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Cardiorespiratory fitness, cardiac morphology and function, and cardiovascular risk factors in long-term breast cancer survivors compared with non-cancer controls

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Abstract

Background Although anthracycline-related cardiotoxicity is widely studied, only a limited number of echocardiographic studies have assessed cardiac function in breast cancer survivors (BCSs) beyond ten years from anthracycline treatment, and the knowledge of long-term cardiorespiratory fitness (CRF) in this population is scarce. This study aimed to compare CRF assessed as peak oxygen uptake ($\dot{V}O_2$), cardiac morphology and function, and cardiovascular (CV) risk factors between long-term BCSs treated with anthracyclines and controls with no history of cancer.

Methods The CAUSE (Cardiovascular Survivors Exercise) trial included 140 BCSs recruited through the Cancer Registry of Norway, who were diagnosed with breast cancer stage II to III between 2008 and 2012 and had received treatment with epirubicin, and 69 similarly aged activity level-matched controls. All the participants underwent blood sampling, blood pressure measurements, echocardiography and cardiopulmonary exercise testing from October 2020 to August 2022.

Results BCSs were aged 59 ± 6 years and had received a cumulative dose of 357 (243 to 366) mg/m^2 of epirubicin on average 11 ± 1 years before inclusion. There was no difference between BCSs and controls with respect to peak $\dot{V}O_2$ (27.6 ± 5.4 mL/kg/min vs. 27.1 ± 5.4 mL/kg/min, $P=0.25$), 2D left ventricular ejection fraction (57 ± 3% vs. 57 ± 3%, $P=0.43$), left ventricular global longitudinal strain (-20.5 ± 1.0% vs. -20.6 ± 1.0%, $P=0.46$) or the proportion with N-terminal pro-brain natriuretic peptide ≥ 125 (22% vs. 20%, $P=0.93$). The proportions with hypertension, dyslipidemia or diabetes did not differ between the groups.

Conclusion We found that CRF, cardiac function, and CV risk profile in BCSs examined a decade after treatment with anthracyclines were similar to that in women with no history of cancer.

Trial registration clinicaltrials.gov (NCT04307407) https://clinicaltrials.gov/ct2/show/NCT04307407.

Keywords Cancer survivorship, Breast cancer, Cardiorespiratory fitness, Echocardiography, Cardiotoxicity

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Introduction

Adjuvant systemic cancer treatments have significantly improved the survival of patients with breast cancer [1]. The mainstay of these treatments is anthracyclines, which entail a dose-dependent risk of irreversible myocardial injury and heart failure [2, 3]. With improved prognosis, long-term (i.e. beyond five years) treatment-related adverse effects are becoming increasingly important among breast cancer survivors (BCSs).

Prior studies have implied that anthracycline-related cardiotoxicity occurs mainly within the first two years after treatment [3], whereas some studies have suggested an anthracycline-related risk of heart failure even beyond five years [4]. A recent large cohort study observed a 10-year cumulative incidence of heart failure of 1.8% in BCSs treated with anthracyclines without trastuzumab compared with 0.9% in BCSs who had not received anthracyclines [5]. Echocardiographic studies on left ventricular (LV) function in BCSs have found a LV ejection fraction (EF)<50% in 3 to 5% 10 years after treatment with anthracyclines [6, 7], but the number of echocardiographic studies with this long follow-up time after modern breast cancer treatment is limited [6–8].

Cardiorespiratory fitness (CRF) reflects the functional reserve of the organ systems involved in oxygen transport and is inversely related to cardiovascular (CV) events and all-cause mortality [9]. Previous studies have found impaired CRF in BCSs within five years after treatment compared with women without cancer [10–13]. But the knowledge on CRF in long-term BCSs is scarce and based on few studies that are either small [14, 15] or heterogeneous regarding cancer treatment or observation time [16].

Cohort studies have shown an increased long-term risk of CV death among BCSs compared with women without breast cancer [17]. This implies a link with anthracycline-related cardiotoxicity, but side effects of other cancer treatments may also contribute, along with conventional CV risk factors. Radiotherapy, especially to those with left-sided breast cancer, has been associated with an increased risk of cardiac disease, although this risk is substantially reduced with modern radiation techniques [18]. Endocrine therapy may interfere with the favourable CV effects of endogenous oestrogen, and aromatase inhibitors are shown to have an unfavourable impact on lipid profile and CV risk compared with tamoxifen [19]. Despite the potentially increased CV risk in this population, few studies have compared CV risk factors between long-term BCSs and women without a history of cancer.

This study aimed to compare CRF assessed as peak oxygen uptake (VO$_2$), cardiac morphology and function, and CV risk factors between long-term BCSs treated with anthracyclines and controls with no history of cancer, by presenting baseline results from the CAUSE (Cardiovascular Survivors Exercise) trial [20].

Methods

Study design and participants

The CAUSE trial was an exercise intervention study including long-term BCSs and similarly aged, activity level-matched females with no history of cancer (controls) [20]. This sub-study compared baseline data in BCSs and controls, corresponding to a cross-sectional study using nonprobability sampling methods.

Inclusion criteria for the BCSs were breast cancer stage II to III diagnosed between 2008 and 2012, age≤60 years at the time of diagnosis and prior epirubicin treatment. Exclusion criteria were >90 min of exercise per week, treatment with trastuzumab, recurrence of breast cancer, other malignancies (except basal cell carcinoma), chronic atrial fibrillation, pacemaker therapy, previous major cardiac surgery, recent or uncontrolled CV disease, health conditions that, by self-evaluation, restricted adherence to study protocols, medical contraindication to exercise, or participation in other exercise trials. Inclusion criteria for the controls were no history of cancer and similar age-group as the BCSs, with the same exclusion criteria as for the BCSs.

BCSs diagnosed with breast cancer stage II to III between 2008 and 2012, aged≤60 years at the time of diagnosis, from a predefined area of South-Eastern Norway surrounding Oslo, were identified from the Cancer Registry of Norway. Living candidates received an invitation letter followed by a phone call to clarify whether they wished to participate and fulfilled all the eligibility criteria. After the baseline assessments, BCSs were randomised to supervised aerobic exercise training or usual care. Those randomised to exercise training were then encouraged to recruit a similar-aged female friend or relative for the control group. Controls were also recruited through advertisements in news media and social media channels, searching for women similarly aged to the BCSs.

