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Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer

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ABSTRACT

Aim: To assess systolic and diastolic function in adult childhood-cancer survivors (CCS) after treatment entailing potential cardiovascular toxicity.

Methods: The study cohort consisted of 277 adult CCS (median age 28 [range 18–48] years), who had been treated with anthracyclines, platinum, and/or radiotherapy between 1976 and 1999, along with 130 healthy sibling controls. The assessments included echocardiography, baroreflex sensitivity measurement, and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP). Echocardiography measurements were shortening fraction (SF) (abnormal < 29%) for systolic function and tissue velocity imaging of early diastole (TVI Et) (abnormal < 8.00) cm/sec for diastolic function; systolic function was also assessed by the wall motion score index (WMSI).

Results: At 18 (5–31) years post-treatment, the prevalence of both impaired SF and abnormal WMSI was increased in CCS compared to controls ($p = 0.003$ and $p < 0.001$, respectively). CCS also had an increased prevalence of diastolic dysfunction compared to the controls (12% versus 1%, $p < 0.001$). Abnormal SF and/or abnormal diastolic function were found in 43% of CCS. NT-proBNP was higher in CCS and was associated to increased WMSI. Baroreflex sensitivity was lower in CCS and was associated with diastolic dysfunction. Systolic as well as diastolic dysfunction was associated with cumulative dose of anthracyclines and mediastinal irradiation.

Conclusion: After treatment with potential cardiovascular toxic therapies, the risk of systolic and diastolic dysfunction in CCS is considerable. Since these abnormalities, in particular diastolic dysfunction, are age related, the observed effects might be considered a sign of precocious cardiac ageing.

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1. Introduction

Cardiovascular toxicity is one of the most devastating late effects in childhood-cancer survivors (CCS).[1] Childhood-cancer survivors are 15 times as likely to develop clinical heart failure compared to controls, and the standard mortality rate for cardiac mortality is significantly increased.[1–3] The incidence of overt heart failure in anthracycline-treated survivors has been found up to 5%.[4] However, subclinical abnormalities in cardiac function are more frequent.[5,6]

Cardiac and cardiovascular toxicity can be caused by several cytostatic drugs, for example vincristine, amsacrine, mitoxantrone, high-dose cyclophosphamide and ifosfamide,[6] but in particular by anthracycline derivates, and also by (concomitant) radiation therapy. In addition, late cardiovascular events have also been described in long-term survivors of testicular cancer, most of them treated with platinum-based chemotherapy.[7,8] Since it is generally assumed that early treatment for cardiac disease might benefit survivors' morbidity and quality of life, early detection of cardiac damage remains a major challenge. Echocardiography is considered the gold standard for detection of cardiac damage, although the predictive value of echocardiographic abnormalities without clinical symptoms remains unclear.[9] Other monitoring strategies for early detection of cardiac damage include biochemical markers (NT-proBNP, troponin) and autonomic function.[10,11] The role of comorbidity also has to be considered as CCS are at risk for metabolic abnormalities.[12]

Cardiomyopathy in CCS is generally expressed as systolic dysfunction.[5,6,12,13] The increased risk of systolic dysfunction in association with previous anthracycline treatment is well known, especially after a higher cumulative dose.[13,14] It has been suggested that cytostatic treatment (i.e. anthracyclines or cisplatin) may also result in diastolic dysfunction, although diastolic cardiac dysfunction in CCS has been described only in a limited number of studies.[15–17] However, as is known from the general population, systolic as well as diastolic dysfunction can be a predictor for clinical heart failure.[18]

Radiation-induced cardiac damage has been recognised especially in long-term survivors of Hodgkin's disease and may manifest itself in the myocardium, the pericardium, or the coronary vessels, or as valvular heart disease.[19,20] Radiotherapy (RT) of the chest has been associated with both systolic and diastolic dysfunction, or with diastolic dysfunction without systolic dysfunction.[19,21] The increased risk of heart failure from mediastinal radiotherapy is further augmented by anthracyclines.[20]

We assessed cross-sectionally the prevalence of systolic and diastolic dysfunction and its association with previous treatment in a large cohort of adult CCS five or more years after completion of treatment characterised by potential cardiovascular toxicity, and we compared the results with those of sibling controls.

