REVIEW

The utility of cardiac stress testing for detection of cardiovascular disease in breast cancer survivors: a systematic review

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Background: Heart function tests performed with myocardial stress, or "cardiac stress tests", may be beneficial for detection of cardiovascular disease. Women who have been diagnosed with breast cancer are more likely to develop cardiovascular diseases than the general population, in part due to the direct toxic effects of cancer treatment on the cardiovascular system. The aim of this review was to determine the utility of cardiac stress tests for the detection of cardiovascular disease after cardiotoxic breast cancer treatment.

Design: Systematic review.

Methods: Medline and Embase were searched for studies utilizing heart function tests in breast cancer survivors. Studies utilizing a cardiac stress test and a heart function test performed at rest were included to determine whether stress provided added benefit to identifying cardiac abnormalities that were undetected at rest within each study.

Results: Fourteen studies were identified. Overall, there was a benefit to utilizing stress tests over tests at rest in identifying evidence of cardiovascular disease in five studies, a possible benefit in five studies, and no benefit in four studies. The most common type of stress test was myocardial perfusion imaging, where reversible perfusion defects were detected under stress in individuals who had no defects at rest, in five of seven studies of long-term follow-up. Two studies demonstrated the benefit of stress echocardiography over resting echocardiography for detecting left ventricular dysfunction in anthracycline-treated breast cancer survivors. There was no benefit of stress cardiac magnetic resonance imaging in one study. Two studies showed a potential benefit of stress electrocardiography, whereas three others did not.

Conclusion: The use of cardiac stress with myocardial perfusion imaging and echocardiography may provide added benefit to tests performed at rest for detection of cardiovascular disease in breast cancer survivors, and merits further research.

Keywords: heart diseases, heart function tests, exercise test, breast neoplasms, review

Introduction

Adjuvant treatment for breast cancer, particularly some chemotherapy regimens and left-sided radiotherapy, are well-recognized to cause direct adverse effects on the cardiovascular system.[1] Thanks to progressively effective antineoplastic therapies, women diagnosed with breast cancer are increasingly living longer, which increases the age-related risk of cardiovascular disease, independent of breast cancer treatment.[2] An important determinant of the increased risk of cardiovascular disease with age in women is the occurrence of menopause;[3] chemotherapy for breast cancer will induce menopause in 21 to 100% of women, depending on age.[4] In light of this combination of risk factors, it is not surprising then that women who have been treated for breast cancer are more likely to die of cardiovascular disease than women who have not had breast cancer.[5,6]

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The cardiovascular toxicity of breast cancer treatment can occur as an early effect, within the first year of treatment, or as a late effect, occurring years to decades after treatment.[7,8] In both instances, individuals may often be asymptomatic before progression to overt disease.[9] Therefore, there is great interest in sensitive heart function tests for detection of occult cardiovascular disease, both during treatment and in long-term follow-up in this population. The utility of resting echocardiography, resting electrocardiography (ECG), resting nuclear imaging techniques, and serum cardiac biomarkers for early detection of cardiovascular disease in cancer survivors has been reviewed extensively.[10–14] Although these diagnostic techniques do appear to have some sensitivity for cancer treatment-induced cardiac abnormalities, cardiac stress tests could be an effective technique for uncovering occult cardiovascular disease related to breast cancer treatment, including coronary artery disease and left ventricular dysfunction.

The human body is a complex, adaptive system with incredible capacity for compensation. Compensatory patterns may maintain homeostasis at rest; however, the introduction of stress challenges the stability of the system, and occult dysfunction may be unmasked. For example, the myocardium may be adequately perfused at rest, despite sub-total occlusion of a major epicardial coronary artery.[15] However, with the heightened metabolic demands of an increased physical workload, and corresponding myocardial blood flow requirements, there is insufficient coronary reserve, resulting in diminished myocardial perfusion and ischemia.[15] Similarly, stress may also uncover systolic dysfunction that may not be apparent at rest. Cardiac stress testing or, more generally, heart function tests performed under myocardial stress, may reveal occult coronary artery disease or left ventricular dysfunction that is not apparent with heart function tests performed at rest, due to compensatory mechanisms. In addition to exercise, a number of pharmacological agents or, less commonly, a cold pressor test may be used to impose myocardial stress.

The purpose of this systematic review was to determine the utility of myocardial stress in combination with heart function tests, or "cardiac stress tests", in detection of evidence of cardiovascular disease among breast cancer survivors. To our knowledge, this is the first review to compare cardiac stress tests against tests performed at rest, for the identification of cardiovascular disease among a population treated for cancer.

Methods
Search strategy
The search strategy was formulated in consultation with a research librarian. Medline (1946 to present) and Embase (1947 to present) were searched up to 21 November 2013. The Ovid interface was used to search the Medline and Embase databases. The detailed search for Medline is provided in Table 1. The general search strategy involved (breast cancer) AND (keywords/MeSH [medical subject heading] terms related to cardiac imaging/heart function tests) AND (keywords/MeSH terms related to cardiotoxicity OR cardiotoxic cancer treatments OR related cardiac issues). The search strategy included search terms for all types of cardiac imaging techniques and heart function tests, with or without stress. The search was limited to human studies and English-language papers published in peer-reviewed journals. Experimental, observational, prospective, and retrospective study designs were included; reviews, editorials, letters to the editor, and comments were excluded. Other inclusion criteria involved: study participants diagnosed with any stage of breast cancer; any age range; at least ten study participants; and count data of heart function test results, or statistical analysis of results between a group who received cardiotoxic treatment and a group who did not.

No studies involving breast cancer survivors were identified that compared cardiac stress tests to the gold standard for diagnosis of cardiotoxicity, endomyocardial biopsy, likely because this technique is invasive and rarely performed. Therefore, in lieu of a reference standard, an alternative technique for assessing the utility of cardiac stress tests in breast cancer survivors was required. An inclusion criterion was added that studies must include a cardiac stress test and at least one heart function test performed at rest. The outcome of the cardiac stress test was compared to that of a test at rest to determine whether the use of stress identified evidence of occult cardiovascular disease that was not detected at rest.