Clinical assessments

Medical history

Details on breast cancer diagnosis, treatments, comorbidities, and CV risk factors at the time of diagnosis were obtained from medical records. Information on comorbidities and current medications at baseline was obtained from case histories and supplemented by case records.

CV risk factors and biomarkers

Body mass index (BMI) was calculated from measured height and weight. Arterial blood pressures (BPs) was measured in supine position. Hypertension was defined as systolic BP≥140 mmHg, diastolic BP≥90 mmHg,

and/or current use of antihypertensive treatment. Blood samples were obtained in a fasted state, details on biochemical analyses are described in the Supplementary Methods. Dyslipidaemia was defined as total cholesterol > 7.0 mmol/L, low-density lipoprotein cholesterol (LDL-C) > 5.0 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.3 mmol/L, triglycerides > 1.70 mmol/L and/or current use of lipid-lowering medication [21]. Diabetes was defined as glycated haemoglobin (HbA1c) ≥ 48 mmol/mol and/or current use of glucose-lowering medication. Cut-off limits indicating a low probability of heart failure were N-terminal pro-brain natriuretic peptide (NT-proBNP) < 192 ng/L in women < 60 years and NT-proBNP < 285 ng/L in women ≥ 60 years [22]. The cardiac biomarkers were also categorised according to the established cut-off limits of NT-proBNP ≥ 125 ng/L and high-sensitivity troponin T ≥ 14 ng/L. Self-reported physical activity was assessed by a modified Godin-Shephard Leisure-Time Physical Activity Questionnaire [23] assessing the frequency and duration of mild, moderate and vigorous leisure-time physical activity during a typical week. The participants were dichotomised into meeting or not meeting the World Health Organization (WHO) recommendation of ≥ 150 min of moderate-intensity, ≥ 75 min of vigorous-intensity physical aerobic activity per week, or an equivalent weekly combination of moderate- and vigorous-intensity aerobic physical activity [24].

Resting echocardiography
A resting transthoracic echocardiography was performed before cardiopulmonary exercise testing (CPET) using Vivid E9 (GE Vingmed) by two different operators. Standard two-dimensional (2D) parasternal and apical views, including a right ventricular (RV)-focused apical four-chamber view, and LV three-dimensional (3D) images were acquired with the participants in the left lateral decubitus position.

Images were analysed offline by a single cardiologist using EchoPac version 202 (GE Vingmed) in accordance with the European Society of Cardiology recommendations [25]. LV mass was estimated from 2D LV dimensions using the Devereux formula [25]. LV 2D volumes and EF were measured by the modified Simpson's method and left atrial volumes by the biplane disk summation technique [25]. LV global longitudinal strain (GLS) was measured by a semi-automatic speckle tracking method using 2D greyscale images from the three standard apical views. 3D LV volumes were obtained by stitching together four to six consecutive heart cycles. RV fractional area change and longitudinal strain were measured in the RV-focused view. RV longitudinal strain was measured by 2D speckle tracking and reported as RV four-chamber longitudinal strain (RV 4CLS), including both free wall and interventricular septum. Diastolic

function was assessed by mitral peak early (E) and late (A) diastolic inflow velocity, deceleration time of the E-wave, and peak early diastolic tissue velocity (e') at the septal and lateral portions of the mitral annulus.

Ventricular mass, dimensions, areas, chamber volumes, stroke volumes (SVs), and cardiac output (Q) were normalised to body surface area. Systolic dysfunction was defined as LV EF < 54% [25] and LV GLS > −18% [26]. The proportion with LV EF < 50% was assessed to enable comparison with previous studies of anthracycline-related cardiotoxicity. LV diastolic dysfunction was defined as the presence of more than two of the following criteria: average E/e' > 14, septal e' < 7 cm/s or lateral e' < 10 cm/s, tricuspid regurgitation velocity > 2.8 m/s and/or left atrial volume > 34 mL/m^2 [27].

Cardiopulmonary exercise testing
The participants performed an incremental treadmill CPET until voluntary exhaustion despite encouragement, following a modified Balke protocol [28]. Gas exchange was measured breath-by-breath using a gas and volume-calibrated metabolic cart (Oxycon Pro, Jaeger GmbH). The electrocardiogram (ECG) was monitored continuously, peak BPs was measured by an automated sphygmomanometer as soon as possible after test termination, and blood lactate was measured one minute after test termination.

Peak VO_2 was defined as the highest volume of oxygen consumed across a period of 30 s. Ventilatory threshold (VT) was determined by the ventilatory equivalent method [28]. Ventilatory efficiency was assessed by the regression slope of minute ventilation (V_E) on carbon dioxide output (VCO_2) (V_E/VCO_2-slope) estimated from the start to the respiratory compensation point. Maximal effort was defined as peak respiratory exchange ratio (RER) (VCO_2/VO_2) ≥ 1.10 and lactate ≥ 7.0 mmol/L in women aged 20 to 49 years, peak RER ≥ 1.05 and lactate ≥ 5.0 mmol/L in women aged 50 to 64 years, and peak RER ≥ 1.00 and lactate ≥ 3.5 mmol/L in women ≥ 65 years [29]. Peak heart rate (HR) was defined as the highest HR reached at the termination of the test.

The participants were laid in the left lateral decubitus position as soon as practically possible after the CPET, and pulsed-wave Doppler velocity spectra were obtained from the LV outflow tract in the apical-5-chamber view to estimate SV and Q. We measured the time from peak exercise to acquisition of measurable Doppler signals. Peripheral oxygen extraction was estimated by the ratio of peak VO_2 to post-exercise Q.

Statistical analysis
The CAUSE trial was designed to demonstrate a change of 3.6 mL/kg/min in peak VO_2 during the intervention period, assuming a standard deviation of 7.2 mL/kg/min

at baseline. To achieve a power of 0.90 with an alpha of 0.05, 70 participants were required in each group, i.e. 140 BCSs and 70 controls, allowing for a drop-out rate of 10% [20].

