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Use of speckle tracking echocardiography to detect late anthracycline-induced cardiotoxicity in childhood cancer: A prospective controlled cross-sectional study

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ABSTRACT

Background: This study aimed to detect late sub-clinical patterns of cardiac dysfunction using speckle tracking echocardiography (STE) in children with cancer remission more than 12 months after the end of anthracycline treatment.

Methods: This prospective controlled study enrolled 196 children, 98 of which had been treated with anthracyclines (mean age 10.8 ± 3.6 years; 51% female) and 98 were age- and gender-matched healthy subjects in a 1:1 case-control design. Conventional echocardiographic variables were collected for left ventricle (LV) and right ventricle (RV). STE analyses were performed in the LV longitudinal, radial, and circumferential displacements and in the RV free wall longitudinal displacement. The association between LV global longitudinal strain (GLS) and the main clinical and biological parameters was evaluated.

Results: After a mean time interval of 5.1 ± 3.2 years since the end of chemotherapy (mean cumulative anthracycline dose of 192 ± 96 mg/m²), conventional echocardiographic measures were normal. GLS was significantly decreased in the anthracycline group (-19.1% vs. -21.5% , $P < 0.0001$), with a higher proportion of children with abnormal values (Z -score < -2 in 18.6% vs. 1.0%, $P < 0.0001$). No association was found between GLS and clinical or biological parameters. Circumferential strain was significantly worse in the anthracycline group (-16.8% vs. -19.4% , $P < 0.0001$), and radial strain significantly better ($+51.4\%$ vs. $+35.9\%$, $P < 0.0001$). RV conventional echocardiography and STE parameters were normal and not different between anthracycline and control groups.

Conclusions: The existence of a modified LV strain despite normal LV function in children treated with anthracyclines represents an important perspective for cardiomyopathy surveillance in childhood cancer survivors.

Clinical Trial Registration -[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02893787) Identifier: NCT02893787.

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Abbreviation's list

2D strain	two-dimensional strain
GE	General Electric healthcare
GLS	global longitudinal strain
IVC %	inferior vena cava collapse index
IVSd	inter-ventricular septum diastolic diameter
LV	left ventricle
LVEF	left ventricle ejection fraction
LVEF	left ventricle ejection fraction (biplane Simpson)
LVIDD	left ventricle internal diastolic diameter
RV	right ventricle
STE	speckle tracking echocardiography
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TEI	myocardial performance index
VCFc	contraction velocity corrected by cardiac frequency

1. Introduction

Nearly half a century after their discovery, anthracyclines remain a widely prescribed anticancer agent [1]. Along with the widespread adoption of multimodality cancer treatment, the efficacy of anthracyclines has contributed to increase life expectancy, and currently, 5-year survival of children diagnosed with cancer exceeds 85% [2], despite their toxic effect on cardiomyocytes [3,4].

The incidence of myocardial dysfunction in the long-term follow-up of children after anthracycline treatment has been estimated between 18% and 57%, and about 5% of them will develop clinical heart failure [5,6]. Delayed cardiotoxicity classically consists in a cardiomyopathy occurring several years or decades after chemotherapy, and is more frequent in patients treated during childhood, with high-dose anthracycline protocols, or requiring radiotherapy [7].

In the modern era, paediatric oncology drug trials require reliable and non-invasive cardiac biomarkers. Currently available tools to evaluate cardiac function may not be very specific (biological blood tests), difficult to perform in paediatric patients (cardiac magnetic resonance imaging), or too invasive (myocardial biopsy) [8]. Left ventricle ejection fraction (LVEF) obtained by conventional two-dimensional (2D) echocardiography is the current gold standard for diagnosis of systolic dysfunction following anthracycline therapy, defined as a decrease from baseline in LVEF of >10 percentage points to a value <53% [9]. Yet, routine paediatric cardiology examinations, and first and foremost conventional echocardiography, are unable to predict whether or not a cardiomyopathy will occur after treatment with anthracyclines [10,11].

Among the modern echocardiographic techniques, 2D and 3D strain using speckle tracking echocardiography (STE) has emerged as an easy to perform, reliable and cost-effective non-invasive functional biomarker in adult onco-cardiology [3,12,13]. STE evaluates the myocardial function with a dynamic regionalized analysis of the overall ventricular contraction. This technique measures localized myocardial movements of natural acoustic markers, also called “speckles” [14]. STE supposedly provides a rapid, precise, and objective assessment of segmental and global myocardial function in the three longitudinal, radial, and circumferential displacements [15].