The reference lists of all studies meeting inclusion criteria and related studies were hand searched for additional relevant publications. Studies with relevant titles but no abstract were included in full text review. Studies with abstracts that reported the use of two or more heart function tests, without enough information to determine whether they were used under resting conditions, were included in full text review. Upon full text review, the methods section of these articles was searched to determine the use of stress with at least one of the tests, in addition to at least one test performed at rest, for comparison. If the methods section did not describe the use of stress, it was assumed that all tests were performed at rest. Authors were not contacted to acquire additional information or data.

Data collection
The following data were extracted from each study: sample size; breast cancer treatments received by study participants;

Table I Ovid Medline search strategy

1	breast neoplasms/ or exp carcinoma, ductal, breast/
2	breast cancer.ti,ab.
3	1 or 2
4	exp cardiac imaging techniques/ or ultrasonography/ or echocardiography/ or echocardiography, doppler/ or exp echocardiography, stress/ or echocardiography, three-dimensional/ or ultrasonography, doppler/ or exp echocardiography, doppler/ or ultrasonography, doppler, duplex/ or ultrasonography, doppler, pulsed/ or diagnostic techniques, cardiovascular/ or heart function tests/ or cardiac output/ or cardiography, impedance/ or echocardiography, stress/ or electrocardiography/ or exercise test/ or heart auscultation/ or heart catheterization/ or magnetocardiography/ or myocardial perfusion imaging/ or oximetry/ or radionuclide ventriculography/ or plethysmography/ or biological assay/ or exp ergometry/ or exp exercise test/
5	cardiac evaluation.ti,ab.
6	card* follow-up.ti.
7	echocardio*.ti,ab.
8	exercise echocardiography.ti,ab.
9	exp dobutamine/du [diagnostic use]
10	dobutamine.ti,ab.
11	doppler.ti.
12	radionuclide.ti.
13	or/4-12
14	exp magnetic resonance imaging/
15	13 and 14
16	15 not (screening or mammogra*).ti.
17	13 or 16
18	exp anthracyclines/ae, po, to [adverse effects, poisoning, toxicity]
19	(anthracyclines or anthracycline antibiotics or doxorubicin or adriamycin or epirubicin or idarubicin or daunorubicin or rubidomycin or daunoxome or myocet or caelyx or doxil).ti,ab.
20	fluorouracil.ti,ab.
21	cyclophosphamide.ti,ab.
22	(herceptin or trastuzumab).ti,ab.
23	exp antineoplastic protocols/ or exp chemotherapy, adjuvant/ or exp radiotherapy, adjuvant/ or exp molecular targeted therapy/
24	chemotherapy-induced.ti,ab.
25	exp radiotherapy, adjuvant/ae [adverse effects]
26	radiation.ti,ab.
27	radiation-induced.ti,ab.
28	cancer treatment.ti.
29	cancer therapy.ti.
30	exp antibodies, monoclonal/ae, po, to [adverse effects, poisoning, toxicity]
31	or/18-30
32	exp drug toxicity/
33	toxicity tests/ or acute toxicity tests/ or cytotoxicity tests, immunologic/ or toxicity tests, chronic/
34	heart diseases/ or arrhythmias, cardiac/ or cardiac output, high/ or cardiac output, low/ or arrhythmogenic right ventricular dysplasia/ or cardiomyopathy, dilated/ or cardiomyopathy, hypertrophic/ or cardiomyopathy, restrictive/ or endomyocardial fibrosis/ or myocarditis/ or heart failure/ or exp myocardial ischemia/ or acute coronary syndrome/ or angina pectoris/ or coronary disease/ or myocardial infarction/ or pericarditis, constrictive/ or exp ventricular dysfunction/
35	heart/de, re, to
36	cardiac dysfunction.ti,ab.
37	cardiomyopath*.ti,ab.
38	cardiotoxic*.ti,ab.
39	cardiac toxic*.ti,ab.
40	heart damage.ti,ab.
41	heart failure/ci
42	cardiovascular injury.ti,ab.
43	(cardiac adj3 injury).ti,ab.
44	or/32-43
45	31 or 44
46	3 and 17 and 45
47	46 not (animal/ not human/)
48	48 limit 47 to english language

Abbreviations: ab, abstract; ae, adverse events; de, drug effects; du, diagnostic use; exp, explode; po, poisoning; re, radiation effects; ti, title; to, toxicity; *, truncation that expands a search term to include all forms of a root word.

dosage and timing of delivery of treatment; timing of heart function tests with respect to treatment receipt; type of each test used with stress; type of stress used; type of each test used at rest; parameters of each test measured; and results for each parameter.

Determination of utility of cardiac stress tests in detection of cardiovascular disease

The findings of the cardiac stress tests were compared to the tests at rest to determine the utility of the stress test within each individual study. Studies were labeled as "no benefit", "possible benefit", or "benefit", based on whether the cardiac stress tests identified evidence of cardiovascular disease in the study participants that was not identified by the heart function tests performed at rest in that study. Where applicable, the reported thresholds for determining cardiovascular dysfunction (eg, LVEF [left ventricular ejection fraction] lower limits of normal) from each individual paper were used. In other cases, the identification of abnormalities was taken as evidence of occult cardiovascular disease (eg, identification of perfusion defects with myocardial perfusion imaging). The study was labeled "no benefit" if: 1) the cardiac stress test did not identify additional study participants with evidence of cardiovascular disease who were not identified with tests at rest, or 2) the cardiac stress tests and the tests at rest were either both statistically different or both not different between treated and non-treated groups. The study was labeled "benefit" if: 1) the cardiac stress test identified study participants with evidence of cardiovascular disease who were not identified by the techniques at rest, or 2) there was a statistically significant difference in cardiac function for the cardiac stress tests, but not for the tests performed at rest. The label "possible benefit" was assigned to studies where the cardiac stress test identified evidence of cardiovascular disease, but it could not be determined from the reported data whether the cases identified with tests performed at rest occurred in the same study participants as the cases identified with stress tests.