Data were presented as mean±SD, median (IQR) or numbers (%). For the present analyses, BCSs and controls were compared by linear regression analyses for continuous normally distributed variables and by

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Invited by letter, n = 698

Phone contact not achieved, n = 279

Contacted by a phone call, n = 419 (60%)

Declined participation, n = 146

  ◦ Time constraint, n = 38
  ◦ Not interested, n = 35
  ◦ COVID-19-related, n = 21
  ◦ Lack of energy, n = 10
  ◦ Too sick by self-evaluation, n = 9
  ◦ Lack of motivation, n = 2
  ◦ Too far to travel, n = 1
  ◦ Fear of needles, n = 1
  ◦ Other reasons, n = 15
  ◦ No reason provided, n = 14

Further screened for eligibility, n = 273 (39%)

Did not meet the eligibility criteria, n = 133

  ◦ > 90 min of exercise per week, n = 45
  ◦ Did not receive epirubicin, n = 38
  ◦ Recurrence of breast cancer or other malignancies, n = 20
  ◦ Health conditions restricting adherence to study protocols, n = 16
  ◦ Treatment with Trastuzumab, n = 9
  ◦ Participation in other exercise trials, n = 3
  ◦ Chronic atrial fibrillation, n = 1
  ◦ Pacemaker therapy, n = 1

Included, 140 (20%)

Fig. 1 Flowchart of recruitment and inclusion of participants

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logistic regression analyses, χ^2-test or Fischer's exact test for dichotomous variables. The linear model fit was assessed by residual analysis. A generalised linear regression model was used when this improved the model fit assessed by Akaike information criterion. A log-link function and gamma distribution were used to account for the right-skewed distribution of insulin and the cardiac biomarkers. Concentrations of cardiac biomarkers below the reporting limit were assigned a value corresponding to half the reporting limit [30].

Comparisons of continuous age-dependent CV risk factors were adjusted for age and current treatment of the respective risk factor. Comparisons of categorical CV risk factors, LV mass, ventricular volumes and areas, measures of longitudinal ventricular function [25, 31], mitral inflow velocities and cardiopulmonary exercise variables were adjusted for age [29, 32]. To account for the varying delay from the peak VO_2 measurement to the post-exercise Doppler echocardiography, post-exercise Doppler-derived Q, SV and HR, and peripheral oxygen extraction were also adjusted for the measured delay.

Exploratory subgroup analyses of the effect of breast cancer treatment modalities on selected outcomes were performed by regression analyses restricted to BCSs, including the treatment modality as a dichotomous explanatory variable, adjusting for the same variables as in the intergroup comparisons.

Two-sided P-values<0.05 were considered significant. No adjustments were made for multiple comparisons. Analyses were performed using StataSE 18 (StataCorp LLC, Texas, USA).

Results
Participants
A total of 698 BCSs were invited, 419 were reached by phone, 273 agreed to participate, of whom 140 met the eligibility criteria. Reasons for not participating are summarised in Fig. 1. One of the BCSs recruited a friend for the control group, 68 controls were recruited through advertisements. Inclusions and baseline study assessments were conducted from October 2020 to August 2022.

Breast cancer characteristics and treatment exposures in BCSs are summarised in Table 1. The BCSs were aged 48 ± 6 years when diagnosed with breast cancer and had received a cumulative dose of 357 mg/m^2 (243 to 366) of epirubicin 11 ± 1 years before the study assessments. 85% of the BCSs had received radiotherapy, with 51% receiving left-sided radiotherapy.

According to the European Society of Cardiology's tool for assessing pre-treatment risk of anthracycline-related CV toxicity [33], 113 participants (81%) were classified as low risk, 26 participants (19%) as medium risk, and one participant as high risk at the time of diagnosis. This risk

Table 1 Breast cancer characteristics and treatment exposures in breast cancer survivors

	($n = 140$)
Age at diagnosis, years	48 ± 6
Time from epirubicin discontinuation to study assessments, years	11 ± 1, range 8 to 14
Hormone receptor-positive, n (%)	109 (78)
Radiotherapy, n (%)	119 (85)
Left-sided radiotherapy, n (%)	72 (51)
Cumulative epirubicin dose [a, b], mg/m^2	357 (243 to 366), range 227 to 598
Cumulative epirubicin dose[a, b], n (%)	
<310 mg/m^2, n (%)	49 (35)
310 to <500 mg/m^2, n (%)	88 (63)
≥500 mg/m^2, n (%)	2 (1)
Taxane therapy[a], n (%)	69 (50)
Endocrine therapy, n (%)	110 (79)
Tamoxifen only, n (%)	54 (39)
Aromatase inhibitor only, n (%)	20 (14)
Tamoxifen and aromatase inhibitor, n (%)	36 (26)

Data are expressed as n (%) for categorical variables, mean±SD for continuous normally distributed variables, and median (IQR) for continuous non-normally distributed variables

[a]Details on chemotherapy regimen are missing from one participant

[b]Administered in combination with 5-fluorouracil and cyclophosphamide

assessment relied on retrospectively obtained information from medical records on cardiovascular risk before initiation of epirubicin treatment. We acknowledge that incomplete data on pre-treatment LV function and the absence of information on cardiac biomarkers may have led to an underestimation of this risk (Supplementary Table S1).

Age at study assessments was 59 ± 6 years in BCSs and 58 ± 5 years in controls. 91% of the BCSs and 94% of the controls had >10 years of education. The proportion that met the WHO recommendation for physical activity was 22% (30 out of 138) in BCSs and 17% (11 out of 66) in controls. One of the BCSs was previously diagnosed with ischemic heart failure, one with paroxysmal atrial fibrillation, and one with left bundle branch block. No controls reported these diagnoses.

Cardiovascular risk factors and biomarkers
CV risk factors and biomarkers are summarised in Table 2. BMI, resting BPs and the proportion with hypertension did not differ between BCSs and controls. HDL-C levels were marginally higher in BCSs compared with controls, but we found no differences between the groups regarding LDL-C, triglycerides, the proportion with dyslipidaemia, HbA1c, glucose, insulin, or the proportion with diabetes. Neither were there any intergroup differences in C-reactive protein, NT-proBNP or troponin T. The proportion of daily smokers did not differ between the groups.

In age-adjusted subgroup analyses of BCSs, neither treatment with tamoxifen nor aromatase inhibitors as the only endocrine therapy was associated with the odds of dyslipidaemia. There was no association between a cumulative epirubicin dose≥310 mg/m^2 or left-sided radiotherapy and the odds of NT-proBNP above the cut-off limit (Supplementary Table S2).

Resting cardiac morphology and function
Echocardiographic variables are summarised in Table 3. The image quality was feasible for 2D EF, 3D EF and GLS assessments in 97%, 83% and 89% of the participants, respectively. The frame rate of greyscale LV apical images was 67±7 frames/s. Body surface area did not differ between the groups.

