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Cardiac function in childhood cancer survivors treated with vincristine: Echocardiographic results from the DCCSS LATER 2 CARD study

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ABSTRACT

Background: Anthracyclines and radiotherapy involving the heart region are cardiotoxic, but the potential cardiotoxicity of vincristine remains unknown. We assessed cardiac function in vincristine-treated >5-year childhood cancer survivors (CCS).

Methods and results: We cross-sectionally compared echocardiograms of 101 vincristine-treated CCS (median age 35 years [range: 17–53], median vincristine dose 63 mg/m^2) from the national Dutch Childhood Cancer Survivor Study, LATER cohort, to 101 age- and sex-matched controls. CCS treated with anthracyclines, radiotherapy involving the heart region, cyclophosphamide or ifosfamide were excluded. Twelve CCS (14%) versus four controls (4%; *p* 0.034) had a decreased left ventricular ejection fraction (LVEF; men <52%, women <54%). Mean LVEF was 58.4% versus 59.7% (*p* 0.050). Global longitudinal strain (GLS) was abnormal in nineteen (24%) CCS versus eight controls (9%; *p* 0.011). Mean GLS was 19.0% versus 20.1% (*p* 0.001). No ≥grade 2 diastolic dysfunction was detected. In multivariable logistic regression analysis CCS had higher risk of abnormal GLS (OR 3.55, *p* 0.012), but not abnormal LVEF (OR 3.07, *p* 0.065), than controls. Blood pressure and smoking history contributed to variation in LVEF, whereas obesity and diastolic blood pressure contributed to variation in GLS. Cumulative vincristine dose was not associated with either abnormal LVEF or abnormal GLS in multivariable models corrected for age and sex (OR per 50 mg/m^2: 0.88, *p* 0.85 and 1.14, *p* 0.82, respectively).

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Conclusions: Vincristine-treated long-term CCS showed an abnormal GLS more frequently than controls. Their risk for future clinical cardiac events and the role of risk factor modification should be further elucidated.

1. Introduction

Cardiotoxicity is an important side-effect of treatments for childhood cancer. Heart failure due to cardiotoxic treatments can become overt in childhood cancer survivors (CCS) even after decades. Anthracyclines and radiotherapy involving the heart region are the main treatment-related risk factors [1]. Mortality due to heart failure in CCS is six-fold higher, compared to the general population [2]. Therefore, a surveillance guideline recommends regular and life-long echocardiography for CCS at risk, to detect left ventricular (LV) systolic dysfunction at an asymptomatic stage [3].

Vincristine, a tubulin-binding drug from the vinca-alkaloid group, is known for its dose-limiting neurotoxicity [4], but cardiotoxicity due to vincristine has been topic of debate. Coronary vascular events after administration of vinca-alkaloids have been reported in case reports on adult patients, often with known cardiovascular risk [5–9]. In long-term CCS, however, vincristine was not shown to entail higher risk of late self-reported myocardial infarction, when adjusted for cardiac radiation dose [10]. Our previous work showed that CCS who developed clinical heart failure more often had received vincristine than CCS without heart failure, but vincristine dose was not associated with incident heart failure after correction for anthracyclines and radiotherapy involving the heart region [11]. A single-centre Dutch echocardiography study in CCS showed a near-significant association between vincristine exposure and reduced fractional shortening. However, this study included high-risk CCS treated with either anthracyclines, radiotherapy involving the heart region, or the potentially cardiotoxic high-dose cyclophosphamide or ifosfamide, which may have attenuated the risk specific to vincristine in multivariable analysis [12].

Since vincristine is still frequently used to treat childhood cancer, we investigated the association between vincristine treatment and LV dysfunction on echocardiography, in the cardiology study of the Dutch Childhood Cancer Survivor Study, LATER cohort (1963–2001) part 2; clinical visit & questionnaire study (DCCSS LATER 2 CARD). Since we aimed to evaluate the effects of vincristine, we excluded CCS who received other potentially cardiotoxic therapy as well.