Results

The process for selection of papers for this review is outlined in Figure 1. Fourteen studies[16–29] met the inclusion criteria for the review and are summarized in Table 2.

Utility of cardiac stress tests

Overall, five studies[16,22,23,25,26] showed a benefit, five[18,19,24,27,28] showed possible benefit, and four[17,20,21,29] showed no benefit

to utilizing cardiac stress tests in identifying evidence of cardiovascular disease in breast cancer survivors.

Cardiac stress test types

Heart function tests that were performed with stress in the selected studies were scintigraphy (n=5),[17,19,20,28,29] single photon emission computed tomography (SPECT) (n=4),[18,22,24,25] echocardiography (n=2),[16,23] cardiac magnetic resonance imaging (cMRI) (n=1),[21] nuclear ventriculography (n=1),[26] and ECG (n=5).[17,19,20,22,27] The utility of stress among each technique is shown in Figure 2A.

Stress myocardial perfusion imaging techniques (ie, scintigraphy or SPECT) were the most commonly used type of cardiac stress test, used in nine studies. The timing and treatment type distributions (ie, chemotherapy, radiotherapy, or trastuzumab) of the effects are shown in Figure 2B. The most common use of myocardial perfusion imaging was for long-term follow-up to radiotherapy, in seven studies, showing a benefit[22,25] or possible benefit[18,19,24] in five of these. Stress echocardiography was used in two studies that both demonstrated a benefit in detecting anthracycline-induced left ventricular dysfunction.[16,23] The timing of imaging in one study was before, during, and after (ie, before each cycle, then 2, 4, 7, and 12–18 months after) chemotherapy,[16] while, in the other study, imaging was a one-time assessment in long-term follow-up to chemotherapy treatment (mean follow-up of 34 months).[23] Stress ECG was utilized in five studies: one demonstrated a benefit,[22] although the benefit in this study was attributed to stress SPECT, not ECG; two demonstrated possible benefit,[19,27] and two no benefit.[17,20] Stress ventriculography was used in one study and demonstrated a benefit, compared to testing performed at rest;[26] while stress cMRI was also used in one study and failed to show a benefit, relative to resting imaging.[21]

Breast cancer treatments

The adjuvant breast cancer treatments included in the studies were chemotherapy, radiotherapy, and a targeted, humanized, monoclonal antibody (trastuzumab). The overall utility of cardiac stress tests among the different treatment types is displayed in Figure 2C. Cardiac stress tests appear to be most beneficial for detecting cardiovascular disease following chemotherapy, or chemotherapy and radiotherapy combined treatment.

Method of inducing myocardial stress

Exercise was used to induce stress in eight studies,[17–20,23,25,27,29] pharmacological agents were used in five studies[16,21,22,24,25]
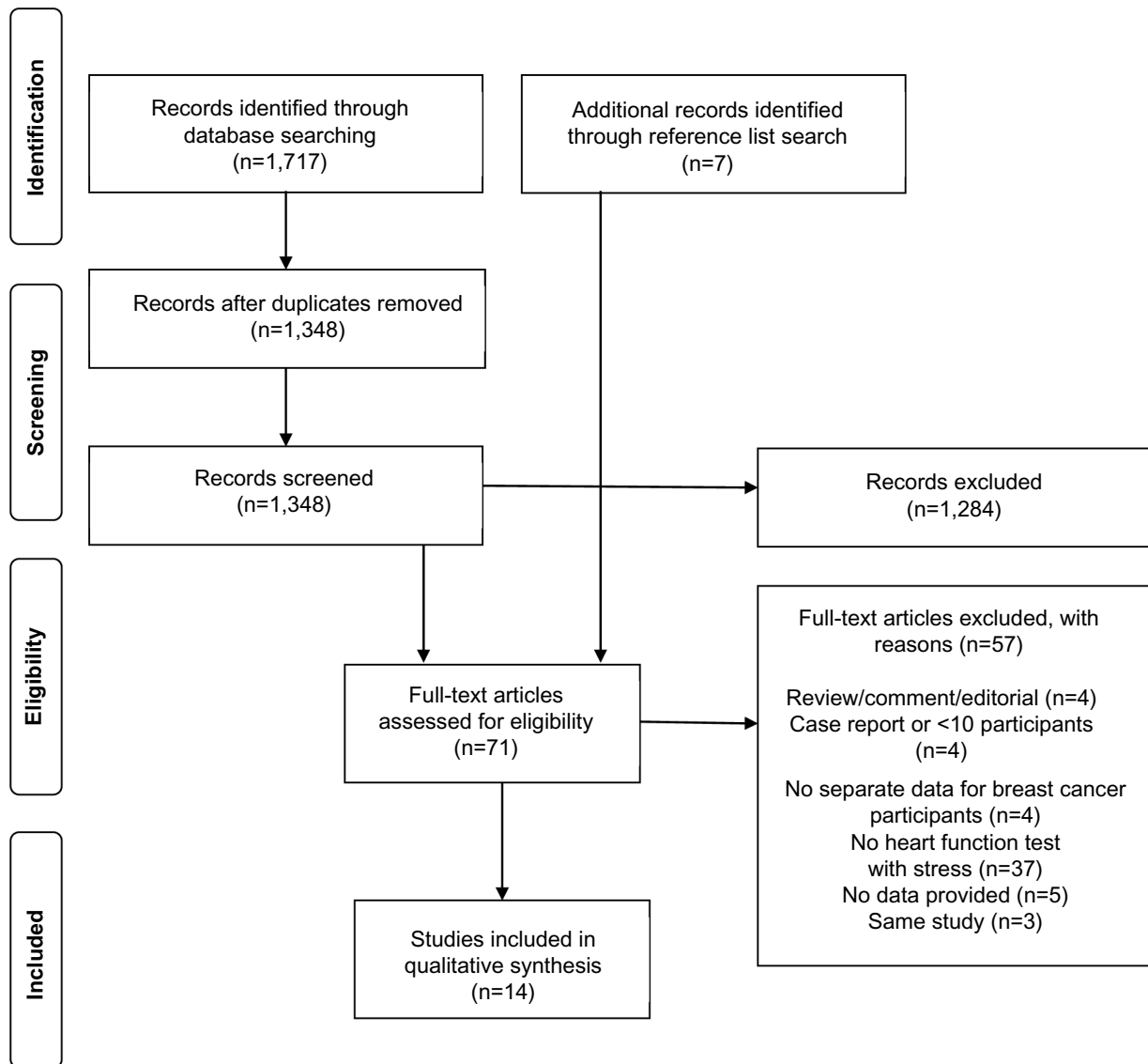
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

