Clinical Research in Cardiology (2019) 108:1000–1008
https://doi.org/10.1007/s00392-019-01427-9

ORIGINAL PAPER

Doxorubicin treatments induce significant changes on the cardiac autonomic nervous system in childhood acute lymphoblastic leukemia long-term survivors

Maxime Caru[1,2,3,4] · Denis Corbin[1] · Delphine Périé[4] · Valérie Lemay[1,4] · Jacques Delfrate[4] · Simon Drouin[4] · Laurence Bertout[4] · Maja Krajinovic[4,5] · Caroline Laverdière[4,5] · Gregor Andelfinger[4,5] · Daniel Sinnett[4,5] · Daniel Curnier[1,4]

Received: 23 August 2018 / Accepted: 29 January 2019 / Published online: 18 February 2019

Abstract

Aims Acute lymphoblastic leukemia (ALL) is one of the leading malignancies in children worldwide. The cardiotoxicity of anti-cancer treatments leads to a dysfunction of the cardiac autonomic nervous system. Protection strategies, with dexrazoxane treatments, were used to counter these adverse effects. The aim of this study was to investigate the effects of the treatments on the cardiac autonomic nervous system.

Methods and results A total of 203 cALL survivors were included in our analyses and were classified into 3 categories based on the prognostic risk group: standard risk, high risk with and without dexrazoxane. A 24-h Holter monitoring was performed to study the cardiac autonomic nervous system. The frequency domain heart rate variability (HRV) was used to validate the cardiac autonomic nervous system modifications. Other analyses were performed using linear HRV indexes in the time domain and non-linear indexes. A frequency domain HRV parameters analysis revealed significant differences on an overall time-period of 24 h. A repeated measures ANOVA indicated a group-effect for the low frequency ($p=0.029$), high frequency ($p=0.03$) and LF/HF ratio ($p=0.029$). Significant differences in the time domain and in the non-linear power spectral density HRV parameters were also observed.

Conclusion Anti-cancer treatments induced significant changes in the cardiac autonomic nervous system. The HRV was sensitive enough to detect cardiac autonomic nervous system alterations depending on the cALL risk category. Protection strategies (i.e., dexrazoxane treatments), which were used to counter the adverse effects of doxorubicin, could prevent changes observed in the cardiac autonomic nervous system.

Keywords Acute lymphoblastic leukemia · Cardiac autonomic nervous system · Heart rate variability · Doxorubicin treatments · Electrophysiology

✉ Maxime Caru
maxime.caru@umontreal.ca

1 Laboratoire de Physiopathologie de l'EXercice (LPEX), Département de Kinésiologie, Université de Montréal, CEPSUM, 2100, boulevard Édouard Montpetit, H3C 3J7 Montreal, QC, Canada

2 Department of Psychology, University of Paris Nanterre, Nanterre, Ile-deFrance, France

3 Laboratoire EA 4430-Clinique Psychanalyse Developpement (CliPsyD), University of Paris Nanterre, Nanterre, Ile-de-France, France

4 Sainte-Justine University Health Center, Research Center, Montreal, QC, Canada

5 Department of Pediatrics, University of Montreal, Montreal, QC, Canada

Introduction

Acute lymphoblastic leukemia (ALL) is one of the leading malignancies in children worldwide. It is described as being a blood cancer treated mainly with doxorubicin treatments [1]. This type of treatment considerably improves the survival rate of children with cancer. However, it has been demonstrated that in the long term, the cumulative dosage of doxorubicin can induce cardiotoxicity [2, 3]. Nearly 65% of childhood acute lymphoblastic leukemia (cALL) survivors live with some comorbidities after the end of their treatments with doxorubicin [4]. The main comorbidity observed among cALL survivors is an alteration in their cardiac system [5, 6]. The cumulative dosage of anti-cancer treatments

and the risk of being affected by a chronic disease have a proportional relationship [7].

It is observed that the cardiotoxicity of anti-cancer treatments leads to a dysfunction of the cardiac autonomic nervous system (ANS) [8], independently of the deterioration of the cardiac contractility [9]. In some cases, when the cumulative doses of doxorubicin are high, dexrazoxane (DEX) treatments are prescribed as a protection strategy to reduce cardiotoxicity [10]. Despite these prevention strategies, the cardiac ANS appears to be excessively activated in patients with cancer [11, 12]. However, the changes observed in the cardiac ANS, and more particularly the activity of the sympathetic nervous system and the parasympathetic nervous system, must be better understood. Therefore, the purpose of this study was to investigate, in a population of cALL survivors, the effects of anti-cancer treatments on the cardiac ANS.

Materials and methods

Participants

All patients were diagnosed between 1987 and 2010 and treated for cALL according to DFCI-ALL 87-01 to 05-01 protocols [13] at Sainte-Justine University Health Center (SJUHC), Montreal (Quebec), Canada. Participants were recruited in the context of the PETALE study, a multidisciplinary research project with the goal to identify and to comprehensively characterize associated predictive biomarkers of long-term treatment-related complications in cALL survivors [14]. Eligible participants were less than 19 years old at diagnosis, without relapse or refractory ALL. They had not received a hematopoietic stem cell transplant and had been diagnosed at least 5 years earlier. These participants were almost exclusively of French Canadian descent (> 95%) [14]. Subjects who suffered from congenital bone disease or who received osteotoxic drugs for non-ALL diseases were excluded. Written informed consent was obtained from every patient or parent/legal guardian. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Review Committee of SJUHC.