2. Material and methods

2.1. Study population

A detailed description of the DCCSS LATER 2 CARD study cohort and methodology has been published [13]. In brief, a nationwide cohort of ≥5-year CCS treated with potentially cardiotoxic therapies from 1963 to 2001 before the age of 18 years, along with an unexposed sibling cohort, were prospectively recruited between 2016 and 2020 for a cross-sectional outpatient clinic evaluation, including echocardiography. The current study focuses on CCS treated with vincristine as the only potentially cardiotoxic agent. CCS who also received anthracyclines, radiotherapy involving the heart region, cyclophosphamide, or ifosfamide were excluded. Since CCS in this exploratory study-arm do not undergo regular echocardiographic surveillance, we included an arbitrary maximum of 100 CCS. This number was slightly exceeded due to concurrent invitation at multiple centres. To account for the background cardiovascular risk, for each CCS, the 'nearest' control subject in terms of age and sex was selected from the LATER CARD sibling cohort in a 1:1 ratio, using propensity score matching. As these were not necessarily all siblings of the vincristine-treated CCS included in the current study, they are further referred to as untreated control group and no paired statistics were performed. Participants with congenital heart disease were excluded. All participants gave their informed consent for use of the study and historical data and the medical ethic boards of all centres approved the study protocol according to the declaration of Helsinki.

2.2. Data collection

Cancer diagnosis and treatment history, including cumulative vincristine dose, were previously obtained retrospectively and available from our central registry. The number of vincristine administrations was noted when registered.

Before their visit, participants completed questionnaires on medical history, cardiovascular risk factors and medication use. Chronic cardiovascular medication use was coded according to the Anatomical Therapeutic Chemical classification. Self-reported history of heart failure, myocardial infarction, hypertension and diabetes were validated against use of appropriate medication. Use of lipid lowering medication was also noted. Being overweight was defined as a body mass index >25.

For 78 CCS and 86 controls that participated in the DCCSS LATER study part 1, self-reported smoking history was available at a mean of, respectively, 4.3 and 3.5 years before the current participation. New participants at the current study completed more extensive questionnaires including smoking history. A participant was considered to ever have smoked when having smoked ≥1 cigarette/week for ≥1 year. At the outpatient clinic, length, weight and resting blood pressure were recorded.

A detailed echocardiography protocol was followed to ensure image quality and frame rate [14]. Two physicians (RM, JL) centrally performed standard structural and functional measurements, including biplane ejection fraction (LVEF) and diastolic function measurements [15,16]. Strain analyses were performed separately in vendor-independent software (2D CPA 1.4, TomTec Imaging Systems, Germany). End-systolic midwall global longitudinal strain (GLS) was calculated from three apical views [14,17,18]. GLS-rate represents the steepest slope of the GLS curve during systole. Global circumferential strain was obtained from the mid-ventricular parasternal short axis view (mid-GCS) and averaged over six segments. Reproducibility and feasibility measures of the primary outcome measurements were previously published. Measurement feasibility was slightly lower in CCS than controls and generally in accordance with the literature [14].

Qualitative references regarding GLS and mid-GCS concern the absolute values (i.e. -18% is lower and worse than −20%). Positive correlations indicate worsening (lower absolute) strain value.

2.3. Outcomes

Primary outcomes were the prevalence of an LVEF below normal (men <52%, women <54%), GLS below software-specific cut-off values, or relevant LV diastolic dysfunction defined as ≥grade 2 [15–17]. Secondary outcomes were LVEF and GLS as continuous values, additional measurements of LV systolic function (lateral mitral annular plane systolic excursion, tissue doppler lateral and septal s', GLS-rate, mid-GCS), diastolic function (E/A ratio, average E/e' ratio, septal and lateral e' and tricuspid regurgitation gradient), and structural measurements of the LV and left atrium.