and the cold pressor test in one study.[26] The utility of the use of exercise, pharmacological agents, or the cold pressor test to induce myocardial stress within the studies is displayed in Figure 2D. Exercise and pharmacological agents demonstrated a benefit or possible benefit in 63% and 80% of the studies they were used in to induce stress, respectively. The one study to use the cold-pressor test to induce stress demonstrated a benefit. No adverse reactions to stress were reported.

Discussion

This review demonstrated that cardiac stress testing may be beneficial in detecting evidence of cardiovascular disease in breast cancer survivors that was missed by heart function tests performed at rest. The primary findings of this review are that, in general, cardiac stress tests appear to be most beneficial in chemotherapy-treated populations (with or without radiotherapy), while, specifically, stress myocardial perfusion imaging appears to be beneficial for long-term follow-up to radiotherapy, and stress echocardiography appears to be beneficial in detecting left ventricular dysfunction following anthracycline treatment.

With an approximate 5-year survival rate of 80% or greater for all stages of breast cancer combined in North America and Europe,[30–32] cancer is beginning to be considered a manageable disease.[33] Short and long-term cardiac effects

Table 2 Summary of articles using cardiac stress testing in breast cancer survivors

Study	N[a]	Treatments	Timing relative to treatment	Stress technique	Stress parameters	Stress findings	Rest technique	Rest parameters	Rest findings	Utility of stress
Cassidy et al 1998[26]	12	Vincristine (4.2 mg/m²) and mitozantrone (77 mg/m²)	2–7 months post	Cold pressor ventriculography	LVEF	9 LVEF$_{stress}$ < LVEF$_{rest}$ by >5%	Ventriculography	LVEF	↓ LVEF <40%	Benefit: stress scintigraphy identified abnormal LVEF response in 9 with normal resting LVEF.
Civelli et al 2006[16]	8	Docetaxel (85 mg/m²), epirubicin (200 mg/m²) and cyclophosphamide (4 g/m²), 3×, 4 weeks apart	Before each cycle, 2, 4, 7, and 12–18 months post	Dobutamine echo	Peak LVEF, LVCR, regional ventricular contractility	↓ peak LVEF and LVCR before 3rd CT cycle, 1, 4, 7 months post-CT in group A[b]	Echo	LVEF, LVEDV, LVESV, LVEDD, LVESD, PWTd, PWTs, IVSd, IVSs, peak E, peak A, E/A ratio, DT, IVRT, regional ventricular contractility	↑ LVEDV in group A[b] at 4, 7 and 12–18 months; no difference in LVEF until final follow-up; ↓ E wave and E/A in both groups	Benefit: stress echo identified ↓ peak LVEF and LVCR as early as 3rd CT cycle in those who had abnormal LVEF at 12–18 months post-CT (group A[b]), whereas resting LVEF did not change significantly.
Cowen et al 1998[17]	17	L-Radiation (50–60 Gy, 2 Gy/day)	Mean follow-up of 57.8 months	Exercise scintigraphy; Exercise ECG	Perfusion defects; Abnormalities	None; ↑ ST-segment depression considered false-positive	Post-stress scintigraphy; ECG	Perfusion defects; Abnormalities	None; None	No benefit: no abnormalities identified by stress scintigraphy or ECG.
Galluci et al 2010[18]	30	Anthracyclines (360–540 mg/m²) and L-radiation (50–60 Gy, 2 Gy/day), trastuzumab (2), hormonal (11)	Median follow-up of 33.8 months	Exercise gated SPECT	Perfusion defects, LVEF	7 RPD	Post-stress gated SPECT; Echo; ECG	Perfusion defects; LVEF, diastolic or valvular dysfunction, septal hypertrophy; Abnormalities	↓ IPD; 2 LVEF ≤50%, 29 diastolic dysfunction, 1 mitral stenosis, 3 septal hypertrophy; 1 atrial fibrillation; 1 ST elevation; 1 pathologic Q-wave; numerous negative T-waves;	Possible benefit: 7 perfusion defects identified by stress SPECT that were not identified by SPECT at rest, but resting echo and ECG identified several abnormalities as well and overlap is not known.

