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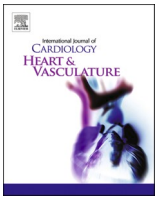

Time course of hypertension and myocardial dysfunction following anthracycline chemotherapy in pediatric patients

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ABSTRACT

Background: Anthracyclines are associated with cardiac dysfunction. Little is known about the interplay of pre-existing hypertension and treatment response. We aimed to investigate the relationship between hypertension and the development of cancer therapy-related cardiac dysfunction (CTRCD) in pediatric patients treated with anthracycline chemotherapy.

Methods: Pediatric patients with cancer who received anthracycline chemotherapy from 2013 to 2021 were retrospectively included. Serial cardiac assessments were conducted during and after chemotherapy. The primary outcome was the development of CTRCD, classified as mild, moderate, or severe according to contemporary definitions.

Results: Among 190 patients undergoing anthracycline chemotherapy, 34 patients (17.9 %) had hypertension (24 patients Stage 1, and 10 patients Stage 2) at baseline evaluation. Patients underwent chemotherapy for a median of 234.4 days (interquartile range 127.8–690.3 days) and were subsequently followed up. Hypertension was frequent during follow-up 31.3 % (0–3 months), 15.8 % (3–6 months), 21.9 % (0.5–1 years), 24.7 % (1–2 years), 31.1 % (2–4 years) and 35.8 % (beyond 4 years) (P for trend < 0.001). Freedom from mild CTRCD at 5 years was 45.0 %, freedom from moderate CTRCD was 87.8 % at 5 years. Baseline hypertension did not increase the risk of mild (HR 0.77, 95 % CI: 0.41–1.42, $P = 0.385$) or moderate CTRCD (HR 0.62, 95 % CI: 0.14–2.72, $P = 0.504$). Patients with baseline hypertension showed different global longitudinal strain ($P < 0.001$) and LVEF ($P < 0.001$) patterns during follow-up.

Conclusions: Pediatric patients often develop CTRCD post-anthracycline chemotherapy. Those with pre-existing hypertension show a unique treatment response, despite no increased CTRCD risk, warranting further investigation.

1. Introduction

The estimated annual incidence of cancer among children and adolescents is about 190 cases per 1 million,[1] with approximately 1 in 285 children diagnosed with cancer prior to 20 years of age. Anthracyclines form the core of numerous chemotherapeutic regimens to treat a broad range of malignancies, including solid organ tumors, leukemias, and lymphomas. Therapeutic advancements have improved the overall survival rate to as high as 85 %,[2] such that every 1 out of 530 young adults is a survivor of childhood cancer.[3] However, some patients who survive the initial 5 year period, depending on the specific malignancy and the type of treatment they received, are still at risk of chemotherapy-related multiorgan dysfunction.[4] Cancer therapy-related cardiac dysfunction (CTRCD) linked to anthracyclines is well known, and represents a spectrum from an asymptomatic reduction in left ventricular ejection fraction (LVEF) to overt heart failure (HF).[4] Other reported complications can include *myo-* or *peri*-carditis and transient subclinical arrhythmias.[4] While the likelihood of these complications depends on the cumulative dose, no specific dosage limitation guarantees safety,[5] as illustrated in the Children's Oncology Group (COG) report that among 1,022 pediatric patients with acute myeloid leukemia approximately 12 % of patients experienced cardiotoxicity, with more than 70 % of

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incident events occurring during on-protocol therapy.[6] However, estimates of the magnitude of the cardiotoxicity risk after anthracycline therapy vary considerably. To help resolve the significant variations in reported cardiotoxicity frequency, a recent consensus statement from the International Cardio-Oncology Society (IC-OS) was formulated which standardize definitions of cardiotoxicity for future research, and to facilitate communication across disciplines to improve clinical outcomes for cancer patients.[7] It is hoped that with enhanced awareness of cardiotoxicity, and its assessment by both LVEF and global longitudinal strain (GLS), cardioprotective measures can be more effectively guided, potentially leading to improved long-term outcomes.[8] In addition, it remains crucial to manage traditional cardiovascular comorbidities such as hypertension, obesity, dyslipidemia, chronic kidney disease, and diabetes, which are known to be associated with subsequent cardiac events in adult childhood cancer survivors.[9] Using contemporary definitions, this observational study aims to evaluate the association of pre-existing hypertension with the onset and progression of CTRCD in pediatric patients treated with anthracycline chemotherapy.[7]

2. Methods

2.1. Study population

We retrospectively identified cancer patients who received anthracycline chemotherapy (specifically doxorubicin, epirubicin, daunorubicin, idarubicin, or mitoxantrone) as part of their tailored regimen at The Johns Hopkins Hospital from January 2013 to September 2021. All patients received a standard regimen including anthracyclines. The cumulative total dose of anthracyclines was converted to a doxorubicin equivalent using evidence-based equivalence ratios.[10] Throughout treatment and subsequent post-chemotherapy follow-up, these patients underwent serial cardiac assessment using conventional 2-dimensional echocardiography when clinically indicated, as determined by the treating oncologist. To be eligible for the study, patients were required to have a baseline assessment not more than 25 days prior to starting chemotherapy, a minimum of 2 total echocardiographic assessments, and longitudinal follow-up at our institution. Patients receiving other medications with potential cardiotoxic effects, and those with inadequate image quality for myocardial deformation analysis, any level of valvular stenosis, valvular regurgitation, or a history of prior heart failure were excluded. The study was approved by the Johns Hopkins Medicine institutional review board with waiver of informed consent due to the retrospective nature of the study.