2.4. Statistical analysis

Continuous variables are presented as mean (±SD) or median [range] where appropriate, and categorical variables as frequencies. Inference tests on matching variables (a good match defined as

standardized mean difference < 0.1) and echocardiographic measurements between CCS and controls were performed with the Student's *t*-test or Kruskall-Wallis test for continuous variables and Pearson chi-square of Fisher's exact test for categorical variables. Non-linearity of dose-response relationships between vincristine and cardiac function measurements was tested with restricted cubic splines with three knots.

Multivariable linear and logistic regression analyses were performed in CCS and controls combined to identify whether being a vincristine-treated CCS was an independent risk factor for cardiac dysfunction. These models always included age at echocardiography and sex, together with covariates with a *p*-value <0.2 in univariable analysis in either CCS or controls, as an exploratory selection criterion. Subsequently, we assessed the differential contribution of covariates in CCS versus controls with interaction terms in the linear models, by stepwise entering interactions with the most significant covariates and omitting any non-significant interactions. Of note, in multivariable analysis comparing risk of cardiac dysfunction in CCS versus controls, time variables regarding cancer diagnosis (age at diagnosis and time since diagnosis) were not considered confounders, since controls did not have cancer.

Two-sided *p*-values <0.05 were considered statistically significant. Since echocardiographic measurements are inter-correlated, we did not correct our secondary outcomes for multiple testing. All statistical tests beyond the primary outcomes should be regarded as exploratory. Analyses were performed in R (version 3.5.3, R Foundation, Vienna, Austria).