2. Patients and methods

2.1. Study design and participant's eligibility and recruitment

Participants were invited to participate in this single centre study with the scope on cardiovascular disease and cardiovascular risk factors in adult CCS, with the following eligibility criteria: (a) childhood cancer diagnosis between 1976 and 1999; (b) treatment characterised by potential cardiovascular toxicity (anthracyclines, platinum, and/or RT) on mediastinum (including mantle field), spine or total body; (c) age at diagnosis $\leqslant$ 20 years; (d) current age $\geqslant$ 18 years; (e) surviving at least 5 years after diagnosis; and (f) no cardiovascular disease pre-existent to the cancer diagnosis and/or down syndrome. These criteria were fulfilled by 467 patients, 46 of whom had died 5 years or more after diagnosis (secondary tumour/late relapse 35, cardiac death one, other causes 10). Exclusion criteria were current treatment for late relapse or secondary tumour ($n = 15$), or mental incapacity ($n = 5$). Consequently 401 CCS were eligible. Seventeen CCS were lost-to-follow-up. The remaining 384 CCS were invited to participate in the study. Two hundred seventy-seven of the invited 384 CCS (72%; 69% of eligible CCS) agreed to participate in the study and 107 (28%) refused. No differences in age at diagnosis, sex, duration of cancer treatment, and type of cancer treatment were found between the 277 participating and 124 eligible non-participating subjects. In participants the median time since diagnosis at the initiation of the study was 17.7 years versus 15.2 years in non-participants ($p = 0.008$). Twenty-seven of the 277 participating CCS (10%) in this study had survived treatment for a relapse. Fourteen CCS were on growth hormone replacement therapy. Eight CCS were receiving cardioactive medication (ACE-inhibitor, β-blocker or diuretic) for systolic heart failure that had been diagnosed previously ($n = 7$) or for renal tubular dysfunction ($n = 1$). At the time of the current assessment, all participating CCS were $\geqslant$5 years off-treatment. The number of participants was based on a power calculation. With an anticipated number of 270 participating CCS and 125 control subjects the power to detect a difference in prevalence of cardiac damage of 15% was 81% with a double sided significance level of $p = 0.05$. Control subjects were recruited among those healthy siblings nearest to them in age ($n = 130$).

The study protocol was approved by the Ethics Committee of the University Medical Centre Groningen. Written informed consent was obtained from all participants. All assessments were performed between August 2004 and April 2007.

2.2. Clinical and cardiac assessments

Childhood-cancer survivors and controls underwent assessment of their medical history, a physical examination, blood sampling, echocardiography, and baroreflex sensitivity (BRS). Within the scope of the study, the participants also underwent vascular assessments, and endothelial and inflammatory marker proteins. The results of the vascular assessments will be published separately.

Medical history was assessed by means of a standardised interview. Details of previous cancer treatment and medication were retrieved from medical records. Blood pressure was measured twice on both arms in supine position in a quiet room after a minimal rest period of ten minutes. The mean of the lowest blood pressure measurements on both arms was taken for analysis. The criteria for hypertension were systolic blood pressure $\geqslant$140 mmHg, diastolic blood

pressure ⩾90 mmHg, and/or treatment with antihypertensive drugs. The eight CCS who received cardioactive medication (ACE-inhibitor, β-blocker, or diuretic) for systolic heart failure ($n = 7$) or renal tubular dysfunction ($n = 1$) were excluded from the assessment of the prevalence of hypertension. Body mass index (BMI; weight (kg)/height^2 (m^2)) was considered to reflect body composition. Underweight was defined as BMI < 18.5 kg/m^2, overweight as BMI ⩾ 25 kg/m^2.

After an overnight fast, blood was drawn in the morning, and analysed for serum electrolytes, liver enzymes, creatinine and lipid levels: total cholesterol (normal < 5.2 mmol/L), LDL cholesterol (normal < 4.7 mmol/L), HDL cholesterol (normal males 0.90–1.50 mmol/L, females 1.10–1.70 mmol/L) and triglycerides (normal males < 2.28 mmol/L, females < 2.05 mmol/L), troponin, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Plasma troponin measurement was by troponin I (normal < 0.04 μg/L) until March 2006 and by troponin T (normal < 0.01 μg/L) afterwards, according to laboratory routine. NT-proBNP was measured in heparin plasma stored at -80°C using an immuno-assay (Elecsys 2010; Roche Diagnostics, Lewes, United Kingdom; normal value ⩽125 ng/L).

Echocardiography was performed by a single skilled technician (masked to the treatment versus the control group) on a General Electric VIVID 7 system with a 2.5 mHz probe, and consisted of two-dimensional echocardiography, colour flow mapping, and 2D-guided M-mode, blood pool, and tissue velocity imaging.[22] Dimensions (intra-ventricular septal thickness end-diastolic [IVSed], left ventricular [LV] posterior wall thickness end-diastolic [LVPW(ed)], LV end-diastolic dimension measured in 2D [LVEDD], LV end-systolic dimension [LVESD], and length and traverse of left atrium (LA)) were measured as previously described in detail,[15] and were corrected for body surface area. LV systolic function was determined by shortening fraction (SF; LVEDD-LVESD/LVEDD × 100%). A SF < 29% was considered abnormal.[23] In addition, we also determined the wall motion score index (WMSI) as a measurement of systolic function. Unlike SF which takes only movement of the septum and the posterior wall of the LV into account, the WMSI takes all LV wall segments into account.[24] WMSI is an accurate index of systolic function, which correlates to ejection fraction (EF) without the variability that is common in EF.[25,26] For measurement of WMSI, the LV wall was divided into 16 segments. Each segment was visually scored between 1 and 4 (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia), and the WMSI was the mean score for all the segments analysed; by definition a normal WMSI is 1.00 and a WMSI >1.00 is abnormal. Diastolic function measurements included mitral valve inflow velocities in early (E) and late (A) diastole (E/A ratio), and diastolic tissue velocity at the mitral valve annulus (Tissue Velocity Imaging of early diastole (TVI Et)). The TVI Et was measured at four segments, that is, septal, lateral, anterior, and posterior, and the mean value of these segments was calculated. A TVI Et mean < 8.0 cm/sec was considered diastolic dysfunction.[27] An additional parameter for diastolic function was E/TVI Et (E/E')-ratio.[27] Cardiac autonomic function was assessed using BRS calculated from Finapres blood pressure and heart rate recordings, as previously described in detail.[28] BRS (ms/mmHg) was determined by the transfer function technique using the CARSPAN software programme, and values were given as natural logarithms.[29] BRS was analysed as a continuous variable without a cut-off value.