Study	N	Treatment	Follow-up	Stress test	Stress test variables	Stress test results	Resting test variables	Resting test modality	Resting test results	Conclusion
Gustavsson et al 1999[29]	34	L-radiation (38–45 Gy, 1.9–2.25 Gy/day) (34); controls: R-radiation (33) and cyclophosphamide only (23)	Median follow-up of 13 years	Exercise scintigraphy	Perfusion defects	None	Perfusion defects / FS, LV mass, LV and LA dimensions, E/A ratio, DT, valvular dysfunction, pericardial effusion	Scintigraphy Echo	L-radiation: 4 IPD; R-radiation: 2 IPD; L-radiation: 1 abnormal relaxation & 1 abnormal restrictive filling; R-radiation: 2 abnormal relaxation; CT only: 1 abnormal relaxation & 1 abnormal restrictive filling; L-radiation: 11 abnormalities; R-radiation: 6 abnormalities; CT only: 1 abnormality	No benefit: stress scintigraphy did not identify any perfusion defects, but resting scintigraphy, echo and ECG identified several abnormalities.
							Abnormalities	ECG		
Gyenes et al 1994[19]	20	L-radiation (45 Gy, 1.8 Gy/day)	Mean follow-up of 18.4 years	Exercise scintigraphy / Exercise ECG	Perfusion defects / ST segment depression and other abnormalities	3 RPD / 7 ST segment depression, 3 other abnormalities	Perfusion defects / Cardiac dimensions, LVEF, IVRT, DT, E/A ratio, valvular dysfunction, pericardial effusion	Scintigraphy / Echo	2 IPD or MPD / 1 LVEF <50% and enlarged LV and LA diameters; 6 LV hypertrophy; 7 abnormal diastolic relaxation;[c] 2 abnormal diastolic filling;[d] 3 significant valvular dysfunction;[e] 1 pericardial effusion	Possible benefit: 3 perfusion defects identified by stress scintigraphy not identified by scintigraphy at rest; 10 abnormalities identified by stress ECG, but resting echo identified numerous abnormalities as well and overlap is not known.

(Continued)

Table 2 (*Continued*)

Study	Nᵃ	Treatments	Timing relative to treatment	Stress technique	Stress parameters	Stress findings	Rest technique	Rest parameters	Rest findings	Utility of stress
Gyenes et al 1997[20]	12	L-radiation (46–50 Gy, 2 Gy/day); previous CT	Pre, post 1 year	Exercise scintigraphy	Perfusion defects	None	Scintigraphy	Perfusion defects	6 IPD	No benefit: all perfusion defects were identified by scintigraphy.
				Exercise ECG	Changes	None	Echo	LVEF, presence of LV hypertrophy, valvular disease or pericardial effusion	None	
Haykowsky et al 2009[21]	17	Trastuzumab (6–8 mg/kg every 3 weeks) and mixed CT	Pre, 4 months later	Dobutamine cardiac MRI	LV volumes, mass, LVEF	↑ peak LVEDV and LVESV, ↓ peak LVEF	Cardiac MRI	LV volumes, mass, LVEF	↑ LV mass, ↑ LVEDV and LVESV, ↓ LVEF	No benefit: identical changes for stress and rest cardiac MRI.
Højris et al 2000[22]	16	L-radiation (50 Gy, 2 Gy/day) and CMF (600/40/600 mg/m²) (9); CMF alone (7)	Median follow-up of 7.9 years	Dipyridamole SPECT	Perfusion defects	L-radiation and CMF: 2 RPD CMF alone: 1 RPD	SPECT	Perfusion defects	L-radiation and CMF: 1 IPD, 1 MPD; CMF alone: 2 IPD, 1 MPD	Benefit: L-radiation and CMF: stress SPECT identified 2 cases of perfusion defects not identified at rest; CMF alone: stress SPECT and ECG identified the same 1 case that was not identified at rest.
				Dipyridamole ECG	ST depression and pathologic Q waves	L-radiation and CMF: 1 ST depression CMF alone: 2 ST segment depression	ECG	ST depression and pathologic Q waves	L-radiation and CMF: 1 Q-wave; 1 partial right bundle block; CMF alone: 2 Q-waves, 1 ST depression	
Khouri et al 2011[23]	38	Doxorubicin (dosage NR) (38); healthy controls (11)	Mean follow-up of 35 months	Exercise echo	SV, LVEF, GLS, exercise-rest % change in GLS	↓ LVEF, ↑ GLS, ↓ exercise-rest percentage change in GLS than controls	Resting echo	SV, LVEF, GLS, GRS	No differences	Benefit: stress echo identified a statistical difference in LVEF and GLS in survivors compared to healthy controls, whereas no differences were identified at rest.
Kirthi et al 2011[28]	12	Trastuzumab (all), anthracyclines (6), taxanes (3) – dosages NR	Post (timing NR)	Stress (type NR) scintigraphy	Perfusion defects	2 RPD	Scintigraphy	Perfusion defects	1 IPD	Possible benefit: stress scintigraphy identified 2 perfusion defects, but with unknown overlap with defects and abnormalities identified by resting scintigraphy or MRI.
							Cardiac MRI	LVEF, LGE, STIR	4↓ LVEF by 10%	

Study	N	Radiation/Population	Follow-up	Stress test	Outcomes measured	Findings	Values	Second test	Outcomes	Findings	Conclusion
Lindahl et al 1983[27]	157	Radiation (L- or R- 42 Gy)	Pre, 6 months post	Exercise ECG	Numerous abnormalities	At 6 months post, +4 ectopic beats, +1 Q-wave, +3 ST depression, +30 T-wave items than baseline		ECG	Numerous abnormalities	At 6 months post, +2 ectopic beats, +7 arrhythmias, +1 AV conduction, +39 T-wave items than baseline	Possible benefit: exercise ECG identified more cases of ST depression, ectopic beats and Q-waves, while resting ECG identified more arrhythmias, AV conduction and T-wave items, but with unknown overlap between cases.
Seddon et al 2002[24]	24	L-radiation (50 Gy, 2 Gy/day) (24); controls: R-radiation (12); prior CT	Follow-up ≥5 years	Adenosine SPECT combined with submaximal exercise	SSS, SRDS, perfusion defects	↓ SSS than controls; 7 RPD		Gated SPECT; ECG	SRS, perfusion defects, LVEF, regional wall motion abnormalities; Abnormalities	↓ SRS than controls; 10 IPD or MPD; 8 wall motion abnormalities; 3 abnormalities	Possible benefit: 7 perfusion defects identified by stress SPECT not identified by SPECT at rest, but gated SPECT at rest identified 8 cases of regional wall abnormalities and 3 with ECG abnormalities with unknown overlap.
Sioka et al 2011[25]	28	L-radiation (60 Gy, 2 Gy/day) (28); controls: R-radiation (18); prior CT in 29; healthy controls (85)	Mean follow-up of 40 months	Exercise, dipyridamole or dobutamine SPECT	SSS, ASSS myocardial ischemia grading (based on SSS), S-RSS	↑ SSS compared to healthy controls but not R-radiation controls; 12 (43%) mild and 3 (11%) moderate myocardial ischemia, whereas 6 (33%) R-radiation controls had mild and 2 (11%) had moderate myocardial ischemia, and 28 (33%) healthy controls had mild myocardial ischemia		Rest SPECT	SRS	No differences between groups	Benefit: exercise, dipyridamole, or dobutamine T-SPECT differentiated between L-radiation and healthy controls, whereas rest T-SPECT did not.