LV 2D dimensions, mass or chamber sizes did not differ between BCSs and controls, neither did LV 3D end-diastolic volume, whereas LV 3D end-systolic volume was marginally larger in BCSs.

LV 2D EF, 3D EF and GLS was similar in both groups, as was the proportion with 2D and 3D EF<54%. In BCSs, 2D LV EF<50% was found in one of 135, 3D LV EF<50% in three of 118 and LV GLS > -18% in three of 122 BCSs, whereas no controls fell into these categories (*P*>0.5 in all). Resting HR, SV and Q did not differ between the groups.

Mitral E, E/A and E/e' was slightly lower, and E-wave deceleration time was shorter in BCSs compared with controls, but no participants met the criteria for LV diastolic dysfunction.

The image quality was feasible for assessment of fractional area change and RV strain in 97% and 89% of the participants, respectively. The frame rate of greyscale RV-focused images was 87±10 frames/s. BCSs had slightly larger RV end-diastolic and end-systolic areas compared with controls. Right atrial area, RV fractional area change, or 4CLS did not differ between the groups.

Table 2 Cardiovascular risk factors and biomarkers in breast cancer survivors and controls

	n	BCSs (n=140)	n	Controls (n=69)	Group comparison[a] (95% CI)		P-value
Body mass							
BMI, kg/m^2	140	26.9±4.5	69	28.1±5.0	-1	(-2.6 to 0.13)	0.077
BMI ≥ 25, n (%)	140	88 (63)	69	51 (74)	0.60	(0.316 to 1.13)	0.11
BMI ≥ 30, n (%)	140	32 (23)	70	18 (26)	0.84	(0.43 to 1.64)	0.61
Blood pressure							
Systolic BP[b], mmHg	140	135±18	69	138±19	-4	(-9 to 1)	0.15
Diastolic BP[b], mmHg	140	82±8	69	81±8	1	(-1 to 3)	0.34
Hypertension[c,d], n (%)	140	54 (39)	69	29 (42)	0.76	(0.41 to 1.40)	0.38
Antihypertensive medication[d], n (%)	140	18 (13)	69	12 (17)	0.59	(0.256 to 1.34)	0.21
High BP[d,e], n (%)	140	48 (34)	69	28 (41)	0.69	(0.378 to 1.28)	0.24
Lipids							
Total cholesterol[f], mmol /L	134	5.9±0.9	68	5.6±1.0	0.2	(-0.0 to 0.5)	0.10
LDL-C[f], mmol/L	134	3.9±0.9	68	3.7±1.1	0.1	(-0.2 to 0.3)	0.65
HDL-C[f], mmol/L	135	1.8±0.4	68	1.7±0.4	0.1	(0.0 to 0.2)	0.049*
Triglycerides[f], mmol/L	134	1.28±0.61	62	1.23±0.51	0.06	(-0.11 to 0.23)	0.48
Dyslipidaemia[d,g], n (%)	136	51 (38)	68	25 (37)	1.01	(0.55 to 1.85)	0.98
Lipid-lowering medication[d], n (%)	140	15 (11)	69	9 (13)	0.77	(0.317 to 1.88)	0.57
Dyslipidaemia by blood test[d,h], n (%)	135	42 (31)	68	19 (28)	1.17	(0.61 to 2.23)	0.63
Glucose metabolism							
HbA1c[i], mmol/mol	132	38 (35 to 40)	67	37 (33 to 40)	0	(-1 to 1)	0.49
Glucose[i], mmol/L	133	5.1 (4.8 to 5.4)	63	5.1 (4.8 to 5.4)	-0.0	(-0.2 to 0.2)	0.78
Insulin[i,j], pmol/L	128	48 (33 to 71)	61	48 (37 to 65)	1.07	(0.87 to 1.31)	0.52
Diabetes[k], n (%)	140	5 (4)	69	3 (4)			0.72[m]
Glucose-lowering medication, n (%)	140	5 (4)	69	2 (3)			1.00[m]
Biomarkers							
NT-proBNP[d,j], ng/L	134	70 (40 to 115)	60	69 (39 to 110)	1.15	(0.87 to 1.50)	0.33
NT-proBNP above cut-off limit[l], n (%)	134	9 (7)	60	4 (7)	1.01	(0.298 to 3.41)	0.99
NT-proBNP ≥ 125 ng/L[d], n (%)	134	30 (22)	60	12 (20)	1.04	(0.48 to 2.24)	0.93
Troponin T[d,j], ng/L	124	5 (4 to 6)	67	5 (4 to 6)	0.90	(0.75 to 1.08)	0.24
Troponin T ≥ 14 ng/L[d], n (%)	124	1 (1)	67	2 (2)			0.28[m]
C-reactive protein, mg/L	134	1.1 (0.6 to 2.2)	65	1.3 (0.6 to 3.2)			0.25[n]
Haemoglobin, g/dL	105	13.8±0.8	68	13.8±0.7	-0.0	(-0.3 to 0.2)	0.93
Creatinine[d], µmol/L	97	63±10	45	63±10	0	(-4 to 4)	0.99
Lifestyle							
Daily smokers, n (%)	138	6 (4)	69	2 (3)			0.72[m]

Data are expressed as n (%) for categorical variables, mean±SD for continuous normally distributed variables, and median (IQR) for continuous non-normally distributed variables. P-values are derived from linear regression analyses for continuous variables and logistic regression analyses for dichotomous variables, unless other specified. *Denotes a P-value<0.05

[a]Intergroup mean difference for continuous normally distributed outcomes, odds ratio for dichotomous outcomes, and exponentated beta-coefficient representing the ratio of means for right skewed variables analysed by generalised linear models using a log-link function and gamma distribution

[b]Adjusted for age and antihypertensive medication administered in the morning at the day of study visit

[c]Systolic BP≥140 mmHg, diastolic BP≥90 mmHg, and/or current antihypertensive treatment

[d]Adjusted for age

[e]Systolic BP≥140 mmHg and/or diastolic BP≥90 mmHg

[f]Adjusted for age and lipid-lowering medication

[g]Total cholesterol>7.0 mmol/L, LDL-C>5 mmol/L, HDL-C < 1.3 mmol/L, triglycerides>1.70 mmol/L, and/or current lipid-lowering medication

[h]Total cholesterol>7.0 mmol/L, LDL-C>5 mmol/L, HDL-C < 1.3 mmol/L, and/or triglycerides>1.70 mmol/L

