiency was associated with reduced oxidative stress and apoptosis as well as decreased circulating cardiac troponin I and improved cardiac contractile function in the hearts of mice treated with 20 mg/kg DOX (37). PAR1 deficiency was also protective in a chronic DOX cardiotoxicity model (5 mg/kg/week for 5 weeks) (37). In line with these observations, PAR1 inhibition with the PAR1 inhibitor Q94 reduced toxic renal effects of DOX (15 mg/kg) in mice (38). Whether PAR2 or PAR4 contribute to DOX cardiotoxicity is the objective of ongoing investigations. Interestingly, PAR2 inhibition with FSLLRY-NH2 reduced nephropathy in a chronic rat DOX kidney injury model (1 mg/kg/day for 6 weeks) suggesting that PAR2 deficiency/inhibition might also be cardioprotective during DOX chemotherapy (39).

ANTHRACYCLINES INDUCE MYOCARDIAL ATROPHY

Anthracycline-based chemotherapies are known to cause abnormalities in heart morphology in cancer patients. Childhood cancer survivors who received anthracycline treatment have reduced ventricular wall thickness and myocardial mass later in life (40, 41). Recent evidence suggests that anthracyclines also cause a reduction in left ventricular mass in adult cancer patients (42–44). Importantly, an early decline in heart mass is associated with worse heart failure outcomes, emphasizing the importance of this phenomenon (42). A decrease in heart mass can be caused by reduced cardiomyocyte size (atrophy) and/or number (i.e., loss of cardiomyocytes due to cell death). Here, we summarize recently identified mechanisms underlying anthracycline-induced atrophy and cell death (**Figure 2**).

Similar to the clinical findings, exposure to the anthracycline DOX also reduces heart weight in mice (44–46). At the molecular level, DOX induces p53 expression, which is necessary for inactivation of mammalian target of rapamycin (mTOR), a serine-threonine kinase essential for protein synthesis (46). Interestingly, DOX-induced reductions in heart weight and myocyte size are abolished by cardiac-specific expression of dominant-interfering p53 or constitutively active mTOR, suggesting that DOX induces cardiac atrophy through p53-dependent inhibition of mTOR (46). Activation of mTOR by vascular endothelial growth factor-B (VEGF-B) gene therapy also prevents DOX-induced cardiac atrophy (47). Conversely, inducible ablation of mTOR in adult heart is sufficient to reduce cardiomyocyte size within 1–2 weeks (48). Taken together, these data indicate that mTOR inhibition is an important mechanism underlying DOX-induced atrophy.

DOX also induces expression of muscle RING finger 1 (MuRF1), a striated muscle-specific ubiquitin ligase and a key mediator of cardiac atrophy (44, 45). Mice lacking MuRF1 are resistant to DOX-induced reduction in heart mass, suggesting that MuRF1 is necessary for DOX-induced atrophy (44). Mechanistically, DOX exposure induces cyclin-dependent kinase 2 (CDK2)-mediated phosphorylation of forkhead box O1 (FOXO1) at Ser 249, resulting in FOXO1 activation and

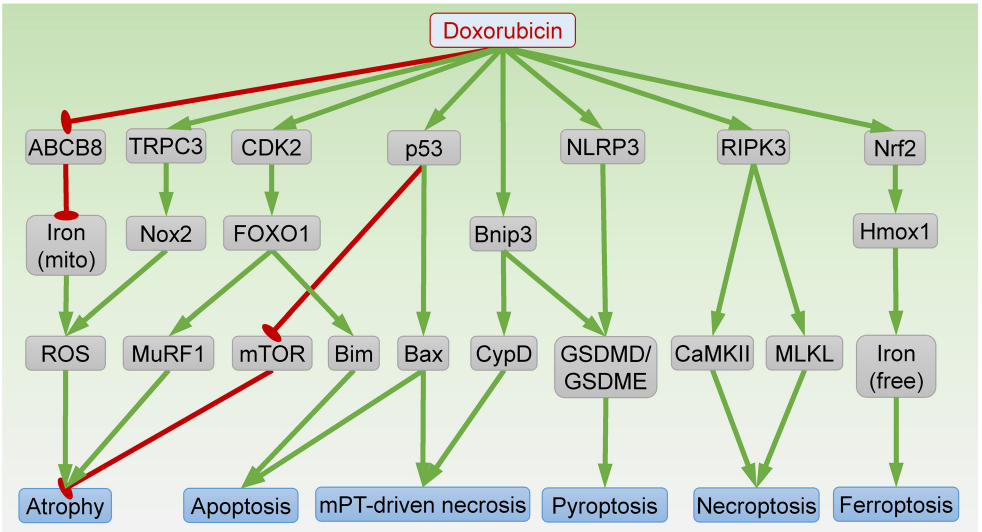

FIGURE 2 | Signaling pathways in DOX-induced cardiomyocyte atrophy and death. ABCB8, ATP-binding cassette protein-B8; CaMKII, Ca^{2+}-calmodulin–dependent protein kinase; CDK2, cyclin-dependent kinase 2; CypD, cyclophilin D; FOXO1, forkhead box O1; GSDMD/GSDME, gasdermin D/E; Hmox1, heme oxygenase-1; mito, mitochondria; MLKL, mixed lineage kinase domain like pseudokinase; mPT, mitochondrial permeability transition; mTOR, mammalian target of rapamycin; MuRF1, muscle RING finger 1; Nox2, NADPH oxidase 2; RIPK3, receptor-interacting protein kinase 3; ROS, reactive oxygen species; NLRP3, NLR family pyrin domain containing 3; TRPC3, transient receptor potential canonical 3. Arrows indicate activation; bar-headed lines indicate inhibition.

transcription of MuRF1 (45). Treatment with a FOXO1 inhibitor prevents DOX-induced cardiac atrophy and dysfunction (45). Collectively, FOXO1-dependent MuRF1 expression mediates DOX-induced atrophy.

Cardiac atrophy can occur as a result of oxidative stress. DOX exposure induces reactive oxygen species (ROS) generation through mitochondrial iron accumulation, owing to repression of ATP-binding cassette protein-B8 (ABCB8)-mediated mitochondrial iron export (49). Cardiac-specific ABCB8 transgenic mice are protected from DOX-induced ROS generation and atrophy (49). In addition, DOX exposure induces transient receptor potential canonical 3 (TRPC3)-dependent upregulation of NADPH oxidase 2 (Nox2) (50). Formation of the TRPC3-Nox2 complex amplifies ROS production and results in cardiac atrophy. Knockdown of TRPC3 or pharmacologic inhibition of TRPC3-Nox2 interaction attenuates DOX-induced atrophy in neonatal rat cardiomyocytes (NRCMs) (50). Moreover, mice lacking Nox2 are also resistant to DOX-induced cardiac atrophy (51). These findings suggest that enhanced ROS production resulting from mitochondrial iron accumulation or TRPC3-Nox2 complex formation also contributes to DOX-induced atrophy.

CONTRIBUTIONS OF PROGRAMMED CELL DEATH TO ANTHRACYCLINE CARDIOTOXICITY

Exposure to anthracyclines triggers a variety of cell death modalities in the heart, resulting in cardiac cell loss. Anthracycline-induced cell death pathways have been reviewed in detail quite recently (52). A brief summary of the novel mechanisms of anthracycline-induced cardiomyocyte death is provided below.

Apoptosis

Apoptosis is undoubtedly the most intensively studied form of cell death in anthracycline cardiotoxicity. DOX targets topoisomerase-IIβ to cause DNA double-strand breaks and initiate the intrinsic apoptosis pathway (53). DNA damage induces p53-dependent oligomerization of the Bcl2 family members Bak and Bax, which forms a pore in the outer mitochondrial membrane, resulting in cytochrome *c* release, caspase activation, and apoptosis. Accordingly, pharmacological inhibition of p53 or Bax blocks apoptosis and prevents DOX-induced cardiomyopathy (54, 55). It is noteworthy that p53 plays complicated roles in DOX-induced cardiotoxicity by modulating apoptosis-independent processes including mitochondrial biogenesis (56) and clonal hematopoiesis (57), as well as atrophy (46). In addition to the pore-forming effectors Bak and Bax, the pro-apoptotic Bcl2 family proteins also include activators (Bim, Bid, and Puma) that directly interact with the effectors to trigger apoptosis (58). DOX induces expression of Bim through CDK2-dependent FOXO1 activation (45, 59). Inhibition of either CDK2 or FOXO1 attenuates DOX-induced apoptosis and cardiac dysfunction (45, 59). Young age, a major risk factor for anthracycline cardiotoxicity in humans, is associated with higher sensitivity to apoptosis, further supporting an important role of apoptosis in anthracycline-related cardiotoxicity (60).

Mitochondrial Permeability Transition Pore (mPTP)-Driven Necrosis

Necrosis driven by opening of the mPTP is characterized by rapid loss of the inner mitochondrial membrane potential and is dependent on cyclophilin D (CypD) (61). Recent evidence suggests that DOX treatment provokes mPTP-driven necrosis in cardiomyocytes (62). Mechanistically, DOX induces expression of Bnip3, which binds CypD to trigger mPTP opening and resultant necrosis (62). Bnip3 null mice are protected from DOX-induced mitochondrial damage, necrosis, and cardiac dysfunction (63). In addition, Bax and Bak are necessary for mPTP-driven necrosis (64, 65). Indeed, a small-molecule Bax inhibitor protects against DOX-induced necrosis *in vivo* (55).

Necroptosis

Necroptosis is programmed cell necrosis that is initiated by binding of a death ligand (typically from the TNF superfamily) to a death receptor (such as Fas, TNFR1, or TRAIL) and culminates in plasma membrane permeabilization mediated by mixed lineage kinase domain like pseudokinase (MLKL) (61). MLKL activation and plasma membrane translocation requires phosphorylation by receptor-interacting protein kinase 3 (RIPK3) (66). DOX exposure upregulates cardiac RIPK3 and MLKL *in vivo* and *in vitro* to induce necroptosis (67). RIPK3 knockout mice are resistant to DOX-induced myocardial necrosis, cardiomyopathy and death (68). In this context, RIPK3 induces activation of Ca^{2+}-calmodulin–dependent protein kinase (CaMKII) to trigger necroptosis (68). Moreover, DOX-induced cardiomyocyte death is blocked by the necroptosis inhibitor necrostatin-1, suggesting that necroptosis contributes to DOX-induced cardiomyocyte injury (67).

Ferroptosis

Ferroptosis is a form of programmed cell death associated with mitochondrial damage owing to iron accumulation and lipid peroxidation (61). DOX induces nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent transcription of heme oxygenase-1 (Hmox1) to trigger heme degradation, resulting in free iron accumulation, and ferroptosis (69). Treatment with the Hmox1 antagonist zinc protoporphyrin IX, the iron chelator dexrazoxane, or the ferroptosis inhibitor ferrostatin-1 protects against DOX-induced cardiomyopathy (69). Interestingly, loss of the E3 ubiquitin ligase tripartite motif containing-21 (TRIM21) enhances Nrf2 antioxidant activity but downregulates Hmox1, resulting in reduced ferroptosis and cardiotoxicity following DOX exposure (70). In addition, DOX reduces the levels of glutathione peroxidase 4 (GPx4), acyl-CoA thioesterase 1 (Acot1), and mitochondrial ubiquitin ligase MITOL, all of which augment lipid peroxidation and ferroptosis, in mouse heart (71–73).

Pyroptosis

The major characteristic of pyroptosis is plasma membrane permeabilization mediated by gasdermin proteins such as gasdermin D (GSDMD) and gasdermin E (GSDME) (61). Cleavage of GSDMD by caspases 1, 3, 4, 5 or 11 results in GSDMD pore formation at the plasma membrane and subsequent pyroptosis. Pyroptosis is often pro-inflammatory owing to secretion of interleukin-1β and interleukin-18. DOX exposure induces cardiomyocyte pyroptosis *in vivo* and *in vitro* through NLR family pyrin domain containing 3 (NLRP3)-dependent activation of caspases 1, 3, and 11 (74, 75). In addition, Bnip3-dependent activation of caspase 3 also contributes to DOX-induced pyroptosis in cardiomyocytes (76).

CONCLUSIONS

Here, we have reviewed our emerging understanding of the contributions of thrombosis, myocardial atrophy, and programmed cell death to the complex and multifaceted pathobiology of anthracycline-induced cardiovascular toxicity. Future work in our labs and others will further explicate the importance of these processes to anthracycline-induced cardiovascular toxicity and define whether they could represent novel therapeutic targets for prevention or treatment of these dose-limiting and potentially life-threatening adverse effects.

AUTHOR CONTRIBUTIONS

All authors drafted, edited, and approved the final version of the manuscript.

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Early Change in Area Strain Detected by 3D Speckle Tracking Is Associated With Subsequent Cardiotoxicity in Patients Treated With Low Doses of Anthracyclines

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Objective: To evaluate the prognostic impact of the parameters of myocardial deformation using three-dimensional speckle tracking echocardiography (3DSTE) in patients with breast cancer who underwent chemotherapy with low doses of anthracyclines.

Background: Chemotherapy-related cardiotoxicity has an important prognostic impact on cancer survivors. Three-dimensional STE has revealed more consistent data than two-dimensional techniques and may represent a more accurate tool in the evaluation of myocardial function in patients who underwent chemotherapy.

Methods: We evaluated patients with breast cancer who were treated with anthracyclines (associated or not with trastuzumab) in five stages: baseline, after cumulative doses of 120 and 240 mg/m^2 of doxorubicin, and then, after 6 months and at least 1 year after anthracyclines. Ultrasensitive troponin I (US-TnI) and a standard echocardiography study were performed at each stage. We analyzed left ventricular ejection fraction (LVEF) by Simpson's method, two-dimensional speckle tracking (2DSTE) with longitudinal and radial strain values, and 3DSTE with longitudinal, radial, and circumferential strain as well as twist, torsion, rotation, and three-dimensional global area strain (3DGAS). Cardiotoxicity was defined as a decrease in LVEF by more than 10 percentage points to a value lower than 53%.

Results: We evaluated 51 female patients who were aged 50.6 ± 11 years. After the cumulative dose of 240 mg/m^2 of doxorubicin, US-TnI was increased (>34 pg/ml) in 21 patients (45%, $p > 0.001$), LVEF remained unchanged ($p = 0.178$), while 2DSTE longitudinal strain was decreased (from −17.8% to −17.1%, $p < 0.001$) and 3DSTE detected changes in longitudinal, radial, circumferential, and area strain. After a lower cumulative dose of doxorubicin (120 mg/m^2), 3DGAS ($p < 0.001$) was the only parameter that was changed. In the follow-up, 7 (13%) patients presented a decrease in LVEF. Three-dimensional GAS early changed to abnormal values was the only variable associated with a subsequent decrease in LVEF (definitive cardiotoxicity).

Conclusion: In patients with breast cancer, 3DSTE detected early changes in area strain after very low doses of doxorubicin. The 3DGAS early changed to abnormal values was associated with a subsequent decrease in LVEF, representing a promising technique to predict chemotherapy-induced cardiomyopathy.

Keywords: cardiotoxicity, chemotherapy, echocardiography, 3D strain, 3D speckle tracking

BACKGROUND

Advances in oncology therapy have increased cancer patient survival rates (1). However, these patients are exposed to the damaging effects of cancer-therapeutic related cardiac dysfunction (CTRCD), which represents a significant cause of morbidity and mortality (2, 3). This complication may result in cancer treatment discontinuation and compromise cancer control or its cure (4). Additionally, chemotherapy-related heart failure (HF) often has a worse prognosis than many cancers, with mortality as high as 60% within 2 years (2). Early detection of cardiotoxicity along with cardioprotection therapy is fundamental to improve the prognosis of these patients (5, 6). However, the usual parameters used for this diagnosis, especially left ventricular ejection fraction (LVEF), have low sensitivity, changing only in the later phases, when the majority of patients do not respond to treatment (5, 7). Thus, there is increased interest in identifying early markers of cardiotoxicity that could predict the subsequent decrease in LVEF and progression to HF.

In this setting, the myocardial deformation assessed by two-dimensional speckle-tracking echocardiography (2DSTE), especially two-dimensional global longitudinal strain (2DGLS), has been demonstrated to play a significant role in the diagnosis of subclinical cardiotoxicity (8–11). Recent expert consensus strongly supports a 2DGLS-based follow-up of adults during and after cancer therapy, and a reduction of this parameter by >15% is likely to be of clinical significance, since it might predict a decrease in LVEF (12, 13). However, the 2DSTE technique presents limitations, which may impair analysis of cardiac mechanics (14).

Three-dimensional echocardiography provides a greater proximity to the cardiac anatomy and a high accuracy and reproducibility as compared to cardiac magnetic resonance (CMR) (15). An important advance was the development of the three-dimensional speckle tracking echocardiography (3DSTE), which has overcome many limitations related to 2DSTE (16, 17). The 3DSTE does not rely on geometric assumptions, and the speckles are tracked by means of the homogeneous spatial distribution of each component of the myocardial displacement vector (16, 17). Previous data suggest that when compared to the 2DSTE, 3DSTE has a higher correspondence with measures of cardiac mechanics, greater accuracy, and efficiency (16, 17). Although reproducibility and applicability of 3DSTE have already been demonstrated in different clinical settings (18–21), this technique has been poorly explored in cancer patients who underwent chemotherapy.

This prospective study evaluated myocardial deformation using 2DSTE and 3DSTE in patients with breast cancer who underwent chemotherapy with low doses of anthracyclines, to identify early markers of cardiotoxicity and its association with a subsequent decrease in LVEF or development of HF.

Abbreviations: 2DGLS, Two-dimensional global longitudinal strain; 2DRS, Two-dimensional radial strain at midpapillary level; 2DSTE, Two-dimensional speckle tracking echocardiography; 3DGAS, Three-dimensional global area strain; 3DGCS, Three-dimensional global circumferential strain; 3DGLS, Three-dimensional global longitudinal strain; 3DGRS, Three-dimensional global radial strain; 3DSTE, Three-dimensional speckle tracking echocardiography; ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker; CMR, Cardiac magnetic resonance; CTRCD, Cancer-therapeutic related cardiac dysfunction; HF, Heart failure; LVEF, Left ventricular ejection fraction; TAPSE, Tricuspid annular plane systolic excursion; US, TnI, Ultrasensitive troponin I.

METHODS

Study Population

In this prospective cohort, patients at least 18 years old, newly diagnosed with breast cancer, and scheduled to receive chemotherapy with anthracyclines were eligible for the study.

Exclusion criteria included previous treatment with chemotherapy or radiotherapy, inadequate echocardiographic image, and the presence of left ventricular systolic dysfunction with an LVEF <55% before chemotherapy.

The Ethics Committee approved the study, and written informed consent was obtained from all patients.

Cancer treatment was scheduled in four chemotherapy cycles with a 21-day interval between them. In each cycle, 60 mg/m^2 of non-liposomal doxorubicin was administered, totaling 240 mg/m^2, together with 600 mg/m^2 of cyclophosphamide, totaling 2, 400 mg/m^2. Human epidermal growth factor receptor 2 (HER-2) positive patients received trastuzumab treatment. In selected cases, patients received cisplatin, paclitaxel, and/or radiotherapy.

Patients underwent a comprehensive echocardiographic study and laboratory collection of serum ultrasensitive troponin I (US-TnI) during the following 5 stages: baseline, after cumulative doses of 120 and 240 mg/m^2 of doxorubicin, and then, after 6 months and at least 1 year after anthracyclines (**Figure 1**). The echocardiographic and laboratory analyses were performed between 3 and 7 days after exposure to the anthracyclines.

Based on current guidelines, cardiotoxicity was defined as a decrease in LVEF by more than 10 percentage points to a value lower than 53% (12, 13).

Standard Echocardiography

Echocardiography was performed using Artida 4D equipment (Toshiba Medical Systems Corporation, Otawara-shi, Japan). Image acquisition and analysis were performed by one experienced echocardiographer who was blinded to prior

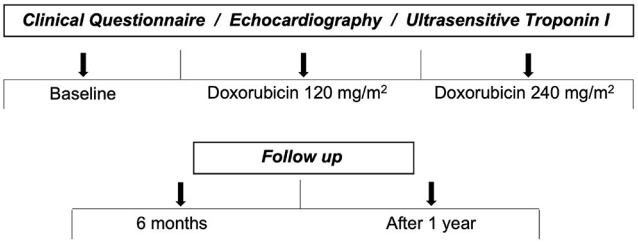

FIGURE 1 | Stages of evaluation.

echocardiographic results. At least three consecutive cardiac cycles were obtained, and the exams were digitally stored for subsequent analysis. LVEF assessed was measured using the Simpson biplane method. From the apical 4-chamber view, E wave velocity, A wave velocity, and E/A ratios were measured using conventional Doppler; peak systolic (s′), early diastolic (e′) mitral annular septal, and lateral velocities were measured using tissue Doppler imaging; and the E/e′ ratio was also calculated. Analysis of LV diastolic function was performed according to the recommendations of the American and European Societies of Echocardiography (22). Right ventricular systolic function was also evaluated.

Speckle Tracking Echocardiography

Peak systolic strain was measured with 2DSTE at a frame rate of 50–90 frames/s or ≥40% of the heart rate. The adequacy of tracking was verified manually, and the region of interest was readjusted to achieve optimal tracking if necessary. Two-dimensional GLS was calculated by averaging the peak systolic strain values in the myocardial segments of the apical 2-, 3-, and 4-chamber views. Additionally, two-dimensional radial strain (2DRS) was calculated by averaging peak systolic strain values in all 6 segments of the parasternal short-axis view at the midpapillary level.

The 3DSTE technique was performed from the apical 4-chamber view (full volume acquisition) using a fully sampled matrix array transducer (PST-25SX). The whole LV was positioned in the pyramidal volume while the depth and width of the sector were reduced to improve spatial and temporal resolution (20–30 volumes/s). After the acquisition, views in five planes in the standard axis were exposed, two longitudinally oriented orthogonally and three transversally oriented. The strain analysis was undertaken based on the marking of three points on the LV myocardium. The endocardial border was detected automatically by the 3D Wall Motion Tracking software (Toshiba Medical Systems Corporation, Otawara-shi, Japan). The tracings were modified manually only in areas where the endocardial borders were not adequately marked. The strain was automatically calculated by the software during the whole cardiac cycle, providing continuous values for 17 myocardial segments simultaneously. The mechanical analysis derived from the 3DSTE was allowed for the following parameters to be calculated: three-dimensional global longitudinal strain (3DGLS), three-dimensional global radial strain (3DGRS), three-dimensional global circumferential strain (3DGCS), three-dimensional global area strain (3DGAS), rotation, torsion, and twist.

Reproducibility

Interobserver and intraobserver variabilities were evaluated in randomized patients using an intraclass correlation coefficient with 95% CIs.

Ultrasensitive Troponin I

The analysis of US-TnI was undertaken with the immunoassay method (chemoluminescence) and expressed in pg/ml, using the Vitros® 5600 (Ortho Clinical Diagnostics, Johnson & Johnson) equipment. Values above 34 pg/ml were considered to be increased.

Statistical Analysis

Continuous data were presented as mean ± SD or median with interquartile range. Categorical data were presented as percentages.

The echocardiographic parameters and the US-TnI values were described according to evaluation stages and compared with generalized estimating equations with normal distribution and identity link function, supposing a matrix of autoregressive correlations of the first-order between the moments. For US-TnI, the logarithmic correction function was used due to the asymmetric distribution of the values. The analyses were followed by multiple Bonferroni comparisons when appropriate.

The follow-up changes in LVEF were created after the use of chemotherapy and verified who suffered and who did not change and compared the deltas of the cardiac parameters of patients according to change in LVEF using Student's t-tests and verified the association of qualitative characteristics with LVEF alteration using Fisher's exact tests or likelihood ratio tests.

The statistical analysis was performed with IBM-SPSS *for Windows* version 20.0. Values of $p < 0.05$ were considered significant.

RESULTS

Study Population

Sixty-eight patients were eligible for the study, with seventeen exclusions (six due to inadequate echocardiographic image, five because they did not wish to follow-up, and two non-cardiac-related death). Accordingly, 51 patients underwent echocardiographic and laboratory analysis at baseline, after cumulative doses of 120 and 240 mg/m^2 of doxorubicin, and then, after 6 months and at least 1 year after anthracyclines. After a cumulative dosage of 120 mg/m^2 of doxorubicin, two patients did not present for evaluation due to fatigue and in the stage just after 6 months of treatment, 4 patients did not present for evaluation because they did not wish to follow-up. The mean follow-up time was 1.6 ± 0.6 years.

All patients were women with a mean age of 50 ± 11 years. The clinical characteristics are summarized in **Table 1**. All patients were treated with a cumulative total dose of 240 mg/m^2 of doxorubicin and 2, 400 mg/m^2 of cyclophosphamide, with an intravenous infusion time of 2 h per cycle. Seven patients

TABLE 1 | Baseline clinical characteristics of the patients.

Variable	*n* = 51
Age (years)	50.6 ± 11.3
Body mass index (kg/m^2)	26.8 ± 4.9
Heart rate (beats/min)	75.8 ± 9
Cardiovascular Risk Factors *n* (%)	
Diabetes	6 (11.8)
Hypertension	13 (25.5)
Hyperlipidemia	2 (3.9)
Smoking	6 (11.8)
Hypothyroidism	2 (3.9)
Overweight/Obesity	12 (23.5)
Previous Heart Disease	0 (0)
Cardiovascular treatment *n* (%)	
ACE inhibitor/ARB	7 (13.7)
Beta-Blocker	6 (11.8)
Diuretics	3 (5.9)
Statins	1 (2)
Diabetes treatment	6 (11.8)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. Data are expressed as the mean ± SD or as number (percentage).

TABLE 2 | Cancer treatment and metastatic stage.

Variable	(*n* = 51)
Doxorubicin	51 (100%)
Cyclophosphamide	51 (100%)
Trastuzumab	7 (13.7)
Paclitaxel	45 (88.2)
Cisplatin	1 (2)
Radiotherapy	45 (88.2)
Surgery	28 (54)
Metastatic Stage	2 (3.9)

Data are expressed as number (percentage).

were treated with trastuzumab and 45 of them with paclitaxel (**Table 2**).

None of the patients presented HF symptoms. After beginning chemotherapy, 13 patients (25%) presented non-specific fatigue.

Echocardiography

All echocardiographic parameters in the 5 evaluation stages are presented in **Table 3**.

The standard echocardiographic parameters in the early stages of evaluation (baseline and after 120 and 240 mg/m^2) during the treatment are summarized in **Table 4**. Mean LVEF, as well as conventional Doppler parameters, were unchanged during treatment of doxorubicin (**Figure 2**). Among tissue Doppler indices, only the e′ septal velocity was decreased after treatment with 240 mg/m^2 of doxorubicin (from 10.7 ± 3.1 cm/s at baseline to 9.6 ± 2.6 cm/s; $p = 0.019$), with no change found for a lower cumulative dosage of doxorubicin ($p > 0.99$). LVEF was changed after the fifth assessment stage (1 year; $p = 0.001$), however, the mean value remained normal. The s′ lateral velocity was decreased after 1 year of chemotherapy (from 10.7 ± 2.9 cm/s at baseline to 8.9 ± 21.8 cm/s after 1 year; $p = 0.001$), however, there was no early change in this parameter ($p = 0.220$; **Table 4**). No changes were observed for LV diastolic function, valvular function, or right ventricular performance during the stages of evaluation.

Speckle Tracking Echocardiography

The 2DGLS presented changes only at the end of the protocol, after the 240 mg/m^2 dosage (from −17.8% ± 1.5 at baseline to −17.1% ± 1.4; $p = 0.001$; **Figure 3** and **Table 5**), with no change after a lower cumulative dosage of doxorubicin ($p = 0.103$). Two-dimensional RS did not present changes during the evaluation stages ($p = 0.47$).

After the cumulative dose of 240 mg/m^2 of doxorubicin, the 3DSTE detected changes in most myocardial deformation parameters: 3DGLS, 3DGRS, 3DGCS, and 3DGAS. There were no changes in rotation, torsion, or twist in any of the evaluation stages (**Table 5**). Alternatively, after a lower cumulative dose of doxorubicin (120 mg/m^2), the only parameter that changed was 3DGAS (from −45.4% ± 4.1 at baseline to −43.2% ± 4.1, $p < 0$, 001; **Figure 4**).

The 3DGAS early changed to below normal values until the period during treatment with doxorubicin was the only parameter that was associated with the subsequent decrease in LVEF during follow-up ($p = 0.009$; **Table 6**).

In our study, the 3DSTE normality values were based on the main studies that report the normal range values for 3D strain parameters from healthy volunteers (23–25).

Ultrasensitive Troponin I

The average US-TnI was increased from 12 to 40.7 pg/ml ($p < 0.001$) after the final evaluation stage. Twenty patients (45%) presented abnormal levels of US-TnI (>34 pg/ml) after cumulative dosage of 240 mg/mg^2 of doxorubicin ($p = 0.001$). After a lower cumulative dose of doxorubicin (120 mg/m^2), there was no change in US-TnI ($p = 0.509$).

Follow-Up

In the follow-up, 7 (13%) patients presented a decrease in LVEF with definitive criteria of CTRCD. None of the patients presented HF symptoms.

Table 6 presents the clinical features and the values of the main echocardiographic parameters identified at an early stage (during chemotherapy, up to the stage after 240 mg/m^2) and their correlation with patients who had a subsequent decrease in LVEF (with definitive cardiotoxicity criteria) in the follow-up.

There was no difference between the clinical characteristics and the presence of cardiovascular risk factors with the development of CTRCD. The use of trastuzumab was slightly associated with a subsequent decrease in LVEF ($p = 0.045$).

Changes in US-TnI during treatment (after cumulative dosage of 240 mg/mg^2 of doxorubicin) were not associated with a subsequent decrease in LVEF ($p = 0.684$).

TABLE 3 | Echocardiographic parameters in the 5 evaluation stages.

Variable	Baseline	120 mg/m^2	240 mg/m^2	6 months	1 year	*p*-value
Heart rate (beat/min)	75.8 ± 9.1	76.1 ± 10.3	75.3 ± 10.5	75.1 ± 9.6	71.5 ± 10.6	0.067
LVEF	0.64 ± 0.02	0.63 ± 0.03	0.63 ± 0.03	0.63 ± 0.03	0.60 ± 0.04	0.001
Diastolic dysfunction†	17 (33.3%)	22 (44%)	22 (44%)	17 (33.3%)	24 (47%)	0.169
E-wave (cm/s)	81.3 ± 18	82.2 ± 18.5	80.5 ± 19.6	83.5 ± 17.6	86.5 ± 18.6	0.455
A-wave (cm/s)	74.2 ± 19.9	75.8 ± 21.7	77.2 ± 20.3	76.8 ± 21.8	74.2 ± 21.3	0.234
DT (ms)	192 ± 42.2	190.5 ± 39.7	180 ± 45.1	207 ± 59.1	208 ± 46.2	0.060
E/A ratio	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	0.120
Septal s′ (cm/s)	9.2 ± 1.4	9.2 ± 1.3	9.1 ± 1.3	8.8 ± 1.7	8.4 ± 1.2	0.058
Septal e′ (cm/s)	10.7 ± 3.0	10.2 ± 3.5	9.6 ± 2.6	9.6 ± 3.7	9.0 ± 2.5	0.021
Lateral s′ (cm/s)	10.8 ± 2.9	10.3 ± 2.0	10 ± 2.1	9.2 ± 1.9	8.9 ± 1.8	0.001
Lateral e′ (cm/s)	13.5 ± 4.2	12.8 ± 4.2	12.7 ± 3.6	13.1 ± 4.1	12.1 ± 4.2	0.247
E/e′ ratio	7.37 ± 1.6	7.1 ± 1.9	7.1 ± 2.2	7.4 ± 1.9	7.5 ± 1.8	0.617
RV s′ (cm/s)	13.7 ± 1.9	13.6 ± 2.4	13.5 ± 2.4	12.7 ± 2.1	12.5 ± 2.0	0.108
TAPSE (mm)	20.6 ± 4.1	19.9 ± 2.3	20.2 ± 2.4	20.3 ± 2.3	20.7 ± 2.9	0.635
2D Speckle Tracking						
2DGLS (%)	−17.8 ± 1.5	−17.4 ± 1.4	−17.1 ± 1.4	−17.0 ± 2.2	−16.6 ± 2.1	<0.001
2DRS (%)	39.3 ± 9.8	36.7 ± 8.6	36.3 ± 14	35.1 ± 12.1	36.5 ± 13.4	0.516
3D Speckle Tracking						
3DGLS (%)	−15.9 ± 2.2	−15.5 ± 2.2	−14.8 ± 1.9	−14.1 ± 6.3	−14.4 ± 3.2	0.043
3DGRS (%)	31.7 ± 12.8	27.5 ± 10.3	26.3 ± 11.6	26.2 ± 11.1	30 ± 13.1	0.043
3DGCS (%)	−33.8 ± 4.7	−32.3 ± 5†	−31.2 ± 4.2	−30.4 ± 6.3	−30.1 ± 6.5	0.023
Twist (°)	6.1 ± 2.8	5.3 ± 3	4.8 ± 2.4	4.5 ± 2.5	5 ± 4.5	0.278
Torsion (°/cm)	2.6 ± 1.4	2.5 ± 1.5	2.4 ± 1.3	1.9 ± 1.1	1.9 ± 1.5	0.068
Rotation (°)	5.2 ± 2.9	5.1 ± 3.4	4.5 ± 2.2	4.4 ± 2.1	3.8 ± 2	0.093
3DGAS (%)	−45.4 ± 4.1	−43.2 ± 4.4	−39.8 ± 3.3	−39 ± 3.1	−39 ± 2.9	<0.001

GAS, global area strain; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial LVEF, left ventricular ejection fraction; DT, E-wave deceleration time; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; data are expressed as the mean ± SD or as number (percentage). Comparisons made by generalized estimation equations with normal distribution and identity link function. †Generalized equations with binomial distribution and logit bond function. p < 0.05 was considered significant.

The 3DGAS early changed to below normal values was the only parameter that was associated with the subsequent decrease in LVEF during follow-up ($p = 0.009$).

The other mechanical indices derived from 2D and 3D speckle tracking analysis, as well as the conventional echocardiographic parameters were not predictors of CTRCD (**Table 6**).

Reproducibility

The intraobserver intraclass coefficients observed were as follows: 2DGLS 0.96 (95% CI, 0.84–0.99), 3DGLS 0.72 (95% CI, 0.21–0.99), 3DGCS 0.97 (95% CI, 0.86–0.99), and 3DGAS 0.99 (95% CI, 0.97–0.99). The corresponding interobserver intraclass coefficients were as follows: 2DGLS 0.92 (95% CI, 0.81–0.98), 3DGLS 0.96 (95% CI, 0.86–0.99), 3DGCS 0.94 (95% CI, 0.82–0.98), and 3DGAS 0.98 (95% CI, 0.92–0.99).

DISCUSSION

This prospective study shows that 3DSTE may provide added value to the evaluation of left ventricular systolic function in women with breast cancer treated with anthracyclines. The early changes in 3DGAS after low doses of doxorubicin represent an early marker of cardiotoxicity and can identify a subgroup of patients with increased risk for future development of LVEF reduction.

Cardiotoxicity is one of the most important complications of cancer treatment. In this setting, HF has a 2-year mortality rate of up to 60% (2). Anthracyclines-induced cardiotoxicity is mainly mediated through the generation of reactive oxygen species, which may result in cardiomyocyte apoptosis, an irreversible condition (26). Prompt beginning of cardioprotective regimens may interfere in this process and possibly avoid the development of HF, improving prognosis (5, 27). As a result, the search for parameters that allow early identification of patients at risk for future LV dysfunction is of paramount importance.

This study comprised a homogeneous population with comparable cardiovascular risk factors and baseline clinical characteristics. To detect early changes in myocardial mechanics, the study design included patient evaluation after a very low cumulative dosage of doxorubicin (120 mg/m^2), distinct from previous studies, which, using a similar population, performed the first post-chemotherapy analysis about 3–6 months after exposure to a higher cumulative dosage of doxorubicin (8, 9).

In the present study, the association of trastuzumab was slightly associated with CTRCD, corroborating the fact that

TABLE 4 | Standard echocardiographic parameters during the treatment.

Variable	Baseline	120 mg/m^2	240 mg/m^2	*p*-value*
LVEF	0.64 ± 0.02	0.63 ± 0.03	0.63 ± 0.03	0.178
Diastolic Dysfunction†	17 (33.3%)	22 (44%)	22 (44%)	0.122
E-wave (cm/s)	81.3 ± 18	82.2 ± 18.5	80.5 ± 19.6	0.466
A-wave (cm/s)	74.2 ± 19.9	75.8 ± 21.7	77.2 ± 20.3	0.262
DT (ms)	192.8 ± 42.2	190.5 ± 39.7	180 ± 45.1	0.269
E/A ratio	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.054
Septal s′ (cm/s)	9.2 ± 1.4	9.2 ± 1.3	9.1 ± 1.3	0.663
Septal e′ (cm/s)	10.7 ± 3.0	10.2 ± 3.5	9.6 ± 2.6	0.019
Lateral s′ (cm/s)	10.8 ± 2.9	10.3 ± 2.0	10 ± 2.1	0.220
Lateral e′ (cm/s)	13.5 ± 4.2	12.8 ± 4.2	12.7 ± 3.6	0.156
E/e′ ratio	7.37 ± 1.6	7.1 ± 1.9	7.1 ± 2.2	0.678
RV s′ (cm/s)	13.7 ± 1.9	13.6 ± 2.4	13.5 ± 2.4	0.937
TAPSE (mm)	20.6 ± 4.1	19.9 ± 2.3	20.2 ± 2.4	0.515
Heart Rate (beat/min)	75.8 ± 9.1	76.1 ± 10.3	75.3 ± 10.5	0.961

*LVEF, left ventricular ejection fraction; DT, E-wave deceleration time; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; data are expressed as the mean ± SD or as number (percentage). *After 240 mg/m^2 dose of doxorubicin compared to baseline. Comparisons made by generalized estimation equations with normal distribution and identity link function. †Generalized equations with binomial distribution and logit bond function. $p < 0.05$ was considered significant.*

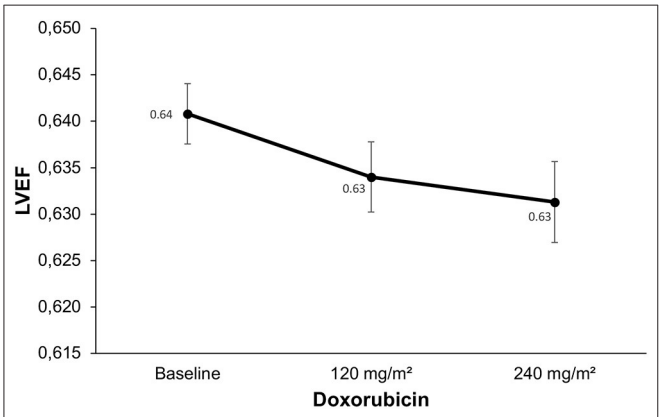

FIGURE 2 | Changes in left ventricle ejection fraction (LVEF) during the treatment. Compared to baseline, LVEF did not change during the chemotherapy with doxorubicin ($p = 0.178$).

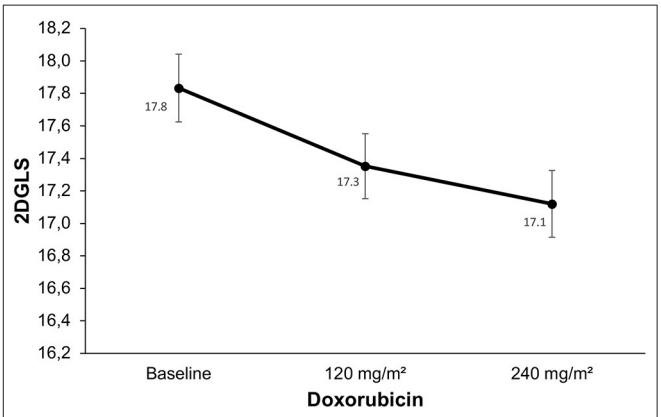

FIGURE 3 | Changes in global longitudinal strain derived from the two-dimensional speckle tracking echocardiography. Compared to baseline, two-dimensional global longitudinal strain (2DGLS) did not change earlier, after 120 mg/m^2 of doxorubicin ($p < 0.103$). There was a decrease in 2DGLS after 240 mg/m^2 of doxorubicin compared to baseline ($p < 0.001$). However, the relative change of 2DGLS was mild, with no patient presenting criteria for the diagnosis of subclinical cardiotoxicity.

the association of drugs in chemotherapy can enhance the occurrence of cardiotoxicity (28).

Myocardial deformation performed by 3DSTE has been shown to be a reliable and reproducible tool for the analysis of LV mechanics in different clinical conditions (18–21). However, this technique has been poorly explored in the scenario of chemotherapy-induced cardiotoxicity. A study evaluated 25 patients with several types of malignancies during chemotherapy and after a 3-month follow-up did not demonstrate changes in any of the 3DSTE indices; however, in this study, only 7 patients were exposed to anthracyclines (29). Another report evaluated 2DSTE and 3DSTE in 55 patients after chemotherapy with anthracyclines and compared to a control group; 3DGAS and 3DGCS were the only parameters that changed. However, in this study, there was no baseline evaluation (30).