2.2. Clinical assessment

Sex- and age-standardized weight, height, and BMI metrics were obtained from Centers for Disease Control and Prevention (CDC) growth charts for the United States.[11] Blood pressure (BP) was measured immediately prior to echocardiography examinations following a standardized protocol. An automated, appropriately sized cuff was chosen and BP was measured in the sitting position, in the right arm, unless otherwise indicated in the standard measurement guidelines. Definitions for hypertension (HTN) as proposed by the American Academy of Pediatrics, were followed.[15] Patients were classified into categories according to the following definitions for systolic − (SBP) and diastolic BP (DBP): normal BP (<90th percentile for age, sex, and height), elevated BP (90–95th percentile, or SBP $\geq$ 120 and/or DBP $\geq$ 80 mm Hg), stage 1 HTN (95th percentile – < 95th percentile + 12 mm Hg, or SBP $\geq$ 130 and/or DBP $\geq$ 80), and stage 2 HTN (SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg, or $\geq$ 95th percentile + 12 mm Hg).[12–15] Age- and height adjusted Z-scores for BP were obtained from the Boston Children's Hospital Z-score calculator.[16]

2.3. Echocardiography measurements and analysis

All patients underwent a comprehensive transthoracic echocardiogram as part of their routine chemotherapy surveillance. Standard images were acquired from standard imaging windows, and measurements were made according to the American Society of Echocardiography guidelines following a standardized protocol.[17] Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane measurement in the apical four- and two-chamber views. Left ventricular fractional shortening (LVFS) was obtained from M-mode imaging in the parasternal long-axis view. Global longitudinal strain (GLS) was measured using speckle tracking echocardiography (STE) in the apical four-chamber, two-chamber, and three-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was obtained from M-mode imaging in the apical four-chamber view. Diastolic dysfunction was assessed by analyzing transmitral and pulmonary venous inflow patterns using pulsed-wave Doppler in the apical four-chamber view, and tissue Doppler imaging at the septal and lateral mitral annuli.

2.4. Study outcomes

Development of CTRCD was the primary outcome and was classified into mild, moderate and severe categories based on the recommendations by the IC-OS Consensus statement.[7,18] Mild CTRCD: LVEF $\geq$ 50 % with a new relative decline in GLS > 15 % from baseline and/or a new elevation in cardiac biomarkers; moderate CTRCD: absolute LVEF reduction $\geq$ 10 % resulting in an LVEF of 40–49 %, or a reduction < 10 % to an LVEF between 40–49 %, with a new relative decline in GLS > 15 % from baseline and/or a new elevation in cardiac biomarkers; severe CTRCD: LVEF < 40 %.

2.5. Statistical analysis

Normality of the distribution of continuous variables was tested using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables were expressed as counts and relative frequency (%). Time-to-event data was plotted using the Kaplan–Meier method. To assess the relationship between baseline variables and CTRCD, we employed Cox regression models. Cox regression models with time-dependent covariates were used to examine how variables assessed during serial follow-up were associated with CTRCD. Repeated measures correlation was used to assess the strength and direction of association between two variables repeatedly measured on the same subject across multiple time points. Longitudinal parameters obtained from clinical evaluations and serial follow-up echocardiograms were visualized using per-patient time profiles, with overall trend lines obtained from locally estimated scatterplot smoothing. Generalized estimating equations with independent correlation structure and robust standard errors were used to model the effect of time and group on these variables using cubic polynomials. A 2-tailed p-value < 0.05 was considered statistically significant. Analysis was completed using R Statistical Software (version 4.1.1, Foundation for Statistical Computing, Vienna, Austria) and Python (version 3.11.3, Python Software Foundation).

3. Results

3.1. Study population

A total of 190 patients (median 15.6 years [IQR: 10.4–18.7], 63.2 % male) were eligible for inclusion in the study. Clinical characteristics of the entire study cohort are summarized in Table 1. Mean follow-up after initiation of chemotherapy was 3.0 years, during which these 190 patients had a cumulative total of 1294 follow-up echocardiograms (6.8 ± 4.1 studies per patient). At baseline, 34 patients (17.9 %) had HTN (24

Table 1
Clinical characteristics of study cohort.