[i]Adjusted for age and glucose-lowering medication

[j]Generalised linear regression analysis with a log-link function and gamma distribution

[k]HbA1c ≥ 48 mmol/mol and/or use of glucose-lowering medication

[l]NT-proBNP≥192 ng/L in women<60 years old, NT-proBNP≥285 ng/L in women≥60 years old

[m]Unadjusted P-values from Fisher's exact test, due to few outcome events

[n]P-value from Willcoxon rank sum test, due to one right-censored observation

BCS, breast cancer survivor; BMI, body mass index; BP, arterial blood pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 3 Resting cardiac morphology and function in breast cancer survivors and controls

	n	BCSs (*n* = 140)	*n*	Controls (*n* = 69)	Group comparison[a] (95% CI)		*P*-value
Morphology							
Body surface area, m^2	140	1.9 ± 0.2	69	1.9 ± 0.2	-0.0	(-0.1 to 0.0)	0.17
LV IVSd, mm	140	9.7 ± 1.3	69	9.8 ± 1.3	-0.2	(-0.6 to 0.1)	0.20
LV IDd, mm/m^2	140	25 ± 2	69	25 ± 2	0	(-1 to 1)	0.79
LV PWd, mm	140	7.5 ± 0.9	69	7.5 ± 0.8	-0.0	(-0.3 to 0.3)	1.00
LV mass, g/m^2	140	73 ± 13	69	74 ± 13	-2	(-5 to 2)	0.38
2D LV EDV, mL/m^2	135	49 ± 5	68	49 ± 7	0	(-1 to 2)	0.73
2D LV ESV, mL/m^2	135	21 ± 3	68	21 ± 3	0	(-1 to 1)	0.59
3D LV EDV, mL/m^2	118	54 ± 7	55	52 ± 7	2	(-0 to 4)	0.067
3D LV ESV, mL/m^2	118	23 ± 4	55	22 ± 4	1	(0 to 3)	0.027*
LA volume, mL/m^2	136	26 ± 4	69	27 ± 5	-1	(-2 to 0)	0.13
RV end-diastolic area, cm^2/m^2	135	8.9 ± 1.2	68	8.5 ± 1.1	0.5	(0.2 to 0.8)	0.004*
RV end-systolic area, cm^2/m^2	134	4.5 ± 0.7	68	4.3 ± 0.6	0.2	(0.0 to 0.4)	0.035*
RA area, cm^2/m^2	137	7.5 ± 0.8	68	7.5 ± 0.9	-0.0	(-0.3 to 0.2)	0.82
Systolic function							
2D LV EF, %	135	57 ± 3	68	57 ± 3	-0	(-1 to 1)	0.43
3D LV EF < 54%, n (%)	135	16 (12)	68	4 (6)	2.15	(0.69 to 6.7)	0.19
3D LV EF, %	118	57 ± 3	55	58 ± 4	-1	(-2 to 0)	0.17
3D LV EF < 54%, n (%)	118	19 (16)	55	8 (15)	1.13	(0.46 to 2.76)	0.79
LV GLS, %	122	-20.5 ± 1.1	63	-20.6 ± 1.0	0.1	(-0.2 to 0.4)	0.46
RV fractional area change, %	134	49 ± 4	68	49 ± 3	0	(-1 to 1)	0.63
RV 4CLS, %	122	-22.8 ± 2.1	64	-23.0 ± 2.2	0.3	(-0.4 to 0.9)	0.41
TAPSE, cm	138	2.3 ± 0.3	69	2.3 ± 0.3	-0.0	(-0.1 to 0.1)	0.97
RV S', cm/s	138	12 ± 2	69	12 ± 1	0	(-0 to 1)	0.21
Diastolic function							
Mitral peak E velocity, cm/s	140	61 ± 13	68	66 ± 14	-5	(-9 to -1)	0.010*
Mitral peak A velocity, cm/s	140	62 ± 12	68	62 ± 11	-0	(-4 to 3)	0.83
Mitral E/A	140	1.0 ± 0.2	68	1.1 ± 0.3	-0.1	(-0.1 to -0.0)	0.040*
E-wave deceleration time, ms	140	180 ± 34	68	193 ± 36	-14	(-24 to -4)	0.006*
E/e'	138	6.5 ± 1.4	66	7.0 ± 1.4	-0.6	(-1.0 to -0.2)	0.004*
TR peak velocity, cm/s	104	2.1 ± 0.3	55	2.1 ± 0.3	0.0	(-0.1 to -0.1)	0.92
Resting cardiac output							
Heart rate, beats/min	139	63 ± 9	69	61 ± 7	2	(-0 to 4)	0.12
Stroke volume, mL/m^2	139	42 ± 5	69	41 ± 5	0	(-1 to 2)	0.72
Cardiac output, mL/min/m^2	139	2.6 ± 0.4	69	2.5 ± 0.3	0.1	(-0.0 to 0.2)	0.11

Data are expressed as n (%) for categorical variables and mean ± SD for continuous normally distributed variables. P-values are derived from linear regression analyses for continuous normally distributed variables, and logistic regression analyses for dichotomous variables. *Denotes a P-value < 0.05

[a]Intergroup mean difference for continuous normally distributed outcomes and odds ratio for dichotomous outcomes. Analyses were adjusted for age, except for BSA, LV IDd, LA volume, RA area, EF and fractional area change

A, peak late diastolic inflow velocity; BCS, breast cancer survivor; E, peak early diastolic inflow velocity; e', peak early diastolic tissue velocity; end-diastolic volume; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; IDd, internal end-diastolic diameter; IVSd, end-diastolic septum thickness; LA, left atrium; LV, left ventricular; PWd, end-diastolic posterior wall thickness; RA, right atrium; RV, right ventricular; S', peak annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; 2D, two-dimensional; 3D, three-dimensional; 4CLS, four-chamber longitudinal strain

There was a minor negative association between left-sided radiotherapy and tricuspid annular plane systolic excursion (β = −0.1 cm, 95% CI -0.2 to 0.0) in BCSs. Otherwise, there were no associations between a cumulative epirubicin dose ≥ 310 mg/m^2 or left-sided radiotherapy and the measures of systolic function (Supplementary Table S2).