Notes: [a]N reflects number of study participants evaluable with stress imaging technique, rather than total in study, and does not include controls; [b]group A (n=8): study participants whose 12–18-month post-CT resting LVEF decreased to <50% and ≥10% drop from baseline; group B (n=39): study participants with follow-up rest LVEF ≥50%; [c]abnormal relaxation defined as two out of three of: E/A ratio ≤0.9, DT >230 m/s, IVRT ≥100 m/s; [d]abnormal filling defined as two out of three of: E/A ratio >1.30, DT <190 m/s, IVRT <80 m/s; [e]significant valvular dysfunction defined as: the regurgitation extended up to the most proximal area of the atrium or the distal third of the LV; [f]grading of myocardial ischemia: mild: SSS of 4–8, moderate: SSS of 9–13, severe: SSS >13.

Abbreviations: echo, echocardiography; LVEF, left ventricular ejection fraction; LVCR, left ventricular contractile reserve; peak LVEF – resting LVEF, calculated as peak LVEF – resting LVEF; CT, chemotherapy; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; pre, before treatment; post, after treatment; PWTd, posterior wall thickness in diastole; PWTs, posterior wall thickness in systole; IVSd, intraventricular septum at diastole; IVSs, intraventricular septum at systole; E, early (passive) diastolic filling velocity; A, late (active) diastolic filling velocity; DT, mitral deceleration time; IVRT, isovolumetric relaxation time; L-radiation, radiation to left breast; Gy, gray, unit of absorbed radiation; SPECT, single-photon emission computed tomography; ECG, electrocardiography; RPD, reversible perfusion defect; R-radiation, radiation to right breast; MPD, mixed perfusion defect; LV, left ventricle; MRI, magnetic resonance imaging; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; STIR, short T1 inversion recovery sequence; TID, transient ischemic dilatation index (ventricular dilatation at exercise); SRDS, summed redistribution score; T-SPECT, translatory single-photon emission computed tomography; SRS, summed rest score; SSS, summed stress score; S-RSS, difference between summed stress score and summed rest score; NR, not reported; SV, stroke volume; ASSS, anterior wall summed stress score; AV, atrioventricular; LA, left atrium; FS, fractional shortening.
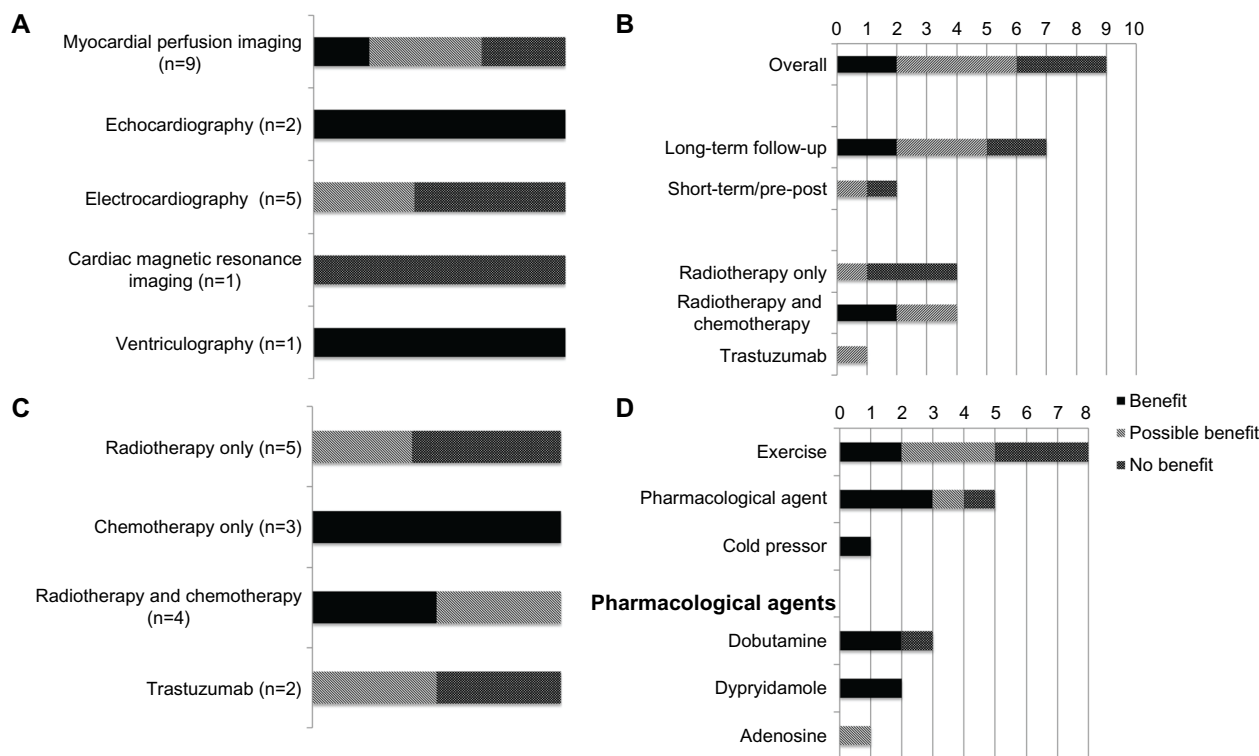
Figure 2 Distribution of utility (ie, "benefit", "possible benefit", or "no benefit") of stress.
Notes: (**A**) Distribution of utility among different techniques. (**B**) Timing of imaging and types of treatment among studies utilizing myocardial perfusion imaging techniques. (**C**) Distribution of utility among different breast cancer treatments. (**D**) Utility of type of stress. Note that one study used exercise, dobutamine, or dipryidamole, and is counted in each category.[25]

of cancer treatment are significant determinants of all-cause mortality rates for cancer survivors.[9] As such, identification of the optimal screening strategies for cardiovascular effects of cancer therapies is a high priority.[9]