All patients were classified into three groups for statistical analysis depending on their gender, age, time from end treatment and prognostic risk group [i.e., standard risk (SR), high risk with and without cardio-protective agent dexrazoxane (HR and HR + DEX)) [13]. The cumulative doxorubicin dose for the SR group was 60 mg/m^2, 300 mg/m^2 for the HR + DEX group and either 360 mg/m^2 (DFCI-ALL protocols 85-01, 87-01 and 91-01) or 300 mg/m^2 (DFCI-ALL protocols 95-01) for the HR group. The main factor that lead to an addition of dexrazoxane was the cumulative dose of doxorubicin (≥300mg/m^2) [13].

Heart rate variability (HRV)

To study the cardiac ANS, we used the heart rate variability acquired from a three-channel 24-h ambulatory Holter monitor. Each electrocardiogram (ECG) was recorded at a sampling frequency of 250 Hz. Data were extracted from the Holter monitor through the MARS software (Mars 8000 scanners, Milwaukee, Wisconsin, USA) with an MIT signal format. Data was then converted into the EDF signal format and read by Kubios HRV premium, version 3.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland). No data compression was performed for pre-analyse solid-state storage, which prevented amplitude and/or phase distortion. Before starting the analyses of linear HRV indexes, an automatic correction of artifacts was performed, by Kubios HRV. The HRV was used as a reliable and non-invasive tool for assessing cardiac ANS in cancer patients [15–17].

The frequency domain was used to validate cardiac ANS modifications [16]. For calculation of the linear HRV indexes in the frequency domain, autoregressive (AR) modeling was used. Frequency domain parameters included the measure of Low Frequency (LF 0.04–0.15 Hz) and High Frequency (HR 0.15–0.4 Hz) ranges. The LF was associated with both the sympathetic and parasympathetic nervous system, whereas the HF was associated only with the parasympathetic branch of the cardiac ANS [18, 19]. The ratio between the LF and HF ranges (LF/HF) was recognized as an important marker of sympathovagal activity.

Other analyses were performed using linear HRV indexes in the time domain and non-linear indexes with Kubios HRV [20] in accordance with established standards [16]. The RR intervals are known as normal-to-normal (NN) intervals [21]. Time domain parameters included the mean value of NN intervals ($\overline{NN}$), the standard deviation of NN (SDNN), the root mean square of successive differences (RMSSD) and the pNN50 which is the percentage of beats that have an interval between 2 beats > 50 ms. Geometric methods included calculation of the HRV RR triangular index and the triangular interpolation of normal-to-normal intervals (TINN). For calculation of the non-linear power spectral density, parametric methods were used. Analysis of non-linear indexes included the approximate entropy (ApEn) which provided a measure of irregularity and complexity within the NN intervals. Amongst the non-linear parameters computed by Kubios HRV, the Poincaré plot was used to visualize non-linear properties of RR interval series. The Poincaré plot included the standard deviation perpendicular to the line-of-identity (SD1) which corresponded to the short-term variability of any non-linear dynamic system. It also included the standard deviation along the line-of-identity

(SD2) which corresponded to the long-term variability of any non-linear dynamic system and to the ratio between SD2 and SD1. The detrended fluctuation analysis (DFA) included the short-term fluctuations, α1 and the long-term fluctuations, α2.

Assessments of ejection fraction

An assessment of the ejection fraction was performed with a cardiac transthoracic echocardiographic measurement (Vivid 9 machine, GE Medical Systems, Milwaukee, Wisconsin) according to recommendations [22]. The M-Mode echocardiography and the biplane Simpson's method were used to measure the left ventricular ejection fraction. Patients with an ejection fraction of less than 55% were considered to have a reduced ejection fraction [23].

Classification of ventricular arrhythmias

A 24-h Holter monitoring was performed to analyze ventricular arrhythmias based on parallel hierarchies of frequency as a categorical variable [24]. The Myerburg classification includes five classes defined as: class 0, no ventricular premature complexes (VPCs); class I, rare VPCs (< 1 VPC/h); class II, infrequent VPCs (1–9 VPCs/h); class III, intermediate VPCs (10–29 VPCs/h); and class IV, frequent VPCs (≥ 30 VPCs/h). The Myerburg classification was chosen, in comparison to the Lown classification [25] for its greater flexibility in characterizing prognostic aspects of ventricular arrhythmias [26]. It should be noted that no patients were in atrial fibrillation at the time of the Holter recordings.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics, version 24.0 (IBM Corp., Armonk, NY, USA). All variables were reported as mean ± standard deviation (SD) and the normal distribution of HRV data was verified using the Shapiro–Wilk test. For clinical characteristics, a series of pair-wise two sample *t* tests with a significance level of 5% was performed over all combinations of the groups under investigation. The effect of the prognostic risk group (i.e., SR, HR + DEX and HR) on the studied variables (i.e., HRV data) was tested by within-subject repeated measures ANOVA. When a significant effect was observed, a post hoc analysis using the Bonferroni correction for multiple comparisons was performed. A Greenhouse–Geisser correction for sphericity was conducted when the hypothesis of sphericity of the data distribution was violated as assessed by Mauchly's test. For all tests, statistical significance was set at an alpha level of $p < 0.05$.