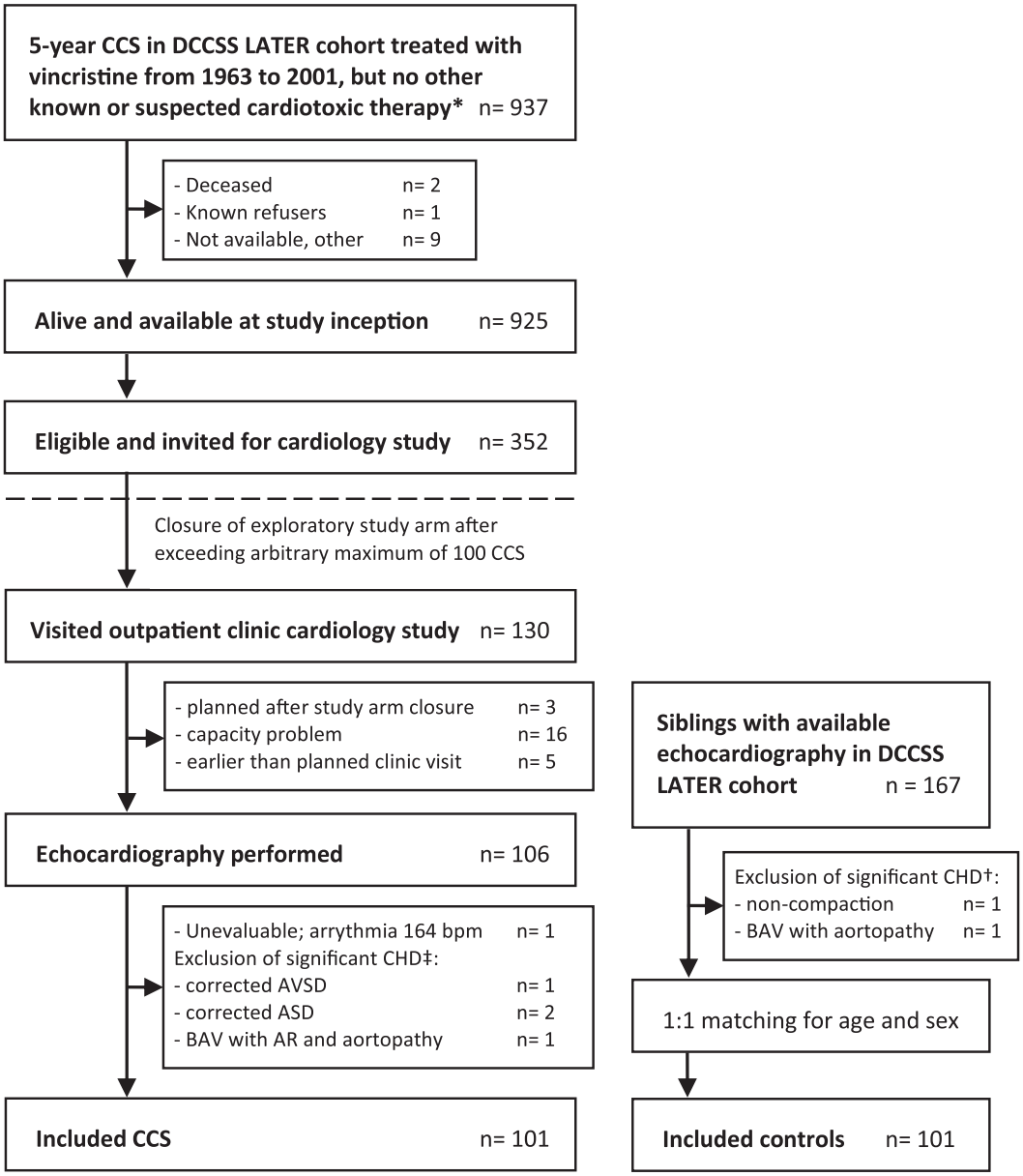

Fig. 1. Inclusion flowchart.
* Neither anthracyclines, radiotherapy involving the heart region, cyclophosphamide nor ifosfamide
†CHD were either known before cancer diagnosis (CCS), reported in LATER questionnaire and confirmed or detected at current echocardiography.
AR = aortic regurgitation; ASD = atrial septal defect; AVSD = atrioventricular septal defect; BAV = bicuspid aortic valve; CCS = childhood cancer survivors; CHD = congenital heart disease.

Table 1
Demography and baseline characteristics of vincristine-treated survivors and controls.

	Vincristine-treated CCS (n = 101)		Unexposed controls (n = 101)		SMD
Demography, diagnosis and treatment history					
Male/ female sex (n (%))	48/53	(48/53)	44/57	(44/56)	0.080
Age at cancer diagnosis, years (median [range])	4.0	[0.2–15.8]			
<5 (n (%))	59	(58)			
5–9	26	(26)			
10–14	15	(15)			
15–18	1	(1)			
Incidence year (median [range])	1987	[1970–2001]			
1970–1979 (n (%))	17	(17)			
1980–1989	40	(40)			
1990–1999	25	(25)			
≥2000	19	(19)			
Primary cancer diagnosis (n (%))					
Leukaemia	72	(71)			
Lymphoma / reticuloendothelial	6	(6)			
Central nervous system, other intracranial, intraspinal	5	(5)			
Renal	16	(16)			
Soft tissue	2	(2)			
Cumulative vincristine dose, mg/m^2 (median [range])	63	[10–138]			
<50 (n (%))	37	(37)			
50–100	61	(60)			
≥100	3	(3)			
Time since cancer diagnosis, years (median [range])	31	[16–48]			
10–19 (n (%))	31	(31)			
20–29	15	(15)			
30–39	42	(42)			
≥40	13	(13)			
Age at echocardiography, years (median [range])	35	[17–53]	35	[17–56]	0.085
15–24 (n (%))	25	(25)	18	(18)	
25–34	24	(24)	33	(33)	
35–44	35	(35)	35	(35)	
≥45	17	(17)	15	(15)	
Questionnaire data					
Self-reported diagnosis of heart failure[a] (n (%))	0		0		
Self-reported diagnosis of myocardial infarction[a] (n (%))	0		0		
Self-reported diagnosis of hypertension[a] (n (%))	4	(4)	0		
Self-reported diagnosis of diabetes[a] (n (%))	2	(2)	0		
Use of lipid lowering medication (n (%))	3	(3)	0		
Ever smoked >1 year[b] (n (%))	28	(30)	28	(35)	
Outpatient clinic data					
Body mass index, kg/m^2 (median [range])	25	[17–42]	25	[19–39]	
Systolic blood pressure, mmHg (mean (SD))	126	(16)	118	(14)	
Diastolic blood pressure, mmHg (mean (SD))	75	(12)	71	(10)	
Heart rate at echocardiography, bpm (mean (SD))	68	(11)	62	(11)	

CCS = childhood cancer survivors; SD = standard deviation; SMD = standardized mean difference (for matching variables only). No p-values are reported in Table 1 following the STROBE recommendations.
[a] Validated with appropriate medication use.
[b] Composite of LATER study part I and II. Valid for 102 CCS and 88 controls.