In the present study, after the end of treatment, with a cumulative dosage of 240 mg/m^2 of doxorubicin, changes in several parameters of 3DSTE were observed: 3DGLS, 3DGRS, 3DGCS, and 3DGAS. These changes, found in almost all 3DSTE-derived indices, suggest that the abnormalities caused by reactive oxygen species in cardiomyocytes can be present throughout all directions of myocardial fibers, concordant with experimental models of doxorubicin-induced cardiotoxicity (31). In addition, these changes included radial and circumferential components, which did not prove to be relevant when evaluated by 2DSTE, demonstrating the superiority of the 3D technique over 2D.

TABLE 5 | Results of myocardial deformation parameters derived from 2DSTE and 3DSTE during the treatment.

Variable	Baseline	120 mg/m^2	240 mg/m^2	*p*-value*
2D Speckle Tracking				
2DGLS (%)	−17.8 ± 1.5	−17.4 ± 1.4	−17.1 ± 1.4	<0.001
2DRS (%)	39.3 ± 9.8	36.7 ± 8.6	36.3 ± 14	0.402
3D Speckle Tracking				
3DGLS (%)	−15.9 ± 2.2	−15.5 ± 2.2	−14.8 ± 1.9	<0.002
3DGRS (%)	31.7 ± 12.8	27.5 ± 10.3	26.3 ± 11.6	0.025
3DGCS (%)	−33.8 ± 4.7	−32.3 ± 5†	−31.2 ± 4.2	<0.012
Twist (°)	6.1 ± 2.8	5.3 ± 3	4.8 ± 2.4	0.059
Torsion (°/cm)	2.6 ± 1.4	2.5 ± 1.5	2.4 ± 1.3	0.659
Rotation (°)	5.2 ± 2.9	5.1 ± 3.4	4.5 ± 2.2	0.423
3DGAS (%)	−45.4 ± 4.1	−43.2 ± 4.4†	−39.8 ± 3.3	<0.001

*GAS, global area strain; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; Data expressed as the mean ± SD. *After 240 mg/m^2 dose of doxorubicin compared to baseline. Comparisons were performed by generalized estimation equations with normal distribution and identity link function. †Multiple comparisons analysis by the Bonferroni method revealing change in 3DGAS after 120 mg/m^2 dose of doxorubicin compared to baseline ($p < 0.001$). $p < 0.05$ was considered significant.*

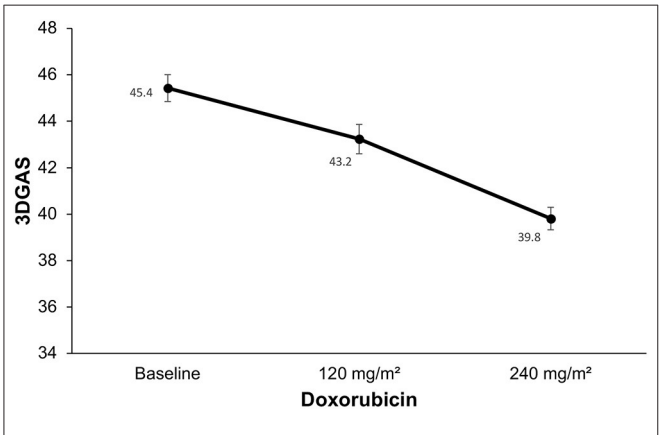

FIGURE 4 | Changes in global area strain derived from the three-dimensional speckle tracking echocardiography. Compared to baseline there was a decrease in three-dimensional global area strain (3DGAS) after a lower cumulative dose of doxorubicin (120 mg/m^2; $p < 0.001$). There was a decrease in 3DGAS after 240 mg/m^2 dose of doxorubicin compared to baseline ($p < 0.001$).

Several factors, such as the absence of geometric assumptions and no need for multiple plane acquisition, may contribute to that. Additionally, because the speckles move in three dimensions according to the translation movement of the heart, 3DSTE allows a homogeneous spatial distribution of each component of the myocardial displacement vector. Thus, analysis of cardiac mechanics may be technically more accurate with the 3D study (16). It is important to highlight that there are already studies that determine normal values for the LV strain by 3DSTE (23–25).

In our evaluation 3DGAS was the only parameter that changed at an earlier stage, after a lower cumulative dosage of doxorubicin (120 mg/m^2). In addition, most importantly, the 3DGAS changed to below normal values was the only parameter that was associated with the subsequent decrease in LVEF during follow-up (**Figure 5**). These data suggest the superiority of this parameter for early detection of CTRCD. Area strain is a new 3DSTE index that has demonstrated applicability in different clinical scenarios; it allows a relatively operator-independent quantitative evaluation of LV function and combines longitudinal and circumferential deformations analysis, probably being more sensitive in detecting anomalies specially in the subendocardium layer, one of the earliest affected areas in several heart conditions (32). In the setting of cardiotoxicity, recent research has evaluated 100 patients with breast cancer under treatment with anthracyclines and demonstrated a potential superiority of 3DGCS and 3DGAS in comparison to other echocardiographic parameters for the subclinical diagnosis of cardiotoxicity. However, the evaluation of these patients was performed after a higher cumulative anthracyclic dosage (mean of 505 mg/m^2 of epirubicin) (33). Another recent study evaluated 89 patients with lymphoma; in comparison to 2DSTE, 3DSTE was superior in the early detection of cardiotoxicity. In this research, the changes were observed after an average cumulative dose of 263 mg/m^2 of epirubicin (34). In **Figure 6**, we have highlighted the main findings of these studies that involve 3DSTE and cancer patients who underwent chemotherapy.

Another point to be highlighted in our study was the evidence of good reproducibility of 3DSTE, especially in 3DGAS and 3DGCS, confirming that they are reliable and accurate indices in the assessment of ventricular mechanics.

The 3DGAS represents a new automatic promissory index, with a more accurate analysis of global and regional left ventricular systolic function. The 3DGAS mainly includes the assessment of myocardial deformation in the subendocardial and endocardial layers (18). The occurrence of cellular oxidative stress, the main pathophysiological mechanism of cardiotoxicity, leads to different degrees of myocyte dysfunction (35). Studies in animal models using 2DSTE and cellular oxidative stress markers have shown that myocyte apoptosis, capillary density reduction,

TABLE 6 | Follow-up. Early changes in variables and clinical features during chemotherapy and its association with a subsequent decrease in LVEF (definite cardiotoxicity).

Variable	Cardiotoxicity		*p*
	No ($n = 44$)	Yes ($n = 7$)	
Diabetes			0.578
No	38	7	
Yes	6	0	
Hypertension			>0.999
No	33	5	
Yes	11	2	
ACE inhibitor/ARB			>0.999
No	38	6	
Yes	6	1	
Beta-Blocker			0.186
No	40	7	
Yes	4	0	
Trastuzumab			0.045
No	40	4	
Yes	4	3	
Radiotherapy			>0.999
No	5	1	
Yes	39	6	
US-TnI >34 pg/mL			0.684
No	23	3	
Yes	17	4	
3DGLS (<16.1%)			>0.999
No	10	1	
Yes	30	5	
3DGRS (<24.4%)			0.381
No	26	3	
Yes	14	3	
3DGCS (<28%)			0.057
No	36	6	
Yes	4	0	
3DGAS (<39, 8)			0.009
No	23	0	
Yes	17	7	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; GAS, global area strain; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; US-TnI, ultrasensitive troponin I; data are expressed as number (percentage). Fisher's exact test. $p < 0.05$ was considered significant. Changes in variables observed during treatment with anthracycline (up to cumulative dose exposure of 240 mg/m^2 of doxorubicin).

inflammatory response in cardiac tissue, and myofilament degradation promote early changes in myocardial deformation, before the decrease in LVEF and LV fractional shortening (36). In our study, the early change in 3DGAS suggests that early oxidative stress injury can affect the different myocardial layers at a very early stage.

Myocardial deformation indices assessed by 2DSTE have played an important role in the early detection of subclinical left ventricular dysfunction in patients who underwent chemotherapy (8–11, 15). The main parameter involved is the 2DGLS, and a relative percentage reduction >12–15% from baseline is very likely to be abnormal (10, 12, 13, 27). In our study, a significant reduction of 2DGLS after a cumulative dosage of 240 mg/m^2 of doxorubicin was observed. However, the relative change of 2DGLS was mild (only 0.7%), with no patient presenting criteria for the diagnosis of subclinical cardiotoxicity (25, 26). Notably, after a low dosage of doxorubicin (120 mg/m^2), there was no significant reduction in 2DGLS. There are little data on the evaluation of these patients after exposure to lower doses of anthracyclines. In a recent study that involves 86 patients, 2DGLS was evaluated after cumulative doxorubicin dosages of 150 mg/m^2 (slightly higher than our study). In this series, 2DGLS was a predictor of cardiotoxicity in the 6 (7%) patients who were presented with LVEF reduction after 1 year of cancer treatment, showing the importance of evaluating the patient at an earlier time (37). In this study, a few patients were exposed also to radiotherapy, increasing the risk of cardiotoxicity; in addition, as the number of patients who developed cardiotoxicity was too small, these data should be confirmed in a larger population sample. Regarding 2DGRS, this parameter did not change after treatment with anthracyclines, corroborating previous studies that demonstrated its low sensitivity for detection of chemotherapy-induced cardiotoxicity (8, 10). Two-dimensional GCS was not evaluated in the present study, considering previous reports that revealed its low reproducibility and less relevance in the scenario of cardiotoxicity (12).

Despite the promising and important results related to the early diagnosis of cardiotoxicity through the 2DSTE, the benefit of cardioprotective treatment based exclusively on the decrease in the 2DGLS is not yet well established. The 1-year results of Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) trial were recently reported (27). This was the first prospective randomized, open, blinded end-point assessment study designed to compare the cardioprotective treatment (beta-blockers plus either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) guided by a decrease in LVEF (>10% to an absolute value <55% or if LVEF drop by 5% accompanied by symptoms) vs. decrease in 2DGLS (relative drop ≥12%). The authors observed that 2DGLS-guided cardioprotective treatment significantly reduced a meaningful fall of LVEF to the abnormal range, supporting the use of 2DSTE in surveillance for CTRCD. However, the study was failed to meet its primary endpoint—the change in LVEF was not different between the two arms. Furthermore, no clinical outcomes were observed (definitive impact still unclear). Additional results are therefore necessary to establish this approach, especially when we consider that unnecessary cardiovascular treatment and inappropriate interruption of cancer treatment can be observed in this context (38). In our study, during chemotherapy with anthracyclines, patients did not have a drop in 2DGLS with criteria of subclinical cardiotoxicity that would justify cardioprotective treatment. We did not observe HF or unfavorable cardiovascular clinical outcomes (probably due to the short follow-up time), limiting the assessment of the clinical impact related to the early decrease in 3DGAS. Patients who had a decrease in LVEF with cardiotoxicity

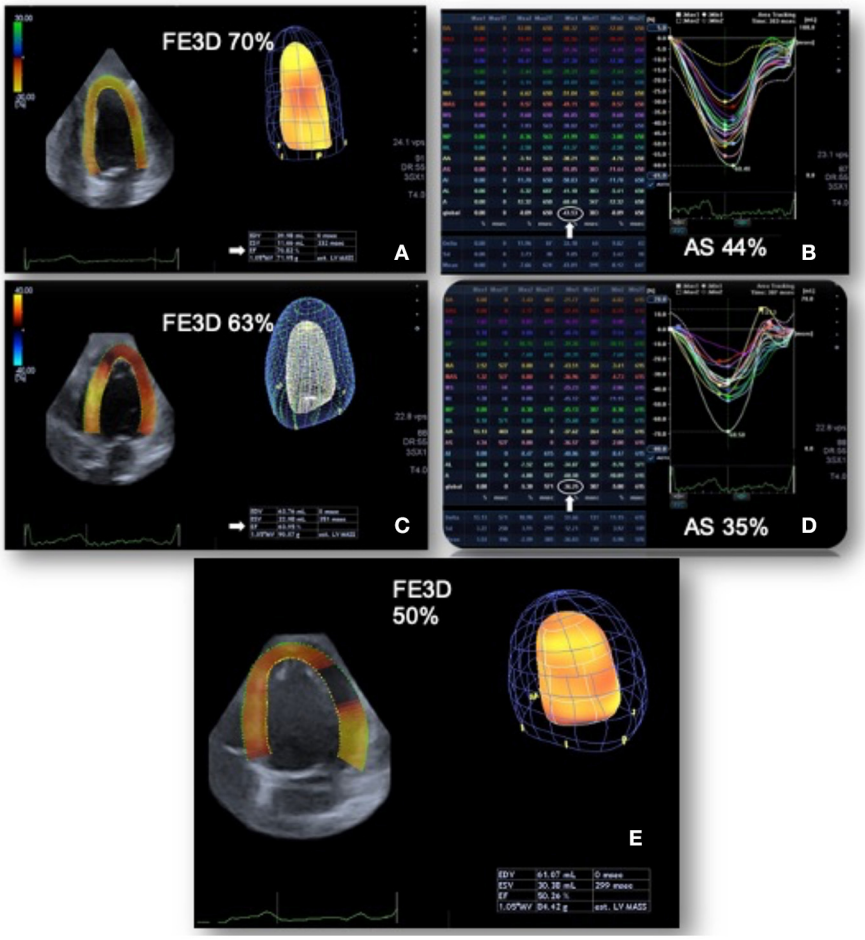

FIGURE 5 | Changes in global area strain derived from the three-dimensional speckle tracking echocardiography. Patient with breast cancer undergoing chemotherapy with doxorubicin. In the baseline evaluation, pre-chemotherapy, left ventricular ejection fraction (LVEF): 0.70 and 3DGAS: −43.5% **(A,B)**. After a low cumulative dose of doxorubicin (120 mg/m^2), LVEF: 0.63 was observed (with reduction, but still preserved) and a significant decrease in three-dimensional global area strain (3DGAS) to −36.2% **(C,D)**. Six months after the end of chemotherapy with doxorubicin (total cumulative dose of 240 mg/m^2), the LVEF dropped to 0.50 **(E)**. GAS, global area strain; LVEF, Left ventricle ejection fraction.

criteria during follow-up were treated with beta-blockers plus either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

No changes were observed in the conventional Doppler indices. In fact, the use of these parameters as early markers of cardiotoxicity is questionable, since they are considerably influenced by load conditions (12).

Troponin I can predict the development of later cardiac events in patients who were treated with high doses of anthracyclines or chemotherapy with trastuzumab, and it is a sensitive and specific marker for myocardial injury in adults who underwent chemotherapy (39). In the present study, after the cumulative dosage of 240 mg/m^2 of doxorubicin, 45% of the patients presented abnormal levels of this biomarker. However, there was no early change in US-TnI, after a lower cumulative dose of doxorubicin (120 mg/m^2). Most importantly, US-TnI was not associated with a subsequent decrease in LVEF ($p = 0.684$). Currently, some challenges remain regarding the widespread application of troponin, such as determining the optimal timing of troponin assessment and defining the cutoff point to define cardiotoxicity.

Early identification of chemotherapy-induced cardiotoxicity is critical to reduce morbidity and mortality in the oncologic population. In this context, adequate clinical risk stratification (identification and control of cardiovascular risk factors and knowledge of the cardiotoxic potential of cancer treatment) is essential (40). Cardiovascular imaging methods will help the pre-treatment risk stratification, in addition to being fundamental in monitoring during and after chemotherapy (41). The 3DSTE, in particular 3DGAS, has the potential to be a future tool incorporated into risk stratification algorithms and can add value in the early recognition of a population at higher risk for the subsequent development of CTRCD.

The clinical implications of the present study are important. The reported findings demonstrate that 3D strain, a non-invasive and easily performed analysis, recognizes subtle myocardial

Author	*n*	*Main Results*	*Note / Limitation*
Tarr A, et al. (2015) (29)	25	3DSTE was not able to detect myocardial damage	Several types of cancer. Only 7 patients were exposed to anthracyclines. Evaluation performed at baseline and only after 3 months of chemotherapy.
Miyoshi T, et al. (2014) (30)	55	Chemotherapy with anthracyclines. 3DGAS and 3DGCS were the only parameters that changed compared to a control group.	There was no baseline evaluation. Analysis performed only after anthracycline treatment.
Santoro C, et al. (2017 (33)	100	Breast cancer patients under treatment with anthracyclines. Potential superiority of 3DGCS and 3DGAS for the subclinical diagnosis of cardiotoxicity.	Evaluation performed only after the end of chemoterapy and with a higher cumulative anthracyclic dosage (505 mg/m^2 epirubicin).
Song FY, et al. (2017) (34)	89	Lymphoma patients. 3DSTE was superior to 2DSTE in the early detection of cardiotoxicity. Changes observed after an average cumulative dose of 263 mg/m^2 of epirubicin.	The predictor impact of 3DSTE was not analyzed. No correlation with LVEF decrease was studied in patients follow-up.

FIGURE 6 | Studies reporting the 3D speckle tracking echocardiography analysis in cancer patients undergoing chemotherapy. GAS, global area strain; GCS, global circumferential strain; LVEF, Left ventricle ejection fraction. STE, speckle tracking echocardiography.

damage and predicts a later decrease in the LVEF in patients receiving anthracyclines.

LIMITATIONS

The study comprised a small sample size and the echocardiographic and laboratory evaluations were performed in a single research center; multicenter studies and a larger population sample are required to validate tour results. Moreover, a longer-term follow-up study would be necessary to determine whether early changes in 3DGAS could correlate with clinical outcomes. In addition, the drop in LVEF was slight and no patient had symptoms of HF. Thus, targeted studies evaluating the comparison of cardioprotective treatment guided by a change in 3DGAS against this treatment guided by a decrease in LVEF are needed to determine the real prognostic impact of this tool. For 2DSTE, we performed the radial strain analysis only from the short-axis mid-papillary level, thus, not representing global radial strain. There was a significant sample loss during patient follow-up.

CONCLUSION

In patients with breast cancer who were treated with anthracyclines, an analysis of myocardial mechanics using 3DSTE detected early changes in 3DGAS after very low doses of doxorubicin. The 3DGAS early changed to abnormal values was associated with a subsequent decrease in LVEF, representing a promising technique to predict chemotherapy-induced cardiomyopathy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitê de ética em pesquisa do Hospital Israelita Albert Einstein. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR and MV: conception and design, acquisition, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of submitted version. CF: conception and design, acquisition of data, drafting the article, and final approval of submitted version. TA: acquisition of data, drafting the article, and final approval of submitted version. ED, FC, TG, and MK: conception and

design, draft the article, and final approval of submitted version. SM: conception and design, interpretation of data, drafting the article, revising the article critically for important intellectual content, and final approval of the submitted version. All authors contributed to the article and approved the submitted version.

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REVIEW
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Genetics of Anthracycline-Associated Cardiotoxicity

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Anthracyclines are a major component of chemotherapies used in many pediatric and adult malignancies. Anthracycline-associated cardiotoxicity (ACT) is a dose-dependent adverse effect that has substantial impact on morbidity and mortality. Therefore, the identification of genetic variants associated with increased risk of ACT has the potential for significant clinical impact to improve patient care. The goal of this review is to summarize the current evidence supporting genetic variants associated with ACT, identify gaps and limitations in current knowledge, and propose future directions for incorporating genetics into clinical practice for patients treated with anthracyclines. We will discuss mechanisms of ACT that could be illuminated by genetics and discuss clinical applications for the cardiologist/cardio-oncologist.

Keywords: anthracycline associated cardiotoxicity, genetics, genetic testing, cardio-oncology, anthracycline

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INTRODUCTION

Anthracyclines are among the most frequently used agents for treating cancer. They serve as the cornerstone for chemotherapy regimens commonly used to treat hematological and solid organ malignancies. Despite their efficacy, their utility is limited by a dose-dependent cardiomyopathy, also known as anthracycline-associated cardiotoxicity (ACT). ACT is commonly detected by imaging studies and may present as anthracycline-associated heart failure. It is estimated that one in ten children exposed to cumulative anthracycline doses >300 mg/m^2 develop anthracycline-induced heart failure (1), and childhood cancer survivors are at a 5–10-fold increased risk of cardiac dysfunction compared to the general population (1, 2). Despite established risk factors such as older age and pre-existing cardiovascular comorbidities, there remains significant inter-individual variability in the development of cardiac toxicity. Some patients tolerate high doses without adverse effects, whereas others develop ACT at relatively low doses. The variable predisposition to ACT between patients suggests that genetic susceptibility may play a role in the development of ACT. Candidate genes with potential contributions to ACT pathophysiology have traditionally been nominated based on mechanistic studies in preclinical models, such as zebrafish and mice. While these models can provide valuable mechanistic data in the setting of *in vivo* treatment, conservation of the pathway and/or specific genetic variant of interest across species remains an important consideration in translating observations to human patients. Cell lines derived directly from human tissues, such as patient-derived human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), offer a unique opportunity to identify genetic variation that may contribute to ACT risk in specific patients. Both animal models and hiPSC-CMs provide mechanistic information that is often complementary to discovery – omics studies in patients.

This review will address the current knowledge of specific genetic associations with ACT, current practice of genetic testing and interpretation in the cardiology clinic and the potential management implications of genetic testing, particularly related to overlap between ACT and other cardiomyopathies.

GENOMIC VARIANTS ASSOCIATED WITH ANTHRACYCLINE ASSOCIATED CARDIOTOXICITY

Efforts to identify genetic variants associated with ACT have been conducted in several studies in pediatric and adult cohorts. Candidate gene approaches and genome wide association studies (GWAS) have yielded several single nucleotide polymorphisms (SNPs) of potential interest. In general, genetic studies in this patient population have been limited by their small sample size and the lack of consensus for clinical or echocardiographic diagnosis of ACT.

Surveillance protocols to detect ACT, as well as the definition of ACT, have not been standardized across studies. As a result, the incidence and timeline of diagnosis of ACT varies considerably in the literature. Clinically, ACT has been identified as new onset heart failure/cardiomyopathy in patients who were treated with anthracyclines. Left ventricular ejection fraction (LVEF) is commonly used in the detection of ACT, but echocardiography surveillance protocols vary considerably from one center to another, and asymptomatic cardiomyopathy is likely underdiagnosed. In addition, LVEF is influenced by preload, afterload and adrenergic state, leading to subjectivity and interpretive variation. A consensus definition of ACT lead by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) defines ACT as a decrease in the LVEF $>10\%$ to an absolute value of $<53\%$ (3).

GENES ASSOCIATED WITH ANTHRACYCLINE-ASSOCIATED CARDIOTOXICITY ACCORDING TO PRESUMED PATHOPHYSIOLOGIC MECHANISM

Several genetic modifiers have been identified as potentially contributing to ACT, which we will review here according to their proposed pathophysiologic mechanism (summarized in **Table 1**).

DNA Damage

DNA topoisomerase I (Top1) and II (Top2) relieve tension in overwound DNA by introducing a single or double-stand DNA break. Anthracyclines target the Top2-cleaved DNA complex, causing accumulation of double-strand DNA breaks (15) ultimately leading to apoptosis. Cardiomyocyte-specific deletion of Top2b protected mice from the development of doxorubicin-induced progressive heart failure (16). Furthermore, disruption of Top2-beta using clustered regularly interspaced short palindromic repeats and associated protein 9 (CRISPR/Cas9) significantly reduced the sensitivity of hiPSC-CMs to doxorubicin-induced double stranded DNA breaks and cell death (17).

Retinoic Acid Receptor Gamma

Although specific genetic variants in Top2-beta have not been identified as associated with anthracycline cardiotoxicity in patients, supporting findings have emerged related to retinoic acid receptor gamma (RARG), which binds to the Top2-beta promoter and participates in DNA damage-associated cell death. RARG binds to DNA regulatory sequences called retinoic acid receptor elements (RAREs) and has been implicated in the development of anthracycline cardiomyopathy in a mouse model (16). Aminkeng et al. performed a GWAS in 280 pediatric patients treated for childhood cancer and identified SNP rs2229774 in RARG to be associated with ACT [odds ratio (OR) 4.7, $P = 5.9 \times 10^{-8}$] (4).

Anthracycline Transportation and Metabolism

Solute Carrier

The solute carrier (SLC) super family of membrane proteins have been described to function as drug transporters for anthracyclines (18–20). Visscher et al. (6) observed consistent association of two variants of the SLC transport protein SLC28A3 (rs7853758 and rs885004) with resistance to ACT in several pediatric cohorts ($P = 1.8 \times 10^{-5}$; OR: 0.35). The association between rs7853758 and ACT was also observed in the Dutch-EKZ cohort (5, 21). The hypothesis is that the proteins encoded by these genes could transport anthracyclines into the cell leading to increased toxicity, whereas reduced function will be protective. The SLC22A17 variants rs4982753 and rs4149178 were also identified to be associated with ACT (6).

UGT1A6

Variants in UDP-glucuronosyltransferase family 1A6 (rs17863783, V209 V) have been associated with ACT in pediatric cohorts (5, 6). UGT1A6 plays a role in drug detoxification through the glucuronidation pathway (22). Although doxorubicin and daunorubicin are not themselves glucuronidated, certain downstream metabolites undergo glucuronidation (23). It can therefore by hypothesized that altered UGT1A6-mediated glucuronidation of anthracycline metabolites might lead to accumulation of toxic anthracycline metabolites in patients carrying UGT1A6*4, resulting in an increased risk of ACT.

Carbonyl Reductase 3

The alcohol metabolite of doxorubicin, doxorubicinol, is thought to be the primary mediator of the cardiotoxic effects of this agent. Carbonyl reductase (CBR) converts doxorubicin to doxorubicinol, leading to its accumulation in cardiomyocytes and a subsequent increase in cellular injury and death (7, 24, 25). These metabolites form a reservoir in cardiomyocytes and impair contractility through inhibition of Ca^{2+} and Na^{+}/K^{+} pump activity (26). Myocardial accumulation of these metabolites has been associated with subsequent cardiomyopathy (27). CBRs

TABLE 1 | Summary of studies investigating the role of genetic modifiers implicated in anthracycline-associated cardiotoxicity.

Genes with SNP	SNP effect	Replication	Authors	Year	Cohort	Case	Control	Study population	Definition of cardiotoxicity	Anthracycline used
DNA damage										
RARG rs2229774	Predisposing	Replicated in similar cohorts	Aminkeng et al. (4)	2015	280 96 80	32 22 19	248 74 61	**Pediatric** ALL, AML, HL, NHL, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, hepatoblastoma, neuroblastoma, Wilms tumor	(i) LVEF < 45% (ii) Dilation of LV-end-diastolic dimension > 117%.	Doxorubicin, daunorubicin, epirubicin
Anthracycline transportation and metabolism										
SLC28A3 rs78537585	Protective	Replicated in two different cohorts	Visscher et al. (5)	2012	156 188 96	38 40 43	118 148 53	**Pediatric** ALL, AML, other leukemia, HL, NHL osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, other sarcoma, Wilms tumor, hepatoblastoma, neuroblastoma, carcinoma	1. FS < 26% 2. Signs and symptoms indicating need for cardiac compromise intervention based on CTCAEv3	Doxorubicin, daunorubicin
UGT1A6 rs17863783	Predisposing	Replicated in same analysis	Visscher et al. (6)	2013	177	46	131	**Pediatric** ALL, AML, HL, NHL osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, other sarcoma, Wilms tumor, hepatoblastoma, neuroblastoma, carcinoma, germ cell tumor	1. FS < 26% 2. Signs/symptoms of cardiac compromise indicating need for intervention based on CTCAEv3	Doxorubicin, daunorubicin
SULT2B1 rs10426377	Predisposing									
CBR3 rs1056892	Predisposing	No replication performed	Blanco et al. (7)	2012	487	170	317	**Pediatric** HL, NHL, bone tumors, soft tissue sarcoma, ALL, AML, other	1. Signs/symptoms of cardiac compromise based on AHA criteria 2. Echo evidence of LV dysfunction (LVEF < 40%; FS < 28%)	Not specified
ABCC1 rs3743527, rs246221, rs3743527	Predisposing	No replication performed	Semsei et al. (8)	2012	234	–	–	**Pediatric** ALL	Change in LV FS	Daunorubicin, doxorubicin/not reported
ABCC2 rs8187710	Predisposing	No replication performed	Armenian et al. (9)	2013	255	77	178	**Pediatric and Adult** Leukemia, myeloma, lymphoma status post-hematopoietic cell transplantation	Sign/symptoms of cardiac compromise indicating need for intervention based on AHA criteria	Not specified

(Continued)

TABLE 1 | (Continued)

Genes with SNP	SNP effect	Replication	Authors	Year	Cohort	Case	Control	Study population	Definition of cardiotoxicity	Anthracycline used
Antioxidant mechanisms:										
HAS3 rs2232228	Predisposing	Replicated in an independent set of 76 patients	Wang et al. (10)	2014	287	93	194	**Pediatric and Adult** HL, NHL bone tumors, soft tissue sarcoma, ALL, AML, other	AHA criteria for cardiac compromise: 1. Symptoms/signs of cardiac compromise 2. Echo evidence of LV dysfunction (LVEF # 40% and/or FS # 28%)	Not specified
GSTM1 null genotype	Predisposing	No replication performed	Singh et al. (11)	2020		75	92	**Pediatric** ALL, AML, HL, NHL, bone tumors, kidney tumor, sarcoma, neuroblastoma	LVEF < 40% and/or FS < 28%	Not specified
NOS3 rs1799983	Protective	No replication	Krajinovic et al. (12)	2016	251	–	–	**Pediatric** ALL	Reduction in FS and EF	Doxorubicin
ABCC5 rs7627754	Predisposing	Replicated in 44 ALL patients								
RAC2 rs1305833	Predisposing	No replication performed	Armenian et al. (9)	2013	255	77	178	**Pediatric and Adult** Leukemia, myeloma, lymphoma status post-hematopoietic cell transplantation	Sign/symptoms of cardiac compromise indicating need for intervention based on AHA criteria	Not specified
Sarcomere dysfunction										
CELF4 rs1786814	Predisposing	Replicated in an independent set of patients	Wang et al. (13)	2016	331 54	112 54	219 0	**Pediatric** HL, NHL, sarcoma, AML, ALL, and others replication HL, NHL, sarcoma, AML, ALL, and others	1. Signs/symptoms of cardiac compromise based on AHA criteria 2. Absence of symptoms/signs with echo evidence of LV dysfunction (EF # 40% and/or FS # 28%)	Not reported
TTNtv	Predisposing	Preclinical replication performed	Garcia-Pavia et al. (14)	2019	213	–	–	**Adult** Breast cancer, AML, other solid tumor	Reduction in EF	Not reported

catalyze cardiotoxic alcohol metabolites and are considered to be major anthracycline metabolizing enzymes. The role of CBRs were investigated by Blanco et al. (7) in pediatric cancer survivors. They found that individuals with CBR3 V244M homozygous G genotype (CBR3:GG) had an increased risk for cardiomyopathy associated with low to moderate dose anthracyclines (1–250 mg/m^2). This is thought to be due to upregulated CBR3 expression mediated by nuclear transcription factor Nrf2, leading to increased synthesis of cardiotoxic anthracycline alcohol metabolites. However, involvement of these enzymes has not been as clearly established in other studies of ACT (4, 5, 9).

ABCC1, ABCC2, and ABCC5

ATP binding cassette (ABC) proteins are membrane-bound transporters involved in the clearance of anthracycline from the cell using energy derived from ATP hydrolysis (28). ABCC1 is highly expressed in the human heart. In mice, its expression is upregulated in the heart following exposure to doxorubicin (29). In a pediatric cohort with acute lymphoblastic leukemia, patients with SNP rs3743527 TT in ABCC1 had decreased LV fractional shortening at follow-up (8). The combination of either the TT or TC genotype was associated with decreased LV fractional shortening as well. Armenian et al. identified ABCC2 SNP rs8187710 to be associated with a 4.3-fold risk of ACT in a retrospective study of a mixed adult and pediatric cohort of patient receiving anthracycline prior to hematopoietic cell transplant (9). ABCC5 has been implicated in ACT with a TT genotype at SNP rs7627754 associated with reduced ejection fraction and fractional shorting in pediatric patients with ALL (12).

Sulfotransferase Family Cytosolic Member 2B1

Sulfotransferase family cytosolic member 2B1 (SULT2B1) is an enzyme that increases drug solubility in water and promotes renal excretion by conjugation of the sulfate group. A possible ACT association (P = 0.054) of the rs10426377 variant in SULT2B1 was reported by Visscher et al. (6). Interestingly, this sensitizing effect was noticed in men but not in women (6). It is possible that the SULT2B1 variant affects anthracycline catabolism and subsequent renal excretion, although additional data will be needed to determine the clinical significance of SULT2B1.

Antioxidant Mechanisms

Oxidative stress has also been implicated in the mechanism of ACT. Cardiomyocytes are particularly vulnerable to ROS induced cellular damage. Anthracyclines are thought to form ROS through dysfunction of the mitochondrial electron transport chain and iron accumulation (30) and by dysregulation of cardiomyocyte autophagy (31).

Hyaluronan Synthase 3

Hyaluronan synthase 3 (HAS3) enzymes synthesize hyaluronan, a glycosaminoglycan which is found in the extracellular matrix and has a role in tissue remodeling post injury. In addition to hyaluronan's tissue remodeling properties, it may also decrease reactive oxygen species–induced cardiac injury. Wang et al demonstrated in a pediatric cohort of cancer survivors that patients with the AA genotype in SNP rs2232228 of HAS3 who were exposed to high doses of anthracyclines (>250 mg/m^2) were at 8.9-fold greater risk of developing ACT compared with those with the GG genotype (10).

GSTM1

Glutathione S-transferases (GST) represent a class of phase II detoxification enzymes that catalyze reduced glutathione and eventually lead to its elimination from the body (32). GST are also scavengers of free radicals, preventing oxidative damage. GSTM1 expression varies by race and ethnicity, with the GSTM1 null genotype identified more frequently in east Asians (70–79%) and less frequently in Europeans (5%) (33–35). In pediatric cancer survivors, Miranda et al. demonstrated an association between the GSTM1 null genotype and the risk of developing cardiomyopathy (11). Similarly, GSTP1 has been reported to be associated with ACT in two small studies (36, 37).

Nitric Oxide Synthase 3

Anthracyclines can bind to nitric oxide synthase 3 (NOS3) leading to the inhibition of its activity. In a mouse model, NOS3$^{-/-}$ mice demonstrated less cardiotoxicity following doxorubicin exposure, whereas mice overexpressing wild type NOS3 exhibited more cardiotoxicity (38). Krajinovic et al. identified a NOS3 variant rs1799983 to be cardioprotective in a cohort of pediatric ALL patient exposed to doxorubicin (12).

NADPH Multienzymes Complex

Anthracyclines are lipophilic molecules which diffuse passively across cell membranes and into the mitochondria. During anthracycline reduction, a superoxide anion is formed. Polymorphism in NADPH oxidase subunits have been associated with the production of ROS. A SNP (rs13058338) in RAC2, which encodes a Rho-GTPase that regulates NADPH oxidase, has been associated with susceptibility to ACT (OR = 2.8, $P < 0.01$) (9). In a report by Wojnowski et al., NADPH oxidase (NOX2) knockout mice were protected against anthracycline induced heart failure (39).

Alternative Splicing of TNNT2/Sarcomere Dysfunction

CELF4

The cytosine-uridine-guanine repeat binding protein (CUGBP) family are splicing regulators that control developmentally regulated tissue-specific splicing events. CELF4 is an RNA protein involved in pre-mRNA splicing, known to mediate the splicing of the gene TNNT2 that encodes cardiac troponin T, which has an essential role in Ca^{2+} signaling in the heart. Wang et al. conducted a GWAS in childhood cancer survivors with and without cardiomyopathy and identified an association of CELF4 SNP rs1786814 with susceptibility to ACT. In patients with an A allele (GA and AA genotypes), cardiomyopathy was infrequent and not dose related. However, among those patients exposed to > 300 mg/m^2 of doxorubicin or equivalent, the rs1786814 GG genotype conferred a 10.2-fold increased risk of cardiomyopathy (95% CI: 3.8 to 27.3; $P < 0.001$) (13).

Impaired Iron Metabolism

Hemochromatosis

Hemochromatosis (HFE) encodes a major histocompatibility complex MHC class 1–like protein that binds to transferrin. This protein regulates the production of hepcidin, a key regulator of the entry of iron into the circulation. Noting that dexrazoxane, an iron chelator, had a cardioprotective effect on patients receiving doxorubicin, Miranda et al. hypothesized that the gene responsible for human HFE could play a role in susceptibility to ACT. Indeed, HFE-deficient mice exhibited greater sensitivity to doxorubicin, with increased serum CK and mortality following chronic doxorubicin treatment (40). In a pediatric cohort where 10% carried the HFE SNP rs1800562 (p.C282Y) and the heterozygous rs1800562 (p.C282Y) genotype, the presence of these variants correlated with an increase in Troponin T and a reduction in fractional shortening at 2-year follow-up (41).

GENE–ENVIRONMENT INTERACTION

The interaction between environmental factors (such as the anthracycline dose) and underlying genetic variation may affect the phenotypic expression of ACT. To date, most studies have not been designed to address this question in detail.

GENETIC OVERLAP BETWEEN ANTHRACYCLINE-ASSOCIATED CARDIOTOXICITY AND OTHER CARDIOMYOCYTES

Overlap in genetic variants between DCM and ACT represents a particularly interesting avenue of investigation (**Figure 1**). Garcia-Pavia et al. (14) demonstrated an increased prevalence of DCM-associated gene variants in the ACT patient population, where 12.2% of patients with ACT were found to have a cardiomyopathy variant. Titin-truncating variants (TTNtv) were identified in 16 of 213 ACT cases (7.5%) and were associated with more heart failure, hospitalizations, and atrial fibrillation, as occurs in patients with DCM caused by TTNtv (42, 43). Other genes associated with DCM such as BAG3, LMNA, and MYH7 have been poorly characterized in patients with ACT (14). As highlighted by the findings of Garcia-Pavia et al. (14), genetic modifiers of ACT overlapping with DCM genes may represent a distinct risk profile in addition to genes specific to ACT pathophysiology, a concept that will be important to consider as genetic testing is integrated into the clinical care of cardio-oncology patients.

TYPE OF GENETIC TESTING

Different types of genetic test are available to analyze changes in genes. At present, commercially available genetic tests do not include most of the genetic modifiers associated with ACT. Here we will focus on molecular testing that might be relevant to ACT gene testing in the future.

Gene Panel Testing

Commercially available gene panels are able to identify specific genetic variants. The number and type of genes offered for sequencing are different between panels. The yield of a panel differs based on the number of genes within a panel, as was demonstrated by Pugh et al. (44). While evaluating 766 patients with DCM, a large gene panel of 47 genes identified an underlying culprit gene in 37% of patients, whereas the yield was less than 10% with a smaller gene panel (44). Broader gene panels have an advantage in evaluating a genetically and clinically heterogeneous disease, but this comes with the expense of a high rate of variants of uncertain significance (VUS). This has been challenged by recent data from Murphy et al. (45), where the most actionable variant in their cohort of patients with inherited cardiac conditions was detected in smaller gene panels. This suggests that larger gene panels may offer little extra sensitivity with a higher burden of VUS (45).

Whole-Exome Sequencing

With the considerable decrease in cost, the clinical use of whole-exome sequencing has increased. Whole-exome sequencing can help identify novel variants that are not known to be involved in the pathogenesis of a disease (46). Importantly, whole-exome sequencing does not include most non-coding regions (intergenic areas and introns); however, these regions can be involved in the regulation of gene expression leading to disease pathogenesis (47). In the future, whole-genome sequencing may enable the characterization of coding and non-coding variation with minimal loss of sensitivity for pathogenic variants and increased opportunity to identify gene-gene or polygenic interactions that influence a patient's risk of developing ACT, as has been done for other cardiovascular diseases (48, 49).

INTERPRETING GENETIC TEST REPORTS

American College of Medical Genetics and Genomics Guidelines

Differences in interpretation are present between laboratories as well as between clinicians. The American College of Medical Genetics and Genomics (ACMG) published a set of guidelines to provide consistent terminology. Using a four-tiered system, somatic sequence variations are categorized based on their clinical significance as being pathogenic, likely pathogenic, a VUS, likely benign or benign (50).