Results

Our study included 250 cALL survivors, among which 47 patients were excluded: 12 refused to carry the ambulatory Holter monitor, 17 did not complete the 24-h recordings because their electrodes either fell off (mostly during the night) or the patients removed their electrodes, and 18 were excluded because their data file was corrupted and could not be read by the software. From these 203 cALL survivors included in our analyses, the patients were classified into three groups (SR, HR + DEX and HR) (Table 1). Using the M-Mode, in the SR group, 19 patients (21.3%) had an ejection fraction < 55%. In the HR + DEX group, 13 patients (20.6%) had an ejection fraction < 55% and in the HR group, 27 patients (52.9%) had an ejection fraction < 55%. Using the biplane Simpson's method, in the SR group, 33 patients (37.1%) had an ejection fraction < 55%. In the HR + DEX group, 25 patients (39.7%) had an ejection fraction < 55% and in the HR group, 26 patients (51.0%) had an ejection fraction < 55%. For both methods, there was no significant difference between the three groups regarding ejection fraction analyses.

Frequency domain HRV parameters

A repeated measures ANOVA revealed significant differences in the frequency domain HRV parameters on an overall time-period of 24 h (Table 2). The results indicated an effect of the groups for the low frequency ($p = 0.029$), high frequency ($p = 0.03$) and LF/HF ratio ($p = 0.029$). Post hoc analyses demonstrated that low frequency was significantly lower in the SR group than in the HR group ($p < 0.05$). Additionally, high frequency was significantly higher in the SR group than in the HR group ($p < 0.05$). The same results were shown with raw values for low and high frequency. The LF/HF ratio was significantly lower in the SR group than in the HR group ($p < 0.01$). It was also lower than in the HR + DEX group ($p < 0.05$).

Time domain HRV parameters

A repeated measures ANOVA revealed significant differences in the time domain HRV parameters on an overall time-period of 24 h (Table 3). The results showed an effect of the groups for RMSSD ($p = 0.012$) and pNN50 ($p = 0.001$). Post hoc analyses demonstrated that RMSSD and pNN50 were significantly higher in the SR group than in the HR group ($p < 0.05$ and $p < 0.001$, respectively).

Non-linear power spectral density HRV parameters

A repeated measures ANOVA revealed significant differences in non-linear power spectral density HRV parameters (Table 4). The results showed an effect of the groups in an

Table 1 Clinical characteristics of cALL survivors

	SR	HR + DEX	HR	*p* value
Total (*n*)	89	63	51	–
Age at visit (years)	19.7 ± 4.9	19.6 ± 5.5[c]	28.3 ± 5.3[a]	< 0.001
Height (cm)	165.8 ± 8.1	165.3 ± 11.7	166.4 ± 10.3	0.670
Weight (kg)	66.8 ± 17.3	64.8 ± 14.4	69.5 ± 14.9	0.391
BMI (kg/m^2)	24.2 ± 5.4	23.6 ± 4.4	25.1 ± 5.2	0.508
Time of treatment (y)	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.3	0.559
Time from end treatment (years)	15.5 ± 5.0	8.7 ± 3.3[c,b]	17.9 ± 3.4	< 0.001
Ejection fraction with M-Mode (%)	57.9 ± 5.0	59.4 ± 5.7	60.7 ± 5.8	0.316
Ejection fraction with biplane Simpson method (%)	56.4 ± 4.9	55.4 ± 5.7	54.9 ± 5.3	0.411
DOX (mg/m^2)	66.8 ± 45.8	284.3 ± 53.7[b]	287.6 ± 68.6[a]	< 0.001
DEX (mg/m^2)		2789.3 ± 469.4		–

Data are expressed as means ± SD

SR standard risk, *HR* high risk, *HR + DEX* high risk with dexrazoxane, *BMI* body mass index, *DOX* cumulative dose of doxorubicin, *DEX* cumulative dose of doxorubicin

[a] $p < 0.05$, SR versus HR group

[b] $p < 0.05$, SR versus HR + DEX

[c] $p < 0.05$, HR versus HR + DEX

Table 2 Frequency domain parameters

	SR	HR + DEX	HR	*p* value
Low frequency (n.u.)	57.3 ± 14.1	62.2 ± 13.9	63.8 ± 11.2[a]	0.029
Low frequency (ms^2)	1764.7 ± 961.5	1671.7 ± 1057.0	1388.4 ± 764.3[a]	0.025
High frequency (n.u.)	42.0 ± 14.1	37.1 ± 14.0	35.4 ± 1.3[a]	0.030
High frequency (ms^2)	1685.9 ± 2119.3	1294.6 ± 1458.9	890.0 ± 767.2[a]	0.032
LF/HF ratio	1.7 ± 1.0	2.1 ± 1.3[c]	2.1 ± 1.2[b]	0.029

Data are expressed as means ± SD

SR standard risk, *HR + DEX* high risk with dexrazoxane, *HR* high risk, *LF* low frequency, *HF* high frequency.