2.3. Treatment variables

To evaluate the late cardiovascular toxic effects of the treatment administered, the following chemotherapy categories were analysed: (1) anthracycline-based combination (doxorubicin, daunorubicin) chemotherapy; and (2) platinum-based combination (cisplatin, carboplatin) chemotherapy. None of the survivors had received epirubicin, idarubicin or liposomal anthracyline derivates. In addition to anthracyclines, two patients also had mitoxantrone and one patient also had mitoxantrone and amsacrine. To evaluate the effect of RT, the following radiation fields were considered: (1) any type of RT, except RT on the extremities, and (2) chest RT (RT of mediastinum, mantle field, spine or total body RT (TBI)). At the time most of the patients in our study group had received RT the data were not stored, precluding accurate retrospective estimation of the radiation dose to the heart. Cardiac radiation dose was considered to be low in the CCS who had received spinal RT (⩽45 Gy spinal RT, estimated RT dose on the heart < 25 Gy) or TBI (⩽12 Gy TBI in one or two fractions, estimated RT dose on the heart equivalent to <20 Gy).[30,31]

2.4. Data analyses and statistics

Since anthracycline cardiotoxicity is related to cumulative dose, the results were analysed for cumulative doses below and above the median of the current study population (i.e. 183 mg/m^2). Platinum was included in the analysis as a yes/no-variable. As the median mediastinal irradiation dose was 25 Gy, the results of the cardiac assessments were analysed for <25 Gy and for ⩾25 Gy. Statistical analyses were performed using SPSS Inc., version 14. Two-sided p-values < 0.05 were considered significant.

Differences between survivors and controls were tested with Chi-square tests (categorical variables, Fisher exact test in case >20% of the cells had an expected count less than 5), Mann–Whitney U tests (non-Gaussian distributed variables), and T-tests (Gaussian distributed variables).

Multivariate logistic and linear regression analyses were used to assess the association between the primary outcome measurements (systolic dysfunction, defined as SF < 29% or as WMSI > 1.00, and diastolic dysfunction, defined as TVI Et mean < 8.00 cm/sec) and the secondary outcomes (abnormal NT-proBNP [>125 ng/L] and BRS [as a continuous variable]) as dependent variables, and the treatment variables as independent variables. First, each of the treatment variables was tested in a separate model with adjustment for possible confounders, that is, age at diagnosis, sex, current age, follow-up period post-treatment, hypertension, BMI, and use of potentially interfering medication (ACE-inhibitor, diuretic, β-blocker or GH-replacement therapy). Second, the treatment variables with a significant association (based on a more liberal p-value < .10) in these separate models were entered simultaneously in the same model in order to correct the effect of the specific treatment for the other treatments.

3. Results

3.1. Study population

Two hundred seventy-seven CCS and 130 sibling controls underwent a cardiac assessment at the median of 18 years post-treatment (range 5–31).

The treatment characteristics of the participants are summarised in Table 1. Basic characteristics and cardiovascular risk factors are summarised in Table 2. Distribution of age and sex was comparable between the CCS and the controls. Serum creatinine levels in CCS and controls were comparable (median 71 (42–146) μmol/L versus 73 (52–109 μmol/L, $p = 0.21$).

Cumulative doses of anthracyclines ranged from 50 to 600 mg/m^2 (median 183 mg/m^2). Thirty-two out of 275 CCS (12%, 2/277 unknown) and none of the controls had cardioactive medication, statins, or growth hormone replacement therapy. Seventeen had cardioactive medication, two had statins and 14 had growth hormone replacement therapy; one of these CCS had cardioactive medication as well as a statin. Although BMI in CCS was comparable to BMI in controls ($p = 0.07$), CCS had more underweight compared to the controls ($p = 0.008$); the prevalence of overweight ($p = 0.46$) and hypercholesterolemia ($p = 0.25$) was not significantly different between the CCS and the controls. More controls than survivors reported ever smoking ($p = 0.04$). Ninety-six percent of the CCS and 99% of the controls were classified as New York Heart Association Class 1; the remaining subjects were classified as Class 2 ($p = 0.11$).[32]

Table 1 – Cancer-related characteristics of the participating 277 survivors.