Characteristic	All Patients (N = 190)	No HTN (N = 156)	Baseline HTN (N = 34)	*p*-value
Demographics				
Age, years	15.6 [10.4, 18.7]	16.6 [12.9, 19.1]	7.76 [3.7, 12.1]	**<0.001**
Male	120 (63.2 %)	100 (64.1 %)	20 (58.8 %)	0.702
Diagnosis				0.190
Lymphoma	50 (26.3 %)	48 (30.8 %)	2 (5.88 %)	
Sarcoma	49 (25.8 %)	43 (27.6 %)	6 (17.6 %)	
AML	16 (8.42 %)	14 (8.97 %)	2 (5.88 %)	
ALL	36 (18.9 %)	24 (15.4 %)	12 (35.3 %)	
Blastoma	9 (4.74 %)	5 (3.21 %)	4 (11.8 %)	
Wilms tumor	10 (5.26 %)	4 (2.56 %)	6 (17.6 %)	
Other	20 (10.5 %)	18 (11.5 %)	2 (5.88 %)	
Duration of chemotherapy, days	234.4 [127.8, 690.3]	215.5 [124.2, 566.1]	372.6 [208.2, 767.0]	**0.015**
Cumulative anthracycline exposure[a], mg/m^2	200 [135.0, 340.0]	204 [150.0, 348.0]	147 [98.3, 196.0]	**0.001**
Duration of follow-up, years	2.7 [1.2, 4.2]	2.9 [1.5, 4.3]	2.3 [0.7, 3.3]	**0.039**
Clinical Assessment				
BMI Z-score	0.52 [-0.65, 1.29]	0.56 [-0.63, 1.27]	0.24 [-0.66, 1.34]	0.830
Height Z-score	0.19 [-0.66, 1.02]	0.19 [-0.64, 1.00]	0.07 [-0.95, 1.11]	0.858
Weight Z-score	0.46 [-0.50, 1.27]	0.56 [-0.49, 1.28]	0.30 [-0.43, 0.85]	0.522
Systolic BP Z-score	0.72 (1.23)	0.51 (1.22)	1.68 (0.71)	**<0.001**
Diastolic BP Z-score	0.65 [-0.03, 1.34]	0.51 [-0.14, 1.02]	2.25 [1.29, 2.98]	**<0.001**
MAP Z-score	0.62 (1.08)	0.35 (0.90)	1.89 (0.93)	**<0.001**
HTN Classification				
Normal	126 (66.3 %)	126 (80.8 %)	0 (0.0 %)	
E levated blood pressure	30 (15.8 %)	30 (19.2 %)	0 (0.0 %)	
Stage 1 HTN	24 (12.6 %)	0 (0.0 %)	24 (70.6 %)	
Stage 2 HTN	10 (5.26 %)	0 (0.0 %)	10 (29.4 %)	
Echocardiography assessment				
LVESV, ml	23.4 [16.7, 31.7]	24.3 [18.5, 33.0]	16.3 [12.6, 21.9]	**0.005**
LVEDV, ml	69.7 [47.5, 87.2]	71.4 [52.9, 90.1]	40.2 [34.0, 59.9]	**0.002**
LVESVi, ml/m^2	15.1 [12.7, 19.1]	15.0 [12.6, 19.3]	15.6 [13.5, 17.8]	0.972
LVEDVi, ml/m^2	42.7 [37.6, 50.2]	43.2 [37.6, 51.6]	41.3 [37.7, 45.1]	0.248
LVFS, %	37.4 [33.7, 40.9]	37.4 [33.8, 41.0]	37.7 [33.3, 40.2]	0.696
LVEF, %	64.7 (5.0)	64.8 (5.0)	64.2 (5.1)	0.534
$LVEF_{3D}$, %	61.9 (3.9)	61.7 (3.9)	62.6 (4.0)	0.385
GLS, %	−20.5 (3.0)	−20.3 (3.1)	−21.3 (2.5)	0.070
TAPSE, cm	2.3 (0.5)	2.4 (0.5)	2.2 (0.4)	**0.045**
Diastolic dysfunction	9 (4.7 %)	6 (3.9 %)	3 (8.8 %)	0.053

LEGEND: Normally distributed variables were presented as mean ± standard deviation while non-normally distributed variables were presented as median (interquartile range). Categorical variables are expressed as frequency (percentage). [a]Cumulative lifetime dose expressed as doxorubicin equivalent. ABBREVIATIONS: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; GLS, global longitudinal strain; HTN, hypertension; LVEF, left ventricular ejection fraction, LVEDV, LV end diastolic volume, LVESV, LV end systolic volume, LVFS, left ventricular fractional shortening; LVEDVi, LVEDV indexed to BSA; LVESVi, LVESV indexed to BSA; MAP, mean arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

patients with Stage 1, and 10 patients with Stage 2). Only one patient had hypotension at baseline (0.5 %), defined as DBP < 5th percentile, while 3 patients (1.6 %) demonstrated DBP < 10th percentile. None of the patients were receiving cardiac medications at baseline. Patients with HTN were significantly younger, had a longer duration of chemotherapy, and lower cumulative anthracycline exposure. Systolic LV function, measured by LVEF or GLS, was not significantly different at baseline between groups. Conversely, systolic RV function was significantly lower in patients with HTN, although there is substantial overlap in the range between these two groups and the sample size in the HTN group is small.

3.2. Clinical outcomes

During longitudinal follow-up, the percentage of hypertensive patients was high during the entirety of follow-up. At 0–3 months, any stage of HTN was present in 31.3 %, between 3–6 months the percentage was decreased at 15.8 %. During subsequent follow-up stages the prevalence increased slowly, 21.9 %, 24.7 %, 31.1 % and 35.8 % at 0.5–1 year, 1–2 years, 2–4 years and beyond 4 years, respectively. Stage 2 HTN was high during the initial 6 months (10.6 % between 0–3 months and 11.0 % between 3–6 months), followed by slightly decreasing numbers up to 4 years follow-up. The percentage of HTN changed significantly during follow-up (P for trend < 0.001). (Fig. 1). Of the 190 patients, 83 developed (43.7 %) at least mild CTRCD during follow-up, with a total of 97 CTRCD events. Of these 97 events, 76 (78.4 %) were due to declines in GLS, whereas the minority was due to changes in LVEF (21.6 %). Freedom from mild CTRCD was 64.9 % (58.2 – 72.4), 56.0 % (48.5 – 64.5), and 45.0 % (35.7 – 56.7) at 1-, 3- and 5-year follow-up respectively (Fig. 2). Moderate CTRCD was less common and occurred in 18 patients (9.5 %). Freedom from moderate CTRCD was 92.7 % (88.9 – 96.6), 89.6 % (84.9 – 94.5), and 87.8 % (82.2 – 93.8) at 1-, 3- and 5-year follow-up respectively (Fig. 2). Severe CTRCD, defined as a new LVEF reduction to < 40 %, occurred in 3 patients (1.6 %). Freedom from severe CTRCD was 98.1 % (95.9 – 100.0) at 5-years follow-up (Fig. 2). Differences in baseline characteristics between patients who developed CTRCD and those who did not are presented in Supplemental Table 1. Patients who developed CTRCD were on average more male (72.3 % vs. 56.1 %, P = 0.032), and had a higher cumulative anthracycline exposure (225 [IQR 150, 371] vs 189 [IQR 124, 295] mg/m^2, P = 0.037). During follow-up, angiotensin-converting enzyme (ACE) inhibitors and β-blockers were initiated in 28 (14.7 %) and 9 (4.7 %) patients, respectively. Rates of initiation of cardiac medications did not differ between patients with baseline HTN and those without (3 [8.8 %] vs. 25 [16.0 %] for ACE-inhibitors [P = 0.420], and 8 [5.1 %] vs. 1 [2.94 %] for β-blockers [P = 1.000]). Two (1.1 %) patients were started on diuretics.