[a] $p < 0.05$, SR versus HR

[b] $p < 0.01$, SR versus HR

[c] $p < 0.05$, SR versus HR + DEX

Table 3 Time domain parameters

	SR	HR + DEX	HR	*p* value
Mean heart rate (bpm)	77.9 ± 9.0	79.3 ± 8.5	79.2 ± 7.1	0.512
$\overline{\text{NN}}$ (ms)	780.7 ± 93.2	765.7 ± 88.9	763.7 ± 74.6	0.501
SDNN (ms)	168.6 ± 42.5	156.9 ± 43.7	154.0 ± 42.7	0.134
RMSSD (ms)	58.7 ± 35.6	49.5 ± 25.7	42.6 ± 18.1[a]	0.012
pNN50 (%)	22.1 ± 12.4	17.7 ± 12.3	13.9 ± 8.9[b]	0.001
HRV triangular index	44.7 ± 12.1	42.9 ± 12.0	40.8 ± 10.4	0.144
TINN (ms)	1119.6 ± 247.7	1035.7 ± 282.0	1049.8 ± 302.1	0.080

Data are expressed as a percentage or as means ± SD

SR standard risk, *HR + DEX* high risk with dexrazoxane, *HR* high risk, $\overline{NN}$ standard deviation of all normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal RR intervals, *RMSSD* root mean square of successive RR interval differences, *pNN50* relative number of successive RR interval pairs that differ more than 50 ms

[a] $p < 0.05$, SR versus HR

[b] $p < 0.01$, SR versus HR

overall time-period of 24 h for SD1, SD2, SD2/SD1 ratio and DFA, long-term fluctuations α1. Post hoc analyses demonstrated that SD1 and SD2 were significantly higher in the SR group than in the HR group ($p < 0.05$ and $p < 0.05$, respectively). The SD2/SD1 ratio was significantly lower in the SR group than in the HR group ($p < 0.01$). This ratio was also lower in the SR group than in the HR + DEX group ($p < 0.05$). The DFA, long-term fluctuations α1 was significantly lower in the SR group than in the HR group ($p < 0.01$).

Classification of ventricular arrhythmias

There were no significant differences in the classification of ventricular arrhythmias of patients in the SR, HR + DEX and HR groups including class 0, class I, class II, class III, or class IV (Table 5).

Discussion

This study investigated the possible effects of doxorubicin treatments on the cardiac ANS. New findings brought to research by this study clarify the role of the sympathetic and parasympathetic nervous system in the alteration of the cardiac ANS in cALL survivors. Therefore, it would seem that cumulative doses of doxorubicin may have a significant negative impact on the cardiac ANS. The dexrazoxane treatments seem to provide an effective protection strategy to counter the adverse effects brought on by doxorubicin to the cardiac ANS.

Our findings completed and specified the results of previous studies in humans [12, 27] and replicated some results of rodent models [28]. Indeed, one of the first studies in this field had observed an autonomic imbalance in cALL survivors, especially in the time domain HRV parameters, which was not resolved when treatments were completed [12]. Previously, in a pilot study, power spectral analyses of HRV had revealed an elevation of the sympathetic modulation without any specification on parasympathetic modulation (Kamath et al., Blood 82: abs. 210, 1993). Recently, the hypothesis of sympathetic dominance in the alteration of the cardiac ANS for acute leukemia was confirmed with time domain HRV parameters [27]. However, the authors pointed out the importance of using frequency domain parameters to consolidate these results [27]; which we did in this study. It should be noted that the involvement of protection strategies in the alteration of the cardiac ANS was not discussed in previous studies

Table 4 Non-linear power spectral density parameters

	SR	HR + DEX	HR	*p* value
ApEn	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	0.529
SD1 (ms)	41.5 ± 25.2	35.0 ± 18.2	30.1 ± 12.8[a]	0.012
SD2 (ms)	70.6 ± 21.2	66.2 ± 21.1	59.9 ± 16.8[a]	0.006
SD2/SD1 ratio	1.9 ± 0.5	2.1 ± 0.5[c]	2.1 ± 0.4[b]	0.018
Detrended fluctuation analysis				
Short-term fluctuations, α1	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.1[b]	0.008
Long-term fluctuations, α2	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.369

Data are expressed as means ± SD

SR standard risk, *HR + DEX* high risk with dexrazoxane, *HR* high risk, *LF* low frequency, *HF* high frequency, *ApEn* approximate entropy

[a] $p < 0.05$, SR versus HR

[b] $p < 0.01$, SR versus HR

[c] $p < 0.05$, SR versus HR + DEX

Table 5 Classification of ventricular arrhythmias

	SR		HR + DEX		HR		*p* value
	Means ± SD	*n* (%)	Means ± SD	*n* (%)	Means ± SD	*n* (%)	
Class 0			0.0 ± 0.0	1.6	0.0 ± 0.0	3.9	
Class I	0.5 ± 0.3	27	0.5 ± 0.3	42.9	0.3 ± 0.2	39.2	0.385
Class II	3.5 ± 2.0	59.6	3.1 ± 2.1	34.9	3.4 ± 2.5	47.1	0.898
Class III	18.1 ± 6.9	7.8	19.7 ± 6.5	14.3	17.6 ± 8.7	9.8	0.989
Class IV	71.9 ± 58.3	5.6	61.2 ± 32.9	6.3			

n (%) is the percentage of cALL survivors in the different class. The *p* value is for differences in means

SR standard risk, *HR + DEX* high risk with dexrazoxane, *HR* high risk

[12, 27] despite the fact that there seems to be an influence in rodent model [28].