Variants of Uncertain Significance: Determining Significance

Genetic testing is frequently inconclusive. This could be attributed to the absence of a pathological variant or the presence of a benign variant. Determining the pathogenesis of a variant using the ACMG criteria is important. At present, it is advised to treat variants in a binary fashion. Pathogenic variants and likely pathogenic variants are regarded as positive results. Benign variants and likely benign variants are considered to be

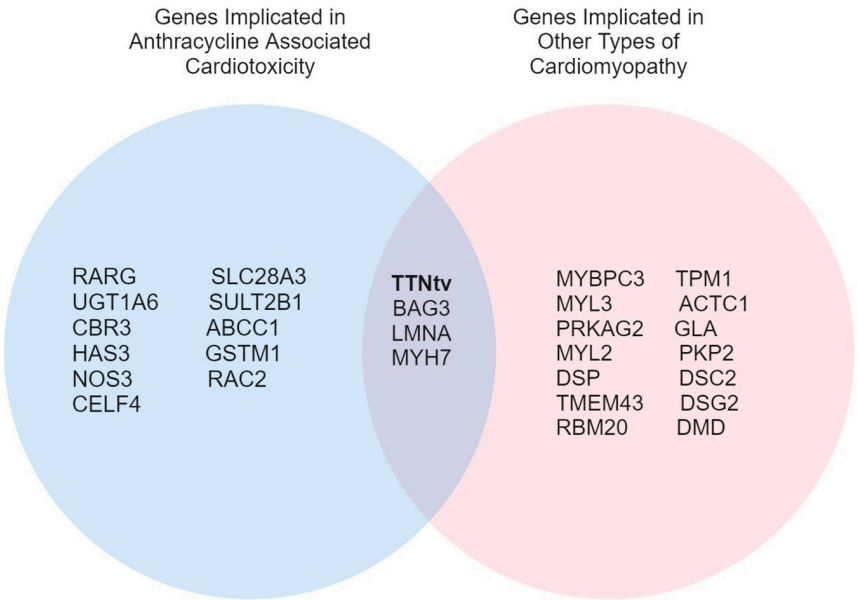

FIGURE 1 | A Venn diagram of overlapping genes implicated in ACT and other types of cardiomyopathies.

negative results. VUSs that have not definitively been classified as pathogenic or benign are open to reclassification as new data become available. VUSs represent a challenge in genetic test interpretation, and this is especially true for ACT where most findings remain investigational. This further demonstrates the need for additional studies with larger sample size. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) may be particularly useful in functional characterization of VUS (51).

GENETIC TESTING RESULTS AND POTENTIAL APPLICATIONS TO PATIENT MANAGEMENT

There is no consensus on the clinical application of genetic testing in the management of patients receiving anthracyclines. With growing data to support genetic predisposition as a key factor in ACT, one might envision future risk assessment tools based on both genetic testing and clinical risk factors. For example, patients with the RARG rs2229774 risk variant and the UGT1A6*4 rs17863783 risk variant may be considered at increased risk of ACT beyond what would be estimated from clinical risk factors alone. This could prompt closer cardiovascular follow-up and echocardiographic imaging during and post-treatment, as well as more aggressive risk factor management.

At present, genetic evaluation has no clinical application in ACT evaluation, unless there is a family history of cardiomyopathy or sudden cardiac death that warrants further investigation. As more data emerge regarding genetic risk factors for ACT, clinicians could consider personalized approaches to cardioprotection as follows:

Dexrazoxane

Dexrazoxane is an iron chelator that protects against oxidative stress. Several RCTs demonstrated the dexrazoxane is effective in preventing anthracycline cardiomyopathy and heart failure, although concern persists among many oncologists regarding mitigation of anthracycline antitumor efficacy and a possible increased risk of secondary malignancies, which has led to restriction of FDA approval for this agent.

Liposomal Encapsulated Anthracyclines

The liposomal formulation of anthracyclines is thought to result in decreased drug delivery to cardiomyocytes, leading to decreased cardiotoxicity. Liposomal doxorubicin was found to have similar efficacy and survival outcomes as regular doxorubicin but with lower risk of ACT and congestive heart failure (52). However, the number of studies is small, and data on long-term follow-up are lacking.

Primary Cardioprotective Agents

Several small RCTs have assessed the efficacy of neurohormonal blockade (beta blockers, ACEI, and ARBs) in preventing ACT (53). Although most suggest a modest attenuation of LVEF decline, these studies have largely been underpowered to detect differences in clinical heart failure. While routine use of neurohormonal blockade for primary cardioprotection is not supported by the current data, there may be some benefit in the setting of high-risk genetic variants and clinical features.

Alternative Chemotherapy Regimens

In a patient with genetic variants that are expected to be high-risk for ACT, particularly if high doses of anthracyclines are

anticipated, it may be reasonable to consider an alternative, less cardiotoxic chemotherapy regimen.

POTENTIAL USES OF GENETIC TESTING IN PATIENTS WHO DEVELOP ANTHRACYCLINE ASSOCIATED CARDIOTOXICITY

In patients with established ACT, treatment is similar to that recommended by standard heart failure management guidelines. The use of neurohormonal blockade as the cornerstone of management is consistent with data demonstrating cardiac reverse remodeling and improved survival in heart failure in general. There has been interest in identifying which patients respond favorably to neurohormonal blockade. Outside the context of ACT, differences in individual response to beta-blockers are thought to be due to genetic polymorphisms in the gene encoding the beta-adrenergic receptor. In the WOSCOPS trial and MERIT-HF trial (54), these polymorphisms were not associated with a change in morbidity or mortality. Similarly, genes encoding angiotensin II and the associated receptors demonstrated polymorphisms associated with different response to therapy. For instance, a homozygous DD genotype for the ACE gene with a polymorphism of AGTR1 might cause higher levels of renin–angiotensin–aldosterone system activation, resulting in worse prognosis despite treatment with ACEI (55) and lower survival (56). The routine use of genetic testing for gene polymorphisms lacks clinical validation at present, but individualized medical therapy holds promise to improve outcomes in patient with ACT.

LIMITATIONS OF THE AVAILABLE DATA

Most genetic studies of ACT have attempted to identify candidate genes and/or genetic modifiers by evaluating the cumulative burden of gene variants to determine which genes were overrepresented for genetic variation in a cohort of patients with ACT. This approach differs from that used for other inherited cardiac diseases in clinical practice, such as DCM, where the evidence for pathogenicity includes the evaluation of individuals SNPs based on prior reported associations for the SNP or location of SNPs in gene mutation "hotspots". To achieve this level of evidence for individual SNPs in ACT will require utilization of genome editing tools such as CRISPR as well as patient-derived *in vitro* models such as hiPSC-CM, as well as accumulating evidence for genetic variants in ACT in clinical practice.

Furthermore, in other types of cardiomyopathy, the evaluation of variant pathogenicity is directed toward a monogenic variant that is otherwise absent (or of very low frequency) in the general population. However, reported variants associated with ACT have typically been common in the general population, with an allele frequency reaching up to 6% (e.g., ABCC2). These genetic modifiers may contribute to the risk of cardiomyopathy, but they likely have a low penetrance for disease in the general population and may require an environmental interaction (such as exposure to anthracycline) as a second hit to produce the clinical ACT phenotype. The uncertainty surrounding genetic testing will necessitate close collaboration with genetic counselors who can help navigate the implications of testing results as genetics is integrated into the cardio-oncology clinic.

FUTURE DIRECTIONS

There continue to be several limitations to the use of genetics in routine clinical care. Above all, the identification of disease causing variants remains challenging. Some genetic variants might be necessary but not sufficient to predispose to ACT, and how these variants interact with other unidentified genetic factors remains to be explored. More studies are needed to identify high risk genetic variants with clinical validation. Recent data suggest that patient derived hiPSC-CM may provide a platform for validation of genes/variants identified through GWAS and to clarify the associated molecular mechanisms predisposing to cardiotoxicity. Ultimately, this approach may allow for tailored doses of chemotherapeutics based on patient genotype (57).

There has also been an increasing interest in understanding the role of complementary approaches, such as epigenetics, proteomics, and metabolomics in the development of cardiomyopathy. An integrated-omics approach has the potential to improve our understanding of ACT. Artificial intelligence methods could be applied to large populations to further improve the diagnosis, prognosis, and treatment of ACT. With improved understanding of genetic predisposition for ACT, a risk assessment model that incorporates genetics and conventional clinical risk factors may be better suited to classify an individual patient's risk.

CONCLUSION

Anthracycline-induced cardiomyopathy is a complex adverse drug reaction that is associated with morbidity, mortality, and increased social and economic burden for patients, their families, and the healthcare system. Recent advances in the field of genetics have led to an improved understanding of ACT, although significant limitations to clinical applicability remain.

AUTHOR CONTRIBUTIONS

AA: conceptualization. TA-O: analysis and data collection. TA-O and BW: writing original manuscript draft. AA and UT: review and editing manuscript. All authors reviewed the results and approved the final version of the manuscript.

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REVIEW
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Novel Therapeutics for Anthracycline Induced Cardiotoxicity

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Anthracyclines remain an essential component of the treatment of many hematologic and solid organ malignancies, but has important implications on cardiovascular disease. Anthracycline induced cardiotoxicity (AIC) ranges from asymptomatic LV dysfunction to highly morbid end- stage heart failure. As cancer survivorship improves, the detection and treatment of AIC becomes more crucial to improve patient outcomes. Current treatment modalities for AIC have been largely extrapolated from treatment of conventional heart failure, but developing effective therapies specific to AIC is an area of growing research interest. This review summarizes the current evidence behind the use of neurohormonal agents, dexrazoxane, and resynchronization therapy in AIC, evaluates the clinical outcomes of advanced therapy and heart transplantation in AIC, and explores future horizons for treatment utilizing gene therapy, stem cell therapy, and mechanism-specific targets.

Keywords: cardio-oncology, anthracyclines, cardiotoxicity, cardiomyopathy, heart failure

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INTRODUCTION

Despite many recent advances in cancer treatments, anthracycline therapies remain an essential component in the successful treatment of multiple hematologic and solid organ malignancies. As cancer survivorship improves, increased efforts have been made to understand and mitigate the short- and long-term toxicities of chemotherapies. Of particular concern for anthracyclines is the development of highly morbid anthracycline-induced cardiotoxicity (AIC), where manifestations can range from asymptomatic electrocardiogram (ECG) changes and left ventricular (LV) dysfunction to profound cardiomyopathy and end-stage heart failure (HF). This narrative review aims to discuss the interplay of proposed mechanisms of anthracycline cardiotoxicity and contemporary evidence for pharmacologic, advanced, and investigational therapies in the prevention and treatment of AIC (Central Illustration, **Figure 1**).

OVERVIEW OF MECHANISMS OF CARDIOTOXICITY WITH PHARMACOLOGIC TARGETS

To understand the current and investigational pharmacologic targets, an understanding of the mechanisms of AIC is essential. Mechanisms of anthracycline cardiotoxicity are multifactorial and involve pathways in DNA damage, mitochondrial dysfunction, oxidative stress, inflammation,

and apoptosis promotion (**Figure 2**). Cardiac samples obtained from autopsy of patients with AIC demonstrate necrotic cells within the ventricular wall, interstitial fibrosis, cytoplasmic vacuolization, and marked reduction in the number of cardiomyocytes and myofibrils (1, 2). As anthracyclines preferentially accumulate in mitochondria and nuclei, the increased mitochondrial density and high energy demands of cardiomyocytes may explain the predilection for cardiotoxicity.

Anthracyclines interfere with many mitochondrial respiratory chain complexes involved in oxidative phosphorylation, leading to ineffective redox reactions and the formation of reactive oxygen species (ROS) (3). ROS production is exacerbated in the presence of iron and ROS interaction with various membrane and mitochondrial DNA constituents leads to alterations in autophagy and promotion of cardiomyocyte apoptosis and necrosis (4). Disruption of the integrity of mitochondrial membranes leads to release of pro-apoptotic factors (3). The depletion of cellular ATP and promotion of inner mitochondrial membrane permeability transition pore opening (mPTP) has also been associated with increased necrotic cardiomyocyte death (5). Anthracyclines also activate pro-inflammatory pathways involving nuclear factor-kB (NF-kB) and tumor necrosis factor alpha (TNF-α) and upregulate the transcription of NLRP3, interleukin (IL)-1β and IL-6, key inflammatory mediators of heart failure pathogenesis (6). Cardiomyocyte death leads to further activation of inflammatory cascades and ROS production, leading to functional and structural changes in the myocardium that is marked by fibrosis and electrical alterations (7, 8).

In addition to oxidative stress and inflammation, DNA intercalation by anthracyclines contributes to cardiotoxicity. Anthracycline binding to topoisomerase 2 beta causes double-stranded DNA breaks and inhibits transcription of several regulators of cardiac metabolism, leading to defective mitochondrial biogenesis and function and thereby indirectly contributing to exacerbation of ROS production (9). The DNA and nuclear damage leads to p53 activation and activation of pro-apoptotic pathways (9). As such, levels of pro-apoptotic molecules, such as Bax and caspase-3, have been found to be upregulated in rat hearts treated with anthracyclines (10).

PHARMACOLOGIC PREVENTION OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

Increasing recognition of the significant morbidity and mortality associated with AIC has led to exploration of treatment modalities to prevent the development of AIC. In preclinical studies, significant acute cardiotoxicity occurs at the time of the initial administration of anthracyclines that starts a cascade leading to the eventual development of LV dysfunction and HF. The most well-studied therapies include conventional heart failure therapies, including angiotensin converting enzyme (ACE) inhibitors and beta blockers, and dexrazoxane; additionally, there are multiple investigational treatments currently undergoing evaluation. The preclinical studies for the various therapies mentioned below are summarized in **Table 1**, while clinical studies are summarized in **Table 2**.

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The renin-angiotensin-aldosterone system has been postulated to play an important role in the development of AIC. Doxorubicin has been shown to increase plasma levels of angiotensin II and increase local myocardial ACE activity, which has been linked to direct myocardial damage *via* myocyte apoptosis, fibrosis, inflammation, and development of ROS (11). Therefore, it is hypothesized that these therapies have a targeted effect in AIC beyond the typical role of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) in neurohormonal regulation and ventricular remodeling in HF. Preclinical studies of ACEI and ARB demonstrated improved hemodynamics, improved cardiac remodeling, reduced incidence of heart failure, and decreased mortality in animal models (11–13). Collectively, these studies demonstrated that ACEI and ARB treatment decreased membrane lipid peroxidation, ROS production, and apoptosis in a variety of rat and mouse models (11). Studies have also compared the effectiveness of various ACEI/ARB therapies in AIC based on molecular structure and bioavailability. For example, zofenopril's presence of a free-radical-scavenging sulfhydryl group and affinity for accumulation in cardiomyocytes provided more effective cardioprotection than enalapril and valsartan in rats (14).

Clinical trial data for ACE inhibitor and ARB therapy has been mixed. The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial was a 2 × 2 factorial, randomized placebo-controlled trial of adjuvant monotherapy and combined candesartan and metoprolol succinate administration during adjuvant epirubicin therapy in breast cancer patients. Early follow up results of this trial immediately following adjuvant therapy demonstrated that candesartan prevented a modest reduction in LV ejection fraction (LVEF) not seen with metoprolol or combination therapy (15). However, the two-year follow up of PRADA showed a modest decline in LVEF in all groups that was not attenuated by candesartan therapy compared to placebo. Compared to patients receiving candesartan monotherapy, patients in the placebo arm experienced a trend toward increase in LV end systolic volume and reduced global longitudinal strain (GLS) (candesartan, 0.2% [95% CI, -0.3 to 0.8] vs. no candesartan, 1.0% [95% CI, 0.5–1.5], $p = 0.046$ (16). A placebo-controlled randomized trial of telmisartan during epirubicin therapy similarly showed improved GLS at 18 months follow up in ARB-treated patients compared to placebo (17). Early levels of serum biomarkers of inflammation and oxidative stress, IL-6 and ROS, were increased compared to baseline in the placebo group but not the telmisartan group, indicating a potential mechanism of cardiotoxicity (17, 18). Additionally, there was an observed correlation between the decrease in GLS and the levels of IL-6 and ROS (17). Similarly, ARB therapy has also been shown to mitigate the production of ROS and inflammatory cytokines

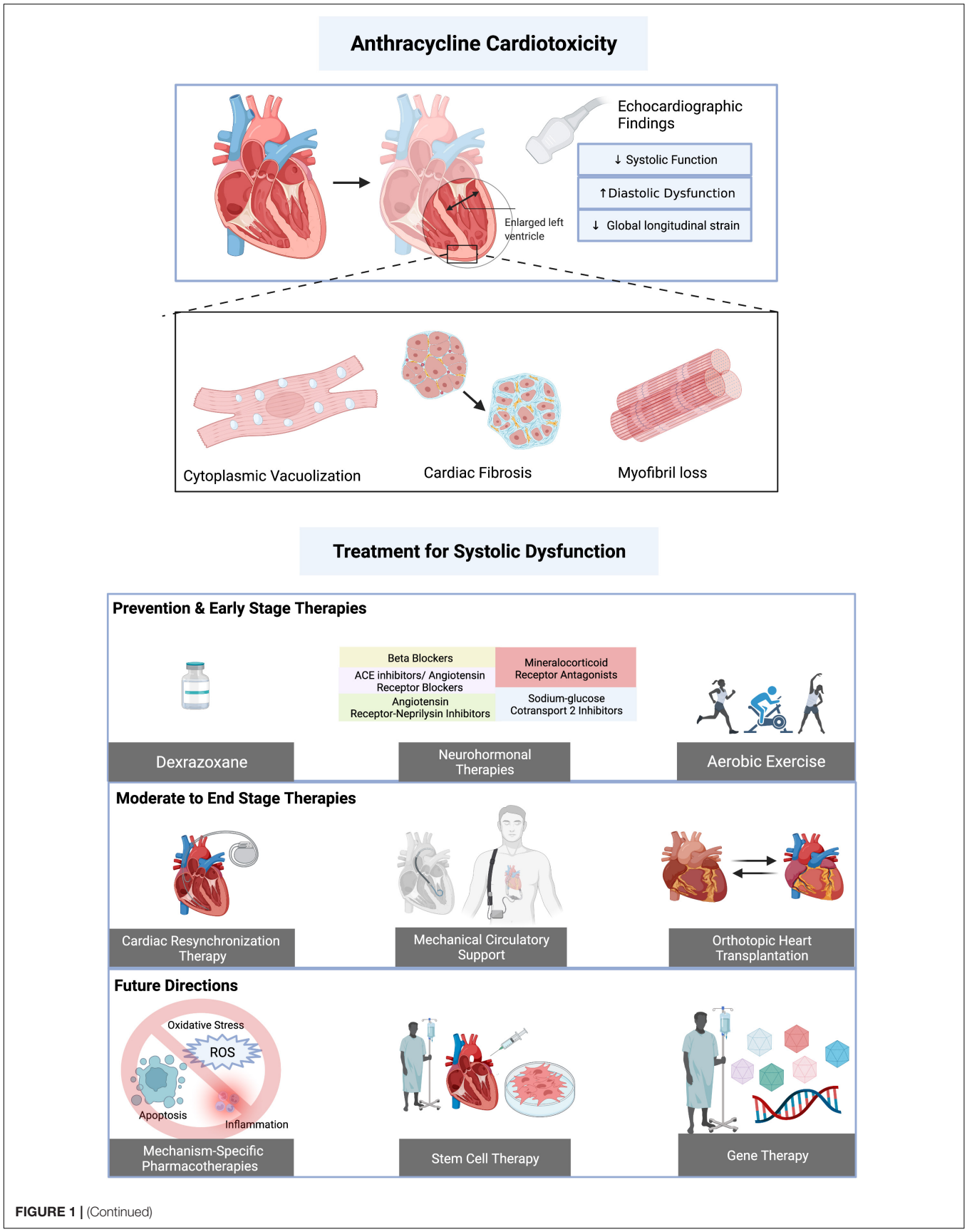

FIGURE 1 | (Continued)

FIGURE 1 | Central illustration. Summary of anthracycline induced cardiotoxicity (AIC) and treatment options. AIC on a cellular level is mediated by cytoplasmic vacuolization, cardiac fibrosis, and myofibril loss and is associated with echocardiographic of decreased systolic function, increased diastolic dysfunction, and decreased global longitudinal strain. Potentially preventative and/or investigational therapies for AIC associated systolic dysfunction include dexrazoxane, neurohormonal pharmacologic therapy, and aerobic exercise. Moderate to end stage therapy considerations include cardiac resynchronization therapy, mechanical circulatory support, and orthotopic heart transplantation. Therapies such as stem cell therapy, gene therapy, and targeting of AIC-specific mechanisms (such as apoptosis, reactive oxygen species production, and inflammation) are under ongoing investigation. Created with BioRender.com.

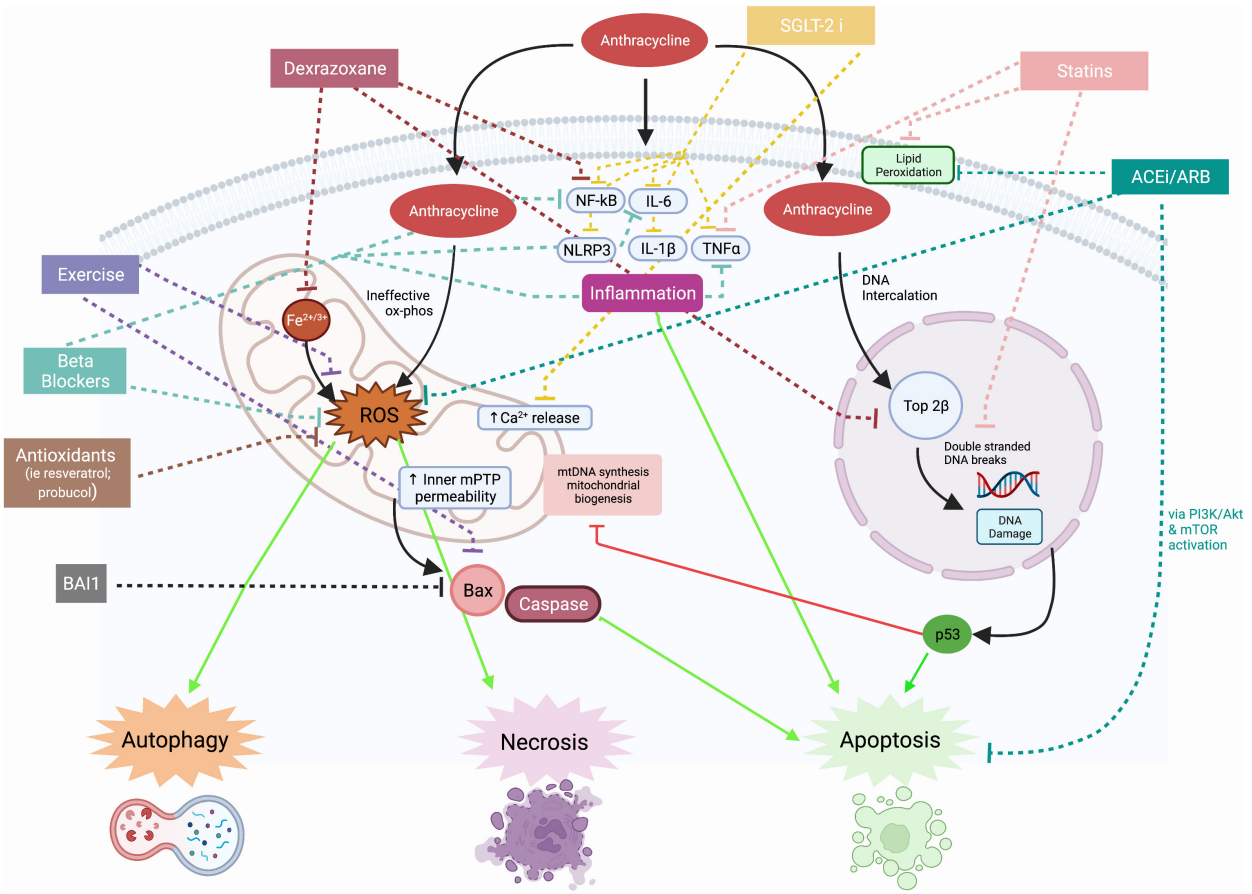

FIGURE 2 | Mechanisms of anthracycline cardiotoxicity and effects of therapies. Mitochondrial effects of anthracycline induced cardiotoxicity include production of reactive oxygen species, calcium dysregulation, impaired mitochondrial biogenesis, and disruption in mitochondrial membrane integrity, leading to release of apoptotic molecules such as bcl-2-associated X protein (Bax). The effects of anthracycline induced cardiotoxicity on nuclei include DNA intercalation and binding to Topoisomerase 2β to cause double stranded DNA breaks. DNA damage releases pro-apoptotic factors such as p53. Anthracyclines increase the expression of pro-inflammatory cytokines such as NF-kB, IL-6, NLRP3, IL-1β, and TNF-α. Proposed therapies have inhibitory effects on inflammation, reactive oxygen species production, DNA damage and apoptosis. Solid lines indicate mechanisms of anthracycline cardiotoxicity and dotted lines indicate mechanisms of proposed therapies. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BAI1, BAX activation inhibitor 1; Bax, bcl-2-associated X protein; Ca, calcium; Fe2+/3+, iron; IL, interleukin; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; NF-kB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; ox phos, oxidative phosphorylation; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha; Top2β, topoisomerase 2β; SGLT2i, sodium glucose cotransporter 2 inhibitor; PI3K, phosphinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin. Created with BioRender.com.

such as IL-6, with higher rates of LVEF recovery (17). This data indicates a potential protective role for ACE inhibitors and ARBs in patients at high risk for cardiotoxicity.

Beta Blockers

Beta blockers play a key role in guideline directed medical therapy for treatment of HF due to their neurohormonal effects, reduction in heart rate, and attenuation of catecholamines and arrhythmias. However, some beta blockers, particularly carvedilol and nebivolol, have additional significant antioxidant effects that reduce ROS and prevent mitochondrial dysfunction, providing a specific advantage in prevention of AIC (19). An initial randomized trial of nebivolol showed higher LVEF, decreased LV end-systolic and end-diastolic diameters, and lower B-type natriuretic peptide (BNP) levels at 6 months than those receiving placebo (20). In the CECCY (Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity) trial, the prophylactic use of carvedilol during anthracycline treatment had no impact

TABLE 1 | Description of example preclinical studies and summary of therapeutic effect on AIC parameters.

Study	Study Design	Therapies	Findings (compared to anthracycline + no therapy)					
			LV systolic function	LV dimension	Fibrosis	ROS	Apoptosis	Other
ACEi/ARB								
Hullin et al. (25)	Mouse model Acute DOX (×1)	Enalapril	↔	↔	NA	NA	NA	
	Mouse model Chronic DOX (weekly ×5)	Enalapril	↑	↓	NA	NA	NA	↑ Activation PI3K/AKT/mTOR
Hiona et al. (12)	Rat model Chronic DOX (weekly ×6)	Enalapril	↑	NA	NA	↓	↔	↑ Mitochondrial function
								↑ %Fractional shortening
Abd El-Aziz et al. (121)	Rat model Acute DOX (×1)	Captopril or enalapril	NA	NA	NA	↓	NA	↓ Lipid peroxidation
Iqbal et al. (13)	Mouse model Acute DOX (×1)	Telmisartan	NA	NA	↓	↓	NA	↓ Lipid peroxidation
								↓ Myocardial edema
Soga et al. (122)	Rat model Chronic DNR (3×/2 weeks)	Candesartan	↑	↔	↓	NA	↓	↓ 28 day mortality (50 vs. 19%)
								↑ %Factional shortening
								↑ E/A ratio
								↑ SERC2A transcription levels
Arozal et al. (123)	Rat model Chronic DNR	Olmesartan	↑	↓	NA	↓	NA	↓ Edema and hemorrhage on histopathology
								↓ AngII and AT-1R cardiomyocyte expression
								↑ %Fractional shortening
								↓ Metalloproteinase II expression
BB								
Chen et al. (124)	Mouse model Chronic DOX (every other day × weeks)	Carvedilol	↑	↓	↓	↓	↓	↑ Mitochondrial preservation
								↑ Cardiac stem cell expression
De Nigris et al. (125)	Rat model Chronic DOX/DNR (every other day × 12 days)	Nebivolol	↑	NA	NA	↓	NA	↑ Diastolic relaxation
		Carvedilol	↑	NA	NA	↓	NA	↑ Diastolic relaxation
MRA								
Lother et al. (24)	Mouse model Acute DOX (×1)	Eplerenone	↑	↓	↓	↔	↔	↑ Cardiac myocyte contraction and development gene expression (i.e., Ankrd1 and Nppa)
	Mouse model Chronic DOX (weekly ×5)	Eplerenone	↑	↓	↔	↔	↔	
Hullin et al. (25)	Mouse model Acute DOX (×1)	Eplerenone/MR gene ablation	↔	↔	↔	NA	NA	↑ Plasma aldosterone, ↑ AngII receptor, ↑ CTGF
	Mouse model Chronic DOX (weekly ×5)	Eplerenone/MR gene ablation	↔	↔	↔	NA	NA	↑ Plasma aldosterone, ↑ AII receptor, ↑CTGF

(Continued)

TABLE 1 | (Continued)

Study	Study Design	Therapies	Findings (compared to anthracycline + no therapy)					
			LV systolic function	LV dimension	Fibrosis	ROS	Apoptosis	Other
ARNI								
Boutagy et al. (29)	Rat model Chronic DOX (every 3 days × 3 weeks)	Sacubitril + valsartan	↑	↓	↓	NA	↔	↑ %Fractional shortening ↓ Metalloproteinase activity ↓ Myofibril vacuolization and inflammatory cell infiltration
SGLT2i								
Quagliariello et al. (33)	*In vitro* cell culture HL-1 mouse cardiomyocytes Acute DOX	Dapagliflozin	↔	↔	↔	↓	↓	↓ Pro-inflammatory cytokines IL-6, NF-kB and NLRP3 ↓ mTORC, FoxO1/O3a pathway expression ↑ Cell viability ↓ Ca^{2-} release
Sabatino et al. (34)	Mouse model Chronic DOX (Weekly ×5)	Empagliflozin	↑	↔	↓	NA	NA	↑ %Fractional shortening ↑ Global longitudinal strain ↓ Cardiac TnT and BNP levels
Quagliariello et al. (35)	Mouse model Chronic DOX (daily ×10) Mouse cardiomyocytes (HL-1)	Empagliflozin	↓	↔	↓	↓	↓	↓ IL-8, IL-6, IL-1β, NLRP3, and leukotriene B4 ↓ NF-kB activation ↓ %Factional shortening
Barış et al. (36)	Rat model Chronic DOX (every other day × weeks)	Empagliflozin	↑	↓	↓	↔	↓	Normal QTc and PR intervals compared to prolonged in DOX toxicity ↑ %Fractional Shortening ↓ Myocardial edema, cell infiltration
Dexrazoxane								
Noel et al. (38)	Mouse model Chronic DOX (weekly ×6)	Dexrazoxane	↑	↔	↓	NA	NA	↑ Global longitudinal strain
Yu et al. (126)	Mouse model Chronic DOX (3× over 1 week)	Dexrazoxane	↑	NA	NA	NA	↓	↑ %Fractional Shortening ↓ Activation of p38MAPK/NFkB apoptotic pathway ↑ miR-15-5p mediated apoptosis
Jirkovsky et al. (127)	Rabbit model Chronic DNR (weekly ×10)	Dexrazoxane	↑	↓	↓	↓	NA	↑ Survival ↓ Cardiac TnT levels ↑ Mitochondrial preservation ↑ Expression mitochondrial ANT1 and NRF1

(Continued)

TABLE 1 | (Continued)

Study	Study Design	Therapies	Findings (compared to anthracycline + no therapy)					
			LV systolic function	LV dimension	Fibrosis	ROS	Apoptosis	Other
Statin								
Riad et al. (48)	Mouse model Acute DOX ×1	Fluvastatin	↑	↓	NA	↓	↓	↓ TNFα expression
Sharma et al. (49)	Rat model Acute DOX ×1	Rosuvastatin	NA	NA	↓	NA	↓	↓ Na+ -K+ ATPase activity ↓ DNA ladder formation ↓ Cytoplasmic vacuolization ↓ LDL and ↑ HDL
Huelsenbeck et al. (50)	Mouse model *in vivo* H9C2 rat cardiomyocytes *in vitro* Chronic DOX (weekly ×3)	Lovastatin	NA	NA	↓	↔	↓	↓ Cardiac TnT levels ↓ DS DNA breaks and DNA damage ↓ CTGF transcription ↑ ANP levels ↑ Doxorubicin antitumor activity in fibrosarcoma model
Aerobic exercise								
Alihemmati et al. (57)	Rat model Acute DOX ×1	High-intensity interval training	NA	NA	NA	NA	↓	↓ BAX/BCL2 levels ↓ Caspase 6, GSK-3β levels
Wonders et al. (128)	Rat model Acute DOX ×1	Motorized treadmill	↑	↓	NA	↓	NA	
Ascensao et al. (129)	Rat model Acute DOX ×1	Motorized treadmill	NA	NA	NA	↓	↓	↑ HSP levels ↓ Cardiac TnI levels ↓ Cytoplasmic vacuolization ↓ Mitochondrial swelling
Ascensao et al. (130)	Mouse model Acute DOX ×1	Swimming	NA	NA	NA	↓	NA	↓ Cardiac TnI levels ↑ HSP60 levels

ACE, angiotensin converting enzyme inhibitor; Akt, Protein kinase B; AngII, angiotensin II, Ankrd1, ankyrin repeat domain 1; ANT1, adenine nucleotide translocase type 1; ARB, angiotensin II receptor blocker; BAI-1, BAX activation inhibitor 1; BAX, Bcl-2-associated X protein; CTGF, connective tissue growth factor; DNR, Danorubicin; DOX, Doxirubicin; IL, interleukin; Fox, Forkhead box; GSK-3β, glycogen synthase kinase-3β; HSP, heat-shock protein; LV, left ventricle; MR, mineralocorticoid receptor; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; NA, not analyzed; NF-kB, Nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; Nppa, Natriuretic Peptide A; NRF1, nuclear transcriptional factor 1; p38 MAPK, p38 mitogen-activated protein kinases; miR, miRNA encoding genes; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha; TnI, troponin I; TnT, troponin T.

TABLE 2 | Summary of results from clinical studies for anthracycline induced cardiotoxicity therapies.

Study	Trial design	Follow up (mean/median)	Disease	Therapies	Findings (compared to placebo or control)				
					Δ LVEF	Myocardial strain	Ventricular remodeling (LVEDD, LVESD)	DD	Other
ACE/ARB									
Dessi et al. (17)	Phase II, placebo-controlled (*n* = 49)	18 months	BC, endometrial Ca, lymphoma, NSCLC, ovarian Ca	Telmisartan	↔	↑	NA	NA	↓ IL-6
									↓ ROS
Cardinale et al. (131)	Randomized, Placebo controlled (*n* = 114)	12 months	AML, lymphoma, MM, BC	Enalapril	↑	NA	↓	NA	↓ HF
									↓ Arrhythmia
Nakamae et al. (132)	Prospective, randomized controlled (*n* = 40)	0.25 months	Lymphoma	Valsartan	↔	NA	↓		↓ BNP
									↓ QTc
BB									
Kaya et al. (20)	Randomized, placebo-controlled trial (*n* = 45)	6 months	Breast cancer	Nebivolol	↑	NA	↓	NA	↓ BNP
CECCY Avila et al. (21)	Randomized controlled trial (*n* = 200)	6 months	Breast cancer	Carvedilol	↔	NA	↔	↓	↔ BNP
									↓Troponin I
Kalay et al. (133)	Randomized, placebo controlled (*n* = 50)	6 months	Lymphoma, BC	Carvedilol	↑	NA	↓	↓	
El-Shitany et al. (134)	Randomized, controlled trial (*n* = 50)	1 months	Pediatric ALL	Carvedilol	↑	↑	NA	↔	↓ Troponin I
									↓ LDH
ACE/ARB ± BB									
Georgakoppulos et al. (135)	Prospective, randomized controlled trial (*n* = 125)	12 months	Lymphoma	Enalapril	↔	NA	↔	↔	
				Metoprolol	↔	NA	↔	↔	
PRADA Gulati et al. (15)	2 × 2 Factoria l, randomized, placebo-controlled trial (*n* = 120)	Treatment duration	Breast cancer	Candesartan	↑	↔	NA	↔	↔ Troponin I and T ↔ BNP
				Metoprolol	↔	↔	NA	↑	↑ BNP
				Combined	↔	↔	NA	↔	
PRADA Heck et al. (16)	2 × 2 factorial, randomized, placebo-controlled trial (*n* = 120)	23 months	Breast cancer	Candesartan	↔	↑	↓	NA	

(Continued)

TABLE 2 | (Continued)

Study	Trial design	Follow up (mean/median)	Disease	Therapies	Findings (compared to placebo or control)				
					Δ LVEF	**Myocardial strain**	**Ventricular remodeling (LVEDD, LVESD)**	**DD**	**Other**
				Metoprolol	↔	↔	↔	NA	
				Combined	↔	↔	↔	NA	
OVERCOME Bosch et al. (23)	Randomized, controlled trial (*n* = 90)	6 months	ALL, AML, lymphoma, MM	Carvedilol + Enalapril	↑	NA	NA	↔	↓ Death or HF
Liu et al. (136)	Randomized, controlled trial (*n* = 40)	4 months	Breast Cancer	Candesartan + Carvedilol	↑	NA	↓	NA	↑ ST and T wave abnormalities on ECG ↓ Arrhythmia ↓ Troponin
MRA									
ELEVATE Davis et al. (26)	Single center, randomized placebo-controlled trial (*n* = 44)	6 months	Breast cancer	Eplerenone	↔	NA	↔	↔	
Akpek et al. (27)	Randomized placebo-controlled study (*n* = 83)	3 week post-treatment	Breast cancer	Spironolactone	↑	NA	NA	↓	↓ Troponin I ↓ TAC
ARNI									
Gregorietti et al. (31)	Prospective trial, serial patients on maximal GDMT (*n* = 28)	24 months	Breast cancer	Sacubitril/valsartan	↑	NA	↓	↓	↓ 6MWT ↑ NYHA class ↓ Mitral regurgitation ↓ BNP
Martín-Garcia et al. (30)	Retrospective multicenter Spanish registry (HF-COH) (*n* = 67)	4.6 months	Breast cancer, lymphoma	Sacubitril/valsartan	↑	↔	↓	↔	↓ NYHA class ↓BNP
Dexrazoxane									
Swain et al. (39)	Multicenter, double blinded RCT phase III (*n* = 682)	532 days	Breast cancer	Dexrazoxane	↑	NA	NA	N A	↓ Cardiac events ↓ Granulocyte and WBC count
	Multicenter, double blinded RCT phase III (*n* = 326)	397 days	Breast cancer	Dexrazoxane	↑	NA	NA	NA	↓ Cardiac events ↓ Granulocyte and WBC count

(Continued)

TABLE 2 | (Continued)

Study	Trial design	Follow up (mean/median)	Disease	Therapies	Findings (compared to placebo or control)				
					Δ LVEF	**Myocardial strain**	**Ventricular remodeling (LVEDD, LVESD)**	**DD**	**Other**
Marty et al. (40)	Multicenter RCT phase III (*n* = 164)	126 days	Breast cancer	Dexrazoxane	↑	NA	NA	NA	↓ Cardiac events ↓ Clinical HF ↑ Cardiac-event free survival time
Asselin et al. (41)	Randomized placebo controlled study (*n* = 573)	9.2 years	Pediatric non-Hodgkin lymphoma, pediatric T-Cell ALL	Dexrazoxane	NA	NA	↓	NA	↓ Troponin T ↑ %Fractional shortening ↔ In infection, hematologic or CNS toxicity
Macedo et al. (44)	Meta-analyses of 7 RCTs and 2 retrospective studies from 1990 to 2019 (*n* = 2,177)	126 days to 7 years	Breast Cancer	Dexrazoxane	↑	NA	NA	NA	↓ Clinical HF ↓ Cardiac events ↔ Overall survival
Sun et al. (137)	Single center, single blinded RCT (*n* = 89)	126 days	Breast cancer w/concurrent T2DM	Dexrazoxane	↔	NA	↔	↓	↓ ROS levels
Ganatra et al. (47)	Single center, consecutive case series (*n* = 8)	13.5 months	T Cell lymphoma, NHL, AML, HL, Ovarian, Breast cancer with pre-existing asymptomatic LVEF <50%	Dexrazoxane	↑[#]	NA	NA	NA	↓ Symptomatic HF[#] ↓ All cause mortality[#]
Statin									
Acar et al. (53)	Single center, randomized placebo-controlled trial (*n* = 40)	6 months	NHL, MM, leukemia	Atorvastatin	↑	NA	↓	NA	↓ Lipid levels ↓ hsCRP levels

(Continued)

TABLE 2 | (Continued)

Study	Trial design	Follow up (mean/median)	Disease	Therapies	Findings (compared to placebo or control)				
					Δ LVEF	Myocardial strain	Ventricular remodeling (LVEDD, LVESD)	DD	Other
Seicean et al. (52)	Single center, retrospective study (*n* = 628)	2.6 years	Breast cancer	Uninterrupted statin therapy (any)	NA	NA	NA	NA	↓ Clinical HF incidence
Abdel-Qadir et al. (55)	Multicenter retrospective study (*n* = 1,332)	5.1 years	Breast cancer	Statin exposure (any) *	NA	NA	NA	NA	↓ LDL level ↓ Hospitalization or ED visit for HF
Chotenimitkhun et al. (54)	Single center prospective cohort study (*n* = 51)	6 months	Breast cancer, leukemia, lymphoma	Prior statin therapy (any)	↑	↔	↓	NA	↔ Blood pressure
Exercise									
Kirkham et al. (64)	Randomized controlled trial (*n* = 24)	24–48 h	Breast cancer	Single session 30 min vigorous intensity exercise 24 h before ANT	↑	↑	↓	↔	↓ SVR, DBP, MAP, pulse ↔ SV, CO ↓ NT-proBNP ↔ Troponin T
Kirkham et al. (65)	Randomized controlled trial (*n* = 24)	7–14 days	Breast Cancer	Single session 30 min vigorous intensity exercise 24 h before ANT	↔	↔	↔	↔	↔ Troponin T ↔ NT-proBNP

6MWT, 6 min walk test; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANT, anthracycline; BC, breast cancer; BNP, brain natriuretic peptide; Ca, Cancer; CO, cardiac output; DBP, diastolic blood pressure; DD, diastolic dysfunction; DOX, doxorubicin; ECG, electrocardiogram; ED, emergency department; HF, heart failure; hsCRP, high sensitivity c-reactive protein; IL, interleukin; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MM, multiple myeloma; NA, not analyzed; NHL, non-Hodgkin's lymphoma; NT-proBNP, N terminal- pro hormone brain natriuretic peptide; NYHA, New York Heart Association; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species; SV, stroke volume; SVR, systemic vascular resistance; TAC, total antioxidative capacity; T2DM, type 2 diabetes mellitus.