3. Results

3.1. Participants

The inclusion flowchart is shown in Fig. 1. Of 130 vincristine-treated CCS that visited the outpatient clinic, 101 CCS were included, along with 101 matched controls. Baseline demographics and clinical data are shown in Table 1 and details of non-participants in Supporting Table 1. Median age at diagnosis was 4.0 [0.2–15.8] years and median time since diagnosis 31 [16–48] years. Dominant cancer type was leukaemia (n = 72; 71%). Median cumulative vincristine dose was 63 [10–138] mg/m^2. The number of vincristine administrations was available for 51 CCS. No participants reported to be diagnosed with or treated for heart failure or myocardial infarction. Included CCS had a higher mean blood pressure and heart rate than controls, and six CCS and no controls were treated for hypertension.

3.2. Left ventricular systolic and diastolic function

Echocardiographic measurements are summarized in Table 2. LVEF could be measured in 88 CCS (87%) and 97 (96%) controls. Twelve CCS (14%) had an abnormal LVEF, compared to four controls (4%; p 0.034), with a lowest measured LVEF of 47% in CCS and 51% in controls. The mean LVEF was 58.4 (±4.7)% in CCS versus 59.7 (±3.7)% in controls (p 0.050).

GLS was measured in 79 (78%) CCS and 92 (91%) controls. Abnormal GLS was encountered in nineteen CCS (24%) and eight controls (9%; p 0.011) and mean GLS values were − 19.0 (±2.4) % versus −20.1 (±2.2)%, respectively (p 0.001). Mild differences were also found in other conventional measurements of LV systolic function, but not in mid-GCS and GLS-rate. Mean GLS was lower in CCS compared to controls in four out of six cardiac walls (Supporting Table 2).

No participants showed echocardiographic findings compatible with ≥grade 2 diastolic dysfunction.

3.3. Associations of LV systolic dysfunction

Table 3 shows the multivariable linear and logistic associations of LVEF and GLS. The univariable analyses underlying our variable selection are shown in Supporting Table 3.

Table 2
Echocardiographic measurements of vincristine-treated survivors and controls.

	Vincristine-treated CCS		Unexposed controls		*p*-value
Primary outcomes					
Abnormal LV ejection fraction[a]	**12**	**(14)**	**4**	**(4)**	**0.034**
Abnormal global longitudinal strain[b]	**19**	**(24)**	**8**	**(9)**	**0.011**
Diastolic dysfunction ≥grade II	0		0		1
Structural measurements					
Interventricular septum thickness, mm	7.8	(1.5)	7.4	(1.2)	0.069
LV end-diastolic diameter index, mm/m^2	24	(2)	25	(3)	0.256
LV end-diastolic volume index, ml/m^2	**50**	**(9)**	**53**	**(11)**	**0.041**
LV mass index, g/m^2	65	(14)	64	(13)	0.655
LA volume index, ml/m^2	23	(7)	25	(6)	0.075
Functional measurements					
LV ejection fraction, %	**58.4**	**(4.7)**	**59.7**	**(3.7)**	**0.050**
Global longitudinal strain, %	**−19.0**	**(2.4)**	**−20.1**	**(2.2)**	**0.001**
Mid-ventricular global circumferential strain, %	−21.9	(2.8)	−22.0	(3.2)	0.813
Global longitudinal strain rate, 1/s	−0.93	(0.12)	−0.95	(0.12)	0.384
Mitral annular systolic plane excursion, mm	**16**	**(3)**	**17**	**(3)**	**0.005**
Tissue Doppler LV septal s', cm/s	8	(1)	9	(1)	0.061
Tissue Doppler LV lateral s', cm/s	10	(2)	11	(2)	0.344
Diastolic dysfunction grade I, normal LV ejection fraction	1	(1)	0		0.466
Mitral inflow E/A ratio	1.6	(0.5)	1.6	(0.4)	0.878
Mitral average E/e' ratio	**5.9**	**(1.3)**	**5.4**	**(1.5)**	**0.020**
Tissue Doppler LV lateral e', cm/s	15	(4)	16	(4)	0.110
Tissue Doppler LV septal e', cm/s	**12**	**(3)**	**13**	**(3)**	**0.003**
TR gradient, mmHg	14	(5)	15	(6)	0.534