	Survivors ($n = 277$)
Age at diagnosis – years [a]	8.8 (0.0–20 1)
Follow-up post-treatment – years [a]	18.2 (5.4–30.8)
Cancer diagnosis, No. (%)	
Leukaemia	113 (41)
Acute lymphoblastic leukaemia 103	
Acute non-lymphoblastic leukaemia 9	
Acute undifferentiated leukaemia 1	
Malignant lymphoma	56 (20)
Sarcoma	48 (17)
Brain tumour	32 (12)
Blastoma[b]	23 (8)
Germ cell tumour	5 (2)
Chemotherapy, No. (%)	
Combination chemotherapy including anthracyclines	199 (72)
Doxorubicin	100 (36)
Daunorubicin	53 (19)
Both doxorubicin and daunorubicin	46 (17)
Anthracycline dose ⩾ median (183 mg/m^2)	100 (36)
Combination chemotherapy including platinum	22 (8)
Radiation therapy, No. (%)	
Radiation therapy	174 (63)
Whole chest RT	69 (25)
Mediastinal RT	33 (12)
TBI	17 (6)
Spinal RT	19 (7)
Dose of mediastinal RT ⩾25 Gy	17 (6)
Combination of treatment modalities, No. (%)	
Anthracylines and platinum	11 (4)
Chest RT and anthracyclines	45 (16)
Chest RT and platinum	6 (2)
Chest RT and anthracyclines and platinum	2 (1)

[a] Median (range).
[b] Nephroblastoma, neuroblastoma; RT, radiotherapy; TBI, total body irradiation.

3.2. Cardiac parameters in CCS and controls (Table 3)

3.2.1. Systolic function

Systolic function was studied using different parameters: SF as well as WMSI. Systolic dysfunction, defined as SF < 29%, was evaluable in 274 CCS and 130 controls. SF was impaired in 100/274 (37%) of the CCS versus 28/130 (22%) of the controls ($p = 0.003$). Median SF was lower in the CCS compared to the controls (31.7% versus 32.7%, $p = 0.007$). WMSI was evaluable in 267 CCS and in 128 controls. Abnormal WMSI, defined as WMSI > 1.00, was found in 39/267 (15%) of the CCS versus 2/128 (2%) of the controls ($p < 0.001$). In both CCS and controls the prevalence of abnormal WMSI was lower than the prevalence of impaired SF (CCS: 15% versus 37%; $p < 0.001$, controls: 2% versus 22%; $p = 0.04$). Results for SF as well as for WMSI were available in 267 CCS. In 80 of them either SF or WMSI were abnormal, in 28 CCS both SF as WMSI were abnormal and in 159 CCS both SF and WMSI were normal. CCS with both abnormal SF and WMSI ($n = 28$) had more often received a cumulative dose of anthracyclines above the median dose of 183 mg/m^2 (odds ratio (OR) 2.64; 95% confidence interval (CI) 1.12–6.25, $p = 0.03$). The combined presence of abnormal SF and WMSI was not associated with prior treatment with any RT or mediastinal RT.

3.2.2. Diastolic function

Diastolic function, expressed as TVI Et, was evaluable in 273 CCS and in 129 controls. Diastolic dysfunction, defined as TVI Et < 8.0 cm/sec, was found in 32/273 (12%) of the CCS versus 1/129 (1%) of the controls ($p < 0.001$). TVI Et mean was lower in the CCS compared to the controls ($p < 0.001$), E/A ratio was lower in the CCS compared to the controls ($p = 0.02$) and E/E′ was higher in CCS compared to controls ($p < 0.001$).

3.2.3. Systolic and diastolic function

Systolic dysfunction was studied using the parameters SF as well as WMSI

1. Systolic function defined as SF < 29%. Both SF and TVI Et were available in 272 CCS and in 129 controls. Systolic dysfunction with normal diastolic function (SF < 29% and TVI Et ⩾ 8.00 cm/sec) was found in 86/272 CCS and in 27/129 controls. Diastolic dysfunction with normal systolic function (SF ⩾ 29% and TVI Et < 8.0 cm/sec) was found in 17/272 CCS and 1/129 controls. Systolic as well as diastolic dysfunction (SF < 29% and TVI Et < 8.0 cm/sec) was found in 14/272 CCS and in 0/129 controls.

Table 2 – General characteristics and cardiovascular risk factors in 277 childhood cancer survivors and 130 controls.

	Survivors	Controls	*p*-Value
Characteristics			
Sex, No. (%)			0.40
Male	155 (56)	67 (52)	
Female	122 (44)	63 (48)	
Age at cardiac evaluation – years[a]	27.5 (18.1–48.2)	25.9 (18.0–51.1)	0.33
NYHA heart failure classification, N[b] (%)			0.11[c]
Class 1	263/274 (96)	129/130 (99)	
Class 2	11/274 (4)	1/130 (1)	
Use of cardioactive medication, N[b] (%)[d]	17/275 (6)	0/130 (0)	0.004
Use of statins, N[b] (%)	2/275 (1)	0/130 (0)	1.00[c]
Growth hormone replacement therapy, N[b] (%)	14/275 (5)	0/130 (0)	0.006[c]
Ever smoking, N[b] (%)	102/275 (37)	62/130 (48)	0.04
Cardiovascular risk factors			
Hypertension[e], N[b] (%)	38/263 (14)	10/130 (8)	0.05
BMI (kg/m^2)[a]	22.8 (16.4–46.3)	23.7 (17.6–35.0)	0.07
Underweight (BMI < 18.5 kg/m^2; N[b] (%))	19/274 (7)	1/130 (1)	0.008
Overweight (BMI ⩾ 25 kg/m^2; N[b] (%))	91/274 (33)	48/130 (37)	0.46
Hypercholesterolemia[f], N[b] (%)	80/245 (33)	33/123 (27)	0.25
Serum creatinine level μmol/L[a]	71 (42–146)	73 (52–109)	0.21

[a] Median (range); No., number; NYHA, New York Heart Association; NYHA Class 1, indicated no symptoms and no limitation in ordinary physical activity; NYHA Class 2, indicated mild symptoms and slight limitation during ordinary activity and comfortable at rest[31]; BMI, body mass index.