[#]Not statistically significant due to limited sample size.

**2 or more statin prescriptions in 1 year prior to index date, 1 of the prescriptions containing index date.*

on LVEF but an attenuation of increased troponin levels and protection against diastolic dysfunction compared to placebo (21). A meta-analysis of six RCTs evaluating prophylactic carvedilol monotherapy confirmed no effect on early changes in LVEF, but there was less increase in LV end-diastolic diameter, indicating a potential protective role in prevention of ventricular remodeling (22). In the beta blocker monotherapy arm of the PRADA trial, metoprolol succinate had no impact on decline of LVEF or GLS in short or long-term follow up (23). Importantly, unlike third generation beta blockers such as nebivolol and carvedilol, metoprolol has not been shown to have significant antioxidant properties. These studies indicate a potential role for beta blockers, particularly carvedilol and nebivolol, however, the small scale and short follow up of the majority of studies limits the wide applicability to all patients undergoing anthracycline therapy.

Combination Therapy

The combination of beta blocker and ACE inhibitor therapy has been hypothesized to provide an increased synergistic effect compared to monotherapy, but the data is conflicting in different populations. In the PRADA trial which focused on breast cancer patients, combined candesartan and metoprolol did not exhibit significant change in LVEF, GLS, or LVESD compared to placebo both in short and long-term follow up (15, 16). Comparatively, the OVERCOME trial found a small benefit of combined enalapril and carvedilol in acute leukemia patients with no significant change in LVEF at 6 months, as compared to an average of 3% LVEF reduction in the placebo group (23). Further large trials are needed to evaluate the optimal patient population who may benefit from combined ACE inhibitor/ARB and beta blocker therapy.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA) are another mainstay of heart failure treatment that has demonstrated conflicting preclinical and clinical results when applied to AIC. In a preclinical mouse model of AIC, both administration of eplerenone and direct cardiac myocyte mineralocorticoid receptor inhibition ameliorate the repressive effects of doxorubicin on cardiac myocyte transcription (24). However, in another mouse model of chronic AIC, eplerenone was not found to be cardioprotective particularly compared to enalapril (25). Clinically, the ELEVATE (Effect of Eplerenone on Left Ventricular Diastolic Function in Women Receiving Anthracyclines for Breast Cancer) trial was a randomized placebo-controlled trial of women with breast cancer to receive eplerenone during chemotherapy which showed no significant effect on LV systolic or diastolic dysfunction (26). Conversely, in Akpek et al., a placebo-controlled randomized controlled trial of spironolactone demonstrated that administration of spironolactone was protective of both systolic and diastolic cardiac function (27). There is an ongoing ATACAR (AuTophagy Activation for Cardiomyopathy Due to Anthracycline tReatment) study evaluating pravastatin and spironolactone in addition to maximally tolerated carvedilol and lisinopril for prevention of AIC (28). Further large-scale randomized controlled trials are needed to clarify the conflicting role of MRA in prevention of AIC.

Angiotensin Receptor-Neprilysin Inhibitors

The angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril-valsartan has been shown to have beneficial effects beyond ACE inhibitors and ARBs in the treatment of heart failure. In AIC, sacubitril-valsartan use in a rat model attenuated the decrease in ejection fraction with histological evidence of reduced myocardial toxicity and fibrosis in comparison with valsartan therapy alone (29). Although multiple small studies have evaluated the role of sacubitril-valsartan in treatment of symptomatic AIC, there is limited data regarding the role of sacubitril-valsartan in prevention of cardiotoxicity (30, 31). To this end, the PRADA II trial has been designed as a multicenter, randomized, placebo-controlled, double blinded clinical trial of sacubitril-valsartan therapy during epirubicin adjuvant chemotherapy to clarify the clinical cardioprotective role (32).

Sodium-Glucose Transport Protein 2 Inhibitors

The newest studies of AIC in mice and *in vitro* human cells have demonstrated that empagliflozin and dapagliflozin protect against LV dysfunction with increased cardiomyocyte viability and reduction in cardiomyocyte apoptosis and inflammatory cytokine expression (33, 34). An *in vitro* cell based study by Quagliariello et al. demonstrated that administration of dapagliflozin reduced myocyte production of pro-inflammatory cytokines, including IL-1β, IL-8 (35). NF-kB and the NLRP3 inflammasome by 25–40%, as well as downregulation of the mTORC mediated pathway to apoptosis. In a rodent model, empagliflozin with doxorubicin administration led to preservation of LVEF and longitudinal strain with histologic evidence of reduced myocardial fibrosis and apoptosis (34–36). Given the mechanistic plausibility and promising preclinical studies of Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors, clinical trials are needed to evaluate their potential role in prevention of cardiotoxicity.

Dexrazoxane

In addition to the aforementioned conventional heart failure therapies, dexrazoxane was the first FDA approved therapy specific to AIC. Despite its early discovery, the mechanism of dexrazoxane cardioprotection continues to be elucidated. It was developed as a water-soluble analog of the iron chelator ethylenediaminetetraacetic acid (EDTA), aimed at reducing the production of ROS by anthracyclines *via* iron sequestration and iron displacement from anthracycline binding sites. However, more recent data involving dexrazoxane and its iron chelating metabolite ADR-925 suggested that topoisomerase IIβ inhibition and depletion, and not iron chelation, is responsible for its cardioprotective properties (37). Dexrazoxane also protects against cardiomyocyte apoptosis and necrosis *via* MAPK/NF-kB pathways inhibition, thereby reducing doxorubicin-induced

inflammation (3). Serial cardiac MRI measurements in mouse models of anthracycline cardiotoxicity treated with dexrazoxane for 8 weeks demonstrated significantly less myocardial edema, improved GLS, and less myocardial deformation compared to no dexrazoxane (38).

Multiple randomized controlled trials have shown a reduced risk of cardiotoxicity with dexrazoxane administration during anthracycline therapy, primarily in children with hematologic malignancies and adults with breast cancer. Two double-blinded randomized controlled trials in advanced breast cancer patients demonstrated that dexrazoxane administered in a 10:1 ratio to anthracycline dose reduces the risk of LVEF decline and heart failure (39). Subsequent trials further solidified the role of dexrazoxane in the reduction in the risk of incident heart failure (11 vs. 1%, $p < 0.05$) and cardiac events (39 vs. 13%, $p < 0.001$) in advanced or metastatic breast cancer, without impeding tumor response rate (40). In children and adolescents with T cell acute lymphocytic leukemia (ALL) or non-Hodgkin lymphoma receiving anthracycline therapy, the addition of dexrazoxane improved LV wall thickness and fractional shortening on echocardiogram (41).

Unfortunately, these early studies indicated a possible increased risk of secondary malignancies and decreased antitumor efficacy (42). However, later studies confirmed the efficacy of dexrazoxane without the associated risk for secondary malignancies and antitumor efficacy (41, 43). The FDA approved usage of dexrazoxane, however, remains restricted to cardioprotection in advanced or metastatic breast cancer with ongoing anthracycline use after a cumulative dose of greater than 300 mg/m^2 of doxorubicin. Off-label use of dexrazoxane in populations beyond metastatic breast cancer is increasing with promising results (44–46). Ongoing observational studies from the Children's Oncology Group are evaluating the long term effects of dexrazoxane on heart failure and cardiomyopathy in children (NCT 01790152). Further studies are needed to further clarify the population of patients that may benefit most from prophylactic treatment with dexrazoxane.

Expanding on the role of dexrazoxane in primary cardiotoxicity prevention, a small case series followed eight patients with pre-existing asymptomatic LV systolic dysfunction for 13.5 months and found that two of three patients who were not treated with dexrazoxane developed cardiogenic shock, and all had markedly reduced ejection fraction (mean 42.5% baseline to 18% after chemotherapy (47). Patients treated with dexrazoxane had less significant LVEF reductions (mean baseline 39% to mean 34% post treatment) and none developed symptomatic HF. Future large scale clinical trials are needed to evaluate the cardioprotective effects of dexrazoxane in patients with established HF.

Statins

In mouse models, fluvastatin and rosuvastatin were associated with improved cardiac function and reduction in cardiac inflammatory response, oxidative stress, and myocardial fibrosis (48, 49). Huelsenbeck et al. demonstrated that lovastatin co-treatment with anthracyclines reduces cardiotoxicity in mice *via* reduced mRNA levels and pro-fibrotic and pro-inflammatory cytokines (50). In comparison to carvedilol, rats pre-treated with rosuvastatin exhibited less LV fibrosis, LVEF reduction, and troponin elevation after 4 weeks of doxorubicin cessation (51). These pre-clinical studies demonstrate promise that the addition of statin therapy may aid in AIC prevention.

Several small single center studies have evaluated the use of statins for primary prevention of cardiotoxicity in breast cancer. In a single center observational cohort study of 628 women with breast cancer treated with anthracyclines, those on uninterrupted statin therapy throughout the 2.5 year follow up period demonstrated reduced incidence of HF (HR 0.3; 9% CI 0.1–0.9, $p = 0.03$) (52). In addition, in a randomized-controlled trial of 40 patients undergoing anthracycline therapy for various malignancies, prophylactic administration of statin for 6 months after anthracycline treatment was cardioprotective, with the placebo group experiencing significantly reduced LVEF (from 62.9 to 55.0%, $p < 0.0001$) while no change in LVEF was found in the atorvastatin group (from 61.3 to 62.6%, $p = 0.144$) on echocardiography (53). Similar results were obtained in a prospective study of 51 patients with various malignancies when assessed with CMR, where patients without statin therapy demonstrated a reduced LVEF (from 57.5 to 52.4%, $p = 0.0003$) while no significant change in LVEF was observed in patients receiving statin therapies (from 56.6 to 54.1%, $p = 0.15$) after 6 months (54). In a propensity score-matched cohort study, breast cancer patients on anthracycline therapy who had received statin therapy had significantly lower rates of heart failure hospital admissions (HR 0.45 95% CI 0.23–0.85, $p = 0.01$) (55). Additional, robust randomized controlled trials evaluating the efficacy of statins in AIC, including the Preventing Anthracycline Cardiovascular Toxicity with Statins (PREVENT; NCT01988571) and the Statins TO Prevent the Cardiotoxicity from Anthracyclines (STOP-CA; NCT02943590) trials are ongoing.

Aerobic Exercise

Recent literature suggests that aerobic exercise may be particularly beneficial in mitigating the cardiotoxic effects of anthracyclines due to the stimulation of antioxidants, reduction of ROS levels, and decrease in activation of apoptotic pathways. Aerobic exercise leads to cardioprotective remodeling by promoting myofilament synthesis and physiologic hypertrophy in various animal models (56). In addition, Alihemmati et al. demonstrated that high intensity interval training in rats treated with doxorubicin led to a reduction in pro-apoptotic proteins, such as BAX and caspase 6, and overall fewer apoptotic cells compared to controls (57). Other pre-clinical studies have shown the benefit of exercise in reducing ROS production, increased gene expression of antioxidant molecules, reduced mPTP susceptibility, increased mitochondrial resilience, and lowered lipid peroxidation in rat models of AIC (58). A variety of pre-clinical studies demonstrated that swimming, forced treadmill and wheel running exercise programs reduced fibrosis and necrosis, decreased myocardial inflammatory markers, and protected against loss of cardiomyocytes and myofibrils among rodents exposed to doxorubicin (59).

In humans, evidence of aerobic exercise in protecting against AIC is limited. Studies have consistently demonstrated that

anthracycline therapy reduces cardiorespiratory fitness in adult breast cancer patients and pediatric patients with hematologic malignancies (60, 61). Additionally, exercise programs are feasible and can improve patient reported cardiorespiratory tolerance and peak VO_2 (62, 63). Despite this, high-quality data demonstrating that aerobic exercise protects against alterations in objective parameters of cardiotoxicity are lacking. Kirkham et al. demonstrated that a single 30-min session of vigorous intensity exercise prior to doxorubicin exposure was associated with improved LV volumes, improved GLS and lowered circulating pro-BNP values compared to controls within 48 h of anthracycline administration (64). However, these protective effects were no longer seen at 2 weeks after anthracycline administration (65). These findings are limited by a short follow up period, small sample size, and confounded by the effects of exercise itself on pro-BNP levels and myocardial strain. Furthermore, these results do not evaluate the effect of longer-term exercise programs on AIC.

Several multicenter studies are currently evaluating the cardioprotective effects of exercise in AIC. The ONCORE study (Exercise-based Cardiac Rehabilitation for the Prevention of Breast Cancer Chemotherapy-induced Cardiotoxicity; NCT03964142) (66), the ATOPE Trial (Attenuating cancer Treatment-related Toxicity in Oncology Patients with a Tailored Physical Exercise Program; NCT 03787966) (67), and the BREXIT trial (Breast Cancer Exercise InTervention) (68) are randomized controlled trials aimed at determining whether exercise-based cardiac rehabilitation in breast cancer patients can mitigate anthracycline cardiotoxicity measured by LVEF and GLS, cardiac biomarkers, and peak VO_2. The results of these robust studies may eventually help define the degree by which aerobic exercise reduces risk for anthracycline induced cardiotoxicity. If the studies demonstrate positive results, they may justify cardiac rehabilitation before or after anthracycline therapy as standard of care even in the absence of overt cardiac dysfunction.

TREATMENT OF ANTHRACYCLINE INDUCED CARDIOMYOPATHY

Alterations in Chemotherapy Regimen

As patients undergo treatment with anthracyclines, cardiovascular monitoring is warranted both during the treatment period and as part of post-treatment surveillance (**Figure 3**). If early signs of cardiotoxicity develop, such as reductions in LVEF or decreased GLS, chemotherapy regimen changes must first be considered as an interdisciplinary team. While prevention or reversal of cardiotoxicity would ideally involve withholding or delaying anthracycline administration, this is often not practical given the risk of malignancy progression.

Additional considerations include changing the anthracycline agent and altering the anthracycline infusion schedule. Early results by Hortobagyi et al. demonstrated that continuous infusion strategies were associated with more than a 75% decrease in the frequency of congestive heart failure in cumulative doses greater than 450 mg/m^2 (69). However, later studies demonstrated equivocal results. In a study comparing continuous intravenous vs. bolus infusion of doxorubicin among breast cancer and sarcoma patients receiving doxorubicin, bolus infusion was associated with lower rates of cardiac events 1–5 years after treatment (4 vs. 5.1% at 1–5 years after treatment, $p = 0.046$), but no significant change was noted for cardiac events within 1 year of treatment or more than 5 years after treatment (6.5 vs. 5.6%, $p = 0.098$ and 0.5 and 0.9%, $p = 0.068$) (70). Similarly, bolus and continuous infusion of doxorubicin among pediatric patients with acute lymphoblastic leukemia demonstrated no difference in rates of cardiotoxicity measured on serial echocardiography monitoring for 8 years (71). Alterations in the anthracycline agent itself may also be considered. Pegylated liposomal doxorubicin has been developed to reduce myocardial anthracycline concentrations, and has been shown in a meta-analysis to be associated with a significant reduction in cardiotoxicity (OR 0.46 95% CI 0.23–0.92) (72). Different anthracycline agents have variable profiles of cardiotoxicity, such as danorubicin and epirubicin showing less long-term cardiotoxicity than doxorubicin in childhood cancer survivor cohorts (72). Thus, agent switching can be employed where applicable to minimize the effects of AIC.

Neurohormonal Pharmacologic Therapy

In patients undergoing anthracycline therapy, serial echocardiography and clinical monitoring for development of LV dysfunction and heart failure is indicated to ensure timely treatment and consideration of changes in chemotherapy regimens. In AIC, the LVEF threshold for initiation of pharmacologic therapy is shifted from the conventional cutoff of an LVEF of 40% to LVEF of less than 50% due to the increased risk of further decline in LVEF in this population. There is evidence for the effectiveness of traditional HF guideline directed medical treatment (GDMT) in this population. In patients with new LVEF of <45%, initiation of enalapril and carvedilol led to complete recovery in 42%, partial recover in 13% and no change in 45% of patients (73). A prospective study of patients undergoing anthracycline chemotherapy monitoring for decline of LVEF showed that for AIC defined as LVEF of <50%, early diagnosis and initiation of combined enalapril and beta blocker therapy has been associated with greater LVEF recovery (74).

Additionally, the role of ARNIs is being elucidated. In a small study of 28 patients who developed AIC and were previously optimized on GDMT, patients were transitioned to sacubitril-valsartan with significant improvement in LVEF, ventricular remodeling and diastolic function indicating a promising role for sacubitril-valsartan (31). A retrospective multicenter registry study identified sixty-seven patients started on sacubitril/valsartan for AIC and similarly found an improvement in LVEF, ventricular remodeling and NT-proBNP levels after initiation of therapy (30).

Current treatment of AIC is largely based on observational studies and adaptation of existing HF guidelines are without specific randomized trials comparing the relative advantages of different guideline-directed therapies in this unique patient

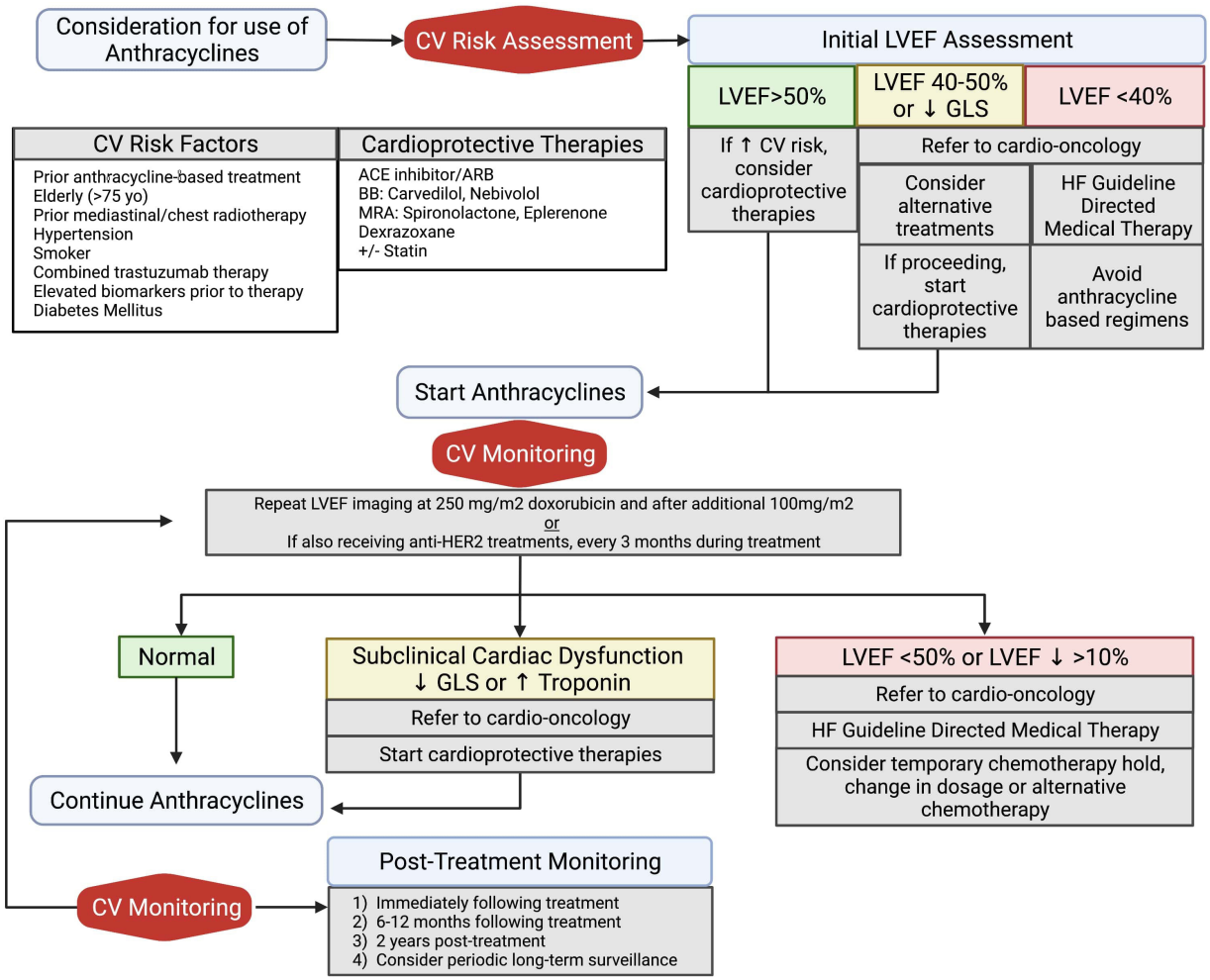

FIGURE 3 | Algorithm of clinical management for prevention and treatment of anthracycline induced cardiotoxicity. All patients should undergo baseline cardiovascular risk assessment, including an echocardiogram. Initiation of cardioprotective medications should be considered in patients with increased cardiovascular risk or abnormal baseline LVEF assessment. Patients with high-risk anthracycline therapy due to high dose (250 mg/m^2 doxorubicin) and concomitant anti-HER2 treatments should undergo serial cardiovascular monitoring during treatment. All patients should undergo post-treatment LVEF monitoring for detection of long-term cardiovascular sequelae. Adapted from ESMO 2020 guidelines (75). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist. Created with BioRender.com.

population, particularly newer agents such as ARNIs and SGLT2i. Current available data have been adapted into clinical surveillance and management guidelines and consensus statements released from the European Society for Medical Oncology (ESMO) and the American Society of Echocardiography (ASE), respectively (75, 76). These guidelines have been summarized into a clinical algorithm proposed in **Figure 3**.

Tolerability Considerations of Pharmacologic Therapy

Compared to conventional heart failure patients, oncology patients with AIC represent a unique cohort of patients vulnerable to hemodynamic intolerance of neurohormonal therapies due to the anemia, dehydration, fatigue and hypotension often associated with their underlying malignancy and treatment regimen. Unfortunately, the tolerability of guideline directed medical therapy in the AIC population is not well-studied. The CECCY trial reported that symptomatic hypotension was the most common side effect of carvedilol administration, affecting three patients (3.1%). While this was an overall low incidence of hypotension, approximately only 9% of the carvedilol arm achieved the dosing goal of 50 mg/day (77). The PRADA trial had reported that candesartan and metoprolol were generally well-tolerated amongst trial participants, but had excluded patients with underlying hypotension with SBP < 110 as well as any history of beta blocker and ACE/ARB intolerance (15, 16). As the PRADA II trial evaluates the efficacy of ARNI in the treatment of AIC, it will be important to understand the potential potent hemodynamic effects of these agents on populations most vulnerable to hemodynamic fluctuation.

Future studies must carefully select populations representative of cancer patients on AIC and compare hemodynamic tolerability of neurohormonal therapy in this population with those of conventional heart failure. Additionally, it remains unclear if optimal or target dosing of medications differs in these patients compared to the general HF population.

Cardiac Resynchronization Therapy

In patients with AIC and standard guideline indications for cardiac resynchronization therapy (CRT), CRT has been found to be safe and effective. CRT reduces myocardial tissue desynchrony, which leads to alterations in perfusion and metabolism that may be particularly beneficial for myocyte toxicity in patients with AIC (78). Small studies, including Multicenter Automatic Defibrillator Implantation Trial-Chemotherapy Induced Cardiomyopathy (MADIT-CHIC), have demonstrated that CRT in AIC patients with dilated cardiomyopathy and left bundle branch block was associated with improvement in LVEF and New York Heart Association (NYHA) functional class during the follow up period (79–81). In retrospective case control studies, patients with AIC and CRT showed evidence of ventricular remodeling (80) and long term mortality (82) similar to patients with alternative etiologies of non-ischemic cardiomyopathy.

Mechanical Circulatory Support

Treatment of end-stage cardiomyopathy may include consideration for advanced heart failure therapies, including ventricular assist devices (VAD) and orthotopic heart transplant (OHT). Evaluation for these invasive therapies can be complicated due to the patient's oncologic history including ongoing chemotherapies, prognosis or, if in remission, risk of recurrence. The use of VADs is still relatively rare and AIC was the etiology of cardiomyopathy in only 0.5% of registry patients on mechanical circulatory support (MCS) (83–85). Compared to idiopathic dilated cardiomyopathy and ischemic cardiomyopathy, AIC patients undergoing left-sided VAD (LVAD) implantation were more likely to be female and more likely to have LVAD as destination therapy (86). One major limiting factor for LVAD implantation is the high risk of right ventricular dysfunction in AIC, which increases the risk for right ventricular failure after LVAD implantation. In fact, in an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis, almost one fifth of patients required biventricular MCS (87). Despite the increased need for biventricular support, survival is similar between AIC patient and other causes of cardiomyopathy and indicates that LVAD may yield acceptable outcomes in those with active cancer (86, 87). Hence, it may be a viable strategy not only in conventional use as support in those with end-stage HF from AIC, but perhaps in highly selected individuals as a bridge during cancer treatment (88).

Orthotopic Heart Transplant

Although OHT remains the definitive treatment for end-stage heart failure, patients with AIC often face barriers to candidacy due to their history of malignancy and concern for recurrence on immunosuppressive medications. To date, 0.8–2.5% of all OHT patients had chemotherapy associated cardiomyopathy (89). OHT recipients with AIC were younger, female, and less likely to have bridge-to-transplant LVAD. Most notably, survival rates after OHT in patient with AIC have been found to be comparable to dilated and ischemic cardiomyopathy (90, 91). Additional studies are needed to better understand how prior malignancy may impact OHT survival and to investigate the role of alternative immunosuppressive regimens that may be useful in this population.

INVESTIGATIONAL THERAPIES

In addition to the investigation into applications of the aforementioned cardioprotective therapies to the treatment of AIC, efforts have been made to design therapies targeting the specific cardiotoxic mechanisms of anthracyclines. However, molecular target selection has proven challenging due to the heterogeneous effects of anthracyclines on many cellular constituents, and the need to select pathways that do not compromise chemotherapeutic efficacy, or cause significant off-target effects. Despite these challenges, several investigational therapies have been proposed, and several with promising preliminary results that are summarized in **Table 3**.

Therapies Targeting Apoptosis

Ongoing investigations are aimed at attenuating the release of apoptotic factors that are integral to the pathophysiology of AIC. Bcl-associated X protein (BAX) is a member of the BCL-2 protein family that has been shown to promote both cellular apoptosis and necrosis. With cellular stress exposure, BAX translocates to the mitochondrial membrane and increases outer membrane permeability to release pro-apoptotic factors and promotes inner membrane mPTP opening to promote cellular necrosis (92, 93). Amgalan et al. utilized BAI1, a small molecular inhibitor of BAX, and demonstrated that the prevention of BAX translocation to the outer mitochondrial membrane leads to reduced apoptotic and necrotic cardiomyocyte death in murine and zebrafish animal models (94). On a cellular level, treatment with BAI1 helped to maintain mitochondrial integrity and ultimately protected against LV systolic dysfunction as measured by echocardiographic parameters (94). Interestingly, BAX inhibition *via* BAI1 did not adversely affect anthracycline cancer cell toxicity in mice; presumably from markedly higher levels of BAX in tumor cells compared to cardiomyocytes.

The use of the phosphodiesterase-5-inhibitor, sildenafil, has also demonstrated anti-apoptotic effects. Pre-treatment with sildenafil prior to doxorubicin initiation in mice was associated with preserved LV function and decreased cellular apoptosis (95). *In vitro* analysis of the underlying mechanisms revealed that sildenafil preserved mitochondrial membrane potentials, reduced intracellular levels of the pro-apoptotic caspase-3 enzyme, and preserved levels of anti-apoptotic Bcl-2 family proteins. These results indicate that sildenafil may be useful in the modulation of apoptotic pathways associated with AIC, however, the safety of the use sildenafil without compromising antitumor efficacy must be better delineated.

TABLE 3 | Summary of findings from clinical and preclinical studies for investigational therapies.

Study	Study design	Anthracycline	Therapies	Findings (compared to anthracycline + no therapy)
Targeting apoptosis				
Amgalan et al. (93)	Mouse model Zebrafish model	Acute DOX (×1) Chronic DOX (every other day × weeks)	BAI-1	↓BAX translocation
				↓ Cardiomyocyte necrosis and apoptosis
				↑ Cardiac contraction
				↓ Pericardial edema
Fisher et al. (94)	Mouse model	Acute DOX (×1)	Sildenafil	↓ *In vivo and in vitro* apoptosis measured by TUNEL
				↑ Bcl-2 expression
				↓ Myofibrillar disarray on immunofluorescence
				↓ ST interval prolongation
				↓ Mitochondrial membrane potential dissipation
				↑ Myocardial contractility
Liu et al. (95)	Mouse model	Acute DOX	Melatonin	↑ Antioxidant activity measured by fluorescence assay
				↑ 5 day survival
				↑ *In vitro* cardiomyocyte function by HR and LVDP
				↑ *In vivo* cardiac function by LVEDP, LVESP, and dP/dt measurements
				↓ Histological cytoplasmic vacuolization, mitochondrial damage, and swelling
				↓ Apoptosis by TUNEL
Yang et al. (97)	*In vitro:* H9c2 rat cardiomyoblasts *In vivo:* mouse model	Chronic DOX (Every other day × weeks)	Melatonin	↓ AMPkα2 activation
				↓ ROS generation
				↑ ATP production
				↓ Apoptosis
				↑ Mitochondria length
				↓ mitochondrial fragmentation
Targeting oxidative stress and inflammation				
Siveski-Iliskovic et al. (98)	Rat model	Chronic DOX (6×/2 weeks)	Probucol	↓ LVEDP, ↑LVEF ↑LVSP
				↑ Levels of antioxidant enzymes GPx and SOD
				↓ Lipid peroxidation
				↓ Mitochondrial swelling, cytoplasmic vacuolization, lysosomal body, sarcotubular deformation
Cao and Li. (99)	*In Vitro:* H9c2 rat cardiomyocytes	Acute DOX	Resveratrol	↑ Antioxidant enzymes SOD, catalase, GSH, and GR activity
		Xanthine		↓ Cardiomyocyte ROS
		HNE		↑ Cell viability
Tatlidede et al. (100)	Rat model	Chronic DOX (every other day × weeks)	Resveratrol	Echo: ↑ LVEF; ↑ %FS ↓LVEDD, ↓LVESD ↑ relative wall thickness
				↓ LDH ↑ CK ↑ AST
				↑ Antioxidant enzyme levels of catalase, SOD, GSH
				↓ ROS
				↓ Capillary vasocongestion and cytoplasmic vacuolization
Liu et al. (101)	*In vitro:* H9c2 rat cardiomyocytes	Acute DOX x1	Resveratrol	↓ Cell apoptosis
				↑ Cell viability
				↓ Pro-apoptotic protein expression of FoxO1, p53, and Bim
				↓ ROS production
				↑ SOD activity
Monahan et al. (102)	*In vitro:* H9c2 rat cardiomyocytes	Acute DOX x1	Resveratrol	↓ ROS production

(Continued)

TABLE 3 | (Continued)

Study	Study design	Anthracycline	Therapies	Findings (compared to anthracycline + no therapy)
				↑ Cell viability (compared to no therapy and compared against carvedilol and dexrazoxane)
Chen et al. (103)	Rat model	Chronic DOX (every 3 days × 3 weeks)	Co-enzyme Q10	↓ Fibrosis on tissue trichrome staining
				↓ Pro-fibrotic CTGF and TGF-β1, MMP2, MMP9, COL1A1 levels
				↓ Pro-apoptotic Bak, BAX, caspase-9, caspase-3 levels
				↓ Apoptosis measured by TUNEL
Akolkar et al. (104)	Rat model	Chronic DOX (6×/3 weeks)	Vitamin C	Echo: ↑ LVEF ↑ %FS ↓ E/A ratio
				Histology: ↓ cytoplasmic vacuole formation; ↑myofibrils ↓ fibrosis s
				↓ Lipid peroxidation; ↓ ROS
				↑ Antioxidant enzyme expression of SOD, GPx and catalase
				↓ TNFα, IL-1β, IL-6
				↓ Proapoptotic Bnip-3, Bak, BAX and caspase-3
				↓ Inflammatory response associated JNK, NF-kB, and IKK levels
				↑Akt and STAT3 levels
Berthiaume et al. (105)	Rat model	Chronic DOX (weekly ×7)	Vitamin E	↔ Mitochondrial oxygen consumption
				↔ Ca loading capacity
				↔ Cardiomyocyte damage and cytoplasmic vacuolization
				↓ ROS protein carbonyls
Arica et al. (106)	Rat model	Acute DOX ×1	N-acetylcysteine	↓ MDA
				↓ AST, LDH, CK
				↔ SOD
				↓ Cytoplasmic vacuolization ↓ myofibril disarray ↓ myofibril loss
Unverferth et al. (107)	Dog model	Chronic DOX (weekly ×16)	N-acetylcysteine	↔ LVEF
				↔ CI, LVEDP, MAP
				↓ Subendocardial and subepicardial fibrosis
EPOCH trial Jo et al. (108)	Single center, randomized controlled clinical study (n = 103) 12 months follow up	DOX Epirubicin	N-acetylcysteine	↔ Troponin I ↔ CK-MB
				↔ LVEF decline ↔LVESD ↔LVEDD, ↔E/A ratio, ↔ E/E'
	Population: adults w/BC, lymphoma			↔ All cause mortality
Inhibiting CYP1				
Asnani et al. (109)	*In vivo:* Mouse model, zebrafish model	Acute DOX	CYP1 inhibition/ Visnagin	↓ Induction of CYP1 enzymes
	In vitro: HL-1 mouse cardiomyocytes			↓ Cardiomyocyte apoptosis
Lam et al. (110)	Zebrafish model	Acute DOX	CYP1 inhibition w/various genes	↓ Pericardial edema
				↑ Cardiac contraction
				↑ Blood flow
Use of Stem Cells				
Bolli et al. (112)	Open-label, phase I, double blind, placebo, randomized control trial (n = 31)	DOX	Allo-MSC	↔ Cardiovascular death ↔ HF hospitalization
	Population: adults w/leukemia, BC, HL, NHL, sarcoma with chronic AIC	Epirubicin, Danorubicin		↔ LVEF, ↔ GLS, ↔LVEDV, ↔ LVESV

(Continued)

TABLE 3 | (Continued)

Study	Study design	Anthracycline	Therapies	Findings (compared to anthracycline + no therapy)
				↔ Scar tissue
				↔ NT-proBNP
				↓ MLHFQ score
				↓ 6MWT*
O'Brien et al. (113)	SENECA trial patient specific iCMs	DOX	Extracellular vesicles from MSCs	↑ Cardiomyocyte viability
				↑ ATP production
				↓ ROS production
				↑ Pro-mitochondrial biogenesis associated PGC-1α

6MWT, 6 minute walk test; Akt, Protein kinase B; AIC, anthracycline induced cardiotoxicity; AMPkα2, AMP-activated protein kinase catalytic subunit alpha-2; AST, aspartate transaminase; ATP, adenosine triphosphate; BAI-1, BAX activation inhibitor 1; Bak, Bcl-2 homologous antagonist/killer; BAX, Bcl-2-associated X protein; Bc, breast cancer; Bcl-2, B-cell lymphoma 2; BIM, Bcl-2-like protein 11; Bnip-3, Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3; CI, cardiac index; CK, creatine kinase; COL1A1, collagen type 1 alpha 1; CTGF, connective tissue growth factor; CYP1, cytochrome P450 family 1; DOX, doxorubicin; FS, fractional shortening; Fox, forkhead box; GSH, glutathione; GPx, glutathione peroxidase; GR, glucocorticoid receptor; HR, heart rate; HL, Hodgkin's lymphoma; HNE, 4-hydroxy 2-non-enal; iCM, induced cardiomyocyte; IKK, IkB kinase; IL, interleukin; LVDP, left ventricular diastolic pressure; JNK, C-Jun N-terminal kinease; LVEDP, left ventricular end diastolic pressure; LVESP, left ventricular end systolic pressure; LVSP, left ventricular systolic pressure; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; MAP, mean arterial pressure; MDA, malondialdehyde; MLHFQ, Minnesota living with heart failure questionnaire; MMP, metalloproteinase; MSC, mesenchymal stem cells; NFkB, nuclear factor kappa B; NHL, non-Hodgkin's lymphoma; NT-proBNP, N terminal- pro hormone brain natriuretic peptide; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor; TNF, tumor necrosis factor; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling.
**Trend toward statistical significance.*

Another apoptotic pathway observed in AIC is *via* AMP-activated protein kinase α2, or AMPKα2. AMPKα2 is overexpressed in fibroblasts treated with doxorubicin and has been shown to activate the transcription of pro-apoptotic molecules including p27, Apaf-1, and Bim. Several studies have shown that melatonin is cardioprotective against AIC, owing to its role as a potent antioxidant and free radial scavenger (96, 97). These studies also suggested that melatonin may also protect against apoptotic cardiomyocyte death, and recent data show that one of the potential mechanisms of this may be *via* inhibition of the upstream pathways of AMPKα2 transcription (97).

Therapies Targeting Oxidative Stress and Inflammation

Multiple antioxidant therapies have been investigated to relieve the oxidative stress and ROS production that is a hallmark in the pathogenesis of AIC. In addition to the antioxidant effects of melatonin as mentioned above, the lipid-lowering agent probucol has been associated with strong antioxidant properties. Probucol administration was shown to increase ROS degradation, which led to prevention of cardiac remodeling, normalization of LV systolic function, and improved overall survival in a murine model of AIC (98). Resveratrol has also demonstrated antioxidant effects that translate to reduced fibrosis and inflammation in cardiomyocytes (99). Resveratrol has been shown to reduce lipid peroxidation and increase mitochondrial stability as prophylactic treatment in rat and mouse models of AIC (100, 101). In fact, Monahan et al. demonstrated that prophylactic resveratrol was associated with increased cell survival and decreased ROS production compared to dexrazoxane and carvedilol in *in vitro* rat cardiomyoblast models (102). Co-enzyme Q10 has also been studied in an *in vivo* rat model of AIC, Q10 co-administration increased cellular survival and reduced fibrosis in cardiomyocytes (103).

In addition, vitamins with potent antioxidant properties have been studied in preclinical AIC models. Prophylactic and co-administration of vitamin C with doxorubicin was shown to increase the LV fractional shortening and LVEF on echocardiography, reduce fibrosis and myofibril loss, and improve overall rat survival *via* reduced lipid peroxidation and superoxide anion production (104). However, while administration of vitamin E in rat models of AIC was also associated with decreased ROS production, it failed to prevent mitochondrial dysfunction or cardiac remodeling on histopathology (105).

While the results above demonstrate generally promising results, studies involving N-acetylcysteine (NAC), a free radial scavenger, have been mixed. While rat models of AIC treated with NAC demonstrated improved myocardial architecture and reduced levels of cardiotoxic biomarkers (106), these improvements were not observed in canine models (107). In addition, NAC was not associated with any improvement in AIC as measured by echocardiographic measures and cardiac biomarkers in a prospective randomized controlled trial in breast and lymphoma patients (108). While the studies on the aforementioned antioxidants suggest that targeting oxidative stress may be cardioprotective in AIC, the equivocal NAC data suggest it is first necessary to determine the most effective antioxidant agents and translate these findings to meaningful clinical parameters.

Cytochrome P450 Family 1 Inhibition

In a zebrafish model of AIC, Asnani et al. demonstrated that doxorubicin treatment significantly increased levels of cytochrome P450 family 1 (CYP1) enzymes, and that various substances inhibiting the CYP1 pathway attenuated cellular apoptosis and exhibited less features of cardiomyopathy under electron microscopy (109). Lam et al. extended these findings to demonstrate that both molecular inhibition of CYP1 and gene

deletion of CYP1A prevented declines in myocardial contractility and perfusion compared with controls in zebrafish treated with doxorubicin (110). Further study is needed to clarify the role of CYP1 inhibition in doxorubicin related anthracycline toxicity, such as whether it is involved in the metabolism of doxorubicin itself or in the clearance of cardiotoxic metabolites.