Cardiopulmonary exercise variables

Cardiopulmonary exercise variables are summarised in Table 4. Peak VO_2 did not differ between BCSs and controls, neither did the proportion with VO_2 below age- and sex-specific reference ranges [32]. In both groups, a large proportion achieved maximal effort (93% of BSCs vs. 95% of controls) during the CPET. Among these, there was no intergroup difference in maximal VO_2. Peak ECG-derived HR was modestly higher in BCSs. Peak pulmonary variables, peak oxygen-pulse, VT and V_E /

Table 4 Cardiopulmonary exercise variables in breast cancer survivors and controls

	n	BCSs (n = 140)	n	Controls (n = 69)	Group comparison[a] (95% CI)		P-value
Submaximal exercise							
Ventilatory threshold, L/min	138	1.70 ± 0.36	68	1.73 ± 0.36	-0.00	(-0.10 to 0.10)	0.94
V_E/VCO_2-slope	139	26.9 ± 3.9	67	26.8 ± 3.7	0.0	(-1.1 to 1.1)	1.00
V_E/VCO_2-slope > 34, n (%)	139	4 (3)	67	2 (3)			1.00[j]
Peak exercise							
VO_2, L/min	140	2.06 ± 0.37	69	2.10 ± 0.34	-0.01	(-0.10 to 0.09)	0.89
VO_2 below reference limit[b], n (%)	140	6 (4)	69	1 (1)			0.43[j]
VO_2[c], mL/kg/min	140	27.6 ± 5.4	69	27.1 ± 5.4	0.9	(-0.6 to 2.4)	0.25
VO_2 below reference limit[d], n (%)	140	16 (11)	69	12 (17)	0.61	(0.272 to 1.38)	0.24
VO_2[e], L/m²/min	140	1.11 ± 0.18	69	1.12 ± 0.17	0.01	(-0.04 to 0.06)	0.62
Time to exhaustion, min	140	8.5 ± 2.0	69	9.0 ± 2.0	0.0	(-0.5 to 0.5)	0.92
SpO_2, %	121	94 ± 3	57	95 ± 2	-0	(-1 to 0)	0.37
Breathing rate, breaths/min	140	41 ± 7	69	42 ± 8	-1	(-3 to 2)	0.62
V_E, L/min	140	77.3 ± 15.8	69	79.8 ± 14.6	-0.9	(-4.8 to 3.0)	0.66
Systolic BP, mmHg	78	198 ± 21	54	187 ± 24	10	(3 to 18)	0.010*
Systolic BP[f], mmHg					10	(2 to 18)	0.012*
Diastolic BP, mmHg	78	78 ± 17	54	72 ± 15	6	(0 to 12)	0.033*
Diastolic BP[f], mmHg					6	(0 to 11)	0.038*
Heart rate, beats/min	139	174 ± 11	69	172 ± 10	4	(1 to 6)	0.016*
Beta-blocked	140	5 (4)	69	0			
O_2-pulse, mL/beat	139	11.8 ± 2.1	69	12.2 ± 1.9	-0.3	(-0.8 to 0.3)	0.33
RER	140	1.20 ± 0.09	69	1.23 ± 0.08	-0.02	(-0.05 to 0.00)	0.052
Lactate, mmol/L	127	8.8 ± 2.7	58	8.4 ± 2.2	0.6	(-0.1 to 1.4)	0.094
Maximal exercise							
Achieved maximal effort[g], n (%)	127	118 (93)	58	55 (95)	0.72	(0.186 to 2.75)	0.63
VO_2[h], L/min	118	2.09 ± 0.37	55	2.10 ± 0.35	0.02	(-0.09 to 0.12)	0.76
VO_2[h], mL/kg/min	118	28.1 ± 5.3	55	27.3 ± 5.7	1.1	(-0.5 to 2.8)	0.18
Post-exercise							
Time to Doppler echocardiography, s	132	37 (30 to 46) range 12 to 130	68	45 (36 to 60) range 25 to 90			< 0.001*[k]
Heart rate[i], beats/min	137	137 ± 16	63	132 ± 19	3	(-2 to 7)	0.26
Stroke volume[i], mL/min/m	137	43 ± 6	68	42 ± 6	1	(-1 to 2)	0.51
Cardiac output[i], mL/min/m	137	5.9 ± 0.9	68	5.6 ± 1.0	0.2	(-0.1 to 0.5)	0.17
Peripheral O_2-extraction[i], mL/dL	137	19.2 ± 3.1	68	20.4 ± 3.5	-0.7	(-1.6 to 0.3)	0.18

Data are expressed as n (%) for categorical variables, mean ± SD for continuous normally distributed variables, and median (IQR) for continuous non-normally distributed variables. P-values are derived from linear regession analyses for normally distributed variables, and logistic regression analyses for dichotomous variables. *Denotes a P-value < 0.05

[a]Intergroup mean difference for continuous normally distributed outcomes and odds ratio for dichotomous outcomes. All analyses were adjusted for age, except for VO_2 below age- and sex-specific reference limits, the achievement of maximal effort and time to Doppler echocardiography

[b]VO_2 (L/min) below age- and sexspecific reference limits

[c]Normalised to body mass

[d]VO_2 (mL/kg/min) below age- and sex specific reference limits

[e]Normalised to body surface area

[f]Adjusted for age and antihypertensive medication administered in the morning at the day of study visit

[g]Achieved maximal effort: RER ≥ 1.10 and lactate ≥ 7.0 mmol/L in women aged 20 to 49 years, RER ≥ 1.05 and lactate ≥ 5.0 mmol/L in women aged 50 to 64 years, and RER ≥ 1.00 and lactate ≥ 3.5 mmol/L in women ≥ 65 years. Of the 24 participants that missed lactate measurements, 23 met the RER-criterium for maximal effort

[h]Included only participants that achieved maximal effort

[i]Adjusted for age and measured time to Doppler echocardiography

[j]Unadjusted P-values from X^2-test, due to few outcome events

[k]P-value from from Willcoxon rank sum test

BCS, breast cancer survivor; BP, arterial blood pressure; O2, oxygen; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; V_E, minute ventilation; VO_2, oxygen uptake

VCO_2-slope did not differ between the groups. Peak BPs were notably higher in BSCs compared with controls, and this difference remained unchanged when adjusted for antihypertensive medication in addition to age. There was no intergroup difference in post-exercise Q, SV or HR, or in calculated peripheral oxygen extraction when adjusted for age and the measured delay from peak exercise to Doppler echo-cardiography.

There were no associations between a cumulative dose of epirubicin ≥310 mg/m^2 or left-sided radiotherapy and peak VO_2 in BCSs (Supplementary Table S2).