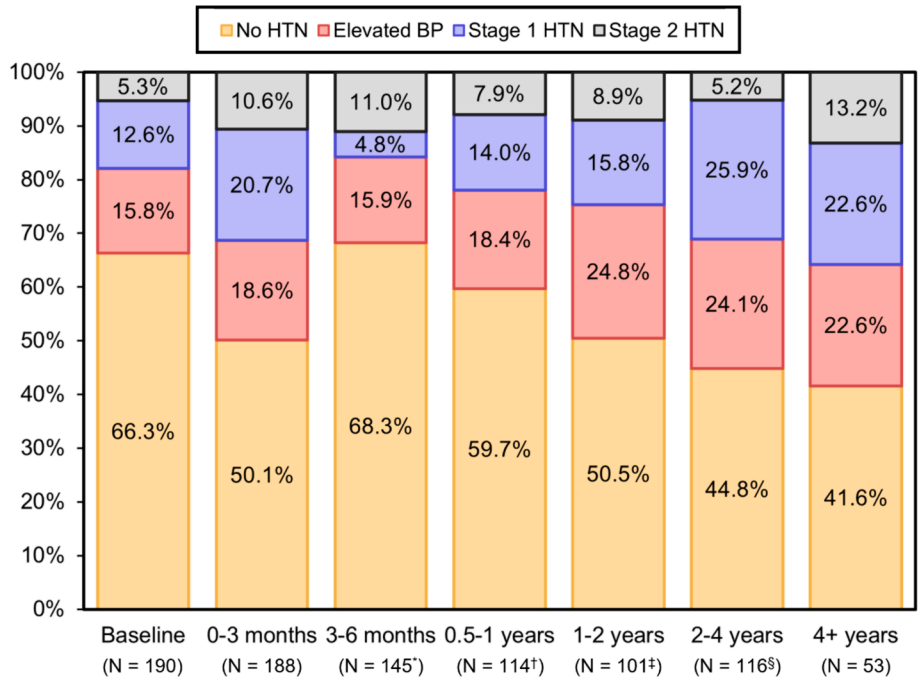

Fig. 1. Cross-sectional representation of hypertension stages during echocardiographic follow-up. LEGEND: Hypertensive stages during follow-up in patients who had a clinical examination within the specified timeframe. *Only 145 patients out of 187 patients (77.5 %) had blood pressure measurements available in this period. †Only 114 patients out of 169 patients (67.5 %) had blood pressure measurements available in this period. ‡Only 101 patients out of 150 patients (67.3 %) had blood pressure measurements available in this period. §Only 116 patients out of 125 patients (92.8 %) had blood pressure measurements available in this period. ABBREVIATIONS: BP, blood pressure; HTN, hypertension.

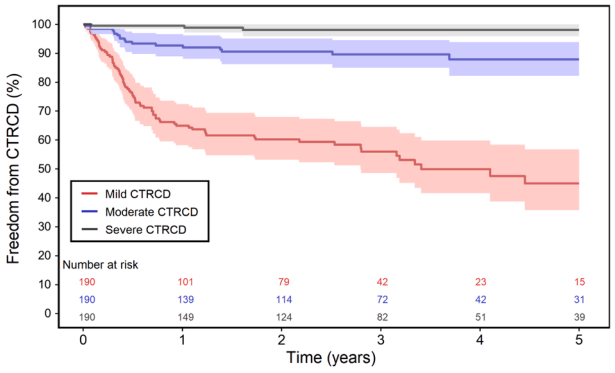

Fig. 2. Freedom from Cancer Therapy–Related Cardiac Dysfunction. LEGEND: Freedom from the primary outcome of CTRCD stratified to severity. ABBREVIATIONS: CTRCD, cancer therapy-related cardiac dysfunction; HTN, hypertension.

Medications were more often prescribed in patients with CTRCD than those without (33.7 % vs 5.6 %, P < 0.001). Comparison of baseline characteristics between patients who received medications versus those who did not are presented in Supplemental Table 2 and 3.

Following the occurrence of mild CTRCD, on average, both GLS (−0.22 % per year, P < 0.001) and LVEF (0.55 % increase per year, P < 0.001) improved significantly (Fig. 3). After moderate CTRCD, on average, both GLS (−0.64 % per year, P < 0.001) and LVEF (2.16 % increase per year, P < 0.001) improved significantly (Fig. 3). As such, over the course of follow-up (3.9 ± 2.3 years), normalization of LVEF (final value of LVEF > 50 %) occurred in 16 patients (88.9 %), with 1 patient showing initial improvement followed by a second deterioration period and another with continued decline up to 2 years follow-up. However, only 5 patients (27.8 %) had a complete recovery (final value of LVEF ≥ baseline).

Assessment of baseline and time-dependent variables associated with CTRCD are presented in Table 2.

Cancer diagnosis was associated with different rates of both mild and moderate CTRCD (P = 0.003 and P = 0.004, respectively), with patients treated for sarcoma or acute myeloid leukemia having the highest cumulative incidence of CTRCD. Baseline hypertension was not associated with an increased risk of mild or moderate CTRCD (HR 0.77 [95 % CI: 0.41–1.42, P = 0.385] and HR 0.62 [95 % CI: 0.14–2.72, P = 0.504], respectively). On longitudinal evaluation, blood pressure measurements (SBP Z-score, DBP Z-score, and MAP Z-score) did not demonstrate noteworthy associations with the risk of CTRCD, with the exception of SBP Z-score on moderate CTRCD (55 % decreased risk with a 1 unit increase in Z-score, HR 0.45 [95 % CI: 0.27–0.75, P = 0.002]. As expected, all echocardiographic measurements of both RV- and LV- function were associated with the occurrence of CTRCD.