Use of Stem Cell Therapies

The Stem Cell Injection in Cancer Survivors (SENECA) trial is an ongoing first in-human randomized controlled trial assessing the effects of allogenic bone marrow derived mesenchymal stromal cell (MSC) administration in the treatment of AIC in breast cancer patients (111). The primary endpoints are assessment of cardiac function on cardiac MRI, cardiac biomarkers, and quality of life questionnaires. To date, the trial has demonstrated no significant difference between the treatment and control groups with regard to clinical outcome, but with a trend toward significantly improved in 6-min walk time (6MWT) ($p = 0.056$) and quality of life questionnaires ($p = 0.048$) in the MSC group (112). In addition, O'Brien et al. demonstrated that in patient-derived cardiomyocytes (iCM) that underwent injury with anthracyclines, treatment with mitochondria-rich extracellular vesicles from mesenchymal stem cells improved mitochondrial biogenesis and contractility, with lower production of ROS (113). While preliminary, these data suggest that mesenchymal stem cell targeting of mitochondrial transfer may be a viable target for reducing anthracycline induced cardiotoxicity.

Use of Gene Therapy

While anthracycline cardiac toxicity is generally dose-dependent, some patients are able to tolerate high doses of anthracyclines, while others develop AIC at relatively lower doses. Differences in patient susceptibility invite consideration of genetic variables that either predispose to or protect against AIC. Several genetic variants have been identified through genomic analysis of both animal models and human trial participants (114–116). These genes affect the synthesis of various important proteins in the mechanisms of AIC, such as the variant *HAS3* that produces the reactive oxygen species neutralizer hyaluronan and *RARG* that derepresses topoisomerase 2β (116).

Gene therapy techniques are rapidly being applied to various disease pathologies, including heart failure, and may have important implications on the future of AIC treatment. The first clinical trial of cardiac gene therapy in conventional heart failure, CUPID (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) utilized an adeno-associated virus (AAV) vector to carry sarcoendoplasmic reticulum calcium ATPase (SERCA2a) transgenes in an attempt to increase cardiac contractility (117). While the phase 2B endpoints were non-significant, CUPID encouragingly demonstrated the safety and feasibility of gene therapy in a large cohort of 250 heart failure patients (118). Kok et al. applies the concepts of cardiac gene therapy to the theoretical treatment of AIC, and proposes methods of developing cardiotropic gene vectors and *in vivo* preclinical delivery models to 1 day feasibly deliver cardioprotective genes to cardiomyocytes while minimizing effects on off-target cancer cells (119). While the concept of gene therapy in AIC is still in its infancy, with further research into appropriate cardioprotective genetic variants and effective gene delivery, gene therapy may one day revolutionize the treatment of AIC.

CONCLUSION AND FUTURE DIRECTIONS

The current treatment of AIC is largely extrapolated from conventional neurohormonal pharmacologic therapy established as guideline directed medical therapy for heart failure with reduced ejection fraction, and evidence of the efficacy of these therapies specific to AIC are primarily from small clinical trials with limited follow up duration. Moreover, a meta-analysis of these clinical trials for neurohormonal therapy in AIC demonstrate only a modest improvement in LV function, and interpretation was substantially limited by highly heterogeneous populations that were studied (120). Thus, large-scale, randomized clinical trials are needed to firmly establish the benefit of these therapies in AIC by targeting hard clinical endpoints and focusing on higher risk populations, including focus on patients with cardiovascular risk factors and/or hematologic malignancies.

The lack of clinically significant improvement with neurohormonal therapy in AIC also raises consideration for the impact of unaddressed pathophysiologic differences between AIC and conventional heart failure. With the exception of dexrazoxane, clinically applicable therapeutics specific to anthracycline cardiotoxicity are still lacking. Though various preclinical studies have demonstrated promising potential therapeutic targets specific to the mechanisms of AIC, further clinical and preclinical studies are needed to substantiate their potential benefit. In addition, the current fragmented understanding of AIC pathophysiology impairs the development of more effective therapies. As the mechanisms of AIC continue to be elucidated, attempts to unify the connections between the various cardiotoxic mechanisms in AIC will help identify potential therapeutic targets that simultaneously address various pathways of toxicity. Further consideration of differences in the genetics and cardiovascular risk profiles of patients with AIC compared to conventional heart failure will help unveil individualized treatment options.

AUTHOR CONTRIBUTIONS

JV, AS-M, RC, and EY contributed to the conception of review article content, review and editing of the manuscript. JV and AS-M wrote the first draft of the manuscript and created figures and tables. All authors have read and approved the final version of the manuscript.

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REVIEW
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Novel Cardiac Computed Tomography Methods for the Assessment of Anthracycline Induced Cardiotoxicity

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Anthracyclines are among the most frequently utilized anti-cancer therapies; however, their use is frequently associated with off-target cardiotoxic effects. Cardiac computed tomography (CCT) is a validated and rapidly evolving technology for the evaluation of cardiac structures, coronary anatomy and plaque, cardiac function and preprocedural planning. However, with emerging new techniques, CCT is rapidly evolving to offer information beyond the evaluation of cardiac structure and epicardial coronary arteries to provide details on myocardial deformation, extracellular volume, and coronary vasoreactivity. The potential for molecular imaging in CCT is also growing. In the current manuscript we review these emerging computed tomography techniques and their potential role in the evaluation of anthracycline-induced cardiotoxicity.

Keywords: computed tomography, anthracycline, doxorubicin, cardiotoxicity, cardiooncology, cardiovascular computed tomography, strain, fibrosis

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INTRODUCTION

Cancer is the second leading cause of death in the United States. Approximately 1.9 million new cancer cases and 600,000 cancer deaths are projected to occur in the United States in 2021 (1). As of 2019, there were an estimated 16.9 million cancer survivors living in the United States and this number is projected to increase to 22.2 million by 2030 (2). In view of the significant improvement in survival, cardiovascular health has become an emerging focus of interest in cancer survivals.

Anthracyclines are among the most frequently utilized anti-cancer agents and they rank high among the most effective antineoplastic therapies (3). The first anthracycline, daunorubicin was discovered in the early 1960s by Di Marco et al. who isolated daunorubicin from a strain of *Streptomyces peucetius* (4). Shortly, this was followed by the discovery of other anthracycline agents which all demonstrated anti-cancer properties, including the most frequently used anthracyclines in addition to daunorubicin: doxorubicin, idarubicin, epirubicin and mitoxantron. The exact mechanism of anthracycline effect on cancer cells remains unclear, however it is likely multifactorial. The following mechanisms have been suggested (1) intercalation into deoxyribonucleic acid (DNA), leading to inhibited protein synthesis; (2) free radical generation leading to inflammation, lipid peroxidation, and DNA damage; (3) DNA binding, alkylation or cross-linking and/or interference with DNA unwinding or DNA strand separation and helicase activity; (4) direct membrane and other cellular cytotoxic effects; and (5) topoisomerase II inhibition leading to DNA damage and apoptosis (3). Despite the fact that it has been almost 60 years since the discovery of anthracyclines, and despite the recent unprecedented

breakthrough in cancer treatment achieved by targeted oncologic therapies, about 30% of breast cancer patients, 50 to 70% of elderly lymphoma patients, and up to 50 to 60% of childhood cancer patients are treated with an anthracycline based regimen (5).

Cardiac computed tomography (CCT) is a validated, rapidly evolving technology for the evaluation of cardiac structures with or without contrast administration, including evaluation of coronary anatomy and coronary atherosclerotic disease with high spatial resolution, evaluation of cardiac function and preprocedural planning for electrophysiologic and percutaneous valvular interventions. This review aims to summarize the current and future CCT applications that could be used for pre-treatment risk evaluation, cardiotoxicity surveillance and early identification during anthracycline therapy (**Figure 1**). Although CCT has value for the evaluation of cancer therapy associated valvular heart disease, pericardial disease and primary/secondary malignancies involving the heart, discussion of these applications is beyond the scope of this review.

MECHANISM OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

Anthracyclines have become one of the most effective antineoplastic agents, however, it was recognized relatively early that their use is associated with increasing incidence of heart failure (6, 7). Importantly, one of these early studies demonstrated the dose dependent association between the most commonly used anthracycline, doxorubicin, and cardiotoxicity, namely that the incidence of clinical heart failure was exponentially higher in patients who were exposed to doxorubicin over a cumulative dose of 550 mg/m^2 (7). This has been confirmed by a later retrospective pooled cohort study showing that the incidence of heart failure varies with exposed cumulative dose of anthracyclines: 4.7% at 400 mg/m^2, 26% at 550 mg/m^2 and 48% at 700 mg/m^2 (8). Importantly, the incidence of anthracycline induced cardiotoxicity (AIC) is influenced by many other factors including genetic variability, age (with children and the elderly at higher risk), previous treatment with cardiotoxic drugs or radiation therapy, and history of cardiovascular disease (9).

The mechanisms responsible for AIC are complex and incompletely understood. Initial observations linked doxorubicin induced cardiotoxicity to the formation of reactive oxygen species (ROS) leading to myocyte damage by oxidative injury (10–13). Myocardial injury by complex formation of anthracyclines with topoisomerase IIb causing double-stranded DNA breaks has been more recently proposed as an alternative main mechanism for AIC (5).

Cardiomyocytes comprise 80% of the cardiac mass, however they only account for less than 20% of the cardiac cells. Other cells, such as endothelial cells, smooth muscle cells, fibroblasts and adipocytes provide structural and functional support and form a unique environment for the cardiomyocytes. Emerging evidence suggests that the deleterious effect of anthracyclines is not limited to cardiomyocytes. As such, anthracycline administration has been linked to microvascular injury by direct endothelial DNA damage (14), by promoting apoptosis through oxidative stress, (15, 16) or by interfering with endothelial nitric oxide bioavailability and nitric oxide signaling (17). Related to this, in rodent models, AIC could be rescued by targeting endothelial inflammation or angiogenesis (18, 19). A recent review concluded that the microvascular endothelium serves an important novel target for the early detection, prevention, and treatment of AIC (20).

The extracellular matrix plays a unique role in cardiac homeostasis, not only by providing structural support, but also by facilitating force transmission and cell to cell communication. Although there are multiple pathways that contribute to anthracycline induced cardiac injury, ultimately all these processes lead to a common downstream pathway that results in alteration of proteolytic pathways leading to disruption in the very fine balance of myocardial matrix metalloproteinases and their inhibitors resulting in deposition of components of the extracellular matrix and tissue fibrosis (21–23).

EVALUATION OF LEFT VENTRICULAR SYSTOLIC FUNCTION AND STRAIN: ROLE OF CT IN ASSESSMENT OF ANTHRACYCLINE INDUCED CARDIOTOXICITY

Multi-phase cardiac computed tomography (CT) with retrospective ECG gating allows for 3-dimensional analysis of the cardiac function with high spatial resolution. Advances in CT technology have resulted in lower radiation dose and higher temporal resolution for cardiac imaging techniques (24). Electrocardiogram pulsing reduces radiation by modulating the tube current during the scan, applying higher amount of tube current during diastole with lower tube current during the rest of the cardiac cycle (25).

Computed tomography based evaluation of left ventricular volumes has been reported as early as 2004, (26); however, the routine use of CT for left ventricular systolic function evaluation has been limited due to the elevated radiation dose associated with retrospectively gated studies.

Left ventricular global longitudinal strain (GLS) as assessed by 2-dimensional transthoracic echocardiography is a well described early predictor of AIC (27, 28). LV GLS is a more sensitive, reproducible measure of LV dysfunction when compared to LVEF. In a recent meta-analysis, measurement of echocardiographic GLS after initiation of anthracycline based chemotherapy with or without trastuzumab had good prognostic performance for predicting subsequent cancer therapy-related cardiac dysfunction defined as clinically significant change in left ventricular ejection fraction (LVEF) with or without new-onset heart failure symptoms (27). The recently published SUCCOR (Strain sUrveillance of Chemotherapy for improving Cardiovascular Outcomes) international multicenter prospective randomized controlled trial evaluated whether echocardiographic GLS guided cardioprotective therapy would

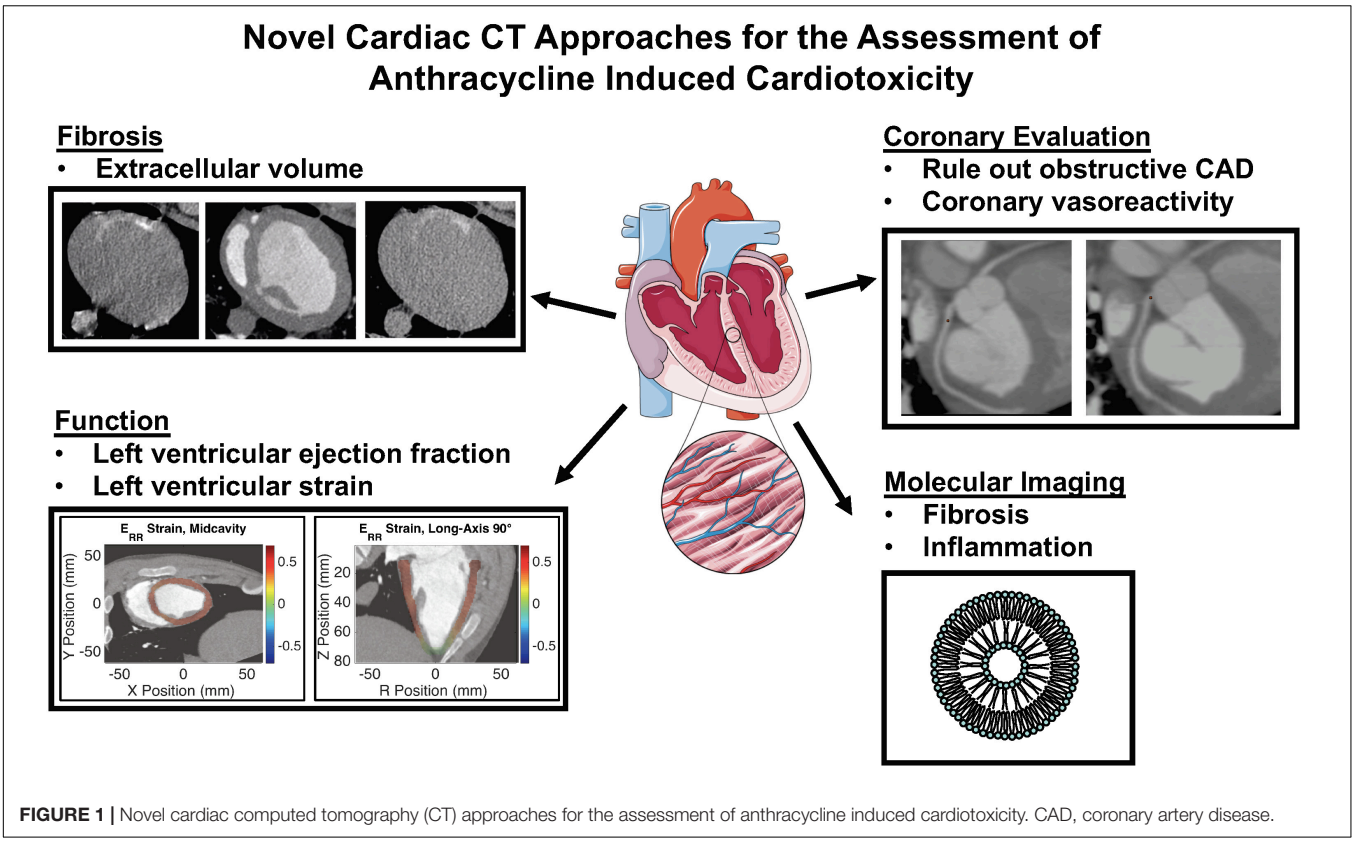

FIGURE 1 | Novel cardiac computed tomography (CT) approaches for the assessment of anthracycline induced cardiotoxicity. CAD, coronary artery disease.

prevent reduction in LVEF and development of chemotherapy induced cardiotoxicity in comparison to standard, LVEF guided care in a high risk population receiving cardiotoxic chemotherapy (29). Despite the fact that the primary outcome, defined as change in LVEF was not significantly different between the 2 arms at 1 year follow-up, in the GLS-guided group fewer patients met the prespecified criteria for chemotherapy induced cardiotoxicity compared to the LVEF-guided group. The LVEF at 1 year follow-up approached achieved a significant difference for the LVEF-guided versus the GLS-guided groups (55 ± 7% versus 57 ± 6%, p = 0.05) (29). In this trial, restricting the analysis to cancer patients who received cardioprotective therapy, the LVEF-guided arm had significantly more reduction in LVEF on follow-up echocardiogram when compared to GLS-guided arm (9 ± 11% vs. 3 ± 7%, p = 0.03).

The possibility of quantitative assessment of regional myocardial deformation from cine CT was demonstrated by Shi et al. using shape-based tracking of the ventricular surface (30) and has been subsequently reported and validated by several other groups (31, 32). Tissue tracking is used to calculate strain between sequential image frames, from systole to diastole, by using techniques adapted from echocardiography and cardiac MRI (30). The feasibility of performing CT strain has been demonstrated in large animal studies (**Figure 2**) (33) and in humans (34–37). A recent study assessing 44 heart failure patients undergoing both ECG gated cardiac CT and cardiac MRI within 24 h, showed good reproducibility of CT strain measurements and detected a good correlation between CT global longitudinal strain (GLS) and MRI GLS (38). In patients undergoing transcatheter aortic valve replacement CT strain was predictive of adverse outcomes, (36) and improvement in CT derived global longitudinal and principal strain has been demonstrated after transcatheter aortic valve replacement (34). The optimal evaluation of regional strain from CT images should employ 3-dimensional tracking of regional myocardial displacements (37), and probably will employ deep learning (39). Automated segmentation of left ventricular cavity in temporal cardiac image sequences (consisting of multiple time-points) is a fundamental requirement for quantitative analysis of cardiac structural and functional changes. A recently published approach employed a spatial-sequential network with bi-directional learning of 4D CT images which out-performed existing approaches for automated LV segmentation (40). Currently, there are commercially available programs for calculation of regional myocardial strain from contrast cine CT but these are based on 2D analysis of stacks of images (41). Although CT imaging holds promise for true high-resolution 3D analysis of regional myocardial strain, to date CT derived strain has not yet been assessed as a tool for the early prediction of AIC.

CT EVALUATION OF EPICARDIAL AND MICROVASCULAR CORONARY INJURY

Cardiac CT plays a central role in the evaluation of coronary artery disease (CAD) in patients presenting with chest pain

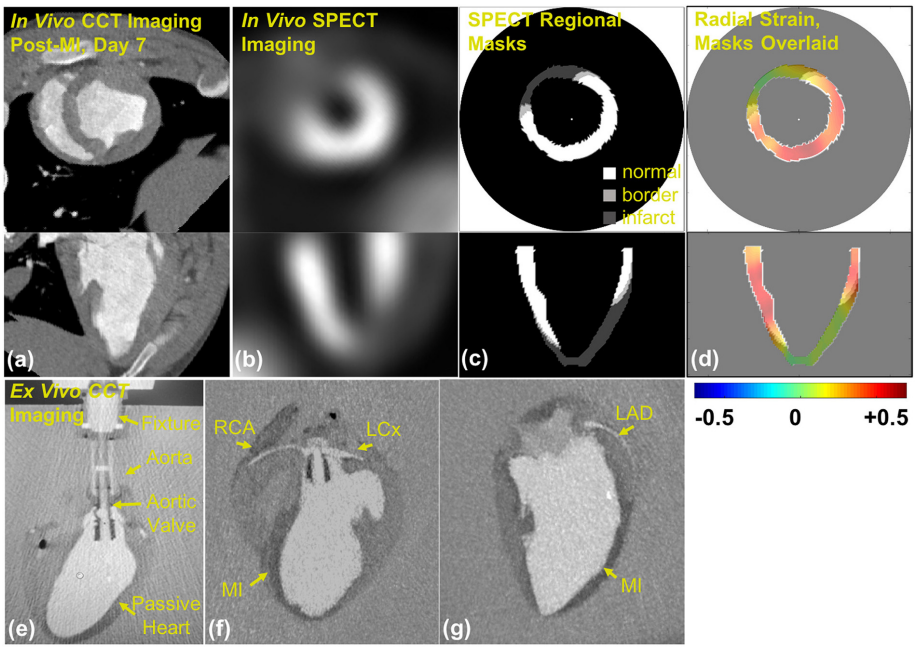

FIGURE 2 | Contrast CineCT and 99mTc-Tetrofosmin SPECT imaging and masking in porcine heart: (a) *in vivo* contrast CineCT short- and long-axis imaging of porcine heart on day 7 after myocardial infarction (MI), (b) *in vivo* SPECT short- and long-axis imaging of the porcine heart on day 7 after MI, (c) SPECT-derived regional masks for strain fields of normal (white, > 60% max intensity), border (light gray, > 50% and < 60% max intensity), and infarct (dark gray, < 50% max intensity) regions, and (d) SPECT strain masks overlaid on radial strain field. *Ex vivo* contrast CineCT imaging of the arrested porcine heart 7 after hydrogel delivery: (e) custom aortic valve insert and suspension fixture, (f) MI region and perfusion of right coronary artery (RCA) and left circumflex coronary artery (LCx), and (g) MI region and left anterior descending coronary artery (LAD). Note: this image is reproduced with permission from Midgett et al. (33).

syndromes. The recent chest pain guideline specifies the use of coronary CT angiography (CTA) as a Class I recommendation for the exclusion of atherosclerotic plaque and obstructive CAD in intermediate-risk patients with acute chest pain and no known CAD (42). Coronary CT angiography also meets Class I recommendation for diagnosis of CAD, risk stratification and guiding treatment decisions for patients with stable chest pain who have an intermediate to high risk of obstructive CAD. Pre-existing CAD is known to increase the risk of development of cardiovascular complications in patients receiving anthracycline-based chemotherapy or receiving chest irradiation as a part of anti-cancer therapy (43), however current guidelines do not recommend routine assessment for evidence of CAD prior to initiation of anthracycline based chemotherapy. On the other hand, heart failure guidelines recommend the exclusion of CAD in patients with a new diagnosis of heart failure with reduced ejection fraction (44). Coronary CTA has been demonstrated to be a highly sensitive tool for the detection of obstructive CAD in patients with dilated cardiomyopathy (45, 46). Therefore, coronary CTA might be utilized to exclude epicardial coronary stenosis in patients with prior anthracycline exposure and newly developed reduced left ventricular ejection fraction. In a single center retrospective study, coronary CTA findings altered the therapeutic plan in 52% of 80 cancer patients undergoing coronary CTA by aiding in the decision of withholding, altering or continuing oncologic therapy (47). Coronary CTA can be used to rule out obstructive CAD in cancer patients with increased troponin levels after undergoing anthracycline treatment, which can be observed in up to 30% of patients receiving high dose chemotherapy (48). In addition, coronary CTA can be particularly helpful with the initial evaluation of patients presenting with chest pain and concurrent severe thrombocytopenia (relatively common side effect of anthracyclines), when invasive evaluation is often not feasible with relative contraindication for the use of heparin containing products. In addition, CT angiography can be further utilized for the evaluation of venous and arterial thrombosis, which are emerging new contributors to the development of AIC (49).

Coronary artery calcium (CAC) scoring by non-contrast CT provides a marker of CAD burden within the epicardial coronary arteries (50). The presence of CAC is a strong predictor of future cardiovascular risk with higher prognostic value than traditional risk assessment tools such as the Framingham risk score and the Atherosclerotic Cardiovascular Disease (ASCVD) risk score (50, 51). Moreover, CAC quantification has been demonstrated to be feasible on non-gated, non-cardiac chest CT scans with excellent correlation with standard CAC score derived from gated cardiac acquisitions (52). El-Sabbagh et al. demonstrated an average increase of 35% in non-gated CAC score in 112 lymphoma patients undergoing chemotherapy when comparing CAC score on pre and post chemotherapy non-gated CT examinations (53). Automated CAC scoring on non-gated non-contrast CT scans could be used as a fast and low-cost tool to identify cancer patients at higher cardiovascular

risk, allowing implementation of cardiovascular risk reduction strategies prior to initiation of anthracycline based therapy. Importantly, the recently published joint guidelines the Society of Cardiovascular Computed Tomography and the Society of Thoracic Radiology recommends visual estimation for presence of CAC and encourages computation of a non-gated CAC score for all non-contrast chest CT examinations (54).

Recently, our group has developed a novel CT based strategy for the evaluation of coronary microvascular dysfunction associated with AIC (28). In this study, we used a canine model of doxorubicin-induced cardiotoxicity, where canines received weekly intravenous doxorubicin (1 mg/kg) for 12–15 weeks resulting in significant reduction in the left ventricular ejection fraction and histological evidence of cardiotoxicity by the end of therapy. Epicardial coronary artery diameters were measured at pre-specified distances from vessel origins from coronary CTA performed during rest, and in the presence of adenosine and dobutamine stress. Adenosine vasodilator responses (increase in epicardial coronary diameter) were impaired after ∼4 mg/kg and ∼8 mg/kg cumulative doxorubicin dosing, whereas dobutamine induced dilation response was preserved at ∼4 mg/kg, but tended to decrease at ∼8 mg/kg of doxorubicin (**Figure 3**). A significant LVEF reduction was observed only at 12–15 mg/kg doxorubicin dosing. These findings suggest an early impairment in microvascular responses in AIC. Adenosine-induced epicardial coronary responses depend on a direct vasodilatory effect on vascular smooth muscle and on subsequent flow-mediated shear stress endothelial dependent vasodilation due to local endothelial nitric oxide secretion. In contrast, dobutamine-induced vasodilation is mostly a result of direct stimulation of myocardial and vascular β-adrenergic receptors. Our results may indicate the susceptibility of the endothelium to anthracyclines leading to an early impairment in endothelium-dependent coronary vasodilation.

CT EVALUATION OF EXTRACELLULAR VOLUME IN ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Assessment and quantification of myocardial late gadolinium enhancement (LGE) using magnetic resonance imaging (MRI) has been well validated for quantitative evaluation of focal myocardial fibrosis in the setting of myocardial infarction and non-ischemic cardiomyopathy (55–58). With cardiac MRI the extracellular volume (ECV) of the myocardium can be estimated by measuring both blood and myocardial longitudinal (T1) relaxation times pre and post gadolinium administration, using the following formula:

$$ECV\ MRI = (1 - hematocrit)\frac{\frac{1}{\text{T1 myo post}} - \frac{1}{\text{T1 myo pre}}}{\frac{1}{\text{T1 blood post}} - \frac{1}{\text{T1 blood pre}}}$$

where, T1 myo and T1 blood represent the myocardial and blood T1 values before (pre) and after (post) gadolinium contrast administration. Several studies reported on excellent correlation between myocardial ECV assessed by MRI and quantitative histopathology (59–61). Importantly, multiple MRI studies have demonstrated that the ECV was elevated in patients treated with anthracyclines compared to matched control populations (62–64). Based on the observed association between increased ECV and decrease in intracellular water lifetime (a marker of cardiomyocyte size) and LV mass in response to anthracycline based chemotherapy, one of these studies suggested that in anthracycline-induced cardiac injury the increase in ECV may be due to a decrease in LV mass from cardiomyocyte loss rather than interstitial fibrosis and edema (64). This hypothesis will require further investigation. MRI has been invaluable for the evaluation of changes in ECV in AIC; however, there are minor drawbacks with the use of MRI for the evaluation of ECV, including: (1) prolonged examination protocols especially with the need of pre and post contrast T1 mapping, (2) associated increased medical cost, and (3) inability to image patients with claustrophobia.

In the last decade, CT has emerged as an additional tool for the assessment of cardiac fibrosis. The evaluation of ECV by CT relies upon the same principle as assessment with MRI. The CT imaging protocol requires acquisition of a low dose ECG-gated cardiac CT prior to contrast administration and repeat imaging following administration of contrast at a delayed timepoint, usually 10 min after iodinated contrast administration (65). The CT derived estimate of ECV is obtained using the following formula:

$$ECV\ CT = (1 - hematocrit)\frac{\Delta\ \text{HU myo}}{\Delta\ \text{HU blood}}$$

where, Δ HU myo and Δ HU blood are the change in Hounsfield unit attenuation pre- and post-contrast administration (e.g., HU post-contrast – HU pre-contrast) in the myocardium and the blood, respectively. ECV estimated by CT has been shown to correlate well with both MRI derived ECV (65–67) and pathological indices of fibrosis (66). Moreover CT derived ECV has been shown to be prognostic of adverse cardiovascular events in aortic stenosis in patients undergoing periprocedural CT evaluation (68).

A handful of studies have investigated the use of ECV CT index in the assessment of AIC (69–74). Zhou et al. compared ECV assessed by CT and MRI in a chronic canine model of AIC (70). In this study canines were administered intravenous doxorubicin every 3 weeks achieving a cumulative dose of 240 mg/m^2 and had follow-up CT and MRI examination at 16 and 24 weeks. CT detected an increase in ECV over time following doxorubicin administration (baseline: 25.2%, 16 weeks: 34.4%, 24 weeks: 37.7%). In this study ECV CT correlated well with both MRI ECV and with indices of fibrosis on histological analysis. In addition to animal models of AIC, a few studies have also looked at CT derived ECV in cancer patients receiving anthracycline-based chemotherapy regimens (71–74). In a small study, Sueta et al. found the ECV CT (33.0 ± 2.5%) elevated in 7 cancer patients with documented AIC which was confirmed by CMR assessment of ECV (**Figure 4**) (74). Another study evaluated 44 patients who previously received anthracycline based chemotherapy regimens, and found significantly higher ECV CT index in the patients with documented AIC ($n = 7$, ECV: 30.3 ± 4.8%) versus patients who received anthracycline without

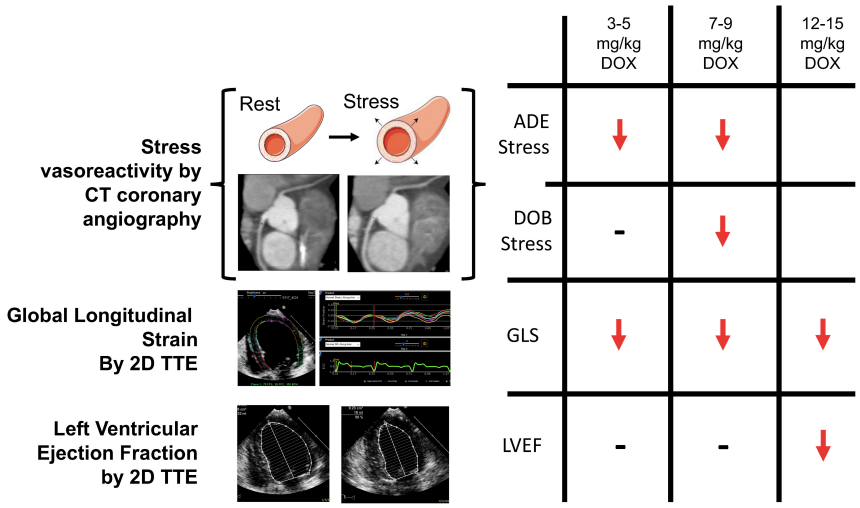

FIGURE 3 | Computed tomography (CT) based assessment of coronary vasoreactivity in a canine model of doxorubicin (DOX) induced cardiotoxicity. Left ventricular ejection fraction (LVEF) was not reduced until a cumulative DOX dose of 12 to 15 mg/kg was administered, whereas impairment in ADE-induced vasodilator responses occurred early in the progression of DOX-induced cardiotoxicity similar to impairment in global longitudinal strain (GLS). 2D = 2-dimensional; TTE = transthoracic echocardiography. Note: this image is reproduced with permission from Feher et al. (28).

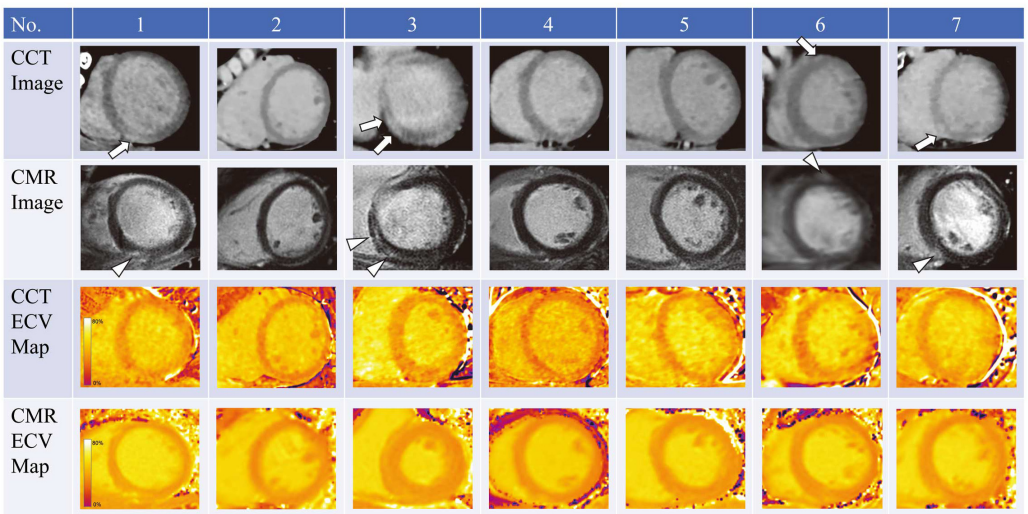

FIGURE 4 | Cardiac computed tomography (CCT) and cardiac magnetic resonance (CMR) imaging in 7 patients who underwent anthracycline treatment. Arrows and arrowheads indicate late iodine and gadolinium enhancements, respectively. ECV, extracellular volume. Note: this image is reproduced with permission from Sueta et al. (74).

cardiac dysfunction (n = 37, ECV: 27.5 ± 3.1%) or control patients who did not receive cardiotoxic chemotherapy (n = 20, ECV: 26.2 ± 2.5%) (73). Monti et al. performed a retrospective study evaluating changes in ECV from serial thoracic non-gated contrast CT scans in 32 female patients with breast cancer who had examination before chemotherapy and repeat examination after completion of anthracycline based chemotherapy regimen (ECV was derived from non-gated pre-contrast and delayed phase scans obtained at 7 min post contrast injection) (71). The authors found increased ECV values post therapy (30.0 ± 5.1%) when compared to pre-treatment ECV values (26.4 ± 3.8%).

The traditional contrast equilibrium method for ECV calculation has some potential technical challenges: (1) this approach requires both pre and post contrast scanning which despite the low dose nature of these scans, increases radiation dose, (2) difficulty in left ventricular segmentation of pre-contrast images, and (3) difficulty in the registration of the pre- and post-contrast images. However, dual source dual energy CT imaging offers a potential solution to these problems by performing a single scan with two orthogonally mounted detectors and tube arrays. This method can not only help with reducing beam hardening and metallic artifacts, but can potentially be

used for quantifying ECV with the potential of eliminating the requirement of pre-contrast images reducing problems with mis-registration as well as reducing radiation dose. Hong et al. evaluated ECV by dual energy CTA in a rabbit model of dilated cardiomyopathy, generated by administering 1.0 mg/kg of doxorubicin twice weekly for 16 weeks (69). The mean ECV values were significantly higher after doxorubicin administration (baseline: 28.5%, 6 weeks: 35.3%, 12 weeks: 41.9% and 16 weeks: 42.1%) (**Figure 5**). ECV obtained with dual energy CT correlated remarkably very well with ECV estimated by CMR and fibrosis extent on histology. Zhao et al. also compared the use of dual energy CT with single energy CT for the estimation of ECV in a canine model of doxorubicin induced cardiotoxicity (75). Dual energy CT ECV analysis was performed by using iodine maps generated from delayed CT images acquired at 100 and 140 kVp. As the authors hypothesized, the ECV CT index derived by dual energy CT correlated well with ECV estimated with single energy CT at 100 kVp and with histological analysis.

CT MOLECULAR IMAGING AND THERANOSTICS

Advancements in basic science and innovations in technology have led to a deeper understanding of the molecular and cellular processes that contribute to the pathophysiology of AIC. Molecular imaging, defined as the visualization, characterization, and non-invasive measurement of biological processes at the molecular and cellular level, has the ability to translate advancements in basic science to humans to facilitate early diagnosis, improve prognostication and guide targeted therapy across the spectrum of cardiovascular disease. Several molecular probes have been evaluated to interrogate molecular mechanisms which have been implicated in the pathophysiology of AIC by using predominantly radiolabeled imaging probes. The higher sensitivity of these radiolabeled probes makes nuclear imaging techniques more suitable for cardiac molecular imaging, however the wide availability of the clinical CT scanners and the fast scanning times coupled with high spatial resolution make CT a promising alternative approach for certain molecular imaging targets with high receptor density.

The currently used iodine-based contrast agents provide excellent tissue contrast for anatomic evaluation; however, these agents show rapid blood clearance and non-specific tissue distribution, both of which limit their use for targeted imaging. To overcome these issues, novel nanoparticles (1–100 nm diameter) have recently been assembled that incorporate high payloads of iodinated or inorganic contrast agents that may also use specific peptides or antibodies for improved sensitivity to detect molecular/cellular targets, while also improving signal-to-noise ratio (76). Moreover, theranostic platforms have also been designed that combine diagnostic properties with the capability of targeted delivery of therapies. As an example Zhu et al. constructed a unique theranostic platform for targeted chemotherapy and *in vitro* cancer cell imaging based on dendrimer-entrapped gold nanoparticles (CT contrast agent) conjugated with doxorubicin (77). Similarly, Lin et al. developed a β-cyclodextrin based micelle system which was successfully loaded with gold nanoparticles and doxorubicin achieving high drug delivery and favorable imaging properties (78). In the future these and similar theranostic agents could be potentially used for pre-clinical investigations to further enhance our understanding of AIC. Nuclear molecular imaging techniques have already been successfully applied to track inflammation by detecting reactive oxygen species formation (12) and matrix metalloproteinase activity (23) in animal models of AIC. Imaging these processes by CT based molecular imaging probes, as well as CT based imaging of molecular processes involved in the pathophysiology of AIC, such as apoptosis, fibrosis and angiogenesis holds great promise for the future. Specifically, pre-clinical molecular imaging with CT has already been applied for the imaging of fibrosis by targeting collagen (79), or imaging inflammation by targeting E-selectin (80).

Nanoparticulate CT agents have been applied successfully in multiple preclinical models in a wide variety of cardiovascular diseases, however the full clinical potential of these probes will not be achieved until these barriers can be overcome, in particular the issue of sensitivity. Multiple liposomal formulations without imageable properties assembled for drug delivery have been successfully translated to clinical applications and used in early phase clinical trials for the delivery of anti-cancer, anti-fungal, anti-inflammatory drugs and for the delivery of therapeutic genes. The use of this nanoparticulate therapy provides local delivery of high therapeutic doses, potentially minimizing systemic toxicity, and this topic has been reviewed extensively (81). Several clinical trials have demonstrated favorable pharmacokinetic and pharmacodynamic profiles for these liposomal agents, along with excellent bioavailability and most importantly favorable safety profile in humans. An intravenously administered product named PEGylated liposomal iodixanol injection (NCTX), which has been previously tested in small and large animal models (82), has entered phase 1 tolerability and pharmacokinetic study in healthy volunteers (ClinicalTrials.gov identifier: NCT02063594).