[b] Number/number evaluable subjects.

[c] *p*-Values based on Fisher's exact test.

[d] Cardioactive medication: ACE-inhibitor, β-blocker or diuretic.

[e] Hypertension: systolic blood pressure ⩾140 mmHg and/or diastolic blood pressure ⩾90 mmHg and/or use of antihypertensive medication (excluding eight survivors with cardiac treatment because of previously diagnosed systolic heart failure ($n = 7$) or renal tubular dysfunction ($n = 1$) and without hypertension).

[f] Hypercholesterolemia: fasting LDL cholesterol ⩾3.4 mmol/L and/or use of cholesterol lowering medication (statins).

When systolic function was expressed as SF, 117/272 (43%) CCS had systolic dysfunction and/or diastolic dysfunction.

2. Systolic function defined as WMSI > 1. Both WMSI and TVI Et were available in 267 CCS and 127 controls. Systolic dysfunction with normal diastolic function (WMSI > 1 and TVI Et ⩾ 8.00 cm/sec) was found in 31/267 CCS and in 2/127 controls. Diastolic dysfunction with normal systolic function (WMSI = 1 and TVI Et < 8.0 cm/sec) was found in 20/267 and in 1/127 controls. Systolic as well as diastolic dysfunction (WMSI > 1 and TVI Et < 8.0 cm/sec) was found in 8/267 CCS and in 0/127 controls. When systolic function was expressed as WMSI, 59/267 (22%) CCS had systolic dysfunction and/or diastolic dysfunction.

3.2.4. *Hypertension*

The prevalence of hypertension was not significantly different between the CCS and the controls ($p = 0.05$) (Table 2). Hypertension was found in 13/92 (14.1%) of evaluable survivors with SF < 29%), in 5/33 (15.2%) of evaluable survivors with WMSI > 1, and in 17/29 (58.6%) of evaluable survivors with diastolic dysfunction.

3.2.5. *Biochemical markers*

NT-proBNP assessment was available in 262 CCS and in 127 controls. NT-proBNP was significantly higher and more often elevated in the CCS compared to the controls (Table 3). NT-proBNP was abnormal in 16/97 evaluable CCS (16%) with systolic dysfunction defined as SF < 29%, in 12/38 evaluable CCS (32%) with systolic dysfunction defined as WMSI > 1.00 and in 4/30 (13%) CCS with diastolic dysfunction, defined as TVI Et < 8.00 cm/sec. Elevated NT-proBNP was associated with systolic dysfunction defined as WMSI > 1.00 ($p \leqslant .001$). NT-proBNP was not associated with systolic dysfunction defined as SF < 29% and diastolic dysfunction. Troponin was abnormal in 3/268 (1%) CCS, all of them with normal renal function, versus none of the controls ($p = 0.55$). None of the CCS with systolic and/or diastolic dysfunction had an abnormal troponin.

3.2.6. *Autonomic function*

The mean BRS was significantly lower in the CCS compared to the controls ($p = 0.01$), indicating autonomic dysfunction in the CCS. A lower BRS was associated with diastolic dysfunction ($p = 0.001$), not with systolic dysfunction (defined as SF < 29%: $p = 0.87$, defined as WMSI > 1.00: $p = 0.29$).

3.3. *Treatment-related factors and cardiac dysfunction*

The results of logistic regression analyses with systolic and diastolic dysfunction as dependent variables are summarised in Table 4.

3.3.1. *Systolic dysfunction (SF < 29%)*

None of the potential confounders was associated with systolic dysfunction, defined as SF < 29%. In the logistic regression models with the different treatment modalities entered

separately and with adjustment for these potential confounders, SF < 29% was associated with anthracyclines (OR 2.15; 95% CI 1.08–4.26), with cumulative dose of anthracyclines ⩾ median (i.e. 183 mg/m^2, OR 2.01; 95% CI 1.17–3.47), and with chest RT (OR 2.04; CI 1.12–3.70), especially mediastinal RT (OR 2.75; 95% CI 1.25–6.05). In the model with the treatment modalities entered simultaneously, these associations remain significant (anthracyclines ⩾ median: OR 2.18; 95% CI 1.25–3.80, mediastinal RT: OR 3.00; 95% CI 1.35–6.67).

3.3.2. *Systolic dysfunction (WMSI > 1.00)*

Of the potential confounders included, only the cardioactive medication (OR 19.6; 95% CI 3.5–108.9) and the GH replacement therapy (OR 5.2; 95% CI 1.4–20.0) were associated with systolic dysfunction, defined as WMSI > 1.00. In the adjusted logistic regression models with the treatment modalities entered separately, a WMSI > 1.00 was only associated with a cumulative anthracycline dose ⩾ median (OR 3.32; 95% CI 1.07–5.04) and this remained significant after adjustment for chest RT by localisation (OR for anthracycline dose ⩾ median 2.40; 95% CI 1.10–5.25).