Interestingly, the repeated measures correlation between GLS and SBP Z-score was statistically significant, with a negative correlation (r = -0.10, 95 % CI: −0.17 – −0.04, P = 0.004, Supplemental Fig. 1), while there was no significant correlation with either DBP- or MAP Z-score (P = 0.100 and P = 0.613, respectively). This significant correlation was also observed for LVEF, with a positive correlation (r = 0.13, 95 % CI: 0.08 – 0.20, P < 0.001, Supplemental Fig. 1). Similarly, there were no significant correlations with DBP- or MAP Z-scores (P = 0.345 and P = 0.178, respectively).

3.3. *Alterations in blood pressure and cardiac systolic function*

Patients were classified based on whether they had HTN at baseline, as described above. Time profiles of parameters obtained from clinical evaluations and serial follow-up echocardiograms are shown in Fig. 4, for the overall population and stratified by HTN status. Volume status of the LV was substantially different between groups over time (P < 0.001 for both LVEDVi and LVESVi). Patients with HTN demonstrated faster progressive increases in their GLS compared to patients without baseline HTN (P < 0.001). A similar pattern was observed for TAPSE, which also

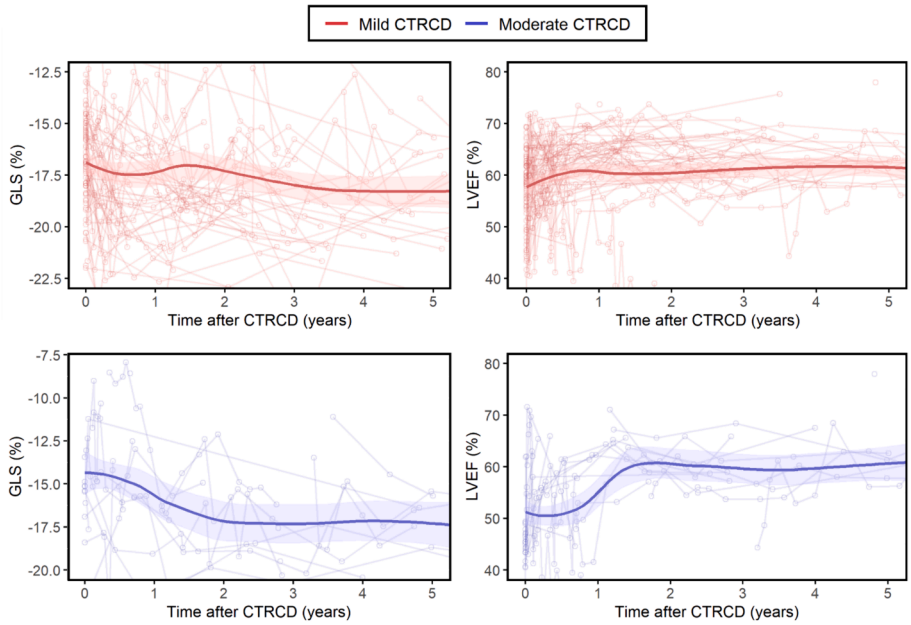

Fig. 3. Changes in LVEF and GLS after the occurrence of CTRCD. LEGEND: Changes in GLS and LVEF following the onset of CTRCD. ABBREVIATIONS: CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain, LVEF, left ventricular ejection fraction.

demonstrated faster progressive decreases compared to those without HTN ($P < 0.001$). On the contrary, LVEF demonstrated slower decreases and recovered faster after chemotherapy in patients with HTN ($P < 0.001$). BP patterns (SBP Z-scores, DBP Z-scores and MAP Z-scores) were also significantly different, overall decreases were observed in both groups during chemotherapy, with significantly larger decreases in patients with baseline HTN ($P < 0.001$, for all respectively). Around 6 months following initiation of chemotherapy, the BP patterns in those with baseline HTN demonstrated progressive increases.

4. Discussion

We demonstrate that baseline hypertension is not associated with the occurrence of ventricular dysfunction and the development of CTRCD during short- to medium-term follow-up post anthracycline chemotherapy in pediatric patients. However, patients with baseline hypertension were significantly younger and had a lower cumulative anthracycline exposure, which might have reduced their risk of CTRCD. Notably, these findings are in contrast to those observed in adult populations, where baseline hypertension, especially when complicated by left ventricular hypertrophy, was significantly associated with CTRCD. [19,20]

4.1. Importance of the early recognition of cardiovascular toxicities of cancer therapies

The incidence of cardiotoxicity has been reported between 30–50 % in children, adolescents and young adults.[21–23] This broad range in the reported incidence of CTRCD is likely explained by the heterogeneity of definitions and study cohorts. The newly recommended definitions of CTRCD by the IC-OS aim to unify the existing definitions and specify criteria to describe disease severity. This is particularly important in overall survival outcomes as demonstrated in the adult literature where a decline in LVEF below 50 % can have detrimental effects on both continuation of cancer therapy, and cancer prognosis itself.[7] More importantly, it is the persistent LV dysfunction (LVEF < 50 %), with lack of recovery despite optimal treatment, rather than transient dysfunction, that plays a role in adverse long term cardiovascular events in adults. [24] In our cohort, 2 patients demonstrated absence of recovery, and will need close longitudinal follow-up to determine if they will have future adverse outcomes. LVEF and GLS are often abnormal in childhood cancer survivors treated with anthracycline chemotherapy. For example, recent results from the DCCSS LATER Study Cohort revealed that in childhood cancer survivors treated with anthracycline chemotherapy, 22 % demonstrated abnormal LVEF, 26 % demonstrated abnormal GLS while only 13 % demonstrated abnormalities in both LVEF and GLS during a median follow-up of 26.7 years, potentially highlighting the incremental benefit of GLS in detecting CTRCD.[25] This incremental value is recognized in the current guidelines, where GLS is an arbiter of whether a decline in LVEF is representative of true deterioration in LV systolic function, and consequently CTRCD. The cumulative incidence of symptomatic heart failure reaches 10.6 % at 40-years following initial cancer diagnosis,[26] which is paramount since these patients demonstrate a 5-year survival of less than 50 %.[27] Additionally, in the DCCSS LATER Study Cohort, 6.4 % developed hypertension during a median of 26.7 years after diagnosis.[25] This is a substantial number, and indicates that hypertension is among the most commonly recognized adverse sequelae, but still lower in comparison to that reported post administration of local radiotherapy to the chest.[25]