The addition of nanoparticulate contrast agents containing inorganic contrast agents provide a unique opportunity for the visualization of a therapeutic agent, referred to as a theranostic. State-of-the-art clinical CT scanners already have the capability for acquiring the images with dual-energy by using either multiple layers of detectors or by employing rapid kilovolt switching from a single x-ray tube or different energy sources from dual source scanners (83). Visualization of materials is facilitated by the availability of modern clinical software equipped with capability for digital subtraction, effective anatomic number imaging and virtual monoenergetic reconstruction. Coupled with the use of novel inorganic agents these technologies can facilitate myocardial tissue characterization by allowing for material decomposition analysis. However, the human use inorganic contrast agents need to face some clinical challenges. Gold containing nanoparticles have been tested in clinical trials for cancer drug delivery demonstrating accumulation of gold

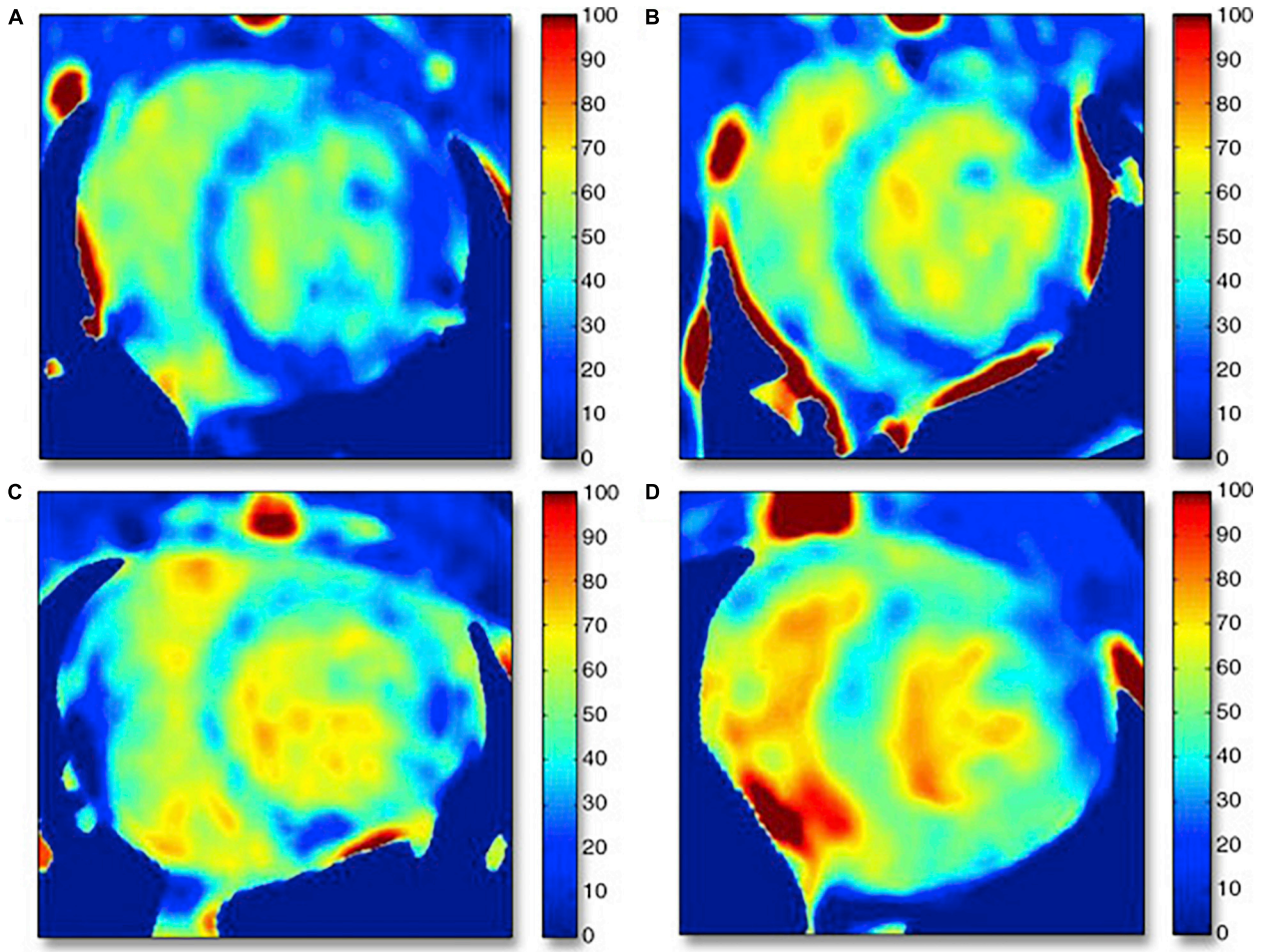

FIGURE 5 | Examples of computed tomography extracellular volume (ECV) maps in control rabbits and rabbits undergoing anthracycline-based chemotherapy generated by dual energy CT acquisition. **(A)** Control subject (Hct = 44.4%), ECV = 27.0%; dark blue normal myocardium shown on the ECV map. **(B)** Six-week treatment model (Hct = 37.4%), ECV = 36.4%; dark blue septal wall changed to bright blue. **(C)** Twelve-week model (Hct = 30.0%), ECV = 44.0%; dark blue area of inferoseptal/inferolateral wall changed to bright blue myocardium. **(D)** Sixteen-week model (Hct = 25.0%), ECV = 46.0%; bright blue myocardium suggests myocardial fibrosis. Hct = hematocrit. Note: this image is reproduced with permission from Hong et al. (69).

nanoparticles in the tumor tissue, but also considerable liver uptake after administration with only about 50% elimination at 120 day after treatment (84). Importantly *in vivo* imaging of nanoparticles was not attempted in these trials, and current concentrations of the gold may be insufficient for *in vivo* imaging. Therefore, while molecular imaging with CT is a promising new avenue, this theranostic approach is not yet ready for widespread clinical application.

ROLE OF MULTIMODALITY IMAGING IN EVALUATION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Anthracycline toxicity can have an insidious presentation, and therefore early recognition of the underlying disease process is very important to initiate preventive measures or to modify the anti-neoplastic therapeutic approach. In addition to the emerging role of CT, other imaging modalities can provide invaluable information about cardiac function that can help with management of AIC. Left ventricular ejection fraction (LVEF) assessment remains the key diagnostic parameter for the monitoring of anthracycline related cardiac dysfunction (85). Transthoracic echocardiography is the first line method for LVEF and strain evaluation (86), however cardiac MRI is emerging as the new gold standard of 3-dimensional quantification of global function and strain and has a growing role in the field (87). Equilibrium radionucleotide angiocardiography remains an accurate technique for LVEF assessment, although being used less frequently clinically for surveillance of cardiotoxicity due to concern of serial radiation exposure. In addition, the assessment of LVEF by CT and 3D echocardiography are newer alternatives for accurate assessment global function

as well as regional function. Growing literature supports the use of echocardiographic LV strain to identify sub-clinical left ventricular dysfunction in patients undergoing anthracycline-based chemotherapy (27). CT and MRI provide alternative methods for the accurate and reproducible assessment of regional myocardial deformation strain. Therefore, a multimodality imaging approach is recommended and often applied.

CONCLUSION

Cardiac CT is a rapidly evolving technology for the evaluation of cardiac structures with or without contrast administration, including the evaluation of the underlying coronary anatomy and/or complicating atherosclerotic or thrombotic disease. With emerging new techniques, CT is rapidly evolving to provide information beyond the evaluation of epicardial coronary arteries including myocardial deformation assessment, extracellular volume quantification, information about coronary vasoreactivity and even potential applications for molecular imaging. These new methodologies hold promise in the future for the early evaluation and management of AIC.

AUTHOR CONTRIBUTIONS

AF drafted the manuscript. LB and AS reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Anthracycline-induced cardiotoxicity: From pathobiology to identification of molecular targets for nuclear imaging

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Anthracyclines are a widely used class of chemotherapy in pediatric and adult cancers, however, their use is hampered by the development of cardiotoxic side-effects and ensuing complications, primarily heart failure. Clinically used imaging modalities to screen for cardiotoxicity are mostly echocardiography and occasionally cardiac magnetic resonance imaging. However, the assessment of diastolic and global or segmental systolic function may not be sensitive to detect subclinical or early stages of cardiotoxicity. Multiple studies have scrutinized molecular nuclear imaging strategies to improve the detection of anthracycline-induced cardiotoxicity. Anthracyclines can activate all forms of cell death in cardiomyocytes. Injury mechanisms associated with anthracycline usage include apoptosis, necrosis, autophagy, ferroptosis, pyroptosis, reactive oxygen species, mitochondrial dysfunction, as well as cardiac fibrosis and perturbation in sympathetic drive and myocardial blood flow; some of which have been targeted using nuclear probes. This review retraces the pathobiology of anthracycline-induced cardiac injury, details the evidence to date supporting a molecular nuclear imaging strategy, explores disease mechanisms which have not yet been targeted, and proposes a clinical strategy incorporating molecular imaging to improve patient management.

KEYWORDS

anthracycline, cardiotoxicity, molecular imaging, nuclear medicine, clinical application

Introduction

Anthracyclines are one of the most commonly prescribed chemotherapies and are used to treat a variety of cancers. Although effective agents, their benefits are sometimes compromised by acute and/or late-onset cardiotoxic side effects. A study that compared adult survivors of pediatric cancer with their siblings found that survivors (that had been treated with anthracyclines and/or radiotherapy) had a 15-fold higher risk of developing heart failure (1). The risk of subsequent heart failure in pediatric patients treated with anthracyclines was demonstrated to be highly dose-dependent, particularly in cumulative anthracycline doses $\geq$300 mg/m^2, and to increase over time (3.3% at 2 years, 4.5% at 10 years, and 9.8% at 20 years after the first dose) (2, 3). Similarly, a retrospective analysis of three phase III clinical trials with adult patients indicated that treatment with a cumulative doxorubicin dose of $\geq$400 mg/m^2 led to a 5% incidence of heart failure, rising to up to 26% at a cumulative dose of 550 mg/m^2 (4). It must be emphasized, however, that (i) no "safe dose" of anthracyclines truly exists, (ii) late effects leading to heart failure can occur and need to be monitored, and (iii) risk assessment needs to be individualized with a particular focus on pre-existing heart disease and/or cardiovascular risk factors such as hypertension. Thus, given the wide individual variability in patient risk of developing anthracycline-induced cardiac injury, risk stratification must be done on a case-by-case basis.

In clinical practice, side effects of anthracyclines are balanced by limiting the dosage while tightly monitoring for clinical manifestations of cardiotoxicity. Typically, imaging modalities such as echocardiography are used to monitor for cardiotoxicity, commonly defined as a decline in LVEF of $\geq$10% to a final value <50% (5). A recent International Cardio-Oncology Society (IC-OS) consensus statement (6) proposed a standardized and more nuanced definition of cancer therapy-related cardiac dysfunction (CTRCD), applicable to anthracyclines, as follows: (1) Asymptomatic CTRCD graded as (i) mild (LVEF $\geq$50% and new decline in GLS >15% from baseline, and/or new rise in troponin I/T, BNP, NT-proBNP), (ii) moderate (new LVEF reduction by $\geq$10 percentage points to a LVEF 40–49%, or new LVEF reduction by <10 percentage points to a LVEF 40–49% and new decline in GLS >15% from baseline, and/or new rise in troponin I/T, BNP, NT-proBNP), and (iii) severe (new LVEF reduction to <40%). (2) Symptomatic CTRCD with supportive LVEF and diagnostic biomarkers, graded from mild to very severe based on heart failure symptoms, requirement for intensification of heart failure treatment, hospitalization, and/or inotropic or mechanical circulatory support.

However, these prognostic/diagnostic tools have several limitations, including their variability, lack of sensitivity, and inadequate detection of toxicity at a subclinical level. One of the main issues is that these parameters detect cardiotoxicity when the myocardium is already damaged and/or cardiac function impaired, which may hinder treatment options. Indeed, histological biopsy samples of patients that underwent doxorubicin treatment demonstrated that the myocardium could incur significant injury despite patients having a preserved/normal LVEF (7).

Therapeutic treatment for AIC remains limited. One of the most well studied agents, dexrazoxane, has been shown to significantly reduce cardiotoxicity in adults and pediatric patients when concurrently prescribed with anthracyclines (8–10). Recent studies have demonstrated the safety of dexrazoxane as a cardioprotective agent and confirmed its lack of interference with the anti-tumor action of anthracyclines. Indeed, an analysis of three Children's Oncology Group (COG) trials that had randomized patients to doxorubicin with or without dexrazoxane (dexrazoxane:doxorubicin dose ratio 10:1, cumulative protocol-specified doxorubicin dose 100–360 mg/m^2) with a median follow-up of 12.6 years demonstrated that dexrazoxane does not compromise long-term survival, and is not associated with mortality from acute myeloid leukemia or cardiovascular causes (11). This was followed by another COG analysis of four trials with pediatric patients that similarly were treated with doxorubicin with or without dexrazoxane (other than one trial in which all patients were assigned to dexrazoxane upfront), and with a median follow-up of close to 20 years, indicating that dexrazoxane does not negatively affect long-term mortality or second cancer risk (12). Angiotensin-converting enzyme inhibitors and beta-blockers have also been studied. In a study of 201 patients with AIC, Cardinale et al. observed that 64% of patients treated early (i.e., 1–2 months after completion of chemotherapy) with enalapril/carvedilol had complete LVEF recovery, while 0% of the patients treated 6 months post-chemotherapy had complete LVEF recovery (13). Whereas these findings were not corroborated in the prospective CECCY trial which randomized 200 HER2-negative breast cancer patients to carvedilol vs. placebo synchronous with anthracycline initiation (total 240 mg/m^2 over 4 cycles), a benefit of betablockade was noted on the development of diastolic dysfunction (14).

These clinical findings underscore the importance of early disease detection and emphasize the need for additional

Abbreviations: AIC, anthracycline-induced cardiotoxicity; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CT, computerized tomography; Dox, doxorubicin; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; GLS, global longitudinal strain; H/M, heart-to-mediastinum; ID/g, injected dose/g; LV, left ventricle; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NLRP3, nucleotide-binding oligomerization domain (NOD-), leucine-rich repeat (LRR-), and pyrin domain (PYD)-containing protein 3; NT-proBNP, N-terminal proBNP; PET, positron emission tomography; PS, phosphatidylserine; ROS, reactive oxygen species; SPECT, single-photon emission computed tomography; TUNEL, terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling; WOR, washout rate.

TABLE 1 Radiotracer, mechanism of uptake, and application for nuclear imaging of anthracycline-induced cardiotoxicity.

Radiotracer	Modality	Target	Cardiovascular application	Preclinical studies	Clinical studies
^{18}F-FDG*	PET	Glucose transporters	Glucose metabolism	32	34–36,38
^{11}C-Acetate	PET	Monocarboxylate transporter	Oxidative metabolism	43	45
^{11}C-Acetoacetate	PET	Monocarboxylate transporter	Ketone body metabolism	44	
^{18}F-DHMT	PET	Reactive oxygen species	Cytotoxicity	59	
^{99m}Tc-Sestamibi*	SPECT	Mitochondrial membrane potential	Cytotoxicity/perfusion	51	
^{68}Ga-Galmydar	PET	Mitochondrial membrane potential	Cytotoxicity/perfusion	52	
^{18}F-MitoPhos	PET	Mitochondrial membrane potential	Cytotoxicity/perfusion	53	
^{99m}Tc-Annexin V	SPECT	Externalized phosphatidylserine	Apoptosis	76	
^{18}F-CP18	PET	Caspase-3 activity	Apoptosis	83	
^{111}In-Antimyosin*	SPECT	Exposed myosin	Necrosis		85,86
^{123}I-MIBG*	SPECT	Norepinephrine transporter	Sympathetic nervous system	94	94–98
^{3}H-CGP12177	PET	Norepinephrine transporter	Sympathetic nervous system	99	
^{13}N-Ammonia*	PET	Passive diffusion	Perfusion		110
^{82}Rb-Chloride*	PET	Na^+/K^+-ATPase	Perfusion		105
^{99m}Tc-MUGA*	SPECT	Red blood cells	Cardiac blood pool		4,102–104
^{68}Ga-FAPI*	PET	Fibroblast activation	Fibrosis		116,117

*U.S. Food and Drug Administration (FDA) approved radiotracer.
References of preclinical and clinical studies examining the role of radiotracers in the context of anthracycline-induced cardiotoxicity.

methods to diagnose subclinical AIC. A promising such strategy is nuclear imaging that can map molecular processes perturbed in AIC using radioactively labeled probes (**Table 1**). Advancements in nuclear imaging have rendered imaging of pathological processes such as mitochondrial dysfunction, sympathetic innervation, and fibrosis, possible. With the ongoing dissection of the pathobiology of AIC at the molecular level, we predict these advances will permit the identification of novel molecular imaging targets and posit a future role for nuclear imaging that will be complementary to that of echocardiography (and/or cardiac MRI). The present review retraces the preclinical and clinical evidence supporting the use of a nuclear molecular imaging strategy in AIC, and offers new avenues for tracer development targeting injury pathways that have not yet been explored.

Nuclear imaging targets

I. Metabolic dysfunction

Anthracyclines induce intracellular ROS through several mechanisms. Fe^{3+} can react with the ketone and hydroxy groups of anthracyclines to form free radicals through the Fenton reaction (15). Anthracyclines also accumulate within the mitochondrial inner membrane, in part due to their high affinity to cardiolipin. In mitochondria, quinone and semiquinone moieties of anthracycline undergo redox cycling, generating large amounts of ROS (16). These events cause oxidative damage to cellular proteins, lipids, and mitochondria, resulting in mitochondrial membrane potential loss, mitochondrial swelling, activation of the mitochondrial-permeability transition pore (mPTP), and the release of cytochrome c (17). Formation of the apoptosome, initiated by cytochrome c release from mitochondria to the cytosol, leads to the cleavage and activation of caspase 3 and cell death (**Figure 1**). Long-term mitochondrial dysfunction also leads to a compensatory shift in cardiomyocyte metabolism, which may be targeted for AIC imaging (18).

Glucose uptake

The most studied PET tracer for AIC imaging is ^{18}F-FDG. Anthracyclines impair mitochondrial phosphorylation and the oxidation of all substrates – including fatty acids, carbohydrates, and ketones – thus driving cardiac myocytes to shift toward utilization of substrates with a more favorable ATP production phosphate/oxygen ratio, such as glucose (18, 19). Cardiomyocyte uptake of the glucose analog ^{18}F-FDG is mediated by glucose transporter (GLUT) −4 and −1 (20). Whereas GLUT-1 is considered responsible for basal intracellular glucose transport, GLUT-4 and to a lesser extent GLUT-1 translocate to the plasma membrane and increase intracellular glucose uptake in response to stimuli such as insulin (21), ischemia (22, 23), anoxia (24), and catecholamines (20). Upon cardiomyocyte uptake, ^{18}F-FDG is phosphorylated by hexokinase and not metabolized further (25). Additionally, the reverse reaction (dephosphorylation by glucose-6-phosphatase) is minimal (25). Thus, phosphorylated ^{18}F-FDG remains trapped

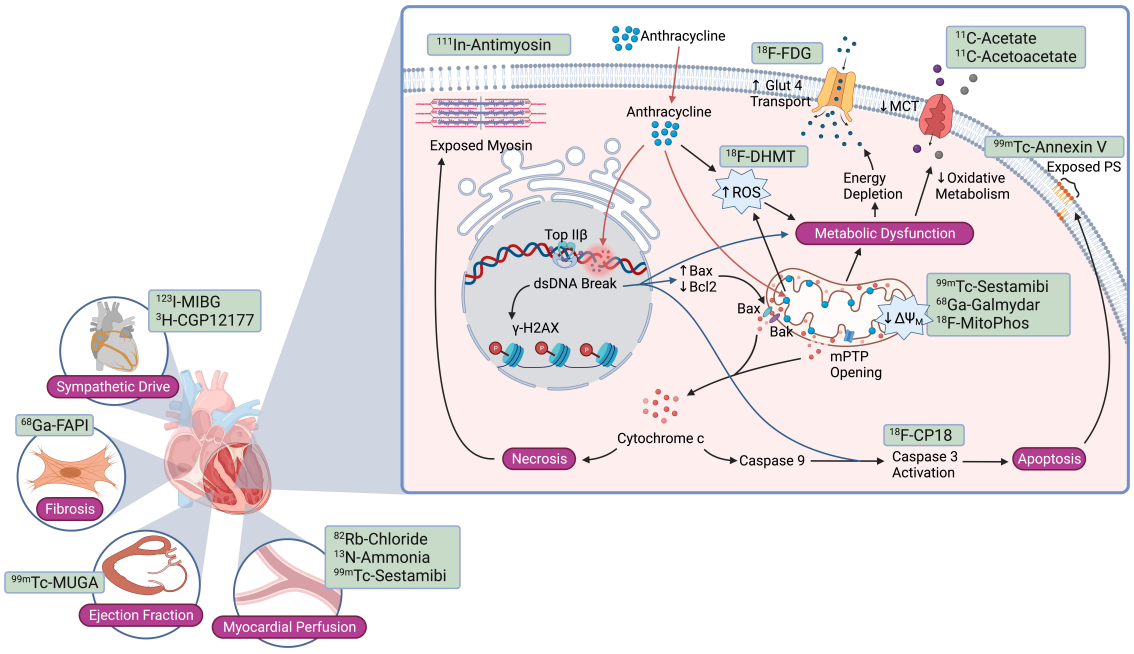

FIGURE 1
Current nuclear molecular imaging strategies targeting pathways and cell injury mechanisms activated in anthracycline-induced cardiotoxicity. Nuclear probes studied to date target anthracycline-mediated cardiomyocyte injury mechanisms such as apoptosis, necrosis, reactive oxygen species, and mitochondrial dysfunction; downstream consequences such as cardiac fibrosis; and more global changes such as sympathetic drive, myocardial blood flow, and left ventricular ejection fraction. Bax, Bcl2 associated X protein; Bak, Bcl2 antagonist/killer; Bcl2, B-cell CLL/lymphoma 2; dsDNA, double-stranded DNA; GLUT1, glucose transporter 1; γ-H2AX, phosphorylated histone variant H2AX; MCT, monocarboxylate transporter; $\Delta\Psi_M$, mitochondrial membrane potential; mPTP, mitochondrial permeability transition pore; PS, phosphatidylserine; ROS, reactive oxygen species; Top IIβ, topoisomerase IIβ.

within cardiomyocytes. To infer glucose metabolic rate from ^{18}F-FDG metabolic rate, a "lumped constant" – initially formulated by Sokoloff et al. (26) – or correction factor, is used. The lumped constant is based on competitive substrate kinetics between glucose and ^{18}F-FDG, and accounts for differences in transport and phosphorylation rates (27). Importantly, the lumped constant for ^{18}F-FDG in the myocardium is dependent on fasting state and serum insulin levels (28–31). The lumped constant has not been evaluated in the setting of anthracycline chemotherapy-induced cardiac injury.

Preclinical studies have assessed the potential utility of ^{18}F-FDG in AIC. Bulten et al. observed a progressive increase in ^{18}F-FDG uptake in mice treated with doxorubicin (15 mg/kg, once every 3 weeks for up to four cycles) (32). They further noted a significant correlation between myocardial ^{18}F-FDG uptake and hypoxia-inducible factor (HIF)-1α, a hypoxia-driven transcription factor that activates GLUTs and glycolytic enzymes. In another study of doxorubicin treated mice, increased ^{18}F-FDG myocardial uptake had a direct correlation with histologically determined myocardial redox stress (33).

Several retrospective clinical studies have documented higher ^{18}F-FDG uptake in patients treated with anthracyclines. Borde et al. observed in lymphoma patients treated with doxorubicin-based chemotherapy a higher post-therapy ^{18}F-FDG uptake than before treatment (34). In a retrospective study of 43 Hodgkin lymphoma patients that developed AIC, Sarocchi et al. observed that a decrease in LVEF several months to years following treatment was inversely correlated with LV uptake of ^{18}F-FDG during doxorubicin containing chemotherapeutic treatment ($R^2 = 0.30$, $P < 0.01$) (35). Similarly, in a recent study of 121 consecutive breast cancer patients undergoing treatment with anthracycline or trastuzumab, Kim et al. found that patients who developed cardiotoxicity had a higher ^{18}F-FDG right ventricular uptake than patients who did not (2.4 ± 1.1 vs. 1.6 ± 0.7, $P = 0.012$) (36). Though it remains unclear whether the observed right ventricular uptake preceded or was a result of LV dysfunction, other have reported that left ventricular and right ventricular global longitudinal strain are both similarly impaired during trastuzumab treatment (37). Additional studies have suggested that baseline LV ^{18}F-FDG SUV may also be an indicator of patient susceptibility to AIC. Baucknehet et al. observed that among a cohort of 36 Hodgkin lymphoma patients that had previously undergone doxorubicin treatment, the 11 patients that developed significant post treatment reduction in ejection fraction had lower pre-treatment LV ^{18}F-FDG

uptake compared to the remaining 25 patients that didn't develop cardiac abnormalities (mean SUV = 1.53 ± 0.9 vs. 3.34 ± 2.54, $P < 0.01$) (38). Heckmann et al. (39) demonstrated in a retrospective study (n = 337 consecutive patients) that Hodgkin's lymphoma (n = 52) was associated with a higher cardiac ^{18}F-FDG uptake (mean SUV = 3.5 ± 3.6, odds ratio = 2.4, $P < 0.01$) whereas non-Hodgkin's lymphoma (n = 57) and non-lymphatic cancer (n = 228) were not. Interestingly, the authors observed that the increase in cardiac ^{18}F-FDG uptake in Hodgkin's lymphoma was not determined by prior chemotherapy and/or serum glucose levels, however, with the caveat that patient preparations were not optimized or standardized for cardiac ^{18}F-FDG PET imaging, in addition to the retrospective nature of the study (39). A significant limitation of these retrospective studies is that protocols were designed for cancer staging and not to measure cardiomyocyte ^{18}F-FDG uptake *per se*, which were done *post hoc* in a retrospective manner. In this setting, patients were only required to fast a minimum of 6 h during which myocardial metabolic patterns still have a high degree of variability (40). Furthermore, the pattern of myocardial ^{18}F-FDG uptake may also need to be taken into consideration when determining physiologic vs. pathologic signals (41). Whereas standardized protocols incorporating adequate nutritional preparation are required (42), these preliminary studies are promising and set the stage for the prospective evaluation of cardiomyocyte ^{18}F-FDG uptake in AIC.

Oxidative metabolism

Acetate is utilized by cardiomyocytes in the tricarboxylic acid (TCA) cycle and can thus serve as a metric to quantify myocardial oxygen consumption. A preclinical model of chronic doxorubicin treatment in rats (2 mg/kg IV weekly for 6 weeks) observed that doxorubicin decreased myocardial oxygen consumption reserve (2.3 ± 0.3 vs. 1.8 ± 0.4, P = 0.02) (43). ^{11}C- acetoacetate, a ketone body that utilizes the same monocarboxylic acid transporter as acetate, exhibited similar changes in an analogous rat model treated with doxorubicin (44).

Nony et al. investigated ^{11}C-acetate uptake to assess myocardial oxidative metabolism and myocardial blood flow in patients treated with anthracyclines (45). The resting myocardial blood flow of 6 patients were serially measured during a doxorubicin treatment course of 50 mg/m^2 every 3 weeks for 15 weeks (cumulative dose of 300 mg/m^2). The investigators observed that compared to baseline, there was no significant change in resting myocardial blood flow during or after completion of doxorubicin treatment. Similarly, no significant changes were noted in K_{mono}, an index of myocardial oxygen consumption (45, 46).

Fatty acid metabolism

Whereas 70 to 90% of cardiac ATP production is derived from fatty acid β-oxidation under physiologic conditions, fatty acid usage decreases significantly in heart failure and cardiomyopathy models (47), thus making it a possible target for AIC imaging. There are no preclinical or clinical studies to date that have applied radiolabeled fatty acids to monitor AIC. Potential candidates include ^{11}C-palmitate, although its clinical utility is hindered by a lack of kinetic data that models and accounts for the redistribution of ^{11}C metabolites within various lipid pools (48). ^{18}F-FTHA (14[R,S]-^{18}F-fluoro-6-thia-heptadecanoic acid) is another PET tracer that could circumvent this limitation by utilizing a sulfur atom in its backbone that prevents it from undergoing further β-oxidation (49).

Mitochondrial membrane potential

^{99m}Tc-sestamibi is a SPECT tracer clinically used to image myocardial perfusion, though its utility as a lipophilic cation has proven useful to detect disruptions in mitochondrial membrane potential. The ability of these cations to accumulate inside the mitochondria has been used as a proxy index for mitochondrial membrane potential ($\Delta\Psi_M$) (50). Animal studies conducted by Safee et al. indicated that rats treated with a single dose of doxorubicin had lower levels of ^{99m}Tc-sestamibi uptake in the myocardium, corresponding to a loss in $\Delta\Psi_M$. A significant 2.5-fold decrease in ^{99m}Tc-sestamibi 2 weeks post-treatment was detected only in rats treated with the highest doxorubicin dose (10 mg/kg), which was associated with a 7% and 9.5% drop in ejection fraction and fractional shortening, respectively, that was also only significant 2 weeks post-treatment (51). While promising, usage of ^{99m}Tc-sestamibi is hindered by its pharmacokinetics and the limited sensitivity inherent to most SPECT tracers. In comparison, PET tracers such as the metalloprobe ^{68}Ga-galmydar have been developed for this same application (52). In live-cell fluorescent imaging of H9c2 cells, Sivapackiam et al. observed a dose- and time-dependent decrease in ^{68}Ga-galmydar that correlated with an increase of caspase-3 activation (52). These findings were subsequently confirmed in *in vivo* models, where the authors reported a nearly 2-fold decrease in myocardial ^{68}Ga-galmydar uptake 5 days following a single doxorubicin dose of 15 mg/kg in rats, verified by post-imaging quantitative biodistribution. Another PET lipophilic cation that bears promise is [1-(2-^{18}F-fluoroethyl),1H[1,2,3]triazole-4-ethylene]triphenylphosphonium bromide (^{18}F-MitoPhos) (53). In a Langendorff perfusion heart model, ^{18}F-MitoPhos exhibited more than double cardiac retention compared to ^{99m}Tc-sestamibi. Moreover, *in vivo* studies in an acute doxorubicin rat model indicated a close to 50% decrease in the left ventricular retention of ^{18}F-MitoPhos compared to controls 48 h after

treatment. While ^{68}Ga-galmydar and ^{18}F-MitoPhos represent encouraging alternatives to ^{99m}Tc-sestamibi for measuring $\Delta\Psi_M$, further studies are needed to corroborate these findings with reference parameters such as ejection fraction and fractional shortening.

An additional promising strategy for the scrutiny of $\Delta\Psi_M$ involves the radiolabeled lipophilic cation ^{18}F-tetraphenylphosphonium (^{18}F-TPP$^+$) (54). Using a pig model, Alpert et al. demonstrated its *in vivo* myocardial applicability *via* a novel method accounting for extracellular space and employing kinetic analysis to estimate tracer volume of distribution (55). Additionally, Pelletier-Galarneau et al. demonstrated excellent agreement of *in vivo* measures of myocardial ^{18}F-TPP$^+$ in healthy humans subjects with previous *in vitro* assessments (56), paving the way for human studies quantifying temporal changes in mitochondrial membrane potential using this radiopharmaceutical in the context of anthracycline-induced cardiotoxicity (57). These tracers require prospective clinical trial evaluation to determine their clinical utility.

Reactive oxygen species

[^{18}F]6-{4-[(1-(2-fluoroethyl)-1*H*-1,2,3-triazol-4-yl) methoxy]phenyl}-5-methyl-5,6-dihydrophenanthridine-3,8-diamine (^{18}F-DHMT), an analog of the superoxide indicator dihydroethidium, has previously been identified as a promising PET radiotracer of ROS generation (58). In a chronic doxorubicin-induced cardiotoxicity rodent model, Boutagy et al. described the significant increase in myocardial ^{18}F-DHMT uptake 4 weeks post treatment which preceded degradation in LVEF that was significant only 6 weeks post treatment (P = 0.0012) (59). Correlation analysis suggested an inverse correlation (r^2 = 0.6; P = 0.01) between LV ^{18}F-DHMT uptake and LVEF as well as a direct correlation (r^2 = 0.72; P = 0.007) between LV ^{18}F-DMHT and LV ESV. These results suggest that ^{18}F-DHMT may be a viable radiotracer for early assessment of cardiotoxicity that precedes left ventricular systolic dysfunction.

II. Cell death

Dox intercalates in the DNA and induces single- and double-strand DNA breaks in target cells in a topoisomerase (Top)-2-dependent manner (60). By producing temporary single- or double-stranded DNA breaks, Top regulates topological changes during DNA replication, transcription, or recombination (61). Top-2α is overexpressed in tumors and is the molecular basis of Dox anticancer activity (62, 63).

Adult cardiomyocytes express Top-2β but not Top-2α (62), and Top-2β is also a Dox target, forming a Top-2β-Dox-DNA ternary cleavage complex that induces DNA strand breaks and ensuing cell death (64, 65). These DNA breaks rapidly result in the phosphorylation of histone variant γ-H2AX, a sensitive marker of the DNA damage response (66, 67) (**Figure 1**). Subsequently, mediator of DNA damage checkpoint protein (MDC)-1 binds to γ-H2AX (68) and facilitates DNA damage repair protein recruitment (69, 70). Furthermore, Dox/Top-2β bind to selective promoters, significantly affecting the cardiomyocyte transcriptome (65, 71). Ensuingly, key antioxidative enzymes are reduced, providing a mechanism linking Dox-induced reactive oxygen species (ROS) production in a Top-2β-dependent manner. For example, peroxisome proliferator activated receptor-γ (PPAR-γ) coactivator –1-α and -β, pivotal transcription factors implicated in mitochondrial biogenesis, are decreased in the setting of Dox cardiotoxicity (65, 71).

Anthracyclines triggers various cell death mechanisms (**Figures 1**, **2**), though the two most well characterized pathways in AIC are apoptosis and necrosis, mediated in part by Bax-induced mitochondrial damage (**Figure 1**). Bax (Bcl-2 associated X protein) is a member of the Bcl-2 family. Under homeostatic conditions, Bax resides in an inactive conformation in the cytosol (72). Upon anthracycline treatment, Bax undergoes a conformational change that results in its translocation to the mitochondrial membrane (**Figure 1**). There, Bax mediates opening of the mitochondrial permeability transition pore (mPTP) located in the inner mitochondrial membrane (73). In turn, mPTP opening leads to swelling of the mitochondrial intermembrane space followed by rupture of the outer mitochondrial membrane, release of intermembrane space proteins – including the small soluble electron carrier cytochrome c – into the cytosol, and cardiomyocyte necrosis (74) (**Figure 1**). Another proposed mechanism of anthracycline-induced, Bax-mediated cytochrome c release is the oligomerization of Bak and Bax within the outer mitochondrial membrane, leading to its permeabilization and activation of apoptotic pathways (72, 75).

Annexin V

Annexin V is a well-established method of detecting externalized phosphatidylserine (PS), a phospholipid that is translocated from the inner to the outer leaflet of the plasma membrane early in apoptosis. ^{99m}Tc-annexin-V was scrutinized by Bennink et al. in an acute doxorubicin-induced cardiotoxicity rat model. Doxorubicin treated rats displayed a significant increase in myocardial ^{99m}Tc-annexin-V uptake, with longer doxorubicin treatment regimens corresponding to an even higher uptake (76). Furthermore, heart-to-body weight ratio decreased in response to doxorubicin treatment, which may have been an indication of cardiomyocyte death. These findings correlated well with cardiotoxicity measured through

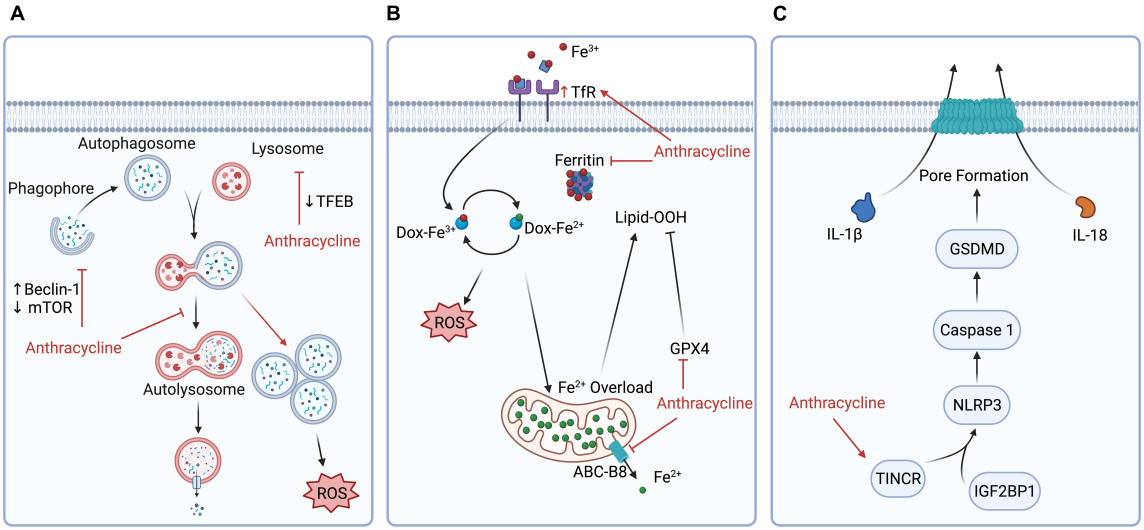

FIGURE 2
Additional anthracycline cardiotoxicity mechanisms for the development of novel molecular nuclear probes. Highlighted mechanisms have not yet been targeted using a nuclear imaging strategy, and certain key molecular or biochemical targets are presented for the potential development of new SPECT/PET tracers. **(A)** Anthracyclines impair autophagy by compromising lysosomal acidification, increasing beclin-1 expression, inhibiting mTOR, and inhibiting transcription factor EB, thereby blocking autophagic flux and causing an accumulation of autolysosomes that leads to increased ROS production. New probes may be developed to target molecules implicated in the accumulation of undegraded autolysosomes. **(B)** Anthracycline-induced ferroptosis is caused by iron overload through upregulation of TfR, inactivation of ferritin, inhibition of ABC-B8, and downregulation of GPX4, which may be targets for probe development. **(C)** Anthracycline induces pyroptosis by upregulating TINCR, which increases the expression of NLRP3 and caspase 1 activation. Future probes may for example target NLRP3 or caspase1. ABC-B8, ATP binding cassette subfamily B member 8; Dox, doxorubicin; GPX4, glutathione peroxidase 4; GSDMD, gasdermin D; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; IL, interleukin; Lipid-OOH, lipid hydroperoxides; mTOR, mammalian target of rapamycin; NLRP3, nucleotide-binding oligomerization domain (NOD-), leucine-rich repeat (LRR-), and pyrin domain (PYD)-containing protein 3; ROS, reactive oxygen species; TFEB, transcription factor EB; TfR, transferrin receptor; TINCR, terminal differentiation-induced non-coding RNA.

immunohistochemistry and the TUNEL assay. Clinical studies utilizing annexin V probes have been limited; ^{99m}Tc-HYNIC-annexin-V, was tested in early clinical trials but its performance in detecting apoptosis in head and neck carcinoma was limited by moderate non-specific binding and slow clearance times (77).

Caspase

A more direct way of measuring apoptosis is by targeting caspase activation. Caspases are intracellular enzymes that are essential for executing apoptosis. Different initiator caspases can be activated extrinsically or intrinsically, though both pathways ultimately converge with caspase-3 and –7 activation. Several analogs of 5-Dialkylaminosulfonylisatins, a potent non-peptide inhibitor of caspase-3 and –7, have been adapted as PET tracers. ^{18}F-ICMT-11, ^{11}C-WC-98, and ^{18}F-WC-IV-3 have demonstrated high caspase-3 affinity *in vitro* but all exhibited poor specificity *in vivo* models, likely due to the dicarbonyl moiety caspase binding region of isatin being recognized by other proteases such as cathepsins (78–80). A substrate-based probe, ^{18}F-CP18, was designed to improve specificity by taking advantage of caspase-3′s unique substrate recognition motif for aspartic acid residues in the P1 and P4 positions (75 - 81). In this probe, the caspase-3 substrate sequence Asp-Glu-Val-Asp connects a radioactively labeled metabolite to a short polyethylene glycol (PEG) chain. The hydrophilic PEG chain facilitates the probe's transport across the cell membrane and upon encountering activated caspase-3 it is cleaved away, leaving the radioactively labeled metabolite inside the cell. While initially developed for visualization of apoptosis in tumors, this radiotracer has also been adapted for AIC imaging (82). Su et al. (83) detected increased accumulation of ^{18}F-CP18 in the myocardium starting at 3 weeks after doxorubicin treatment in mice, which was histologically validated using a TUNEL assay. The authors also observed that ^{18}F-CP18 detects myocardial apoptosis at a stage prior to significant changes in LVEF. Clinical studies are required to further expand on these promising results.

Necrosis

^{111}In-antimyosin is a tracer that binds to the exposed myosin of damaged cells, an indicator used to quantify regions

of myocardial necrosis. Early clinical studies evaluated ^{111}In-antimyosin in AIC (84–86). Carrió et al. studied 30 sarcoma patients who underwent serial ^{111}In-antimyosin imaging prior to chemotherapy and at intermediate (240–300 mg/m^2) and maximal (420–600 mg/m^2) cumulative doxorubicin doses. Whereas an abnormal heart-to-lung ^{111}In-antimyosin uptake ratio was observed with both doxorubicin dosages, maximal exposure to doxorubicin led to a more pronounced ^{111}In-antimyosin uptake with a ratio of 2.02 ± 0.3 ($P < 0.01$) and was associated with a significant ≥10% decrease in LVEF (85). Furthermore, in a follow up study of patients that had discontinued anthracycline treatment due to a decrease in LV function leading to a LVEF <50%, Olmos et al. demonstrated that patients with an ^{111}In-antimyosin heart-to-lung uptake ratio ≥1.87 experienced a persistent decline in LVEF at 2–26 weeks follow-up, with 4 out of 11 of these patients subsequently developing congestive heart failure (86). In contrast, patients with a transient change in LVEF following the discontinuation of anthracycline treatment had a mean ^{111}In-antimyosin heart-to-lung uptake ratio of 1.52. Despite these promising results, interest in ^{111}In-antimyosin cardiac imaging has waned and this tracer is not commonly used in contemporary practice due to its detection of necrotic cell death which occurs at more at more advanced stages of the disease process and thereby limits options for clinical intervention.