Analyses of linear HRV in the frequency domain revealed a possible alteration of the cardiac ANS in our population. Indeed, the SR group had a low frequency value significantly inferior to the HR group. The opposite was observed for high frequency analysis, where the SR group was significantly superior to the HR group. However, no significant difference was observed between the SR and HR + DEX groups. This observation seems to support the effectiveness of dexrazoxane treatments, which were used to counter the adverse effects of doxorubicin in high risk cALL survivors. Dexrazoxane treatments allowed a reduction of cardiotoxicity and a prevention of a possible change in the cardiac ANS [10]. However, no significant difference was observed between the HR + DEX and HR groups, which could be explained by the lack of statistical power. The analysis of the 24-h Holter data provided comprehensive and more robust information about all daily activities of patients [19, 29]. Previous studies have published data on the healthy population, with the same parameters as our research [30]. Overall, our data in low frequency seemed to be higher in the HR + DEX and HR groups, but in high frequency they were lower. The absence of a healthy control group in our study does not allow us to confirm this trend. The sensitivity of our results in cALL survivors for LF/HF ratio was similar to previous studies [12, 31]. Nevertheless, the LF/HF ratio increased with the risk level but was slightly higher than those reported previously [12]. These findings could be due to differences in cancer treatments between studies. For example, Kamath study [12] used ALL survivors who had vincristine and methotrexate treatments while our study focused on doxorubicin treatments. Thus, our results in the frequency domain suggested that the cardiac ANS alterations in cALL survivors could be due to an increase in sympathetic activity and a decrease in parasympathetic activity. These observations were confirmed by the analysis of the linear HRV in the time domain and non-linear HRV indexes.

Indeed, we observed a significant decrease of the pNN50 index with the prognostic risk group. These results were similar for the RMSSD index, suggesting that the parasympathetic activity of the cardiac ANS was impaired. Additionally, the analysis of non-linear HRV indexes showed that short-term variability was affected. The results in the SR group were significantly higher than the ones in the HR group. The results were similar for long-term variability, as well as for DFA, α1. The changes observed in the cardiac ANS may be considered as short-term compensatory responses to hemodynamic alterations resulting from abnormal cardiac function [32]. The literature suggests that there is a similar rate of ventricular arrhythmias in cancer survivors and in non-ischaemic cardiomyopathy patients [33]. However, it should be noted that the prognostic risk group did not seem to influence the number of ventricular arrhythmias in our study, as shown by the analysis of ventricular arrhythmias based on the Myerburg classification. Previously, a study observing an alteration of cardiac autonomic function in acute leukemia patients did not detect episodes of sustained atrial or ventricular arrhythmias [27]. Recently, a study highlighted the developed incidence of atrial fibrillation during follow-up in patients with chronic lymphocytic leukemia [34]. It should be noted that the average age of the patients in this study was superior to the one in our study (median age at diagnosis in Shanafelt study was 65 years) which might explain differences in the results obtained from each study. Indeed, the incidence of atrial fibrillation increases with the age [34–36]. Thus, results of our study suggest that there may be processes other than the doxorubicin doses involved in the deterioration of the cardiac function in cALL survivors. The cardiotoxicity associated with chemotherapy treatments involves multiple complex mechanisms [37]. Other studies are necessary to determine the physiopathological role of the cardiac ANS imbalance in cALL survivors.

The major clinical implication of our findings was that measuring the HRV, in cALL survivors, was sensitive enough to discriminate changes in the cardiac ANS depending on the doxorubicin doses mediated by dexrazoxane protection. The cumulative dosage of doxorubicin induced cardiotoxicity in cALL survivors, but our results seemed to show that in the long term, the impact was subclinical since there was a slight deterioration of the ejection fraction. A high proportion of left ventricular dysfunction assessed by global longitudinal strain has been shown in apparently healthy cALL survivors previously exposure to high doses of anthracyclines [38]. In patients treated during childhood and adolescence with doxorubicin, the myocardial sympathetic activity was not associated with a reduction in the left ventricular ejection fraction [39]. In that sense, a follow-up of the sympathetic and the parasympathetic nervous system activity could allow monitoring and prevention of an inappropriate remodeling of the myocardium and of a deterioration of the cardiac function [40]. As in the first stage of heart failure, we could hypothesize that the cardiac ANS began to compensate for subclinical cardiac remodeling in cALL survivors [41]. Nevertheless, this adaptive mechanism could, in the long term, result in a misadaptation and in a worsening of the cardiac function [41]. This is an important point because it has been reported that cancer survivors have a considerably increased risk for premature cardiovascular diseases such as congestive heart failure [42]. There are strategies to reduce the imbalance of the cardiac ANS in cALL survivors in an anti-adrenergic way, even in low doses of doxorubicin. These should be considered as exploratory therapies, similarly to early beta-blockade [43] or to exercise training [44–46].