3.3.3. *Diastolic dysfunction (TVI Et < 8.0 m/sec)*

Of the potential confounders included, age (OR 1.3; 95% CI 1.2–1.6), female sex (OR 0.3; 95% CI 0.1–0.97), hypertension (OR 8.4; 95% CI 2.9–24.1), and BMI (OR 1.1; 95% CI 1.0–1.2) were associated with diastolic dysfunction, defined as TVI ET < 8 cm/sec. In the adjusted logistic regression models with the treatment modalities entered separately, diastolic dysfunction was associated with a cumulative anthracycline dose ⩾ median (OR 3.04; 95% CI 1.02–9.03) and with chest RT (OR 4.27; 95% CI 1.42–12.87), especially mediastinal RT (OR 12.33; 95% CI 2.97–51.14) and mediastinal RT ⩾ 25 Gy (OR 28.12; 95% CI 4.69–168.74). In the model with the treatment modalities entered simultaneously, these associations remain significant (anthracyclines ⩾ median: OR 4.05; 95% CI 1.16–14.09, mediastinal RT: OR 15.21; 95% CI 3.40–68.01).

Additional adjustment for blood creatinine and glucose levels did not change the results of the analyses on systolic and diastolic dysfunction (data not shown). A statistical analysis was also performed after exclusion of the CCS who were on cardiac medication. The results were not different from those of the entire cohort (data not shown).

3.3.4. *NT-proBNP and BRS*

The results of the regression analyses performed with an elevated NT-proBNP (logistic regression) and BRS (linear regression) as dependent variables showed that an elevated NT-proBNP was associated with cumulative anthracycline dose ⩾ median (OR 4.0; 95% CI 1.5–11.0) and with mediastinal RT

Table 3 – Cardiac parameters in 277 childhood cancer survivors and 130 controls.

	Survivors	Controls	P-value
Echocardiography			
Systolic function			
SF (%), median (range)	31.7 (16.7–57.9)	32.7 (21.4–48.0)	0.007
SF < 29%, n[a](%)	100/274 (37%)	28/130 (22%)	0.003
WMSI > 1.00	39/267 (15%)	2/128 (2%)	<0.001
Diastolic function			
E/A ratio	1.63 ± 0.50	1.74 ± 0.41	0.02
E/A ratio < 1.00, n[a] (%)	14/273 (5.1%)	2/130 (1.5%)	0.08
TVI Et mean (cm/sec)	10.6 ± 2.2	12.4 ± 1.6	<0.001
TVI Et < 8 cm/sec, n[a] (%)	32/273 (12%)	1/129 (1%)	<0.001
E/E′ median (range)	8.6 (5.1–30.0)	7.7 (4.7–12.5)	<0.001
Cardiac dimensions (in mm; BSA corrected)			
BSA median (range)	1.85 (1.28–2.64)	1.92 (1.55–2.42)	0.001
IVSed, mean ± SD	4.3 ± 0.5	4.3 ± 0.6	0.85
LVPWed, mean ± SD	4.3 ± 0.6	4.2 ± 0.5	0.13
LVEDD, mean ± SD	25.3 ± 2.4	25.1 ± 2.0	0.41
LVESD, mean ± SD	17.3 ± 2.3	16.8 ± 2.1	0.03
LA parasternal, mean ± SD	17.5 ± 1.9	17.5 ± 1.7	0.98
LA length, mean ± SD	28.2 ± 2.8	28.0 ± 2.6	0.37
LA transverse, mean ± SD	21.0 ± 2.8	21.0 ± 2.4	0.92
Autonomic function			
Natural log mean BRS (ms/mmHg), mean ± SD	2.4 ± 0.6	2.6 ± 0.6	0.01
Range	0.6–4.1	0.9–5.3	
Biochemical markers			
NT-proBNP (ng/L), median (range)	47 (11–4758)	34 (11–257)	<0.001
NT-proBNP > 125 ng/L, n[a] (%)	32/262 (12%)	4/127 (3%)	0.004
Abnormal troponin, n[a] (%)	3/268 (1%)	0/130 (0%)	0.55

[a] Number/number evaluable subjects. SF, shortening fraction; SD, standard deviation; WMSI, wall motion score index; BSA, body surface area; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrium; BRS, baroreflex sensitivity; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4 – Logistic regression analysis[a] with systolic (SF, WMSI) and diastolic function (TVI Et) as dependent variables.