Continuous data are mean (standard deviation), proportions are n (%).
CCS = childhood cancer survivors; LA = left atrium; LV = left ventricle; TR = tricuspid regurgitation.
Bold values indicate statistical significance ($p < 0.05$).
[a] <52% for men, <54% for women.
[b] Age-, sex- and vendor specific cut-off values.

Abnormal LVEF was not significantly associated with being a CCS versus control (OR 3.07) but had wide 95% confidence intervals (1.0 to 11.6). The model for LVEF as a continuous outcome showed a significant interaction between CCS status and age at echo, which should be interpreted as younger CCS having a significantly lower LVEF than controls. The difference between CCS and controls for abnormal GLS, but not GLS as a continuous outcome, did reach significance (OR 3.55, 95%CI 1.37 to 10.1 and β 0.69, 95%CI -0.03 to 1.4, respectively).

Factors that significantly contributed to variation in LVEF were sex, age at echocardiography (in CCS), diastolic blood pressure and smoking history, whereas sex, obesity and diastolic blood pressure contributed to variation in GLS. Hypertension was too rare ($n = 4$) to include in the models. Instead, continuous blood pressure values were included. Since only few CCS used antidiabetics or lipid lowering medication, these variables were not included in the models, but sensitivity analyses showed similar results when these subjects were excluded from the models for GLS. In the linear regression model for GLS, no significant interactions were found between the included covariates and being a CCS versus control.

Within the CCS group, cumulative vincristine dose and the number of vincristine administrations did not satisfy our univariable selection criterion to be included in our multivariable models for either LVEF or GLS (Supporting Table 3 and Supporting Fig. 1). No significant non-linearity was observed. After adjusting for age and sex, cumulative vincristine dose and the number of vincristine administrations were not associated with abnormal LVEF (OR 0.88 per 50 mg/m^2, 95%CI 0.24 to 3.4; OR 0.58 per 10 administrations, 95%CI 0.23 to 1.3) or abnormal GLS (OR 1.14 per 50 mg/m^2, 95%CI 0.40 to 3.4; OR 1.04 per 10 administrations, 95%CI 0.48 to 2.6). Including diastolic blood pressure in the models did not alter these findings. Results in multivariable linear regression analysis were similar.

4. Discussion

Our systematic approach addressed mild echocardiographic abnormalities in long-term CCS treated with vincristine, but without other established or potentially cardiotoxic therapies. We showed an increased prevalence of abnormal GLS in these CCS compared to untreated controls, independent of other cardiovascular risk factors. Only mild LVEF abnormalities were found and important diastolic dysfunction was not encountered in these CCS. Although vincristine treatment is the common denominator in this sub-population of CCS, we did not find a dose-response relationship of measures of vincristine exposure with any of the systolic dysfunction measurements.

It is encouraging that none of the CCS in the current study reported a diagnosis of clinical heart failure, although this small cross-sectional cohort study prevents drawing conclusions on heart failure incidence. The prevalence of an abnormal LVEF (14%) in vincristine-treated CCS may seem higher than the 4.3% in anthracycline-treated CCS [19], but we emphasize that we defined abnormal LVEF with a higher cut-off value than in previous reports, following the latest chamber quantification guidelines [15]. Only two CCS showed an LVEF just below 50% in our cohort.