III. Sympathetic innervation

The clinical signs of early myocardial cell injury are often masked by a compensatory rise in sympathetic drive. Indeed, an increase in chronotropy and inotropy preserve LVEF during the early stages of AIC (87, 88). While initially beneficial, long term cardiac sympathetic activation is detrimental, with cardiac sympathetic dysinnervation occurring in cardiomyopathy and heart failure (89). The main catecholamine released by sympathetic postganglionic fibers is norepinephrine which accounts for 70% of circulating levels, with the remainder mainly released by the adrenal gland (90, 91). The majority of clinical tracers that monitor sympathetic innervation are radiolabeled analogs of norepinephrine.

^{123}I-metaiodobenzylguanidine

^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), a norepinephrine analog that shares with it similar release and uptake mechanisms, can be used to identify areas of abnormal adrenergic innervation in the myocardium. Approximately 80–90% of norepinephrine released at sympathetic nerve terminals is taken up again *via* norepinephrine transporter uptake-1 (89). Reduction of norepinephrine uptake at these sites has been documented in various cardiovascular diseases (92, 93). Like norepinephrine, reuptake of ^{123}I-MIBG is mediated by norepinephrine transporters along myocardial sympathetic nerve terminals. Given ^{123}I-MIBG is not metabolized, its retention can be used as an indicator for neuronal integrity.

^{123}I-metaiodobenzylguanidine uptake is reduced in preclinical models of AIC. In a chronic doxorubicin rat model (2 mg/kg IV weekly for 1, 2, 3, 4, 5 and 8 weeks), a significant decrease in cardiac ^{123}I-MIBG uptake was detected at week 4, which correlated with histologically examined myocardial tissue damage (94). A comparative study of ^{123}I-MIBG with ^{18}F-FDG in a chronic doxorubicin-induced cardiotoxicity rat model (15 mg/kg cumulative dose) indicated that ^{18}F-FDG uptake decreased significantly in doxorubicin treated groups at weeks 4 and 6 (4.2 ± 0.5%ID/g vs. 9.2 ± 0.8%ID/g at week 6), which correlated with LVEF ($r = 0.49$, $P = 0.002$) (95). In contrast, a significant decrease in ^{123}I-MIBG heart-to-mediastinum (H/M) ratio between groups was detected earlier at week 2 (∼1.9% vs. ∼1.4%, $P < 0.05$), maintained at weeks 4 and 6, but was not correlated with LVEF decrease at week 6 ($r = 0.24$, $P = 0.15$). While promising, a limiting point of these preclinical studies is the large variability in anthracycline doses and temporal administration patterns which may lead to systemic toxicity in animals.

Early and late H/M ratios of ^{123}I-MIBG uptake were proposed as an index for stratifying prognosis and risk in patients with chronic heart failure (96). Carrió et al. (96) observed a significant 1.5-fold decrease in cardiac ^{123}I-MIBG uptake in sarcoma patients undergoing maximal cumulative doxorubicin treatment (420–600 mg/m^2), which also corresponded with a significant (≥10%) reduction in LVEF. A similar reduction in ejection fraction was not detected in patients at intermediate cumulative doxorubicin doses (240–300 mg/m^2), though 25% of patients exhibited slight decreases in ^{123}I-MIBG uptake that were not significant compared to baseline. A study by Laursen et al. (97) further reinforced that ^{123}I-MIBG imaging is only applicable in patients undergoing high cumulative doxorubicin doses. Moreover, the authors observed that patients undergoing intermediate cumulative doses of doxorubicin had a non-significant increase post therapy on both background-corrected WOR – which reflects norepinephrine retention in adrenergic neurons, closely connected to sympathetic tone (18.6% vs. 23.4%, $P = 0.09$), and H/M$_{early}$ – a measure of the anatomical distribution of functioning myocardial adrenergic neurons (2.7% vs. 2.9%, $P = 0.4$). No association was observed between follow-up decreases in LVEF and WOR ($P = 0.5$). Moreover, in a study of asymptomatic patients who had completed anthracycline treatment ≥2 years prior, ^{123}I-MIBG uptake did not differ between anthracycline treated patients (cumulative anthracycline dose 257.6 ± 117.1 g/m^2) and control patients, as assessed either by mean H/M$_{late}$ – which reflects overall neuronal functioning, i.e., the product of norepinephrine uptake,

storage, and release (2.24% vs. 2.26%, P = 0.5) – or WOR (10.32% vs. 9.64%, P = 0.8) (98). These results suggest that the myocardial adrenergic activation initially detected by ^{123}I-MIBG during treatment is reversible upon discontinuation of anthracycline treatment. Overall, ^{123}I-MIBG adrenergic imaging is not presently a clinically applicable strategy for the early detection of AIC, though further clinical studies may be warranted to investigate its sensitivity at lower cumulative anthracycline doses.

Additional tracers

Other PET radiotracers for cardiac sympathetic innervation have been studied in animal models. *Ex vivo* biodistribution studies 3 weeks after chronic doxorubicin treatment in rats found no change in cardiac uptake of the norepinephrine analog ^{11}C-*meta*-hydroxyephedrine (^{11}C-HED) or the phosphodiesterase-4 inhibitor (*R*)-^{11}C-rolipram (which provides an index of myocardial cyclic AMP activity, downstream of norepinephrine) (99). On the other hand, the authors noted a decreased uptake of the β-adrenergic antagonist ^{3}H-CGP12177 3 weeks post treatment while there was no change in ejection fraction or heart-to-weight ratio. Similarly, Kizaki et al. also reported that β-adrenergic receptor gene expression decreases following doxorubicin treatment in rats (100).

IV. Myocardial function, perfusion, and blood flow

^{99m}Tc-MUGA imaging is an accurate method to assess ventricular contraction. While generally avoided in pediatric patients due to radiation concerns, ^{99m}Tc-MUGA may be used to monitor cardiotoxicity in adult patients due to its high accuracy and low inter-observer variability (101–103). In a prospective study of 28 non-Hodgkin lymphoma patients undergoing doxorubicin treatment, Nousiainen et al. observed that a decrease of ≥4% in LVEF quantified by ^{99m}Tc-MUGA following a cumulative doxorubicin dose of 200 mg/m^2 predicted AIC with 90% sensitivity and 72% specificity (104). However, these findings were not supported by a large-scale retrospective study of 630 patients grouped according to increasing doxorubicin doses or placebo (4). Overall, assessment of LVEF – even if done accurately by ^{99m}Tc-MUGA – is not a favored approach to assess AIC as it only provides a global and often delayed assessment of cardiac mechanical abnormalities following injury.

Microvascular dysfunction is a possible complication of AIC (105). The SPECT myocardial perfusion imaging tracer ^{99m}Tc-sestamibi was assessed in AIC in a prospective study of breast cancer patients undergoing radiation therapy and doxorubicin treatment (106). Hardenbergh et al. observed that 7 out of 10 patients developed new visible perfusion defects 6 months post-radiation. More recently, PET tracers such as ^{13}N-ammonia and ^{82}Rb-chloride have become more common for myocardial perfusion assessment due to their superior diagnostic accuracy compared to SPECT (107–109). In a small prospective study (n = 10) using ^{13}N-ammonia, Nehmeh et al. reported decreased MFR 1-year post-radiation in 50% of breast cancer patients (n = 4) receiving radiotherapy and anthracycline (110). However, these findings are suggested by a small dataset only, and it is unknown if the observed cardiotoxic effects were caused by the anthracycline treatment or the radiation. PET myocardial perfusion tracers are amenable to myocardial blood flow quantitation, an integrated measure of epicardial and microvascular coronary artery disease (109). ^{82}Rb-chloride assessment of myocardial blood flow in lymphoma patients by Laursen et al. revealed a mild reduction in myocardial flow reserve (MFR: 2.69 vs. 2.51, P = 0.03) – calculated as the stress/rest ratio of myocardial blood flow – 3 days after initial doxorubicin treatment, with 13 out of 54 patients exhibiting low cardiotoxicity threshold (>20% decline in MFR) (105). Importantly, the MFR decline was independent of perfusion defects determined using the summed stress score and summed difference score. Stratifying patient risk of developing AIC in this manner is relevantly new, and additional studies are needed to determine whether an acute reduction in MFR shortly after anthracycline administration may identify patients at higher cardiotoxicity risk. Furthermore, the PET tracers ^{13}N-ammonia (110), ^{15}O-water (111) and ^{18}F-flurpiridaz (112, 113) should also be considered to assess myocardial blood flow changes in AIC given their higher myocardial extraction fractions (108).

V. Cardiac fibrosis

Myocardial fibrosis (114) may occur as a result of AIC. While the exact role cardiac fibroblasts play in AIC remains underexplored, doxorubicin was recently reported to induce fibroblast differentiation (115). ^{68}Ga-fibroblast activation protein inhibitor (FAPI) is a robust fibroblast PET tracer that was initially developed to detect high FAP-expressing, cancer-associated fibroblasts. In a retrospective study of n = 32 patients, Siebermair et al. evaluated the cardiac uptake of ^{68}Ga-FAPI in a heterogenous population of cancer patients treated with various anticancer therapies (116). While only 3 patients with FAPI uptake had been treated with anthracyclines, the authors observed a significant association of myocardial FAPI uptake with CAD and LVEF. Using modeling (n = 185) and confirmatory (n = 44) consecutive cohorts of patients with cancer metastasis who had FAPI-positive PET scans, Heckmann et al. (117) did not observe an association of focal myocardial FAPI uptake with anthracycline treatment, however, noted a correlation of high signal intensities with cardiovascular risk

factors and metabolic disease. Additional studies are warranted to investigate cardiac fibroblast FAP expression patterns in the context of AIC (116).

Additional anthracycline cardiotoxicity mechanisms for future development of candidate molecular targets

Several AIC mechanisms have not been targeted to date using a nuclear imaging strategy. Anthracycline-induced cardiac injury is multi-factorial and -genic, with no single mechanism fully explaining all aspects of the injury process. Importantly, anthracyclines induce all forms of cell death (118, 119). We highlight below three additional injury pathways that may lead to the development of new radiotracers for nuclear molecular imaging in AIC.

Autophagy

Autophagy is a homeostatic process in which cells utilize lysosomes to remove unnecessary or damaged cellular components (75). Anthracyclines block cardiomyocyte autophagic flux by impairing lysosomal acidification – critical for lysosomal hydrolytic enzyme activity and lysosomal maturation (120) – leading to the accumulation of undegraded autolysosomes (121) (**Figure 2A**). Another mechanism of anthracycline interference with autophagic flux is the inhibition of transcription factor EB expression which is a regulator of lysosomal proteolysis mediated primarily by cathepsin B activity (122). Furthermore, phosphoinositide 3-kinase γ (PI3Kγ) is induced downstream of Toll-like receptor 9 by cardiomyocytes following anthracycline treatment (123). PI3Kγ leads to Akt phosphorylation and inactivation of mTOR (mammalian target of rapamycin) targets, thus causing autophagy inhibition and a reduced ability to remove damaged organelles such as mitochondria (123). Expression of beclin-1, a mediator of autophagy initiation, increases following doxorubicin treatment in mice (121). Furthermore, Li et al. indicated that haploinsufficiency of beclin-1 diminishes autophagy initiation, leading to fewer unprocessed autolysosomes and decreased ROS production. Conversely, doxorubicin-induced cardiac injury is accentuated in mice with beclin-1 overexpression. Taken together, these mechanisms indicate the contribution of autophagy perturbation to AIC-induced cardiomyocyte death, cardiac remodeling, and failure (124).

Ferroptosis

Ferroptosis is a type of cell death characterized by the iron-related accumulation of lipid peroxides (75). Iron plays a significant role in AIC injury (125) (**Figure 2B**). Heart biopsies of patients who experienced anthracycline-related heart failure demonstrated excessive mitochondrial iron accumulation (126). This excessive iron load in the mitochondria can be explained by doxorubicin downregulation of ATP-binding cassette protein-B8 (ABC-B8), which mitigates iron transport out of the mitochondria (126). Doxorubicin also downregulates the key anti-ferroptosis protein glutathione peroxidase-4, resulting in lipid peroxidation. Additionally, doxorubicin can interact with the iron response elements of ferritin, reducing cytosolic ferritin and increasing labile iron (127).

Pyroptosis

Pyroptosis is a cell death mechanism characterized by increased proinflammatory signaling and activation of caspase-1, −4, −5, and −11, leading to plasma membrane rupture mediated by gasdermin D (GSDMD) (75). Previous research has determined that doxorubicin induces pyroptosis *via* induction of terminal differentiation-induced non-coding RNA (TINCR) and activation of the NLRP-3-caspase-1 pathway (128–130). Specifically, doxorubicin upregulation of TINCR leads to recruitment of the adapter protein IGF2BP1 (insulin-like growth factor 2 mRNA-binding protein 1) and stabilization of NLRP3 mRNA (128). This increases NLRP3 expression and activates caspase-1, thereby leading to GSDMD cleavage, plasma membrane rupture, and interleukin (IL)-1β and IL-18 release (**Figure 2C**).

Need for improved cardiac imaging approaches in the context of contemporary anthracycline use

While cancer affects more than one in three people over their lifetime, improved long-term cancer survival has led to an increase in the incidence of adverse cardiac side-effects of cancer treatments (131). The U.S. National Cancer Institute estimates that in 2022 there will be ∼ 18 million cancer survivors which mounts to >5% of the U.S. population (132). Anthracyclines are a cornerstone of chemotherapy in various cancers (133), however, their use is complicated by anthracycline-induced cardiotoxicity (134, 135) which has been appreciated for decades (4, 136–138).

Despite the continued discovery of alternative chemotherapeutic strategies, and their known cardiotoxic side-effects, anthracyclines remain a mainstay of many cancer treatments (139, 140). Indeed, anthracyclines are used in 30–35% of breast cancer patients (141–143) and 60–70% of elderly lymphoma patients (144, 145). Moreover, 50–60% of childhood cancer survivors were treated with a chemotherapy

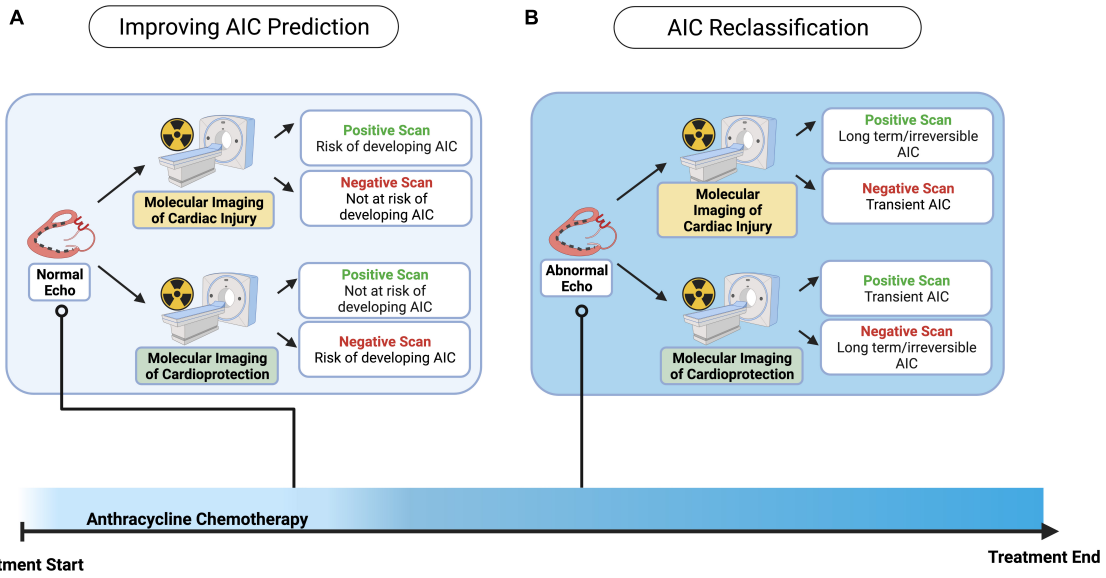

FIGURE 3
Potential clinical applications of nuclear molecular imaging in predicting and reclassifying cardiotoxicity in cancer patients undergoing anthracycline treatment. Different clinical algorithms may be followed according to the mechanistic pathway targeted for imaging – whether expression of cardiac injury related proteins, or alternatively activation of cardioprotective pathways – and the presence or absence of abnormal echocardiographic features suggestive of cardiotoxicity. **(A)** Molecular imaging may be used to predict the risk of developing cardiotoxicity during and/or following anthracycline treatment in patients with a normal echocardiogram. **(B)** In patients with an abnormal echocardiogram suggesting a new impairment in cardiac function, molecular imaging may be able to finetune the cardiotoxicity diagnosis with implications on the duration of anthracycline-induced cardiac dysfunction, or to reclassify the echocardiographic diagnosis, thereby providing oncologists and cardiologists greater diagnostic certainty with ensuing clinical implications.

regimen containing anthracyclines (146, 147). In parallel, continued advances in cancer therapy have increased the survival rate of childhood cancer to ∼ 80% (132). Furthermore, long-term follow-up of childhood cancer survivors indicate that up to 30% of patients treated with anthracyclines have signs of cardiac dysfunction in adulthood that are unmasked when more sensitive detection techniques are used (148), indicating significant under-estimation of long-term complications. These observations highlight the need for additional and improved imaging strategies in the context of AIC.

While echocardiography continues to be the most widely used tool for AIC monitoring, it is important to consider the limitations and advantages of each modality when selecting the proper screening exam for an individual patient. Echocardiography enjoys attractive features such as wide availability, rapid interpretation, lack of ionizing radiation exposure and relatively low cost which have firmly established it as the staple of AIC monitoring (6). However, the quality of the study is highly dependent on patient anatomy, acoustic windows, technician skill, and interobserver variability to a greater degree than other available methods (149–151).

In contrast, automated segmentation and ventricular volume algorithms offer precise and accurate evaluations of chamber function in cardiac MRI and multi-detector gated cardiac CT. However, cardiac MRI is more expensive and less widely available at many clinical centers. It is also a time-consuming exam that requires significant patient cooperation and can be undermined by rapid heart rates, arrhythmias, or by the presence of intrathoracic hardware such as implantable pacemakers or defibrillators that can introduce excessive signal artifact (152, 153).

Cardiac CT is also challenged by susceptibility to gating artifacts with rapid or irregular heart rhythms, need for iodinated contrast which is limiting in patients with kidney disease, as well as less robust data on the assessment of muscle strain or mechanics that can indicate early toxicity as compared to echocardiography or cardiac MRI (154).

Lastly, although largely fallen in clinical desuetude, patients with poor echocardiographic acoustic windows and contraindications to MRI or CT imaging may be referred for a radionuclide MUGA scan. This modality has proven to be a viable alternative to cardiac MRI or CT in patients where the precision or accuracy of echocardiographic measurements are in question, and thus remains a clinical option when choosing a strategy to monitor for AIC (155, 156). However, the advent of unique and specific markers in the growing field of nuclear molecular imaging may offer an additional toolset to detect and treat early manifestations of AIC.

Whereas the utility of perfusion-based imaging and myocardial blood flow quantitation for the detection of subclinical or early AIC has been studied in several small trials, additional research is needed to bring the evidence to the level of routine clinical utility. In particular, PET-derived myocardial blood flow has been examined as a potential marker of patients who may be at increased risk for AIC (157, 158). Whether changes in myocardial blood flow metrics are a sign of early cardiac stress or indicative of irreversible toxicity in response to anthracyclines require further scrutiny (157). If the value of myocardial flow reserve assessment in AIC can be further demonstrated in large-scale clinical studies, it could be added as an early evaluation strategy in company of echo-derived left ventricular global longitudinal strain or biomarkers such as plasma troponin levels.

Similarly, although no societal guidelines exist for routine myocardial perfusion imaging of patients undergoing anthracycline based chemotherapy regimens, the high correlation of CAD and subsequent acute coronary syndromes in cancer patients often prompts clinicians to screen patients with intermediate or high risk of CAD prior to initiation of therapy. In one retrospective analysis of 6.5 million cases of acute coronary syndromes, 9% of the patients had a diagnosis of cancer, either active or in remission, suggesting that pre-chemotherapy evaluation and revascularization, if indicated, may be appropriate in this patient group (159).

Several of the probes discussed in this review such as ^{18}F-FDG and ^{68}Ga-FAPI are used for cancer staging or progression evaluation. Retrospective analyses of these clinical studies suggest abnormal myocardial uptake in certain patients, paving the way for dedicated cardiac studies to detect and monitor AIC. There is also an opportunity to investigate these probes for oncologic and cardiac assessment in tandem. Doing so, however, will require patients to have a standardized preparation and clinicians to follow a more rigid imaging protocol that adheres to both oncologic and cardiac quality control requirements.

Echocardiography, including the segmental assessment of myocardial function by strain or displacement vectors, remains the first imaging modality of choice for AIC screening. Therefore, we posit a complementary role – dependent on the imaging targets – for the clinical utilization of nuclear molecular imaging applications in cardio-oncology, that we separate into two aims: 1) improving the prediction of AIC development in the setting of a normal echocardiogram, and 2) improving AIC reclassification in the setting of an abnormal echocardiogram (**Figure 3**). The clinical adoption of nuclear molecular imaging approaches remains limited at present, however, is poised to significantly affect current imaging strategies that have limitations in both sensitivity and specificity to screen and monitor AIC.

Conclusion

Anthracycline-induced cardiotoxicity involves a broad range of pathophysiological pathways that lead to cardiomyocyte injury and that may be further complicated by cardiomyopathy and heart failure. Mechanisms implicated in the disease process, as well as molecular responses thereto, can be probed for nuclear imaging, e.g., metabolic dysfunction, cardiomyocyte death, sympathetic innervation, and changes in myocardial blood flow. Detecting these AIC-induced processes at a subclinical level, prior to the onset of irreversible cardiac impairment, may provide clinicians with valuable information permitting changes in chemotherapeutic strategies and/or timely initiation of cardioprotective strategies.

Author contributions

JJ, JP, and RP wrote the manuscript. JJ drew the figures and wrote the table. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Cardiac MRI assessment of anthracycline-induced cardiotoxicity

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The objective of this review article is to discuss how cardiovascular magnetic resonance (CMR) imaging measures left ventricular (LV) function, characterizes tissue, and identifies myocardial fibrosis in patients receiving anthracycline-based chemotherapy (Anth-bC). Specifically, CMR can measure LV ejection fraction (EF), volumes at end-diastole (LVEDV), and end-systole (LVESV), LV strain, and LV mass. Tissue characterization is accomplished through T1/T2-mapping, late gadolinium enhancement (LGE), and CMR perfusion imaging. Despite CMR's accuracy and efficiency in collecting data about the myocardium, there are challenges that persist while monitoring a cardio-oncology patient undergoing Anth-bC, such as the presence of other cardiovascular risk factors and utility controversies. Furthermore, CMR can be a useful adjunct during cardiopulmonary exercise testing to pinpoint cardiovascular mediated exercise limitations, as well as to assess myocardial microcirculatory damage in patients undergoing Anth-bC.

KEYWORDS

cardiac MRI, anthracycline, cardiotoxicity, cardiac assessment, cancer treatment

Introduction

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging method that produces 3-dimensional images without using ionizing radiation and may accurately assess left ventricular (LV) myocardial structure, function (strain, volumes, ejection fraction), perfusion, and tissue characteristics across a variety of disease processes including heart failure, ischemic heart disease, non-ischemic cardiomyopathy, myocarditis, pericardial disease, and congenital heart disease (1).

Recently, CMR has been used to assess LV myocardial injury and identify cardiotoxicity in patients receiving anthracycline-based chemotherapy (Anth-bC) for the treatment of various cancers including breast, leukemia, lymphoma, bladder, and ovarian cancer (2). Cardiotoxicity is a condition defined as change in LV performance which can be assessed through CMR and is most commonly identified as a left

ventricular ejection fraction (LVEF) absolute decline of ≥ 10%, or a decline to a value < 50% (3–6). CMR can determine LVEF and extracellular volume fraction (ECVF) and assess LV myocardial injury, helping to identify cardiotoxicity. Furthermore, CMR tissue-based characterization, such as late gadolinium enhancement (LGE) imaging, detects myocardial fibrosis, which can be indicative of LV injury, and T1/T2 mapping with CMR allows for accurate spatial visualization while assessing for cardiotoxicity.

This article will review the utilization of CMR for identifying cardiotoxicity in patients receiving Anth-bC, discuss recent clinical data and parameters that can be detected *via* CMR, address challenges, and finally, consider recent breakthroughs and new frontiers of research.

Anthracyclines and cardiotoxicity

Anthracyclines are a class of anti-tumor agents including daunorubicin, doxorubicin, epirubicin, idarubicin, and valrubicin (2). Anthracyclines are commonly used as components of curative therapy for various types of cancers (2). For example, adjuvant chemotherapy containing anthracyclines decrease the 10-year risk of breast cancer recurrence from 47.4 to 39.4% when compared to breast cancer patients who received no chemotherapy (7), and increase overall survival among patients with Non-Hodgkin's lymphoma (112 months, on average) when compared to lymphoma cancer patients who received a non-anthracycline regimen (94 months, on average; $p = 0.0004$) (8).

Although effective in eradicating tumors in breast, lymphoma, and soft tissue sarcoma cancers, anthracycline-related treatments may have a negative impact on LV function and promote heart failure (HF) (7, 9, 10). The mechanism by which anthracycline-induced LV myocardial injury occurs is multi-factorial and includes (a) inhibition of topoisomerase (Top) 2β, (b) generation of reactive oxygen species (ROS) (11), (c) downregulation of adiponectin (12), (d) promoting LV myocardial fibrosis (13), (e) promoting mitochondrial toxicity (14), and (f) promoting microvascular disease (15).

What is cardiac magnetic resonance imaging and how can it assess anthracycline-induced cardiotoxicity?

Mechanistically, CMRs are based on the detection of signals from hydrogen nuclei (1). When a patient enters a scanner, hydrogen nuclei align with, and "precess" about the axis of the magnetic field and small magnetic pulses are delivered. Cine images used to evaluate cardiac volumes are acquired using steady state free precession (SSFP) pulse sequences, which allows for signals to be received and processed to produce an image of the spatial distribution of the spins of protons within the body (16). CMR is unique in its use of various imaging sequences: cine imaging determines morphology, T2-weighted imaging describes myocardial edema, perfusion characterizes ischemia, and LGE is used for scar and tagging for myocardial strain imaging (17). While CMR imaging techniques can identify cardiac structure, measure cardiovascular function, and characterize tissue, these techniques do not use ionizing radiation, which is particularly advantageous for use in oncology patients.

Measuring left ventricular ejection fraction with cardiovascular magnetic resonance

Two common techniques to determine LVEF with CMR are the Simpson's rule technique and the area-length technique (18). The Simpson's rule technique (19, **Figure 1**) uses multiple short axial slices from the base to the apex of the myocardium. Next, the endocardial border is identified, and each intraventricular area is multiplied by slice thickness to determine LV volumes which are summed to calculate total LV volume without requiring assumptions about LV shape. Therefore, this method is especially useful among patients who exhibit cardiomyopathy or similar abnormalities of the myocardium. In situations in which the left ventricle assumes the shape of a prolate ellipsoid, the area-length technique may be used, as it encompasses only two slice acquisitions in LV apical views. Once LV volumes are determined, LVEF is calculated with the following formula: ([left ventricular end-diastolic volume (LVEDV)—left ventricular end-systolic volume (LVESV)]/LVEDV) *100. LVESV is the LV volume at the end of systole, with an average indexed value of 26 ± 6 mL/m^2 for males and 24 ± 5 mL/m^2 for females, whereas LVEDV is the LV volume at the end of diastole, with an average indexed value of 81 ± 12 mL/m^2 for males and 76 ± 10 mL/m^2 for females (19).

In 53 men and women with breast cancer, leukemia, or lymphoma, LVEF decreased within 6 months after low to moderate doses of Anth-bC (10) (**Table 1**). Moreover, Ferreira de Souza et al. (20) used CMR to determine that among 27 women with breast cancer, the average LVEF declined by 12 absolute LVEF units ($p < 0.001$) at 351–700 days after anthracycline therapy of 240 mg/m^2 (20). Additionally, the average LV mass index decreased by 19 g/m^2, from 51.4 ± 8.0 to 36 ± 6 g/m^2 ($p < 0.001$), and cardiac troponin T significantly increased ($p < 0.001$). Therefore, based on these studies, patients being treated with Anth-bC obtained CMRs before, 6, 12, and/or 24 months after anthracycline treatment.

Furthermore, a study by Melendez et al. (21) used CMR to determine that among 112 cancer patients (72% of whom received anthracyclines), 26 patients developed significant declines in LVEF of > 10% or to values < 50% at 3 months

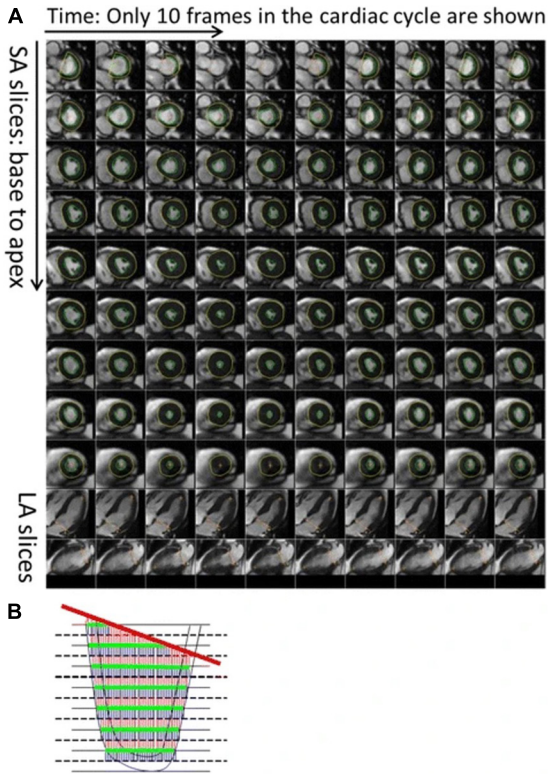

FIGURE 1
Description of the automatic process to calculate left ventricular (LV) volume and strain. As shown, **(A)** the LV endocardium and epicardium are automatically contoured on the LV short axis slices. The mitral valve base plane is detected on the long axis slices of the left ventricle and projected onto the LV short axis slices. **(B)** To calculate the LV volumes, slices are stacked and contoured areas are summed up. At the same time, the mitral valve base plane is intersected with the stack of slices to remove portions of the volume that are above the base plane and inside the left atrium. From (38) with permission.

(21). Among these 26 patients, 19% were determined to have a decline in LVEF due to a decline in LVEDV, whereas 60% were determined to have a decline in LVEF due to an increase in LVESV. Systolic heart failure is associated with LVEF drops given by LVESV changes, but changes in LVEDV may be due to volume depletion, which is a common occurrence in cancer patients. Thus, the LVEF may decrease due to a decline in LVEDV or an increase in LVESV, and CMR allows for clinical determination of which case is present in a patient (**Figure 2**).

Measuring left ventricular mass with cardiovascular magnetic resonance

In cancer patients, LV mass may decrease and result in greater end systolic wall stress, known as the Grinch Syndrome. Typically, indexed LV mass ranges from 50 to 86 g/m^2 for males and 36–72 g/m^2 for females (22) and can be determined by CMR, but in patients with the Grinch Syndrome, these values can decline and adversely affect the myocardium. The mechanism of cardiac atrophy involves suppression of pro-growth pathways, such as signaling events controlled by myocyte-enriched calcineurin-interacting protein-1 (hMCIP1) or Thioredoxin1 (Trx1), or direct stimulation of protein degradation (23–27).

LV mass can be calculated by subtracting LVEDV from epicardial volume and multiplying by 1.05 g/mL (28). The Grinch Syndrome has been observed in patients receiving Anth-bC as early as 1 (29) and 6 months (31, **Figure 3**) after initiating treatment (30). Specifically, researchers conducted a cohort analysis with 61 cancer patients initiating Anth-bC, and assessed their cardiac function with CMR before and 6 months after initiating chemotherapy (31). The researchers observed a 5% decline in LV mass (p = 0.03) and LVEF (p < 0.0001) but did not observe this decline in patients receiving non-Anth-bC (n = 15) or control patients (n = 24). Additionally, patients receiving Anth-bC experienced a decline in Minnesota Living with Heart Failure Questionnaire scores over the 6-month period, which was associated with LV mass declines (r = –0.27; p < 0.01), yet not with LVEF declines (r = 0.11; p = 0.45), thus indicating that patients with declining LV mass while undergoing treatment with Anth-bC may experience worsening heart failure symptomatology that's independent of LVEF (31).

Furthermore, in a study with 91 patients receiving Anth-bC, researchers found an inverse association between anthracycline dose and indexed LV mass (r = –0.67, p < 0.001; 32). The researchers also determined if patients experienced a major adverse cardiovascular event (MACE), which was defined as cardiovascular death, implantable cardioverter defibrillator therapy, and admission for heart failure (30). Among patients who experienced a MACE during the 27-month study period, indexed LV mass and glomerular filtration rate were lower while anthracycline dose was higher (30). Additionally, indexed LV mass had the strongest association with MACE (HR = 0.89, chi-squared = 26, p < 0.001) in a multivariable model (30). Therefore, determination of LV mass by CMR may be a predictor of adverse cardiovascular events (30).

However, LV mass has been shown to decrease in conditions of weightlessness, bed rest, and other situations of ventricular unloading. For example, LV mass index decreased by 15% after 12 weeks of bed rest in healthy individuals (32), and another study by de Groot et al. (33) reported a 25% decrease in LV mass in patients with spinal cord injury who did not exercise (27, 33). Therefore, both general status and Anth-bC may affect LV mass, so general status may be a confounding factor while observing LV mass decline in patients treated with Anth-bC.

TABLE 1 Summarizes the number of cancer patients, cancer type, chemotherapy, techniques to measure LVEF and/or LV mass, and the outcome of each study cited in this manuscript.

References	Number of cancer patients (male/female)	Cancer type	Chemotherapy	Techniques to measure LVEF and/or LV Mass	Outcome
Drafts et al. (10)	53 (31/22)	Breast cancer, leukemia, or lymphoma	50–375 mg/m^2 of doxorubicin equivalent chemotherapy	CMR: cine white blood steady state free precession techniques with 256×128 matrix; 40 cm field of view; 10-ms repetition time; 4-ms echo time; 20-degree flip angle; 8 mm thick slice; 40-ms temporal resolution	LVEF decline from 58 ± 1 to 53 ± 1% in 6 months ($p = 0.0002$)
Ferreira de et al. (20)	27 (0/27)	Breast cancer	Anthracycline therapy of 240 mg/m^2	CMR: cine imaging (steady-state free precession with TR 3.4 ms, echo time 1.2 ms, and in-plane spatial resolution 1.5 mm)	Mean LVEF decline by 12% to 58 ± 6% ($p < 0.001$) at 351–700 days after anthracycline therapy LV mass index decreased by 19 g/m^2, from 51.4 ± 8.0 g/m^2 to 36 ± 6 g/m^2 ($p < 0.001$)
Melendez et al. (21)	112 (78/34)	Breast cancer, Leukemia, Lymphoma, Renal Cell, or Sarcoma	Mixture of anthracyclines (72%), antimicrotubule agents (60%), alkylating agents (74%), and tyrosine-kinase inhibitors (51%)	CMR: cine white blood steady-state free precession techniques with a 256 × 128 matrix; 40-cm field of view; 10-ms repetition time; 4-ms echo time; 20-degree flip angle; slice 8-mm thick; 40-ms temporal resolution	26 patients developed significant declines in LVEF of >10% or to values <50% at 3 months Participants who dropped their LVEF due to decreases in LVEDV lost more LV mass than those who dropped their LVEF due to an increase in LVESV ($p = 0.03$)
Jordan et al. (31)	61 (19/42)	Breast cancer, hematologic malignancies, or sarcomas	Average cumulative doxorubicin dose equivalent of 232 ± 103 mg/m^2	CMR: cine short-axis white-blood steady-state free precession images were acquired encompassing the LV in 8-mm thick planes separated by 2-mm gaps; 40-cm field of view, 192 × 109 matrix, 10-ms repetition time, 1.12-ms echo time, 20° flip angle, 930 Hz/pixel bandwidth, and 40-ms temporal resolution	5% decline in both LVEF ($P <$ 0.0001) and LV mass ($P = 0.03$)
Neilan et al. (30)	91 (53/38)	Not reported	Anthracycline dose of 276 ± 82 mg/m^2	CMR: successive short-axis cine images at end-diastole and systole LV mass by CMR was derived by the summation of discs method by multiplying myocardial muscle volume by 1.05 g/cm^3	Inverse association between anthracycline dose and indexed LV mass ($r = -0.67$, $p < 0.001$) Indexed LV mass had the strongest association with MACE (HR = 0.89, chi-squared = 26, $p <$ 0.001)
Sawaya et al. (36)	43 (0/43)	Breast cancer	Doxorubicin (240 mg/m^2), Epirubicin (300 mg/m^2)	Transthoracic echocardiography using the Vivid 7 or E9 LVEF calculated from apical 4- and 2-chamber views using a modified Simpson's biplane method	LVEF change from 0.65 ± 0.06 at baseline to 0.63 ± 0.06 at 3 months, 0.59 ± 0.05 at 6 months ($p < 0.0001$) Circumferential strain (%) from 18 ± 4 at baseline to 15 ± 4 at 3 months, 14 ± 3 at 6 months ($p =$ 0.001)
Jolly et al. (38)	72 (24/48)	Breast cancer (39%), lymphoma (49%), or sarcoma (12%)	Anthracycline (68%), Antimicrotubular agents (67%), Alkylating agents (78%), Tyrosine-kinase inhibitors (39%), Antimetabolites (6%)	Cine balanced steady state free precession (bSSFP) imaging was performed using breath-hold retrospective ECG gating to acquire a stack of short axis slices as well as 2 long axis views (2-chamber and 4-chamber)	The LVEF declined from 65 ± 7% at baseline to 62 ± 7% at 3 months ($p = 0.0002$). LV Strain changed from −18.81 ± 2.89 at baseline to −17.58 ± 3.08 at 3 months ($p = 0.001$) The correlation between LV strain from cine imaging and LVEF was $r = -0.61$ ($p < 0.0001$), and the 3-month changes in each measurement also correlated ($r =$ −0.49, $p < 0.0001$)

(*Continued*)

TABLE 1 (Continued)

References	Number of cancer patients (male/female)	Cancer type	Chemotherapy	Techniques to measure LVEF and/or LV Mass	Outcome
Higgins et al. (42)	20 (15/5)	Lung cancer (30%), renal cell carcinoma (25%), melanoma (15%), other (30%)	Nivolumab (50%), pembrolizumab (40%), ipilimumab (30%)	CMR: Steady state free precession (SSFP) cine imaging (repetition time = 3 ms, echo time = 1.5 ms, flip angle = 60°, 30 cardiac phases, 1.4 × 1.4 × 8 mm^3 resolution) with retrospective ECG gating was acquired in the two-chamber, three-chamber, and four-chamber views, and in contiguous short axis slices of the left ventricle	LV strain was negatively correlated with LVEF (r_s = −0.64, $p < 0.002$)
de Barros et al. (47)	112 (1/111)	Breast cancer	Doxorubicin and Cyclophosphamide, Paclitaxel, Trastuzumab	Transthoracic echocardiogram, including longitudinal strain assessment with 2D speckle-tracking echocardiography	LVWMA (OR = 6.25 [CI 95%: 1.03; 37.95], $p < 0,05$), LV systolic dimension (1.34 [CI 95%: 1.01; 1.79], $p < 0,05$) and global longitudinal strain by speckle tracking (1.48 [CI 95%: 1.02; 2.12], $p < 0,05$) were strongly associated with cardiotoxicity
Tahir et al. (49)	39 (0/39)	Breast Cancer	Epirubicin-based chemotherapy	CMR: T2 mapping was performed using a free-breathing navigator-gated black-blood prepared gradient and spin-echo (GraSE) hybrid sequence in three short-axis slices; T1 mapping performed using a 5 s (3 s) 3 s MOLLI sequence with parameters: voxel size 2 × 2 × 10 mm^3, echo time=0.7 ms, time to repetition=2.3 ms, partial echo factor =0.8, flip angle =35°, SENSE factor =2, linear phase encoding.	T1/T2 myocardial relaxation times increased at therapy completion when compared to baseline, thus indicating myocardial injury, and when assessed with other CMR parameters (LVEF), this predicted anthracycline-induced cardiotoxicity [sensitivity (78%, 44–95%) and specificity (84%, 72–92%)]
Toro-Salazar et al. (51)	46 (33/13)	Acute myelogenous leukemia (21.7%), osteosarcoma (13%), Hodgkin lymphoma (10.9%), Ewing sarcoma (10.9%)	Average total cumulative dose of anthracyclines of 328 mg/m^2	CMR: standard multislice, multiphase cine imaging using a steady-state free-precession acquisition technique (fast imaging employing steady-state acquisition [FIESTA]) in the 2-chamber, 4-chamber, and contiguous short-axis planes T1 mapping using modified Look-Locker with saturation recovery sequence (MLLSR	Post contrast T1 values of cancer patients were significantly lower than control patients (458 ± 69 versus 487 ± 44 milliseconds; P = 0.01)
Modi et al. (54)	298 (108/190)	Breast cancer (38.6%), lymphoma (95%), leukemia (55%), sarcoma (21%), or other (4%)	Anthracyclines or trastuzumab	Cine CMR images were acquired in short-axis (every 10mm to cover the entire LV from the mitral valve plane through the apex) and three long-axis views using a steady-state free precession sequence LGE CMR was performed 10–15min after administration of gadolinium contrast (0.1–0.15mmol/kg), using 2D segmented inversion-recovery gradient-echo sequence in identical views as cine CMR	31 patients (10.4%) had LGE that ranged from 3.9–34.7% in extent, and an ischemic pattern was present in 20 (64.5%) of the 31 patients, yet these were no different in age-matched control patients
Jordan et al. (56)	37 (8/29)	Breast cancer (57%), hematologic (43%)	Anthracyclines	CMR: Cine imaging parameters included a 360–400 mm field of view collected with a 256 × 160 matrix, a 20° flip angle, a 6 mm slice thickness with 4 mm slice gap, a 3–5 ms echo time, and an 8–10 ms repetition time T2 mapping: 360 × 360 field of view, 192 × 60 matrix, 70° flip angle, 6 mm slice thickness, acceleration factor of 2, T2 preparation pulses of 0, 24, 55 ms T1 mapping: Look-Locker inversion recovery sequence in mid-cavity short-axis slice pre-contrast and again at 12 and 25 min after contrast administration in contrast eligible participants	T1 and ECVF remain elevated 3 years after anthracycline-based treatment, independent of cardiovascular comorbidities or underlying cancer

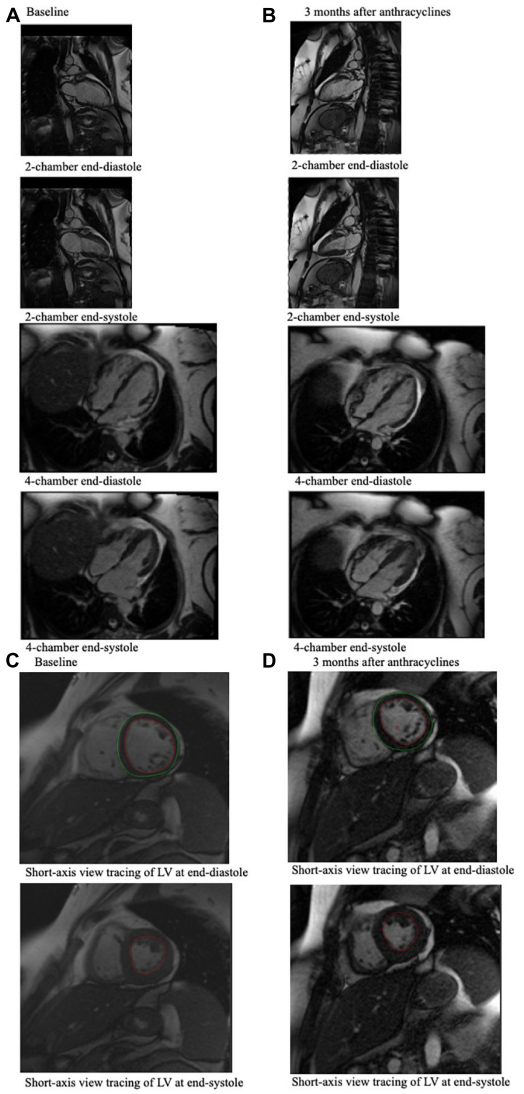

FIGURE 2
CMR end-diastole and end-systole frames from a cine loop for a 49-year-old breast cancer patient who experienced an associated LVEF decline from 61% at baseline **(A)** to 43% 3 months after anthracycline-based chemotherapy **(B)**, which was measured using these CMR images. **(A)** Shows 4-chamber and 2-chamber view CMR imaging of the cancer patient pre-chemotherapy, and **(B)** shows CMR imaging of the same cancer patient 3 months after chemotherapy. **(C)** Shows the short-axis view tracing of the LV at end-diastole and at end-systole at baseline, which can be compared to **(D)** which shows short-axis view tracings of the LV at end-diastole and end-systole of this patient at 3 months after chemotherapy. In these tracings, the red tracing outlines the blood pool in the left ventricle, and the green tracing outlines the left ventricle. These tracings, which indicate LVEDV and LVESV, are used to calculate LVEF.