Discussion

In this study, investigating baseline data from an exercise intervention study, The CAUSE trial [20], we found no clinically meaningful differences when comparing CRF, cardiac morphology and function, and CV risk factors between long-term BCSs and non-cancer controls. Importantly, we assessed several aspects of CV health by partly complementary methods and found consistent results.

Cardiorespiratory fitness

In contrast to our expectation, peak VO_2 was preserved in long-term BCSs compared with controls, and so were the determinants of peak VO_2, measured as peak pulmonary variables, Doppler-derived post-exercise Q, SV and HR, and peripheral oxygen extraction derived from Fick's principle.

Consistent with our results, Koelwyn et al. found no difference in peak VO_2, SV or HR when comparing 30 BCSs treated with anthracyclines without trastuzumab on average seven years earlier with non-cancer controls. Lakosky et al. studied a diverse sample of 180 BCSs less than a year to 39 years after diagnosis and found no difference in CRF between BCSs and non-cancer controls, and no difference between BCSs assessed before and after five years from treatment [15]. In contrast, another study observed lower peak VO_2 and Q in nine elderly BSCs 10 years beyond anthracycline treatment compared with controls [14].

A prior metanalysis reported substantially impaired CRF in BCSs measured less than five years from cancer treatment compared with normative values for age-matched sedentary women [10]. Three studies, which included hemodynamic measurements, found impaired peak VO_2, SV and Q in BCSs within three years after anthracycline treatment compared with controls [11–13]. Indirectly derived peak peripheral oxygen extraction did not differ [11–13], supporting a cardiac limitation of peak VO_2.

CRF measured within a short interval from cancer treatment may reflect early and transient side effects, such as anaemia, asthenia and a temporary decline in physical activity, which may have less impact on CRF in the long term. Furthermore, many of the studies on CRF in BCSs have limited generalisability due to small sample sizes [12, 14], and a direct comparison of pooled CRF values to normative data [10] are challenging due to methodological variations, such as different exercise modalities, estimated vs. directly measured VO_2 and considerable variations in exercise effort.

In our study, peak HR derived from ECG monitoring was higher in BSCs compared with controls, although the exercise effort was similar. This may to some extent be explained by the non-significant difference in BMI between the groups, as the difference in peak HR was attenuated in a post hoc analysis adjusted for both age and BMI (β=3 beats/min, 95% CI -0 to 5). Correspondingly, a large cross-sectional population-based study showed that maximal HR is modestly lower in obese individuals compared with overweight and normal weight individuals [34].

The BSCs also had notably higher peak BPs than the controls. As systemic vascular resistance can be estimated as the ratio of mean BP to Q, higher peak BPs could either reflect higher peak Q and VO_2 [35] or higher peak systemic vascular resistance. Given the similar resting LV function, post-exercise Q, and peak VO_2 between the groups, we performed a post-hoc analysis of peak systemic vascular resistance. We found no difference between the groups, either when comparing the ratio of peak mean BP to post-exercise Q, with adjustments for age and time to Doppler echocardiography (β=89 dynes · s · m^2/cm^5, *P*=0.18), or when comparing the ratio of peak mean BP to peak VO_2 adjusted for age (β=0.14 mmHg · min · kg/L, *P*=0.48). The latter estimate is confounded by potential differences in peripheral O2-extraction. However, we consider peak VO_2 to be a more robust measure than the Doppler-derived post-exercise Q.

Furthermore, the validity of the differences in peak BPs is compromised by a high proportion of missing data (44% in BSCs vs. 22% in controls) (Table 4). The higher proportion of missing values in BSCs compared with controls may reflect that many of the BSCs were assessed during the initial phase of the study. As the study progressed and personnel became more experienced, the proportion of missing measurements decreased. Previous studies have found that higher peak BPs are associated with higher resting BPs [36, 37], higher BMI [36, 37] and higher LV mass [37]. Resting BPs were higher in the controls with missing peak BPs measurements compared with those with complete measurements, whereas this pattern was not observed in BSCs (Supplementary Table S3).

A large cohort study has shown that a higher workload-indexed increase in systolic BP in response to exercise was predictive of all-cause mortality [35]. Regarding

cardiotoxic cancer treatments, some previous studies have suggested that treatment with anthracyclines [38] and radiotherapy [39] is associated with impaired vascular function in the long term, whereas other studies have not found affection of vascular function in BCS one [40] and seven [14] years after anthracycline therapy.

Resting cardiac morphology and function

We found no differences in cardiac biventricular function between BCSs and controls. There were minor differences in mitral inflow pattern, but no participants met the criteria for diastolic dysfunction. RV areas were slightly larger in BCSs compared with controls, with no other differences in right-sided measures. These findings were supported by similar levels of the cardiac biomarkers NT-proBNP and troponin T in BCSs and controls.

In our study, 12% of the BCSs had a 2D LVEF<54%, with 1% having a 2D LVEF<50%. In comparison, a study of 350 BCSs from Boerman et al. reported a 2D LV EF<54% in 15% of all BCSs, and in 16% of the 142 BCSs treated with anthracyclines, which was higher than found in non-cancer controls [6]. Also in that study, the proportion with a 2D LV EF<50% was low and did not differ between the groups [6]. Consistent with our findings, the proportion with LV diastolic dysfunction or RV function measured by tricuspid annular plane systolic excursion and peak annular systolic velocity did not differ between BCSs and controls [6]. Data on RV function in long-term BSCs are scarce, and to our knowledge, our study is the first to do a broad assessment of the RV in this population.

Jacobse et al. observed a 2D LV EF<54% in 10% of BCSs treated with anthracyclines in their study of 569 BCSs, and reported a higher proportion with 2D LV EF<54% and LV GLS > -17% in BCSs who had received anthracyclines compared with those who had not [8]. Both that study and the study from Boerman et al. [6] are comparable to our study regarding age, cumulative anthracycline dose, and follow-up time, although a minor proportion of the BCSs in those studies had also received trastuzumab.

NT-proBNP reflects cardiac wall stress and is thus an indirect and less investigator-dependent measure of cardiac function. We found that NT-proBNP was elevated in 7% of both BCSs and controls according to age- and sex-specific cut-off limits for the general population [22]. The proportion with NT-proBNP≥125 ng/L in BCSs was 22%, compared with 33% in the study from Boerman et al. [6] and 23% in the study from Jacobsen et al. [8]. Analogous to LV 2D EF, the proportions with NT-proBNP≥125 ng/L in those studies were higher in BCSs compared with non-cancer controls [6], and higher in BCSs who had received anthracyclines, compared with those who had not [8].