The prevalence of abnormal GLS (24%), however, is comparable to that found in anthracycline-treated CCS [19]. GLS is considered an earlier indicator of systolic dysfunction compared to LVEF, with superior predictive value for future heart failure and related events in various populations with (risk of) cardiovascular disease and adult cardio-oncology [20,21]. The occurrence of abnormal GLS among young survivors warrants investigation of its natural course and the clinical consequences later in life. Clinicians should be aware that also these CCS may have an elevated risk of future cardiovascular events.

Whether vincristine causes direct cardiac damage has been investigated in preclinical studies. In rats, interstitial cardiac endothelial cells went into arrest or apoptosis hours after high dose vincristine or vinblastine administrations, but no myocardial necrosis was found [22]. Endothelial cell damage was confirmed in porcine aortic cells [23]. Tochinai et al., by contrast, did show cardiomyocyte necrosis in rats and indeed suggested endothelial damage as causative mechanism [24]. Clinical studies may support the hypothesis of vascular toxicity, but

Table 3
Multivariable associations of systolic function measurements.

	Linear regression[a]			Logistic regression[a]		
	Multivariable β (95%CI)		*p*	Multivariable OR (95%CI)		*p*
LV ejection fraction						
CCS (vs no)	**−5.76**	**(−11.0 to −0.53)**	**0.031**	3.07	(1.0–11.6)	0.065
Female sex (vs male)	**1.67**	**(0.34–3.0)**	**0.014**	1.07	(0.37–3.2)	0.896
Age at echo (per year)	0.04	(−0.06–0.16)	0.426	0.94	(0.88–1.0)	0.075
BMI >25 kg/m^2 (vs ≤25)	−0.70	(−2.0–0.63)	0.300	[b]		
Diastolic BP (per 10 mmHg)[c]	**−0.70**	**(−1.4 to −0.05)**	**0.032**	1.42	(0.85–2.4)	0.182
Ever smoked >1 year (vs no)	**−2.21**	**(−3.6 to −0.77)**	**0.003**	[b]		
Interaction term:						
Age at echo*CCS	**0.15**	**(0.01–0.30)**	**0.041**			
R-squared[d]	*0.158*			*0.082*		
Global longitudinal strain [e]						
CCS (vs no)	0.69	(−0.03–1.4)	0.060	**3.55**	**(1.37–10.1)**	***0.012***
Female sex (vs male)	**−0.90**	**(−1.6 to −0.18)**	**0.015**	1.76	(0.70–4.62)	0.237
Age at echo (per year)	−0.03	(−0.07–0.02)	0.212	1.02	(0.97–1.08)	0.490
BMI >25 kg/m^2 (vs ≤25)	**0.80**	**(0.08–1.5)**	**0.031**	1.89	(0.76–4.94)	0.178
Diastolic BP (per 10 mmHg)[c]	**0.65**	**(0.31–0.99)**	**< 0.001**	1.39	(0.92–2.18)	0.130
Ever smoked >1 year (vs no)	0.09	(−0.68–0.86)	0.815	[b]		
R-squared[d]	*0.195*			*0.131*		

Childhood cancer survivors and controls were combined in the models.
BMI = body mass index; BP = blood pressure; CCS = childhood cancer survivors; LV = left ventricle.
Bold values indicate statistical significance ($p < 0.05$).
[a] All variables in the linear models were tested for interactions with being a CCS by stepwise addition starting with the most significant variable. No tests for interactions were performed in logistic regression due to the limited number of events.
[b] Univariable $p > 0.2$.
[c] Multicollinear with systolic blood pressure and equally related to cardiovascular risk in the general population under age 50 years [33]. Diastolic blood pressure had a slightly better fit in most of the models and was therefore chosen. Too few participants were diagnosed with hypertension.
[d] Adjusted R-squared for linear models, Nagelkerke pseudo-R-squared for logistic models.
[e] Global longitudinal strain is a negative number. Negative correlations indicate 'better' values and vice versa.

mainly in peripheral vasculature and vinca-alkaloids were only part of a regimen [25,7].