Independent variables	SF < 29%			WMSI > 1.00			TVI Et < 8.0 m/sec		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Each treatment variable entered separately									
Anthracyclines (n = 199)	**2.15**	**1.08–4.26**	**.03**	1.59	0.58–4.40	.37	1.46	0.43–4.99	.55
Dose anthracyclines ⩾ median (183 mg/m^2) (n = 100)	**2.01**	**1.17–3.47**	**.01**	**3.32**	**1.07–5.04**	**.03**	**3.04**	**1.02–9.03**	**.05**
Platinum (n = 22)	0.67	0.25–1.84	.44	0.67	0.16–2.72	.57	2.29	0.33–15.95	.40
Any RT (n = 174)	0.92	0.53–1.61	.78	0.82	0.37–1.81	.62	0.84	0.27–2.61	.76
Chest RT (n = 69)	**2.04**	**1.12–3.70**	**.02**	1.05	0.45–2.45	.92	**4.27**	**1.42–12.87**	**.01**
Dose of mediastinal RT ⩾ 25 Gy (n = 17)	2.34	0.83–6.60	.11	2.58	0.71–9.44	.15	**28.12**	**4.69–168.74**	**<.001**
Chest RT by localisation									
Mediastinal RT (n = 33)	**2.75**	**1.25–6.05**	**.01**	1.40	0.45–4.29	.56	**12.33**	**2.97–51.14**	**.001**
TBI (n = 17)	1.70	0.59–4.93	.33	0.78	0.17–3.50	.74	1.62	0.10–25.14	.73
Spinal RT (n = 19)	1.23	0.36–4.18	.74	0.79	0.12–5.25	.81	0.74	0.08–6.92	.80
Treatment variables entered simultaneously *Dose anthracyclines ⩾ median (183 mg/m^2) and chest RT by localisation*									
Dose anthracyclines ⩾ median	**2.18**	**1.25–3.80**	**.006**	**2.40**	**1.10–5.25**	**.03**	**4.05**	**1.16–14.09**	**.03**
Mediastinal RT	**3.00**	**1.35–6.67**	**.007**	1.61	0.51–5.02	.42	**15.21**	**3.40–68.01**	**<.001**
TBI	1.89	0.64–5.60	.25	0.82	0.18–3.78	.80	2.89	0.18–46.77	.45
Spinal RT	1.40	0.40–4.90	.60	0.79	0.11–5.57	.81	1.12	0.11–11.54	.93

Bold: significant. SF, shortening fraction; WMSI, wall motion score index; RT, radiotherapy; TBI, total body irradiation; OR, odds ratio; CI, confidence interval.

[a] Corrected for age at diagnosis, sex, current age, follow-up period post-treatment, hypertension, BMI, and use of potentially interfering medication (ACE-inhibitor, diuretic, β-blocker or GH-replacement therapy).

((OR 4.4; 95% CI 1.3–17.7) ORs given are for the model with both treatment modalities entered simultaneously). No association was found between BRS and the different treatment groups (data not shown).

4. Discussion

In this cross-sectional long-term follow-up study we found a significantly higher prevalence of systolic and diastolic dysfunction in a large cohort of adult CCS compared to sibling controls. At a median follow-up of 18 years post-treatment, the prevalence of systolic and/or diastolic dysfunction was as high as 43%, when SF was used to measure systolic function and 22% when WMSI was used to measure systolic function. Most survivors with diastolic dysfunction (TVI Et < 8.00 cm/sec) had normal systolic function (SF ⩾ 29%). These results are of importance, since in the general population not only systolic dysfunction, but also diastolic dysfunction predicts clinical heart failure and sudden cardiac death.[18]

Diastolic function is not well established in CCS and has been described in only a few studies.[15,16,33] The major drawbacks of those studies are their limited size, their use of load-dependent echocardiography parameters such as E/A-ratio or the lack of healthy controls. Load-dependent diastolic parameters have the disadvantage that differences in LV filling may interfere with correct interpretation, thus prompting conflicting results.[34] Diastolic dysfunction of the heart is ideally assessed by an invasive approach.[27] However the invasive approach is burdensome and therefore a non-invasive approach is preferable for the assessment of a cancer survivor population and healthy controls. TVI Et, being independent of LV filling, is currently considered the most reliable non-invasive technique for assessing diastolic dysfunction.[34] In our data, we found no difference in prevalence of an abnormal E/A ratio between the CCS and the controls, whereas TVI was significantly more often abnormal in CCS (12% versus 1%). In survivors of adult cancer, TVI showed progressive impairment several years after anthracycline treatment when compared to baseline before treatment.[35]

In our study we found that systolic and diastolic dysfunctions were associated with a higher cumulative dose of anthracyclines and with mediastinal irradiation (Table 4). This is in accordance with the results of several other studies which suggested that diastolic dysfunction, measured by load-dependent variables, was associated with both anthracyclines and chest RT,[15,19,36] other studies showed conflicting results, however. Hudson and colleagues found that in CCS a decreased SF was associated with a cumulative anthracycline dose ⩾270 mg/m^2 but not with whole heart RT; others, however, demonstrated earlier that systolic dysfunction, expressed as ejection fraction, was associated with RT of the cardiac region.[13,21,37] In the current study systolic and/or diastolic dysfunction was not associated with platinum, whereas in an earlier study on platinum treated survivors of testicular cancer we found a significant decrease in TVI Et and E/A ratio 1 year after treatment.[8] As the number of platinum treated CCS in the current study was only 22, lack of power could play a role, as well as a difference in duration of follow-up.

Plasma NT-proBNP, troponine and BRS were evaluated as additional parameters in the cardiac risk assessment. NT-proBNP was higher in the CCS compared to the controls, and a higher cumulative anthracycline dose as well as mediastinal RT was associated with an elevated NT-proBNP. There was no relationship between diastolic dysfunction and NT-pro-BNP. As for systolic dysfunction, NT-proBNP was related with WMSI, but not with SF. This could suggest that WMSI is a more precise measurement of systolic function than SF. Troponine levels were not different in CCS and

controls and we found no association of troponine levels with systolic or diastolic dysfunction. In this study only three long-term CCS had elevated troponine levels, and none of them had echocardiographic abnormalities. Compared to the sibling controls, BRS was lower in CCS, suggesting autonomic cardiac dysfunction. A lower BRS was associated with diastolic dysfunction. None of the treatment factors in this study was found to be associated with BRS. In a previous study we did in high-dose anthracycline-treated bone tumour survivors who were found to have systolic and diastolic dysfunction, we also observed autonomic dysfunction.[15] As a low BRS is known to be a predictor of all-cause mortality and sudden death in various patient groups,[38] autonomic dysfunction in CCS may be a sensitive early parameter of cardiac morbidity.