Our study was the first to include a large number of patients and to take into account anti-cancer treatments. Cardiotoxic protection therapies for chemotherapeutic treatments were also taken into account. Despite our interesting findings, some limitations should be mentioned. The physical fitness and age, which were considered as confounding factors, were not included in the analysis. However, the patients were close in age at the time of the study, in comparison to previous studies which compared patients with many decades of age difference. This was also observed for the time from the end of chemotherapy, which could have an impact on our HRV data. In that sense, the age and the time from end treatment should not be considered as a bias in our interpretation of data. Additionally, it is reported that BNP and NT-proBNP are important markers of cardiotoxicity in cancer patients [47, 48] in addition to an echocardiographic evaluation [49]. Thus, it would be interesting to consider these cardiotoxicity markers in future statistical analyses. Finally, the use of the myocardial strain imaging to detect left ventricular dysfunction should be considered for its sensitivity to chemotherapy cardiotoxicity [50].

In conclusion, doxorubicin induced significant changes in the cardiac ANS in our population. Our findings suggested that regulation of the cardiac ANS is compromised in cALL survivors depending on their treatments. Protection strategies (i.e., dexrazoxane treatments), which were used to counter the adverse effects of doxorubicin, could prevent changes observed in the cardiac autonomic nervous system. Finally, whether the measurement of the HRV can be used in cALL survivors to monitor cardiac remodeling from subclinical stages to heart failure remains an open question.

Acknowledgements This work was supported by the Institute of Cancer Research (ICR) of the Canadian Institutes of Health Research (CIHR), in collaboration with C17 Council, Canadian Cancer Society (CCS), Cancer Research Society (CRS), Garron Family Cancer Centre at the Hospital for Sick Children, Ontario Institute for Cancer Research (OICR) and Pediatric Oncology Group of Ontario (POGO) (grant number: TCF 118694). This research was also supported in part by PhD study grants from Cole Foundation, Fonds de Recherche du Québec—Santé (FRQS), Sainte-Justine University Hospital Center Foundation and Foundation of Stars. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We appreciate the invaluable assistance of Ariane Levesque (McGill University) for her review of the article in the English language.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

References

1. Iarussi D, Indolfi P, Casale F, Martino V, Di Tullio MT, Calabro R (2005) Anthracycline-induced cardiotoxicity in children with cancer: strategies for prevention and management. Paediatr Drugs 7(2):67–76
2. Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, Orav EJ, Gelber RD, Colan SD (1995) Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 332(26):1738–1743. https://doi.org/10.1056/nejm199506293322602
3. Lipshultz SE, Cochran TR, Franco VI, Miller TL (2013) Treatment-related cardiotoxicity in survivors of childhood cancer. Nat Rev Clin Oncol 10(12):697–710. https://doi.org/10.1038/nrclinonc.2013.195
4. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP (1991) Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 324(12):808–815. https://doi.org/10.1056/NEJM199103213241205 doi
5. Van Brussel M, Takken T, Lucia A, van der Net J, Helders PJ (2005) Is physical fitness decreased in survivors of childhood leukemia? A systematic review. Leukemia 19(1):13–17. https://doi.org/10.1038/sj.leu.2403547
6. Tilemann LM, Heckmann MB, Katus HA, Lehmann LH, Muller OJ (2018) Cardio-oncology: conflicting priorities of anticancer treatment and cardiovascular outcome. Clin Res Cardiol 107(4):271–280. https://doi.org/10.1007/s00392-018-1202-x
7. Søgaard M, Thomsen RW, Bossen KS, Sørensen HT, Nørgaard M (2013) The impact of comorbidity on cancer survival: a review. Clin Epidemiol 5(Suppl 1):3–29. https://doi.org/10.2147/clep.S47150
8. Walsh D, Nelson KA (2002) Autonomic nervous system dysfunction in advanced cancer. Support Care Cancer 10(7):523–528. https://doi.org/10.1007/s00520-002-0376-x
9. Viniegra M, Marchetti M, Losso M, Navigante A, Litovska S, Senderowicz A, Borghi L, Lebron J, Pujato D, Marrero H et al (1990) Cardiovascular autonomic function in anthracycline-treated breast cancer patients. Cancer Chemother Pharmacol 26(3):227–231
10. Kremer LC, van Dalen EC (2015) Dexrazoxane in children with cancer: from evidence to practice. J Clin Oncol 33(24):2594–2596. https://doi.org/10.1200/jco.2015.61.7928
11. Guo Y, Koshy S, Hui D, Palmer JL, Shin K, Bozkurt M, Yusuf SW (2015) Prognostic value of heart rate variability in patients with cancer. J Clin Neurophysiol 32(6):516–520. https://doi.org/10.1097/wnp.0000000000000210
12. Kamath MV, Halton J, Harvey A, Turner-Gomes S, McArthur A, Barr RD (1998) Cardiac autonomic dysfunction in survivors of acute lymphoblastic leukemia in childhood. Int J Oncol 12(3):635–640
13. Silverman LB, Stevenson KE, O'Brien JE, Asselin BL, Barr RD, Clavell L, Cole PD, Kelly KM, Laverdiere C, Michon B, Schorin MA, Schwartz CL, O'Holleran EW, Neuberg DS, Cohen HJ, Sallan SE (2010) Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985–2000). Leukemia 24(2):320–334. https://doi.org/10.1038/leu.2009.253
14. Marcoux S, Drouin S, Laverdiere C, Alos N, Andelfinger GU, Bertout L, Curnier D, Friedrich MG, Kritikou EA, Lefebvre G, Levy E, Lippe S, Marcil V, Raboisson MJ, Rauch F, Robaey P, Samoilenko M, Seguin C, Sultan S, Krajinovic M, Sinnett D (2017) The PETALE study: late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors. Pediatr Blood Cancer. https://doi.org/10.1002/pbc.26361
15. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213(4504):220–222

16. Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93(5):1043–1065
17. Arab C, Vanderlei LCM, da Silva Paiva L, Fulghum KL, Fristachi CE, Nazario ACP, Elias S, Gebrim LH, Ferreira Filho C, Gidron Y (2018) Cardiac autonomic modulation impairments in advanced breast cancer patients. Clin Res Cardiol 107(10):924–936
18. Berntson GG, Bigger JT Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW (1997) Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34(6):623–648
19. Malik M (1996) Heart rate variability. Circulation 93(5):1043–1065
20. Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA (2014) Kubios HRV–heart rate variability analysis software. Comput Methods Progr Biomed 113(1):210–220. https://doi.org/10.1016/j.cmpb.2013.07.024
21. Heart rate variability (1996) Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Euro Heart J 17(3):354–381
22. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 29(4):277–314. https://doi.org/10.1016/j.echo.2016.01.011
23. Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Uemura S, Saito Y (2015) Left ventricular ejection fraction (EF) of 55% as cutoff for late transition from heart failure (HF) with preserved EF to HF with mildly reduced EF. Circ J 79(10):2209–2215. https://doi.org/10.1253/circj.CJ-15-0425
24. Myerburg RJ, Kessler KM, Luceri RM, Zaman L, Trohman RG, Estes D, Castellanos A (1984) Classification of ventricular arrhythmias based on parallel hierarchies of frequency and form. Am J Cardiol 54(10):1355–1358
25. Lown B, Wolf M (1971) Approaches to sudden death from coronary heart disease. Circulation 44(1):130–142
26. Bethge K-P (1991) Classification of arrhythmias. J Cardiovasc Pharmacol 17:S20
27. Nevruz O, Yokusoglu M, Uzun M, Demirkol S, Avcu F, Baysan O, Koz C, Cetin T, Sag C, Ural AU, Isik E (2007) Cardiac autonomic functions are altered in patients with acute leukemia, assessed by heart rate variability. Tohoku J Exp Med 211(2):121–126
28. Potocnik N, Perse M, Cerar A, Injac R, Finderle Z (2017) Cardiac autonomic modulation induced by doxorubicin in a rodent model of colorectal cancer and the influence of fullerenol pretreatment. PLoS One 12(7):e0181632. https://doi.org/10.1371/journal.pone.0181632
29. Kleiger RE, Stein PK, Bigger JT Jr (2005) Heart rate variability: measurement and clinical utility. Ann Noninvasive electrocardiol 10(1):88–101. https://doi.org/10.1111/j.1542-474X.2005.10101.x
30. Nunan D, Sandercock GR, Brodie DA (2010) A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing Clin Electrophysiol PACE 33(11):1407–1417. https://doi.org/10.1111/j.1540-8159.2010.02841.x
31. Kamath MV, Fallen EL (1993) Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 21(3):245–311
32. van Bilsen M, Patel HC, Bauersachs J, Bohm M, Borggrefe M, Brutsaert D, Coats AJS, de Boer RA, de Keulenaer GW, Filippatos GS, Floras J, Grassi G, Jankowska EA, Kornet L, Lunde IG, Maack C, Mahfoud F, Pollesello P, Ponikowski P, Ruschitzka F, Sabbah HN, Schultz HD, Seferovic P, Slart R, Taggart P, Tocchetti CG, Van Laake LW, Zannad F, Heymans S, Lyon AR (2017) The autonomic nervous system as a therapeutic target in heart failure: a scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 19(11):1361–1378. https://doi.org/10.1002/ejhf.921
33. Fradley MG, Viganego F, Kip K, Martin A, Patel AA, Ismail-Khan R, Chae S, Herweg B, Labovitz A (2017) Rates and risk of arrhythmias in cancer survivors with chemotherapy-induced cardiomyopathy compared with patients with other cardiomyopathies. Open Heart 4(2):e000701
34. Shanafelt TD, Parikh SA, Noseworthy PA, Goede V, Chaffee KG, Bahlo J, Call TG, Schwager SM, Ding W, Eichhorst B, Fischer K, Leis JF, Chanan-Khan AA, Hallek M, Slager SL, Kay NE (2017) Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leukemia Lymphoma 58(7):1630–1639. https://doi.org/10.1080/10428194.2016.1257795
35. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM (2006) Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 27(8):949–953. https://doi.org/10.1093/eurheartj/ehi825
36. Benjamin EJ, Levy D, Vaziri SM, D'agostino RB, Belanger AJ, Wolf PA (1994) Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. Jama 271(11):840–844
37. Poreba M, Poreba R, Gac P, Usnarska-Zubkiewicz L, Pilecki W, Piotrowicz E, Piotrowicz R, Rusiecki L, Kuliczkowski K, Mazur G, Sobieszczanska M (2014) Heart rate variability and heart rate turbulence in patients with hematologic malignancies subjected to high-dose chemotherapy in the course of hematopoietic stem cell transplantation. Ann Noninvasive Electrocardiol 19(2):157–165. https://doi.org/10.1111/anec.12108
38. Christiansen JR, Massey R, Dalen H, Kanellopoulos A, Hamre H, Fossa SD, Ruud E, Kiserud CE, Aakhus S (2016) Utility of global longitudinal strain by echocardiography to detect left ventricular dysfunction in long-term adult survivors of childhood lymphoma and acute lymphoblastic leukemia. Am J Cardiol 118(3):446–452. https://doi.org/10.1016/j.amjcard.2016.05.021
39. Dos Santos MJ, da Rocha ET, Verberne HJ, da Silva ET, Aragon DC, Junior JS (2017) Assessment of late anthracycline-induced cardiotoxicity by (123)I-mIBG cardiac scintigraphy in patients treated during childhood and adolescence. J Nucl cardiol 24(1):256–264. https://doi.org/10.1007/s12350-015-0309-y
40. Floras JS, Ponikowski P (2015) The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J 36(30):1974–1982b. https://doi.org/10.1093/eurheartj/ehv087
41. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J (2009) The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol 54(19):1747–1762. https://doi.org/10.1016/j.jacc.2009.05.015
42. Faber J, Wingerter A, Neu MA, Henninger N, Eckerle S, Münzel T, Lackner KJ, Beutel ME, Blettner M, Rathmann W, Peters A, Meisinger C, Linkohr B, Neuhauser H, Kaatsch P, Spix C, Schneider A, Merzenich H, Panova-Noeva M, Prochaska JH, Wild PS (2018) Burden of cardiovascular risk factors and cardiovascular disease in childhood cancer survivors: data from the German CVSS-study. Eur Heart J 39(17):1555–1562. https://doi.org/10.1093/eurheartj/ehy026