Heart function tests, in combination with exercise or pharmacological stress, are commonly used for diagnostic and prognostic cardiac care,[34,35] and have been used to a limited extent for long-term follow-up in childhood cancer survivors treated with chemotherapy.[36–43] In this review, two studies[16,23] demonstrated the benefit of parameters of global systolic function measured via stress echocardiography in identifying left ventricular dysfunction in breast cancer survivors who have received a cardiotoxic systemic treatment. Khouri et al[23] demonstrated that the change in global longitudinal strain from rest to peak exercise was significantly different between anthracycline-treated breast cancer survivors and healthy controls. In addition to long-term cardiac effects, anthracyclines are also associated with acute or early cardiac effects, defined as occurring between treatment initiation and 1 year later.[8] Early identification of left ventricular dysfunction is critical, as it allows for earlier intervention in the form of dose reduction or initiation of therapeutic measures. Civelli et al[16] monitored patients for early cardiotoxicity

during ongoing anthracycline chemotherapy treatment, and demonstrated the ability of dobutamine echocardiography to identify subclinical left ventricular dysfunction with a reduction in left ventricular contractile reserve (LVCR) (stress–rest LVEF) before the third chemotherapy cycle. This study also demonstrated the predictive value of LVCR for traditional diagnostic parameters of cardiotoxicity (resting LVEF decrease to <50% and ≥10% drop from baseline) at 12–18 months post-chemotherapy.

Radiation to the breast can cause ultrastructural damage to myocardial capillaries and valves, atherosclerosis in coronary arteries, valvular abnormalities, and myocardial fibrosis leading to diastolic and systolic dysfunction, pericardial inflammation, or effusion.[44–47] There is a 1.27 excess rate ratio of heart disease in women treated with radiation for breast cancer relative to those who were not.[48] Mortality from coronary artery disease and risk of cardiovascular disease has decreased for breast cancer survivors diagnosed after 1980,[6,49] although more follow-up data is need to determine long-term risk associated with more modern treatment techniques. The cardiac injury associated with radiotherapy for breast cancer is typically a "late effect", occurring years to decades after treatment.[7] Long-term cardiac follow-up is

suggested for breast cancer survivors who receive radiotherapy.[50] In this review, myocardial perfusion imaging was used in several studies of long-term follow-up to radiotherapy. To perform this type of imaging, a radioactive tracer substance is injected, and its accumulation in the myocardium, as detected by a gamma camera, is considered proportional to the myocardial blood flow.[15] A perfusion defect can be identified on the image produced as an area of decreased perfusion or injured heart tissue resulting from a diseased coronary artery. A perfusion defect that is detected at rest and does not change during stress imaging is considered fixed or irreversible, and suggests non-viable myocardium; while a perfusion defect that is absent at rest but detected during stress is considered reversible, and indicates ischemic myocardium.[51] Five studies[18,19,22,24,28] in this review identified reversible defects with stress tests that would not have been discovered with tests performed at rest alone in breast cancer survivors treated with left-sided radiotherapy and other systemic treatments. This suggests that stress myocardial perfusion imaging could be an effective method of long-term follow-up for detection of coronary artery disease in radiation-treated breast cancer survivors. Gyenes et al[20] reported several fixed perfusion defects, but no reversible defects at 1 year post-radiotherapy. An incidence of fixed perfusion defects of 60% has been reported 6 months following radiotherapy for left-sided breast cancer.[52] It may be that the utility of stress myocardial perfusion imaging for screening purposes is limited to long-term follow-up only.

It is unclear from this review whether stress ECG is beneficial for identifying cardiovascular disease in breast cancer survivors. Two studies demonstrated possible benefit. In one of these,[27] ECG was used under stress and at rest, and stress did appear to better detect specific abnormalities, namely ectopic beats and, not surprisingly, minor ST depressions that developed 6 months after radiotherapy to the sternum. However, numerous arrthymias and more T-wave items were detected only at rest and there was unknown overlap between abnormalities detected under each condition. A similar case of unknown overlap between abnormalities detected with stress ECG and resting echocardiography occurred in the other study of long-term follow-up.[19] The lack of ability to detect occult cardiovascular disease may be attributed to the temporally late occurrence of electrocardiographic changes in the cascade of occurrences in the development of ischemia.[53]

Baseline and periodic monitoring of cardiac function is recommended in individuals treated with trastuzumab.[50] Haykowsky et al[21] used cMRI, at rest and with dobutamine stress, at baseline and 4 months into trastuzumab treatment.