In the present study, the similar LV function in BCSs and controls contrasts with our hypothesis [20], but is consistent with the similar peak VO_2 and V_E/VCO_2-slope found between the groups. The low proportion with cardiac pathology assessed by echocardiography and biomarkers is consistent with the low proportion with peak VO_2 below the age- and sex-specific reference ranges in this study, and the low proportion with LV dysfunction in comparable studies [6, 7, 41].

Cardiovascular risk factors

We found no relevant differences between BCSs and controls regarding CV risk factors. A recently published cohort study of more than 14 000 BCSs reported that BCSs had a slightly higher cumulative incidence of diabetes, and slightly lower cumulative incidences of hypertension and dyslipidaemia 10 years after diagnosis compared with age-matched non-cancer controls. These results did not differ by prior exposure to chemotherapy, left-sided radiotherapy or endocrine therapy [42]. There were only minor differences in CV risk factors at the time of breast cancer diagnosis [42]. Corresponding trends were not apparent in our limited sample of BCSs.

Limitations

Our study had the limitations of a cross-sectional design, including potential for survival and sample selection bias. As the CAUSE trial involved an exercise training intervention, there was a risk of recruiting the healthiest individuals from both sampling populations, and thereby missing candidates with anthracycline-related adverse effects (Fig. 1). However, by identifying BCSs through the Cancer Registry of Norway, which provides nearly complete and accurate data on the Norwegian cancer population [43], we ensured that all eligible BCSs in the recruitment area were invited to participate. Nevertheless, only 20% of the invited BCSs were included in the study, which restricts the generalisability of our study results.

The different recruitment procedures for BCSs and controls may have affected the internal validity of our results. Whereas the BCSs were personally contacted, the controls actively volunteered in response to advertisements to take part in a training study. Hence, the controls may have had a stronger motivation for the exercise intervention, potentially reflecting higher activity levels and better health. However, differences in physical activity between the groups were mitigated by excluding the most physically active candidates. The similar findings between the groups do not support a selection bias towards fitter or healthier controls. Furthermore, the CV risk profile of the controls did not substantially deviate from the estimates for similar-aged women in Norwegian population-based studies [44, 45]. Few exclusion criteria

concerning CV health strengthens the generalisability of our findings but may have attenuated differences attributable to the breast cancer treatment.

This study did not have the power to detect differences in rare outcomes or to adequately assess the effect of the different breast cancer treatment modalities on outcome variables. Therefore, the explanatory analyses must be interpreted with caution.

SVs measured after CPET were likely underestimated due to the challenge of acquiring Doppler spectra during post-exercise ventilation. Furthermore, post-exercise Q was influenced by the delay between peak exercise and the Doppler-measurement, which was shorter in BCSs compared with controls. After a participant fell during the transfer from the treadmill to the examination bench, resulting in multiple fractures, we increased our focus on ensuring a safe transfer. This change led to increasing delays in Doppler-echocardiography for the subsequent participants, which to some extents may have contributed to the difference between the groups, as a higher proportion of BCSs were examined during the initial phase of the study compared with controls. However, we sought to account for this difference by adjusting for the measured time delay, which yielded similar results as adjustment with the ratio of Doppler-derived heart rate to ECG-derived HR (data not shown).

Clinical implications

This study utilised a spectrum of diagnostic tools to elucidate the various elements of CV health in long-term BCSs, yielding corresponding key findings. Along with a sufficient sample size, this strengthens the validity of our findings, suggesting that overall CV health is not considerably worse in long-term BCSs exposed to first-line anthracycline treatment, and having low to moderate pre-treatment risk of anthracycline-related CV toxicity [32], compared with women without cancer. Within the limitations of the study design, our results reflect a low risk of clinical anthracycline-related cardiotoxicity in this patient population. Banke et al. illustrated this by pointing out that the incidence rate of heart failure after epirubicin treatment is less than half that in a population with hypertension [4]. Our study does not support concerns of an accentuated age-related decline in CRF or a slow subclinical deterioration of cardiac function several years after treatment with anthracyclines. From this perspective, it is important to identify subgroups in need of long-term surveillance, both to ensure adequate management of high-risk individuals and to prevent over-surveillance of the whole group. Large longitudinal data are needed to elucidate this topic.

Conclusion

CRF, cardiac morphology and function, and CV risk profile in BCSs examined a decade after first-line treatment with anthracyclines were similar to that in women with no history of cancer. These findings are reassuring for the growing population of BCSs and those involved in the follow-up care of these individuals.

Abbreviations

BCS	Breast Cancer Survivor
BMI	Body Mass Index
BP	Arterial Blood Pressure
CV	Cardiovascular
EDV	End-Diastolic Volume
EF	Ejection Fraction
ESV	End-Systolic Volume
GLS	Global Longitudinal Strain
HbA1c	Glycated Haemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
LA	Left Atrium
LDL-C	Low-Density Lipoprotein Cholesterol
LV	Left Ventricular
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
Q	Cardiac Output
RER	Respiratory Exchange Ratio
RV	Right Ventricular
SpO_2	Saturation of Peripheral Oxygen
SV	Stroke Volume
$\dot{V}CO_2$	Carbon Dioxide Output
$\dot{V}_E$	Minute Ventilation
$\dot{V}O_2$	Oxygen Uptake
VT	Ventilatory Threshold
WHO	World Health Organisation
2D	Two-Dimensional
3D	Three-Dimensional
4CLS	Four-Chamber Longitudinal Strain

Author contributions

TSN (principal investigator for the CAUSE trial), LT, KVR and SIS made the conception and design of the study. MS and SIS performed the echocardiograms. MS collected clinical data from medical records and case histories, analysed the echocardiograms, analysed the data and wrote the main manuscript text. SHJ conducted the majority of the CPETs. All authors reviewed the manuscript. All authors have approved the submitted version of the manuscript and have agreed to be personally accountable for the author's own contributions.

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Declarations

Ethical approval
Written informed consent was given by all study participants. The study complies with the Declaration of Helsinki and was approved by the Regional Committees for Medical and Health Research Ethics (2019/1318) and the Data Protection Services for Research (865175).

Competing interests
The authors declare no competing interests.

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