4.2. Cellular and molecular pathways of CTRCD and hypertension: A vicious cycle

Anthracycline-related cardiac toxicity is a multifactorial process, and theories vary about exact pathophysiological mechanism. Earliest reports have focused on the oxidative stress response model for the development of both hypertension and CTRCD.[28] However other mechanisms have also been described, including reduced nitric oxide generation, endothelial dysfunction, increased sympathetic outflow, as well as renal effects of anticancer therapy. Genetic polymorphisms in vascular endothelial growth factor receptors have also been implicated in vascular endothelial growth factor inhibitor-induced hypertension. Regarding CTRCD development, one of the most important mechanisms include iron-mediated generation of reactive oxygen species, with resulting mitochondriopathy and cellular apoptosis.[28] Other mechanisms such as the targeting of cardiomyocyte components like topoisomerase-IIβ, leading to breakage of DNA and subsequent impairment of transcription and translation have also been described.[29] It has also

Table 2
Cox regression model and time-dependent Cox regression model for the risk on outcomes.

Baseline variables	Moderate CTRCD (N = 18/190) HR (95 % CI)	p-value	Mild CTRCD (N = 83/190) HR (95 % CI)	p-value
Demographics				
Age, years	1.07 (0.98–1.17)	0.096	1.04 (1.01–1.08)	**0.014**
Male	1.15 (0.43–3.06)	0.781	1.66 (1.03–2.69)	**0.033**
Diagnosis		**0.004**		**0.003**
Lymphoma	Reference		Reference	
Sarcoma	1.65 (0.39–6.89)		2.28 (1.20–4.31)	
AML	9.03 (2.33–35.0)		3.82 (1.74–8.37)	
ALL	0.87 (0.14–5.19)		1.57 (0.77–3.18)	
Blastoma	NA		0.46 (0.06–3.48)	
Wilms tumor	NA		0.57 (0.13–2.48)	
Other	0.76 (0.08–7.27)		2.12 (0.97–4.62)	
Cumulative anthracycline exposure[a], per 10 mg/m^2	1.03 (1.00–1.07)	**0.045**	1.02 (1.00–1.03)	0.089
Clinical Assessment				
BMI Z-score	0.94 (0.67–1.31)	0.705	1.04 (0.90–1.19)	0.633
Height Z-score	1.02 (0.75–1.39)	0.895	0.95 (0.83–1.08)	0.411
Weight Z-score	0.94 (0.65–1.37)	0.760	0.98 (0.83–1.16)	0.817
HTN Classification		**0.046**		0.703
Normal	Reference		Reference	
Elevated blood pressure	NA		1.26 (0.71–2.24)	
Stage 1 HTN	0.35 (0.05–2.64)		0.77 (0.36–1.62)	
Stage 2 HTN	0.87 (0.12–6.58)		0.89 (0.32–2.45)	

Time-dependent variables	Moderate CTRCD (N = 18/190) HR (95 % CI)	p-value	Mild CTRCD (N = 83/190) HR (95 % CI)	p-value
Clinical Assessment				
Systolic BP Z-score	0.45 (0.27–0.75)	**0.002**	0.90 (0.72–1.13)	0.347
Diastolic BP Z-score	0.85 (0.48–1.49)	0.565	1.07 (0.87–1.30)	0.532
MAP Z-score	0.59 (0.31–1.12)	0.108	1.00 (0.99–0.79)	0.989
HTN Classification				
Normal	Reference		Reference	
Elevated blood pressure	0.27 (0.03–2.18)	0.222	0.71 (0.36–1.39)	0.312
Stage 1 HTN	0.71 (0.16–3.13)	0.649	0.91 (0.48–1.72)	0.773
Stage 2 HTN	NA		1.18 (0.48–2.89)	0.718
Echocardiography assessment				
LVFS, %	0.59 (0.54–0.66)	**<0.001**	0.85 (0.81–0.89)	**<0.001**
LVEF, %	0.62 (0.56–0.68)	**<0.001**	0.86 (0.83–0.89)	**<0.001**
$LVEF_{3D}$, %	0.60 (0.50–0.72)	**<0.001**	0.84 (0.80–0.89)	**<0.001**
GLS, %	1.78 (1.53–2.06)	**<0.001**	1.40 (1.30–1.50)	**<0.001**
TAPSE, cm	0.13 (0.05–0.36)	**<0.001**	0.46 (0.28–0.75)	**0.002**
Diastolic dysfunction	8.37 (3.22–21.8)	**<0.001**	2.91 (1.86–4.56)	**<0.001**