We generated working hypotheses on the associations and pathophysiology of the observed systolic dysfunction. An absent dose-response relation between vincristine (cumulative dose or number of administrations) and systolic function measurements, does not exclude a 'single-hit' or threshold association, individual variation in pharmacokinetics or vincristine-susceptibility, or indirect toxicity. GLS was more often abnormal in vincristine-treated CCS than in controls, independent of sex, age at echocardiography and diastolic blood pressure; such residual confounding likely results from unmeasured risk factors. Investigating GLS in CCS who received only surgical treatment, may provide useful insights in whether CCS are at higher risk of cardiac dysfunction, irrespective of received chemotherapy.

We found GLS and LVEF to be associated with diastolic blood pressure. Hypertension is highly prevalent in young CCS [26], but since only few CCS in our cohort used antihypertensive medication, analysis of blood pressure as a continuous variable, rather than a binary indicator of hypertension, was more feasible. Both LVEF and GLS are known afterload-dependent measurements, and blood pressure can influence GLS measurement [17,27–29], even independent of arterial hypertension [30]. The hypothesized vascular toxicity of vincristine may as well result in an increased afterload. However, the cross-sectional nature of our study precludes any conclusion on the possible contributions of afterload dependency of the outcome measurements and of cardiac damage due to longitudinal exposure to higher blood pressures. The association of being overweight with decreased GLS has also been previously shown in CCS and the general population [31,29].

In CCS treated with anthracyclines and/or radiotherapy to the heart region, Armstrong et al. showed less increasing risk ratios for abnormal GLS than for abnormal LVEF with increasing cardiotoxic doses, and a stronger correlation of abnormal GLS than abnormal LVEF with traditional cardiovascular risk factors [32]. As such, GLS may be representative of the traditional cardiovascular risk factors present in a long-term CCS, rather than being a sole indicator of treatment-related cardiotoxicity. Modification of common cardiovascular risk factors may thus be one key strategy to prevent future cardiovascular events for young patients whose chances to survive their respective childhood cancer depend on treatment modalities that may be cardiotoxic.

4.1. Limitations

In this heterogeneous historical cohort, many unknown potential confounders that may explain the difference in abnormal GLS between CCS and controls remained unmeasured. These confounders may relate to the cancer diagnosis and treatment period as well as the long period until the current study, and may include other somatic late effects, lifestyle and environmental factors. A dose-response relation is one of the few signs suggestive of causality in observational studies. We assessed alternative dose-response hypothesis with the number of vincristine administrations, but data were limited. Logistic regression analysis of abnormal LVEF may have been underpowered due to few events. Three-dimensional LVEF measurements were not systematically obtained in all participating centres and carried a high risk of selection bias [14]. Questionnaires were currently the best data source for medical history and medication use, since new diagnoses of heart failure, diabetes or hypertension at the current visit required referral, follow-up visits or additional investigations which were not recorded.

5. Conclusions

Long-term CCS treated with vincristine, but without anthracyclines, radiotherapy involving the heart region, cyclophosphamide or ifosfamide, showed an increased prevalence of abnormal GLS compared to controls, independent of age, sex, obesity and blood pressure. This finding remained partially unexplained since there was no dose-response relation between vincristine exposure and LVEF or GLS. Traditional cardiovascular risk factors contributed to abnormal GLS and LVEF. Whether vincristine-treated CCS with abnormal GLS are at risk of cardiovascular events later in life and would benefit from early

cardiovascular risk factor modification, should be evaluated.

Availability of data

De-identified data may be shared with investigators who would like to collaborate after the main analyses of the LATER CARD study are finished. Applications of intent can be sent to the LATER study group via e.a.m.feijen@prinsesmaximacentrum.nl.

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Protocol registration

Netherlands Trial Registry number 7481.

Author statement

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Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

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