Measuring left ventricular strain with cardiovascular magnetic resonance

LV strain is the percent change in length per unit of initial length (18). Two techniques are typically used to assess LV strain: Strain Encoding magnetic resonance imaging (SENC) and Displacement Encoding with Stimulated Echos (DENSE) (34). SENC imaging uses tagging of short-axis images with different z phases to calculate longitudinal strain, and DENSE imaging relies on tagging of short-axis images acquired with echoes to modulate pixels to their position in space. Both techniques have high spatial resolution and fast post-processing, but low temporal resolution. Both measure contraction in the longitudinal, circumferential, and radial directions (35). A study by Sawaya et al. (36) determined that an early decrease in longitudinal strain from baseline to 3 months among chemotherapy-treated breast cancer patients was an independent predictor of cardiotoxicity development at 6 months (36). As a decrease in LVEDV may lead to a decline in LV strain (37) (**Figure 4**), LV strain may also be affected by changes in LV volume. A study by Jolly et al. (38) determined that the correlation between LV strain from cine imaging and LVEF was $r = -0.61$ ($p < 0.0001$), and the 3-month changes in each measurement also correlated ($r = -0.49$, $p < 0.0001$) (38). Moreover, in a study by Houbois et al. (39), the authors suggest that feature-tracking strain can function as a confirmatory prognostic measure in addition to LVEF measurements when assessing for cardiotoxicity (39).

Tissue tracking

LV strain can also be quantified and tracked with post-processing semi-automated methods, such as tissue tracking. Specifically, LV strain can be tracked over time with CMR feature tracking (CMR-FT), as CMR-FT follows myocardial boundaries and automates strain calculation. The tracked features are anatomic elements along the cavity-myocardial interface and throughout the cardiac cycle, and each feature is tracked by algorithms (40). Tissue tracking technology depends on a post-processing method known as optical flow, which recognizes features in an image to track and follow in a sequence of successive images (41). A comparable technique for image tracking is known as speckle tracking echocardiography (STE), which is used when the ventricular myocardium has a speckled appearance.

Tissue tracking methods initially identify a small window on an image, and the search for the most comparable image pattern in the subsequent frame (41). Any displacement that's determined between the two tissue patterns is considered the local displacement (41). Typically, the minimum window dimension used in cardiology is 8 by 8 pixels, and it's essential to optimize image quality, temporal resolution, and speed and magnitude of displacement while performing tissue tracking (41). Furthermore, circumferential strain has been shown to have better reproducibility in CMR-FT than STE, but STE produces more accurate results for longitudinal strain due to the high echogenicity of the fibrous annulus (41). A study by Higgins et al. (42) measured LV strain, *via* CMR-FT, and LVEF of 20 patients undergoing cardiotoxic chemotherapy, and

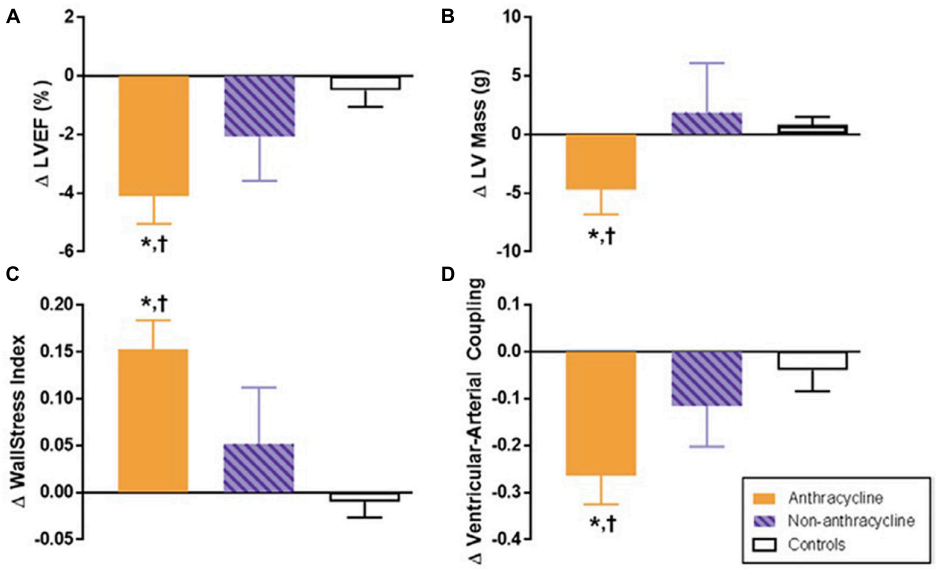

FIGURE 3
Six-month change in cardiovascular magnetic resonance (CMR)-derived left ventricular (LV) remodeling measurements after anthracycline-based chemotherapy. Six-month change in CMR-derived measurements of left ventricular remodeling in adults treated with anthracycline-based chemotherapy (Anth-bC, orange), non-Anth-bC (purple) for breast cancer or hematologic malignancy and cancer-free comparators of similar age (white). Compared with cancer-free comparators, those receiving Anth-bC had a significant decrease in LV ejection fraction (LVEF; **A** $P < 0.01$) and LV myocardial mass (**B**; $P = 0.03$) that occurred concurrently with increased end-systolic wall stress index (**C**; $P < 0.01$) and reduced ventricular-arterial coupling (**D**; $P < 0.01$). Changes among patients with cancer who received non–Anth-bC were not statistically different than those observed in non-cancer comparators ($P > 0.15$ for all). Data shown as mean ± SEM. *$P < 0.05$ for change from baseline. †$P < 0.05$ vs. change in control. From Jordan et al. (31) with permission.

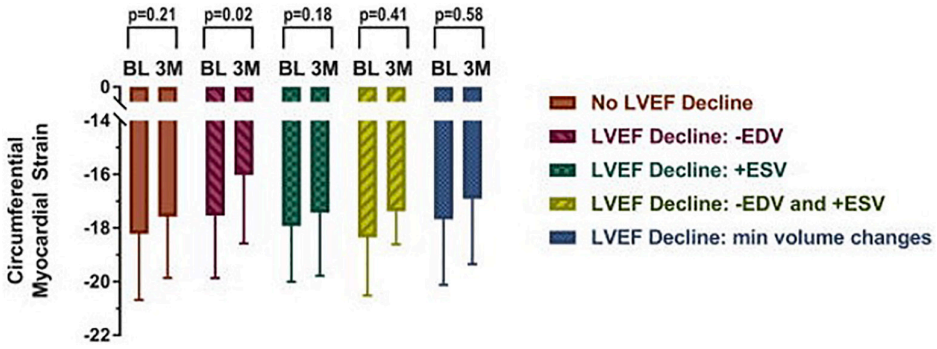

FIGURE 4
Mid-wall circumferential myocardial strain measured with CMR in cancer patients prior to (BL) and 3 months (3M) after initiation of chemotherapy categorized by underlying cause for left ventricular ejection fraction (LVEF) decline. Participants with a decline in LVEF due to a > 5 ml decrease in end diastolic volume exhibited subclinical deteriorations in myocardial strain. Myocardial strain changes were not observed in any other subgroup, including those with end systolic volume changes. From Jordan et al. (37) with permission.

among these patients, LV strain was negatively correlated with LVEF ($r_s = -0.64$, $p < 0.002$) (42).

The reproducibility and validity of CMR-FT have been assessed extensively (43). For example, CMR-FT was used to assess LV radial and circumferential strain in patients 5 years after undergoing Anth-bC, and it was found that circumferential strain was a reliable and reproducible measure of myocardial deformation, whereas radial strain measurement were unreliable (44).

Measuring left ventricular wall motion with cardiovascular magnetic resonance

Because cine loops can be acquired during breath holding from nearly any tomographic plane, CMR also allows for visualization of LV wall motion (18). Moreover, LV wall thickening may be assessed using the center line method and

myocardial tissue tagging. The center line technique creates a line down the center of the myocardium and draws evenly distributed perpendicular chords, where the length of each chord corresponds to the local wall thickness. However, when an imaging slice is not positioned perpendicular to the long axis of the left ventricle, the center line method may overestimate wall thickness. Tagging, on the other hand, can determine wall thickness across the LV myocardium by accounting for separation or intersections of tag lines.

Peak radial, longitudinal, and circumferential velocities are some of the parameters of LV wall motion (45). Typically, LV wall thickness is greater in males and younger patients, and systolic wall thickening (SWT) is highest in the lateral and apical myocardium, while wall motion (WM) is greatest in the lateral and basal myocardium (46). Additionally, if there is a wall motion abnormality in greater than two of seven parameters, then alterations to treatment progression may be recommended.

In a study by de Barros et al. (47), the LV wall motion of 112 cancer patients was analyzed to determine cardiotoxicity. Patients with LV segmental wall motion abnormalities (LVSWMA) were strongly associated with cardiotoxicity (47). Additionally, in a study by Jordan et al. (31), end-systolic wall stress index increased in cancer patients treated with anth-bC ($p < 0.01$; **Figure 3**) (31). LV wall motion abnormalities continue to be analyzed with CMR in cancer patients treated with anth-bC, and this remains an area of active study.

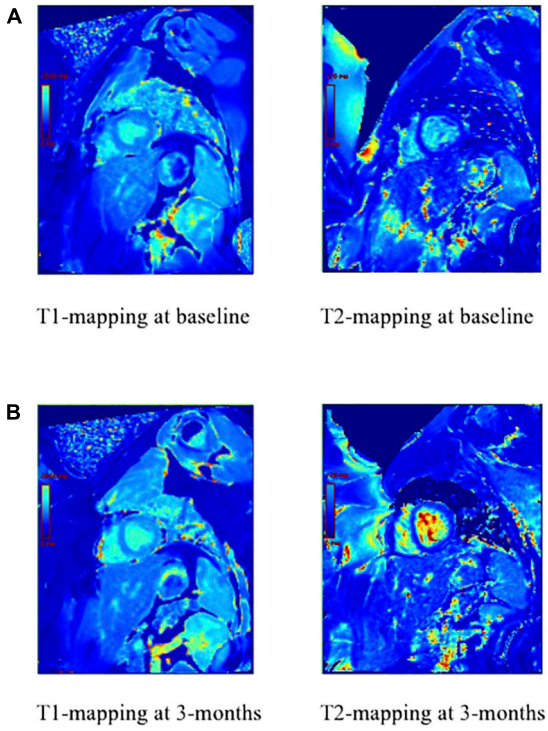

FIGURE 5
T1 and T2-mapping of the myocardium prior to anthracycline-based chemotherapy **(A)** and 3 months after anthracycline-based chemotherapy **(B)**. T1 has changed, which indicates active injury or ongoing fibrosis. T2 has also changed, which indicates increased water and active inflammation of the myocardium.

Tissue characterization

While CMR provides data regarding LV function, such as EF, strain, volume, and mass, it also provides tissue characterization data to assess myocardial fibrosis through methods that utilize gadolinium contrast and methods that do not use gadolinium contrast (native T1), such as T1 and T2 mapping. Longitudinal relaxation time (T1) and transverse relaxation time (T2) are properties determined by a tissue's molecular composition (**Figure 5**). Thus, changes in T1 and T2 relaxation times, when compared to a healthy myocardium, may indicate cardiovascular injury such as edema and fibrosis. T1 and T2 measures have been validated by histological analysis to represent myocardial injury, interstitial fibrosis, inflammation, and edema of myocardial biopsy with anthracycline-induced cardiotoxicity (48). For example, a study by Tahir et al. (49) determined that among 39 women receiving chemotherapy, T1/T2 myocardial relaxation times increased, thus indicating myocardial injury, and when assessed with other CMR parameters, this predicted anthracycline-induced cardiotoxicity (49). Thus, T1/T2 mapping have clinical implications in potentially predicting cardiotoxicity following anthracycline treatment. Furthermore, Galan-Arriola et al. (50) found that in 20 pigs, T2 mapping during doxorubicin treatment detects intra-cardiomyocyte edema at 6 weeks, which is earlier than T1 mapping, LV motion, and extracellular volume quantification (50). A study by Toro-Salazar et al. (51) determined that among 46 long-term childhood cancer survivors who received cumulative anthracycline dose $\geq$ 200 mg/m^2 and exhibited normal systolic function, post contrast T1 values were significantly lower than control patients (458 $\pm$ 69 vs. 487 $\pm$ 44 ms; $P = 0.01$) (51).

One CMR technique that assesses myocardial fibrosis using gadolinium contrast is LGE, and inversion recovery (IR) with magnitude reconstruction is the pulse sequence most widely used for LGE (52). Roughly 10 min after gadolinium contrast injection, it is evenly distributed, and fibrosis will show with high signal intensity due to the increase in stroma. Anthracycline use has been associated with LGE in some studies, yet the extent of this association is still being researched. For example, in an animal model of doxorubicin cardiotoxicity, greater LGE signal intensity in the myocardium was associated with future LV systolic dysfunction, vacuolization, and extracellular volume (53) (**Figure 6**). However, Modi et al. (54) determined that among 298 patients receiving anthracyclines or trastuzumab, 31 (10.4%) had LGE that ranged from 3.9 to 34.7% in extent, and

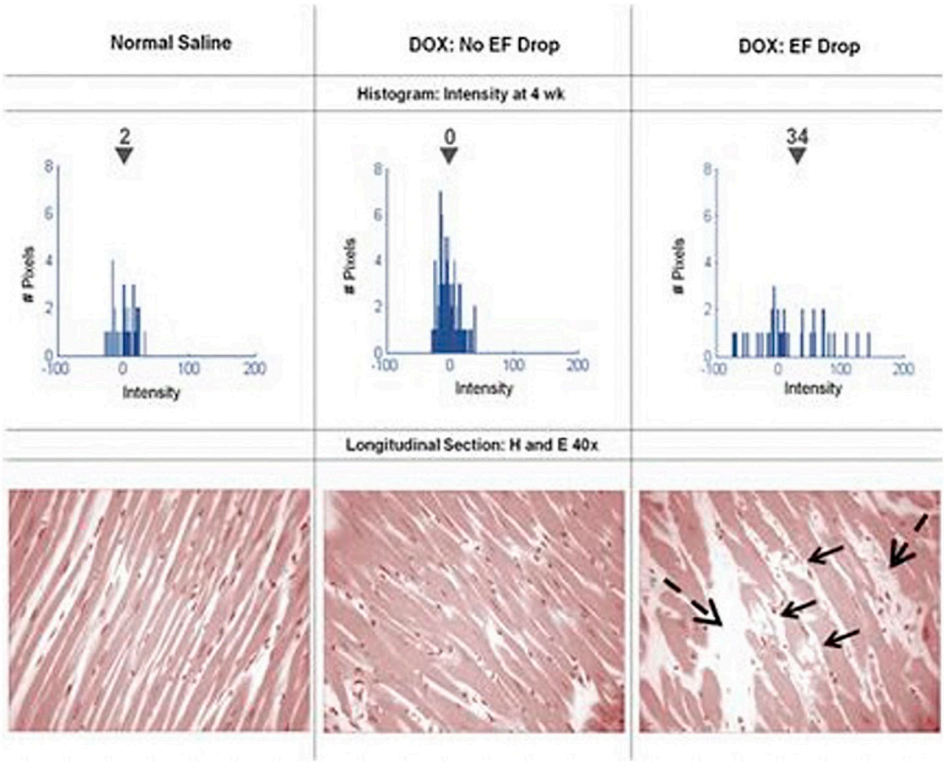

FIGURE 6
Serial histograms of myocardial LGE signal intensity (**top**, mean intensity shown above the *inverted black triangles*) and corresponding histopathology **(bottom)** of individual animals 4 weeks after receipt of normal saline **(left)**, doxorubicin without an LVEF drop **(middle)**, and doxorubicin with an LVEF drop **(right)**. Vacuolization (*arrows*) and increased extracellular space (*dashed arrows*) were observed in animals with doxorubicin cardiotoxicity. From Lightfoot et al. (53) with permission.

an ischemic pattern was present in 20 (64.5%) of the 31 patients, yet these were no different in age-matched control patients (54).

When T1-maps are collected both with and without contrast in a patient, the extracellular volume fraction (ECVF) can be calculated by first determining the partition coefficient from the slope of $1/T_{myocardium}$ vs. $1/T1_{blood}$, and then using the following formula: $ECVF = (1 - hematocrit)\frac{(\frac{1}{T1_{myo\ post}} - \frac{1}{T1_{myo\ pre}})}{(\frac{1}{T1_{blood\ post}} - \frac{1}{T1_{blood\ pre}})}$ (55). A blinded CMR analysis of T1 and ECVF was conducted among 327 individuals (37 breast cancer patients, 54 cancer survivors, and 236 cancer-free patients) by Jordan et al. (56). **Figure 7** (56) shows T1 images and ECVF measurements from a participant in each of the three study groups (no cancer, cancer pre-treatment, and cancer post-treatment). The researchers determined that T1 (56) (**Figure 8**) and ECVF (56) (**Figure 9**) remain elevated 3 years after anthracycline-based treatment, independent of cardiovascular comorbidities or underlying cancer, thus indicating that this T1 and ECVF elevation are related to receipt of anthracyclines.

CMR perfusion imaging can further characterize tissue (57). Perfusion defects can identify coronary artery disease (CAD), which shares many risk factors with cardiotoxicity (58, 59). Additionally, a retrospective study by Li et al. (60) determined that patients with cancer have higher risk of developing CAD when compared to non-cancer patients (OR: 2.024, 95% CI: 1.475–2.778, $p < 0.001$; 60). Perfusion imaging may also allow for assessment of myocardial perfusion reserve (MPR), which is the maximum increase in myocardial blood flow above baseline conditions, by quantifying myocardial blood flow at rest and during stress. Changes in MPR may elucidate the underlying pathophysiology of cardiomyopathies, such as coronary microvascular dysfunction and CAD, which increases risk of cardiotoxicity for patients undergoing potentially cardiotoxic chemotherapy.

Clinical decision-making

CMR accurately assesses LV function and structure, and this allows for physicians to use findings in clinical decision-making. Cardiotoxicity is defined as a decline in LVEF by > 10% to a value < 50% while undergoing cancer treatment (59). Probable subclinical cardiotoxicity is defined as an LVEF decline by > 10% to a value ≥ 50% with a fall in global longitudinal strain (GLS) > 15% while undergoing cancer treatment (61). Possible subclinical cardiotoxicity is defined

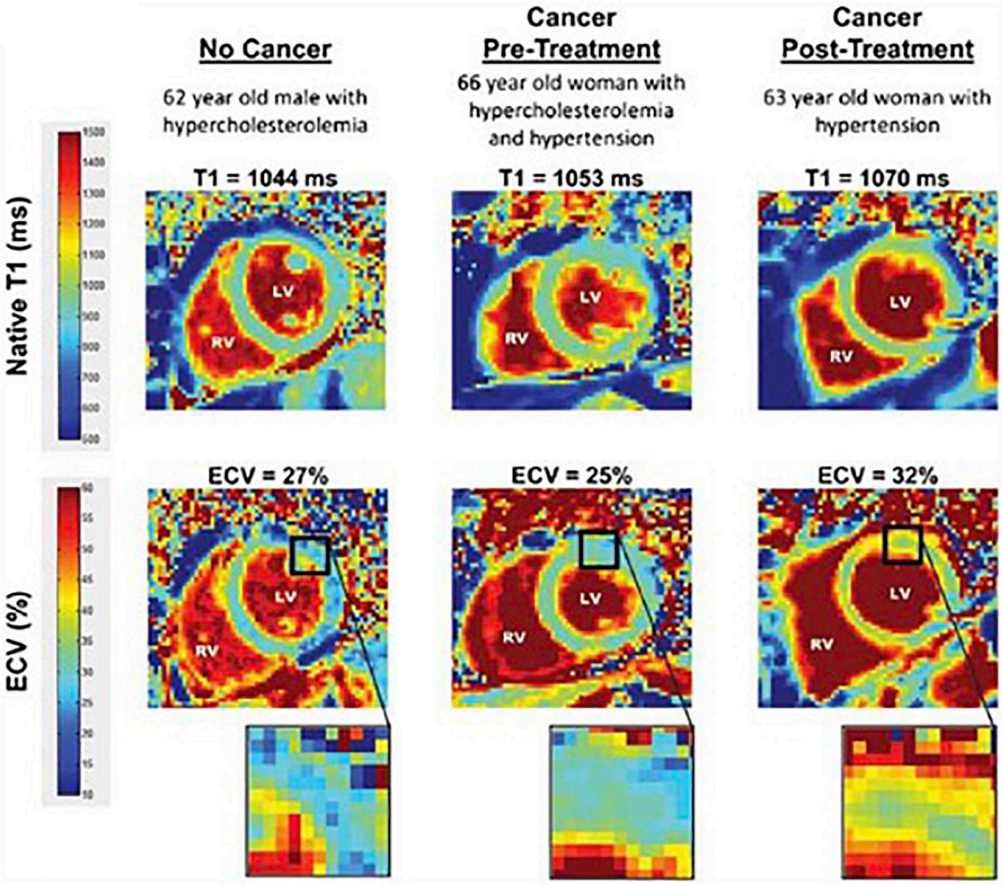

FIGURE 7
Comparison of T1 and ECV map images. Representative left ventricular (LV) short-axis native T1 (top row) and extracellular volume (ECV, bottom row) maps are shown in similarly aged participants. The LV and right ventricular (RV) blood pool cavities are noted. On each image, the color of pixels in the images (color scales on left) identifies the native T1 (milliseconds) and ECV (%). Insets on the ECV maps demonstrate the change in color intensity within the anterolateral wall of each ventricle. As shown, ECV is elevated in the cancer survivor previously treated with anthracycline-based chemotherapy. From Jordan et al. (56) with permission.

as an LVEF decline by < 10% to a value < 50% or a relative percentage reduction in GLS by > 15% from baseline while undergoing cancer treatment (61). If a patient falls into the cardiotoxicity, probably subclinical cardiotoxicity, or possible subclinical cardiotoxicity categories, as defined above, then a referral to cardio-oncology should be considered (61). However, if they do not fall into these categories, then treatment may continue as planned and surveillance imaging should be maintained (61). It's important to note that clinical suggestions may vary depending upon consensus statements. Generally, in clinical practice, echocardiography remains the first line myocardial imaging technique due to access and affordability.

Challenges

Although CMR is the gold standard for assessing myocardial function, challenges persist. CMR availability and portability are limited, which may contribute to less widespread use of CMR. A CMR scanner is 4–10 times the cost of a standard 3D echocardiography system (62). However, a retrospective study with 361 patients indicated that the use of CMR to assess myocardial function and structure saved roughly $2,308/patient due to avoidance of invasive procedures and further diagnostic testing (63). Additionally, CMR exams may take up to an hour longer than echocardiography exams. Thus, cost, accessibility, and time are all factors that may affect a patient's decision to proceed with CMR imaging.

Feasibility to perform CMR on all patients must also be considered. Specifically, some patients require anxiolytics for claustrophobia while undergoing CMR, which may lower their heart rate and blood pressure during the exam, and thus affect findings. Additionally, patients with certain implants may not undergo magnetic resonance imaging, as artifacts can affect imaging outcome.

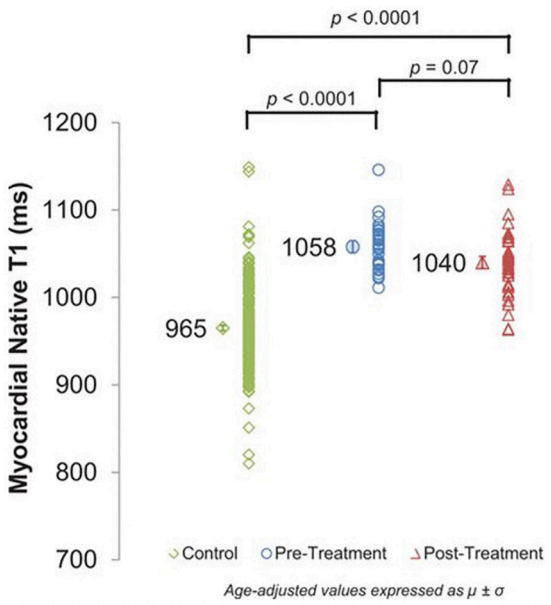

FIGURE 8
Cardiovascular magnetic resonance (CMR) assessments of myocardial T1. Myocardial native T1 of control participants without cancer (965 ± 3 ms) and cancer pretreatment participants (1,058 ± 7 ms) compared with cancer survivors treated with anthracycline chemotherapy (1,040 ± 7 ms). Myocardial T1 is elevated in both cancer groups, reflecting potential myocardial fibrosis compared with cancer-free control participants ($P < 0.0001$ for both). From Jordan et al. (56) with permission.

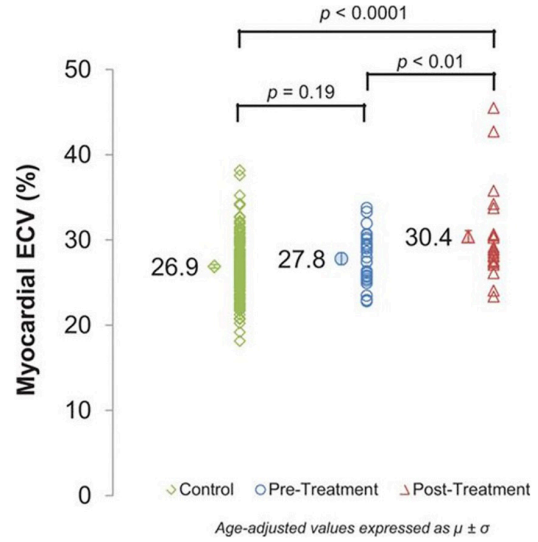

FIGURE 9
Cardiovascular magnetic resonance (CMR) assessments of myocardial extracellular volume (ECV). Myocardial ECV measured by cardiovascular magnetic resonance in controls (26.9 ± 0.2%) and cancer pretreatment participants (27.8 ± 0.7%) compared with cancer survivors treated with anthracycline chemotherapy (30.4 ± 0.7%). ECV incrementally increases across the groups ($P < 0.0001$) with a significant increase in post-treatment ECV values compared with pretreatment ECV values ($P < 0.01$). From Jordan et al. (56) with permission.

New frontiers and next avenue of research

As CMR continues to serve as a robust and reliable tool for monitoring a patient's progression through cardiotoxic treatment, as well as other myocardial injuries, the imaging modality continues to improve. Artificial intelligence (AI) and machine learning (ML) have become increasingly prominent in the field of CMR, improving the efficiency and accuracy of assessing cardiac function (64). A deep learning algorithm was developed to automatically segment right and left ventricular endocardium and epicardium to measure mass and function- a process that is often time-consuming and challenging to perfect (65–67). The algorithm was tested on various datasets, and it was found that measurements acquired by the algorithm were comparable to those of human experts in the field. Automating segmentation would save time and resources while assessing CMRs for cardiotoxic changes in cancer patients, and this would be especially useful in a clinical setting.

Moreover, the applications of CMR expand well beyond the field of cardio-oncology. Stress CMR images may be obtained to assess patients' heart function under myocardial stress, which provides prognostic insight. Specifically, a retrospective cohort study by Antiochos et al. (68) obtained vasodilator stress perfusion CMRs in 1,698 patients without a history of coronary artery disease (CAD) (68). Stress CMR perfusion imaging reclassified 60.3% of patients who were in the intermediate

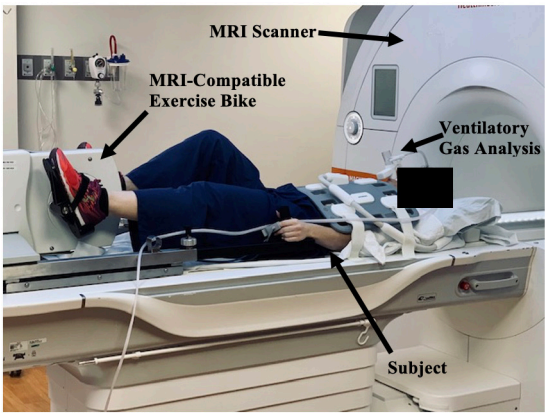

FIGURE 10
Study set-up with magnetic resonance imaging (MRI)-compatible exercise bike positioned in CMR imaging scanner. The subject, MRI scanner, MRI-compatible exercise bike, and ventilatory gas analysis are indicated by black arrows. The subject lies outside the MRI scanner and will pedal on an exercise bike as they move through the scanner. Ventilatory gas analysis is simultaneously performed while a cardiac MRI is obtained.

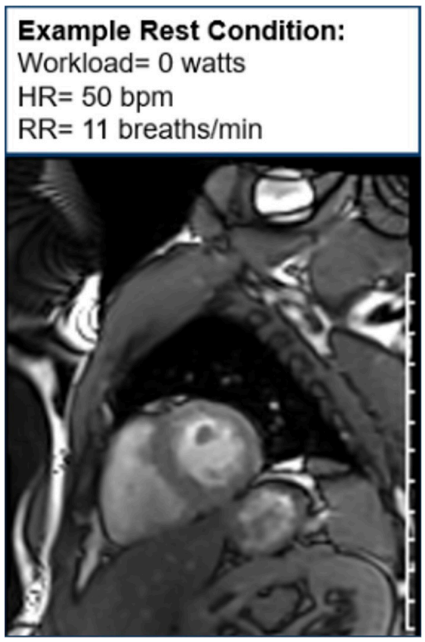

FIGURE 11
Cine image at rest. One image of a cine loop at the end short-axis view of the myocardium. The left ventricle is gray, while the blood pool is white. At rest, the workload is 0 w, and the patient's heart rate is 50 bpm and respiratory rate is 11 breaths/min.

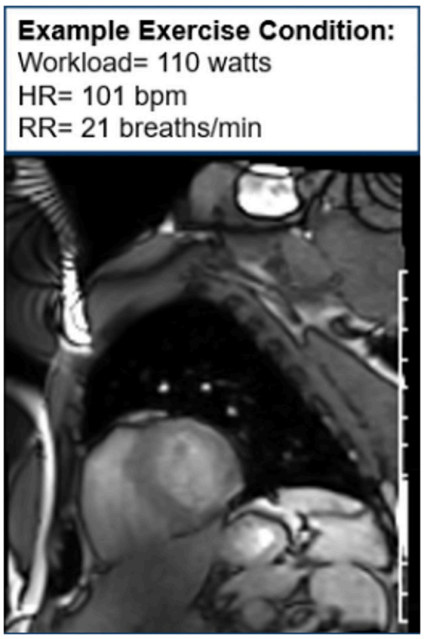

FIGURE 12
Cine image during exercise. One image of cine loop at the end short-axis view of the myocardium. The left ventricle is gray, while the blood pool is white. During exercise, the workload is 110 w, and the patient's heart rate is 101 bpm and respiratory rate is 21 breaths/min.

pretest risk category, thus indicating that stress CMR imaging provides valuable information beyond clinical factors in risk stratifying patients at intermediate risk for cardiovascular death and non-fatal myocardial infarction (69). Additionally, CMR stress perfusion imaging, which allows for quantification of myocardial blood flow at rest and during stress, may help with identifying early vascular changes following Anth-bC (57). Myocardial perfusion defects have been detected 6–24 months post-radiation therapy in 40% of cancer patients using nuclear SPECT imaging, which were found to be associated with corresponding wall-motion abnormalities (70). Furthermore, Sioka et al. (71) conducted a multiple regression analysis which showed more abnormalities in myocardial perfusion imaging of left breast cancer patients who underwent radiation therapy when compared to controls ($p = 0.0001$); (71). Thus, analysis of CMR stress perfusion imaging may help refine clinical practice of radiation therapy in cancer patients.

Moreover, CMR can be used to assess cardiac function during exercise testing (72) and has even been utilized in hematologic cancer survivors by placing an exercise bike in the magnetic resonance imaging (MRI) scanner (**Figure 10**). Cine images at rest and during exercise are depicted (**Figures 11**, **12**), as this technology allows for myocardial function to be compared at baseline and during exercise (73).

Another new application of CMR in oncology patients may be to evaluate microcirculatory damage, as one of the effects of cardiotoxic chemotherapy is microcirculatory damage

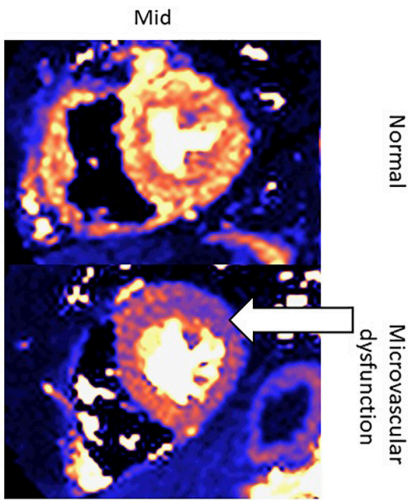

FIGURE 13
Quantitative perfusion CMR assessment of myocardial microcirculatory damage in a normal patient vs. cancer patient undergoing cardiotoxic chemotherapy. These are two left ventricular short-axis images of the mid-segment myocardium. The top row contains an image from a healthy patient, whereas the bottom row contains an image from a patient with microvascular dysfunction due to chemotherapy. The white arrow indicates the area of the left ventricle with the greatest microvascular dysfunction.

to the myocardium (74). Studies have shown that cardiotoxic chemotherapies lead to a decrease in nitric oxide-mediated dilation in endothelial cells, which is associated with increased

risk of various cardiovascular risk factors, such as heart failure and hypertension (75). One study assessing the direct effect of doxorubicin on human coronary microvascular function *ex vivo* found that among adult human coronary microvessels treated with doxorubicin, flow-mediated dilation (FMD) and coronary arteriolar function were significantly impaired (76). Moreover, CMR has been used to assess microcirculatory damage, as seen in **Figure 13** (76–79).

With the development of real-time (RT) CMR, advances are also being made in CMR efficiency. By allowing for high spatial and temporal resolution during free breathing and without ECG synchronization, RT CMR reduces the total exam time from 12 to 15 min for SSFP to evaluate LV function in under 2 min. Although there have not been many studies assessing the accuracy of SSFP vs. RT CMR among cancer patients, the RT CMR technique may be useful in improving efficient resource utilization.

Discussion and conclusion

As a non-invasive cardiac imaging technique, CMR assesses LV function, tissue characterization, and myocardial injury. LV function is accurately assessed through determination of LVEF, volumes at end-diastole (LVEDV), and end-systole (LVESV), strain, mass, and wall motion. Various techniques may be used for tissue characterization, some of which use gadolinium contrast (LGE and T1-mapping), and some of which are non-contrast methods (T1/T2 mapping). Significant clinical changes in LV function may correlate with cardiotoxicity, and CMR is especially useful in monitoring cardiac function throughout treatment with potentially cardiotoxic chemotherapy.

When compared to other modalities, CMR provides a variety of information while being non-ionizing, non-invasive, and accurate, thus making it advantageous for routine cardiac monitoring among oncology patients in a clinical setting. Additionally, CMR assesses LV volumes and can characterize tissue to assess myocardial fibrosis. Challenges persist, however, while using CMR in cancer patients, such as cost, efficiency, and accessibility. As new frontiers of research with CMR are constantly discovered, its applications and techniques continue to expand and improve, respectively.

Author contributions

LM drafted the initial manuscript. WH, WB, and JJ critically reviewed the manuscript. All authors approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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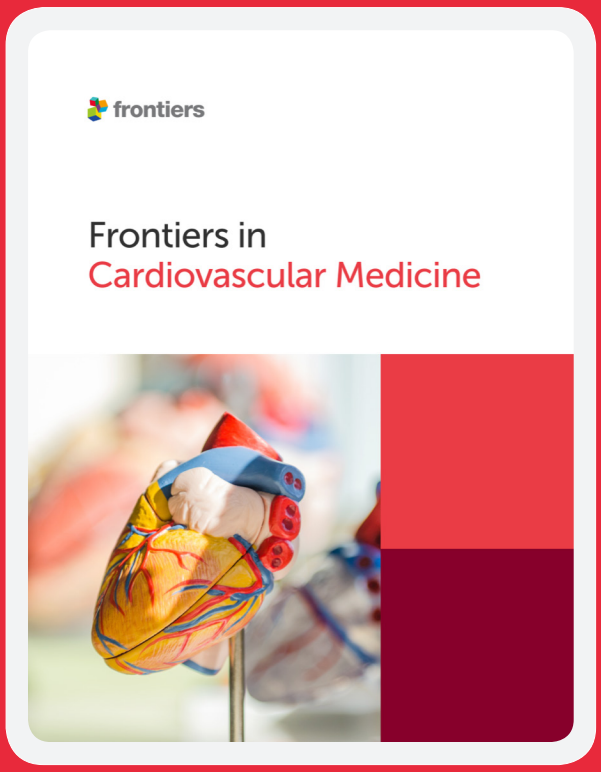

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