LEGEND: Normally distributed variables were presented as mean ± standard deviation while non-normally distributed variables were presented as median (interquartile range). Categorical variables are expressed as frequency (percentage). [a]Cumulative lifetime dose expressed as doxorubicin equivalent. ABBREVIATIONS: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index; BP, blood pressure; CI, confidence interval; CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; HR, hazard ratio; HTN, hypertension; LVEF, left ventricular ejection fraction, LVEDV, LV end diastolic volume, LVESV, LV end systolic volume, LVFS, left ventricular fractional shortening; LVEDVi, LVEDV indexed to BSA; LVESVi, LVESV indexed to BSA; MAP, mean arterial pressure; TAPSE, tricuspid annular plane systolic excurs.

been reported that C-13 alcohol metabolites of anthracyclines, can negatively impact calcium regulation and cardiac contractility through inhibition of the sodium-calcium exchange and increased L-type calcium channel activity.[30] All of these mechanisms have important genetic determinants, which might additionally explain interpatient variability in incidence of CTRCD.[30] Lastly, both hypertension and cardiac dysfunction are intertwined in a complex and reciprocal relationship, often resulting in a vicious cycle that exacerbates both conditions.

4.3. Ventriculo-vascular interplay and its impact on anthracycline-related CTRCD

Hypertension at baseline, characterized by increased afterload, can lead to cardiac remodeling,[19,31] which can potentially cause further decreased systolic function when exposed to increased stress on exposure to anthracyclines. In earlier stages, concentric remodeling, defined as a normal level of left ventricular mass and increased relative wall thickness, is a common cardiac geometrical change.[32] However, in our study population, patients did not have longstanding HTN, as demonstrated by the young age, leading to potentially lower SBP load for adverse remodeling.[33] Additionally, another interface where HTN can be associated with CTRCD is the increased reported incidence of diastolic dysfunction in patients with HTN.[34] The relationship between CTRCD and diastolic dysfunction is complex and still poorly understood, especially in the pediatric population where diastolic assessment may be limited.[19] At baseline, we did not observe significant differences in diastolic function in our population between patients with and without HTN. However, diastolic dysfunction was significantly associated with the occurrence of CTRCD. Furthermore, our study observed an initial compensatory response associated with baseline HTN. Further investigations could clarify whether this response is sustained over time or if negative remodeling would eventually lead to reduced contractility. The latter seems plausible, as multiple adult studies have demonstrated long-term poor prognosis with pre-existing HTN, as HTN increased the risk of myocardial infarction, coronary artery disease, heart failure, or cerebrovascular accident 4-fold in one report.[21] Secondly, some long-term studies have reported the relationship between follow-up DBP and abnormal GLS, however, it remains unclear whether this observed association represents cardiac damage from hypertension or is only a reflection of the load dependency of GLS.[25] We observed a contrasting relationship with SBP and GLS, with higher SBP being correlated with better GLS values, this was further confirmed by a positive correlation between SBP and LVEF. This is interesting since most studies have shown that with preserved contractile function, strain can increase with higher preload, but decrease with greater afterload or heart rate.[35] However, in the clinic, preload,

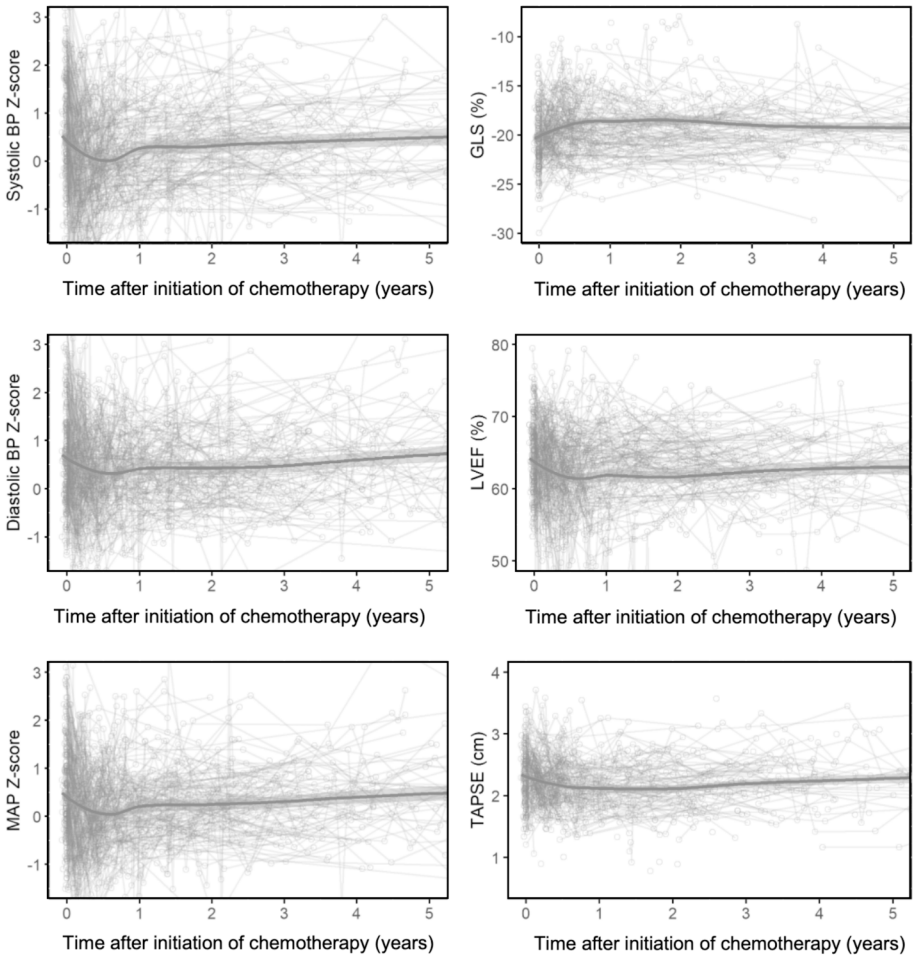

Fig. 4A. Changes in Blood Pressure and Systolic Function after initiation of Anthracycline Chemotherapy. ABBREVIATIONS: BP, blood pressure; GLS, global longitudinal strain; HTN, hypertension; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

afterload, and compensatory structural remodeling are in a reciprocal relationship.[35] One of the potential mechanisms of our observed results might also be explained by changes in preload due to loading conditions, for example, from decreased oral intake or increased fluid loss (diarrhea or vomiting). As such, the exact impact of baseline BP on the development of CTRCD caused by anthracycline therapy, remains incompletely understood.[18]