Although hypertension is known to be of predictive value in the development of diastolic dysfunction,[27] in the current study more than 40% of CCS with diastolic dysfunction had no hypertension. This suggests that there are additional mechanisms that play a role in the oetiology of diastolic dysfunction in CCS which have still to be unravelled. One of those mechanisms could be precocious cardiovascular ageing, since in the general population diastolic dysfunction is associated with advanced age,[18,39] with increased vascular and ventricular stiffness as integral manifestations of ageing.[34] The finding of an increased prevalence of diastolic dysfunction at a median age of 28 years in our population of young adult CCS is a good fit with the concept of precocious cardiovascular ageing. Recently, Maccormick and colleagues elaborated the theoretical mechanisms of ageing and its potential acceleration by chemotherapy.[40] One of the ageing theories is based on free-radical damage. Anthracycline metabolism generates free-radical intermediates that can damage cardiac tissue.[40] Radiation has been described in association with atherosclerosis, which is an integral component of ageing.[41] The exact mechanism needs to be elucidated, but RT-induced endothelial injury has been suggested as an initiator in the development of atherosclerosis.[30,31] Further research is warranted to explore the hypothesis of accelerated ageing in CCS and its effect on vital organs such as the heart and the vascular system.

Although treatment for asymptomatic systolic dysfunction has been well established in patients with cardiac problems due to causes other than childhood cancer treatment,[42] treatment for symptomatic and asymptomatic diastolic dysfunction in patients with cardiac problems due to causes other than childhood cancer treatment is still controversial, and has yet to be evaluated in clinical trials.[43] Thus far, the approach to subclinical diastolic dysfunction has been limited to identification and treatment of the underlying cause(s) of diastolic dysfunction (e.g. hypertension, overweight).

Cardiac toxicity further unfolds to become a considerable problem in CCS. Cardiac mortality is reported to be about six times higher in CCS compared to controls,[1] while data on cardiac morbidity show variable results.[5,6] Thus far, cardiac dysfunction has mainly been characterised by parameters of systolic function.[5,12,37,44] In paediatric oncology and in studies of CCS, systolic function is commonly expressed as measured by SF. However, in many studies in cardiology the WMSI is used rather than SF. This is based on the fact that the WMSI is actually a more precise measurement of systolic function than SF, since it takes all 16 segments of the LV wall into account as opposed to essentially only two segments in SF. We therefore decided to use the WMSI in addition to SF. Abnormal WMSI was found in 15% of CCS versus 2% of controls, whereas an abnormal SF was found in 37% of CCS and in 22% of the controls. The high prevalence of abnormal SF in apparently healthy sibling controls suggests the possibility of false-positive findings and challenges the appropriateness of SF as a reliable marker of systolic function in adults.

The strengths of our study are its large sample size, the extended follow-up period, the sibling controls, and the advanced contemporary echocardiography. Moreover, all the echocardiograms were performed by a single skilled technician, thus reducing inter-observer variability. However, there are some limitations. First of all, the cohort is very heterogeneous. Indeed, due to the rarity of paediatric cancer, most single-institutional long-term follow-up studies of childhood cancer survivors involve heterogeneous patient populations. To overcome this, we used regression analyses to adjust for possibly confounding variables. Another limitation is the cross-sectional nature of the study design, which precludes showing changes over time. Furthermore, RT dosimetry could not be evaluated due to the fact that at the time most of the patients had received RT the data were not stored, precluding accurate retrospective estimation of the radiation dose to the heart. Finally, a selection bias cannot be ruled out. Twenty-eight percent of the invited patients refused to participate, which may have resulted in a selection bias as the prevalence of cardiac failure in non-participants is unknown. It cannot be ruled out that survivors who are sicker feel more encouraged to participate compared to those who feel healthy. Non-participants had a somewhat shorter duration of follow-up compared to the participants, which may have resulted in overestimation of the prevalence of cardiac damage, since an association has been suggested between duration of follow-up and cardiac damage.[15,44]

We concluded that childhood cancer survivors who have been treated with potentially cardiovascular-toxic treatment have an increased prevalence of both systolic and diastolic dysfunction as compared to sibling controls. Moreover, a higher anthracycline dose and chest RT were associated with both systolic and diastolic dysfunction. Since these abnormalities, in particular diastolic dysfunction, are more common in the elderly, these observed effects might be interpreted as a form of precocious cardiac ageing. Further research is warranted to test this hypothesis. In addition studies are also needed to determine the most appropriate and usable method for determination of systolic function in CCS. To determine the clinical relevance of diastolic dysfunction in this particular population of cancer survivors, there is a need for prospective longitudinal studies on systolic and diastolic cardiac function in CCS. In addition, associated risk factors, such as hypertension and overweight, require further exploration as potential intervention targets.

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Conflict of interest statement

None declared.

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