This study did not demonstrate the utility of cardiac stress, as the cMRI findings were the same at rest and with stress. However, left ventricular contractile reserve was not reported, which is a more sensitive measure of early left ventricular dysfunction, as evidenced by Civelli et al.[16] Kirthi et al[28] used scintigraphy at rest and with stress, in addition to resting cMRI, following trastuzumab treatment. One additional case of cardiovascular dysfunction was identified with stress scintigraphy, compared against scintigraphy at rest, demonstrating a benefit for this technique alone; however, cMRI at rest also identified four cases of cardiovascular dysfunction.[28]

Myocardial stress can be induced by exercise, a number of pharmacological agents, or a cold pressor test. Pharmacological-induced stress minimizes factors such as movement artifact that may degrade cardiac imaging quality and decrease accuracy, but incurs the additional cost of the pharmacological agent.[53] The cold pressor test would likely carry similar advantages, but does not incur additional costs. However, the clinical significance of a cold pressor-induced change in cardiovascular function is unclear. Dynamic exercise tends to be the preferred method to induce myocardial stress, because it is less expensive, perceived to be safer, and the equipment (ie, cycle ergometer or treadmill) is widely available in clinical settings.[54] Exercise stress also provides additional ancillary prognostic, diagnostic, and therapeutic information, such as peak oxygen consumption, heart rate, and blood pressure response, and variables required for exercise prescription. However, the inability to reach maximal exercise capacity will limit the sensitivity of stress tests, in which case pharmacological stress is a suitable alternative.[54]

There is additional cost involved in cardiac stress tests with either exercise or pharmacological stress. For example, stress echocardiography is approximately double the cost of resting echocardiography,[55] but is reported to potentially enhance overall cost-effectiveness for diagnosis and management of suspected cardiovascular disease.[56] Stress myocardial perfusion imaging is often performed in addition to imaging at rest; however, the use of stress myocardial perfusion imaging alone would decrease the cost, radiation exposure, and time of testing, and is not associated with differences in prognosis or mortality outcomes.[57]

In ten of the 14 studies in this review, evidence of cardiovascular disease was missed by heart function tests performed at rest, but detectable with cardiac stress tests. This information is relevant to those involved in the treatment and care of breast cancer survivors, including family physicians, medical and radiation oncologists, and cardiologists.

Lack of change in the most common oncological clinical parameter of cardiac function, resting LVEF, is often equated to a lack of cardiotoxicity, despite convincing evidence in the literature that substantial myocyte damage can occur before a change in LVEF results.[58] However, when exercise stress is used to evaluate change in LVEF, sensitivity for detection of anthracycline-induced left ventricular dysfunction in cancer survivors is dramatically increased.[59] Similarly, in this review, the sensitivity of LVEF, perfusion defects, and global longitudinal strain is increased by cardiac stress tests.[16,18,19,22–26] This preliminary evidence that cardiac stress tests may be more sensitive for detection of evidence of cardiovascular disease and may also be used to inform the type of heart function tests utilized to address cardiovascular safety in future clinical trials of antineoplastic therapies.

The parameters of cardiac stress tests that were shown to be beneficial in this review were perfusion defects, measured during stress myocardial perfusion imaging, as well as global longitudinal strain reserve and LVCR measured during stress echocardiography. These parameters are associated with negative clinical outcomes. Perfusion defects are reported to be a significant predictor of cardiac events and cardiac death in cancer survivors, and those with reversible perfusion defects (ie, those detected only with stress tests) have a lower probability of 3-year cardiac event-free survival than those with fixed perfusion defects.[60] Further investigation into the utility of stress myocardial perfusion imaging as a cardiovascular surveillance tool for radiation-treated breast cancer survivors is warranted, given the demonstrated benefit of stress tests in identifying prognostically valuable reversible perfusion defects.

The parameters assessed by stress echocardiography that were beneficial in identifying cardiovascular disease in breast cancer survivors in this review were peak LVEF,[16] LVCR,[16] and global longitudinal strain.[23] Strain imaging is an advanced echocardiographic technique that is new to evaluation with stress.[61] Strain or strain rate has prognostic and diagnostic value in cardiac disease and surgery,[61] but its value in the evaluation of anthracycline-induced left ventricular dysfunction is unknown. Additionally, the absence of LVCR (ie, no change or a decrease in LVEF when stress is applied) is associated with decreased myocardial blood flow and oxygen consumption, at rest and under stress,[62] a maladaptive response predictive of heart failure patient survival.[63] Although there has been limited research on the use of stress echocardiography for detection of chemotherapy-associated left ventricular dysfunction in breast cancer survivors, the two initial studies[16,23] highlight the potential for this technique to be used both for prognosis and follow-up in this population.

Future studies are required, investigating the use of sensitive stress echocardiographic parameters, including LVCR, strain, and diastolic function for identification of left ventricular dysfunction associated with anthracyclines and other chemotherapeutic agents.

This review is subject to some limitations. Firstly, no studies involving breast cancer survivors were identified that compared a cardiac stress test to the gold standard for diagnosis of cardiotoxicity, endomyocardial biopsy, which required that a nontraditional method of synthesizing results be developed. Additionally, there was considerable variability in the format of data reported within each study, which made data synthesis difficult. The small number of available studies that fit the inclusion criteria, as well as the small sample sizes (8 to 38) within these studies limit the interpretation and generalization of the results. Lastly, the findings of this review only provide information as to whether or not cardiac stress tests are beneficial, but do allow for specific recommendations on the optimal timing of this technique with specific breast cancer treatments. However, despite the shortcomings of this review, it demonstrates that there appears to be some benefit to the use of cardiac stress testing of breast cancer survivors to uncover occult cardiovascular disease, and that this technique merits further investigation.

In summary, this is the first review to evaluate the utility of cardiac stress tests in breast cancer survivors. Although few studies of breast cancer survivors have employed cardiac stress tests to monitor cardiac function, and no studies have compared stress tests to the reference standard, the available evidence suggests that myocardial stress may be beneficial in identifying evidence of cardiovascular disease in breast cancer survivors. In particular, stress myocardial perfusion imaging appears to be beneficial in long-term follow-up to left-sided radiotherapy for breast cancer, and stress echocardiography may be beneficial in early and late follow-up to anthracycline treatment. Further research is needed to determine the optimal heart function tests and parameters to be measured during a stress test, the optimal timing of stress tests with different treatments, and the cost-to-benefit ratio of performing a stress test over a heart function test at rest in this population.

Disclosure

The authors declare that there is no conflict of interest.

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