4.4. Study limitations

Firstly, the study's retrospective design, relied on existing echocardiograms captured based upon clinical indications prior to, during, and after chemotherapy, which introduces potential biases. Moreover, the precise timing of cancer onset remains uncertain. Beyond the BP response related to anthracyclines, numerous other medications could contribute to undesired BP fluctuations. A pertinent example is corticosteroids, frequently used in contemporary cancer treatment protocols, which can substantially elevate BP, either independently or in conjunction with other prohypertensive treatments. Other confounders that might introduce bias include anemia, cardiac medication use and anthracycline dose adjustments made during follow-up in response to BP and cardiac dysfunction. A further constraint pertains to BP measurements taken in the office setting, which are known to be prone to inaccuracies. Unfortunately, 24-hour ambulatory blood pressure monitoring data was not available in our cohort. Furthermore, the potential for selection bias exists, because not all patients had identical consistent follow-up. This could potentially bias the results, as individuals with more pronounced response to anthracyclines or patients with CTRCD might have undergone longer observation periods.

5. Conclusions

While it has been shown that anthracyclines offer clear benefits in cancer therapy, enhancing survival rates, our results emphasize the importance of monitoring for the occurrence of CTRCD. More than 50 % of patients in our cohort developed at least mild CTRCD, while 22 % developed moderate CTRCD at 5-year follow-up. Furthermore, we demonstrate that patients with pre-existing hypertension showed distinct treatment responses.

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CRediT authorship contribution statement

Xander Jacquemyn: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Junzhen Zhan:** Writing – review & editing, Investigation, Data curation. **Jef Van den Eynde:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Kyla Cordrey:** Writing – review & editing, Data curation, Conceptualization. **Rita Long:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Sruti Rao:** Writing – review & editing, Writing – original draft, Supervision, Investigation,

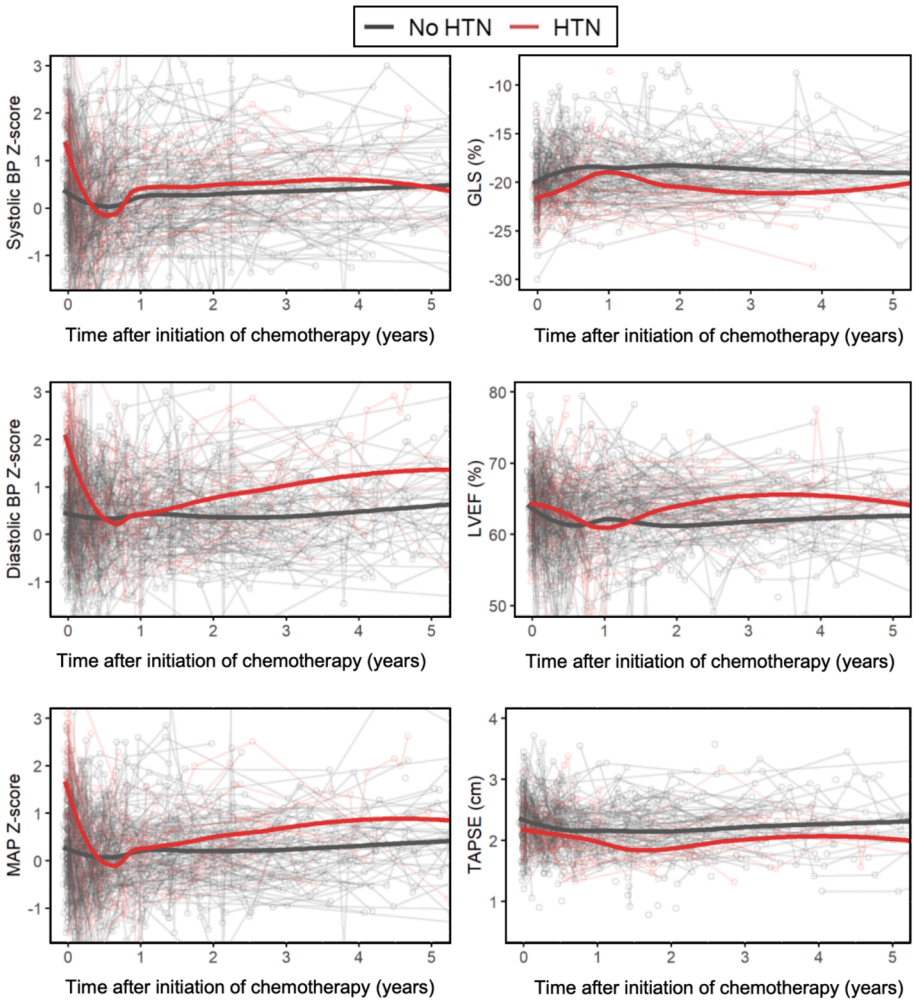

Fig. 4B. Changes in Blood Pressure and Systolic Function after initiation of Anthracycline Chemotherapy. ABBREVIATIONS: BP, blood pressure; GLS, global longitudinal strain; HTN, hypertension; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

Formal analysis, Data curation, Conceptualization. **Benjamin T. Barnes:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **W. Reid Thompson:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **David Danford:** Writing – review & editing, Supervision, Methodology. **Shelby Kutty:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101436.

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