43. Packer M (1998) Beta-adrenergic blockade in chronic heart failure: principles, progress, and practice. Progr Cardiovasc Dis 41(1 Suppl 1):39–52
44. Hsu CY, Hsieh PL, Hsiao SF, Chien MY (2015) Effects of exercise training on autonomic function in chronic heart failure: systematic review. BioMed Res Int 2015:591708. https://doi.org/10.1155/2015/591708
45. Ricca-Mallada R, Migliaro ER, Silvera G, Chiappella L, Frattini R, Ferrando-Castagnetto F (2017) Functional outcome in chronic heart failure after exercise training: possible predictive value of heart rate variability. Ann Phys Rehabilit Med 60(2):87–94. https://doi.org/10.1016/j.rehab.2016.12.003
46. Zhou W, Wan YH, Chen Q, Qiu YR, Luo XM (2017) Effects of Tai Chi exercise on cancer-related fatigue in patients with nasopharyngeal carcinoma undergoing chemoradiotherapy: a randomized controlled trial. J Pain Symptom Manag. https://doi.org/10.1016/j.jpainsymman.2017.10.021
47. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, Colan SD, Neuberg DS, Dahlberg SE, Henkel JM, Asselin BL, Athale UH, Clavell LA, Laverdiere C, Michon B, Schorin MA, Sallan SE (2012) Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol 30(10):1042–1049. https://doi.org/10.1200/jco.2010.30.3404
48. Bando S, Soeki T, Matsuura T, Tobiume T, Ise T, Kusunose K, Yamaguchi K, Yagi S, Fukuda D, Iwase T, Yamada H, Wakatsuki T, Shimabukuro M, Muguruma N, Takayama T, Kishimoto I, Kangawa K, Sata M (2017) Plasma brain natriuretic peptide levels are elevated in patients with cancer. PLoS One. https://doi.org/10.1371/journal.pone.0178607
49. Dodos F, Halbsguth T, Erdmann E, Hoppe UC (2008) Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. Clin Res Cardiol 97(5):318–326. https://doi.org/10.1007/s00392-007-0633-6
50. Riffel JH, Keller MG, Aurich M, Sander Y, Andre F, Giusca S, Aus dem Siepen F, Seitz S, Galuschky C, Korosoglou G, Mereles D, Katus HA, Buss SJ (2015) Assessment of global longitudinal strain using standardized myocardial deformation imaging: a modality independent software approach. Clin Res Cardiol 104(7):591–602. https://doi.org/10.1007/s00392-015-0822-7