In the paediatric population, several studies have shown the ability of STE to detect preclinical myocardial dysfunction, such as after septic shock [16], cardiac ischemia [17], dilated cardiomyopathy [18], Duchenne muscular dystrophy [8], or heart transplantation [19]. STE also detects subclinical LV systolic dysfunction in adult survivors of childhood cancer [10,20–22]. Changes in myocardial strain have been observed in acute cardiotoxicity [23–25], however, STE is not routinely used for cardiomyopathy surveillance in children receiving cancer therapy. Indeed, the ability of early STE changes during childhood to predict delayed anthracycline-induced cardiomyopathy remains undetermined, and the frequency of cardiac follow-up in asymptomatic patients is still not consensual [26]. Nevertheless, our group has recently

shown, using an animal model of juvenile rats treated with different cumulative doses of doxorubicin, that screening of the contractile defaults of the base of the heart by regional 2D strain was useful to detect subclinical myocardial dysfunction, prior to the development of delayed anthracycline-induced cardiomyopathy [27].

Therefore, we aimed to perform a complete 2D strain analysis using STE in children in complete cancer remission, at least one year after the end of chemotherapy, to investigate the potential of STE in identifying late subclinical cardiac dysfunction, and to compare the results to age and gender-matched healthy control subjects. We also intended to identify, in this population, the clinical and biological markers associated with 2D strain parameters.

2. Method

2.1. Study design and patients

This prospective cross-sectional study was carried from July 2015 to September 2017 in a tertiary care paediatric centre. All children <18, in complete remission after anthracycline treatment, were screened. To ensure to guarantee a late cardiac functional assessment, only patients with a discontinuation of treatment with chemotherapy for over 1 year were eligible for the study. We did not include children with any progressive malignancy, and those with any cardiac, pulmonary, or muscular chronic diseases, that were not secondary to anthracycline treatment. The Paediatric Oncology Group guidelines were used to determine the anthracycline toxicology equivalence ratios [28].

The control group consisted of age and gender-matched healthy children aged 0 to less than 18 years old, and who were referred to the outpatient paediatric cardiology consultation for minor symptoms (e.g., innocent murmur, chest pain, palpitations, or sports certificate). Only subjects with normal physical examination, electrocardiogram, and conventional echocardiography were eligible for the study. Children with any chronic disease, or under any treatment, were not included in the control group [8,29].

All children, in both groups, have been enrolled consecutively, and all clinical and biological study assessments were performed on the same day.

2.2. Biological markers of cardiotoxicity

The two main cardiotoxicity biomarkers, cardiac troponin T (cTnT) and N-Terminal pro-brain natriuretic peptide (NT-proBNP), were assessed in the anthracycline group [30,31].

Standard blood test with measure of haemoglobin was also performed in the anthracycline group to identify biological anomalies, which could influence cardiac parameters.

2.3. Cardiac risk stratification

In the anthracycline group, patients were categorized using the cardiac risk stratification by anthracycline and/or chest radiation dose from the “International late effects of childhood cancer guideline harmonization group” [32]. Patients with cumulative anthracycline dose ≥ 250 mg/m² or chest radiation dose ≥ 35 mSv were at high risk to develop anthracycline-induced cardiomyopathy. Patients with cumulative anthracycline dose ≥ 100 mg/m² and radiation dose ≥ 15 mSv had moderate cardiac risk. Remaining patients had low cardiac risk.

2.4. Conventional echocardiography

Echocardiographic examinations were performed in both groups using the Vivid E9 ultrasound system (General Electric Healthcare, Little Chalfont, United Kingdom). Echocardiographic examinations were performed by senior paediatric cardiologists, and following the current guidelines [33]. No additional imaging techniques were performed in

the two groups.

The following conventional LV function variables were measured: LVEF by the Simpson biplane method; inter-ventricular septum diastolic diameter (IVSd) and left ventricle internal diastolic diameter (LVIDd) using the M-mode; mitral inflow with peak early filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, and E wave deceleration time; early diastolic velocities of the lateral mitral annulus (E') measured by pulsed Tissue Doppler Imaging (TDI); E/E' ratio; velocity of circumferential fiber shortening (VCFc); and LV wall stress, determined by the pressure in the ventricle using cuff blood pressure at the time of echocardiography, the internal radius of the ventricle by M-mode, and the thickness of the wall [34].

The following conventional RV function variables were measured: tricuspid annular plane systolic excursion (TAPSE), TDI myocardial performance index (TEI), and inferior vena cava collapse index (IVC%) [35].

2.5. Two-dimensional speckle tracking echocardiography (2D-STE)

Strain analysis was performed off-line by an investigator who was blinded to subject information, using the EchoPAC software from General Electric (version 203). The following global and segmental STE variables were measured: LV longitudinal, radial, and circumferential peak systolic strain from the 17-segment model [36]; RV longitudinal peak systolic strain from the free wall basal, mid, and apical segments in apical and sub-xiphoid views [37]; and peak systolic strain rate for both ventricles in all displacements [37].

A second off-line analysis was performed on a sample of 40 randomly selected ultrasound examinations, by the same investigator to assess intra-observer reproducibility, and by a second investigator to assess inter-observer reproducibility, with no access to the results of first analysis.

The investigators manually traced the endocardium in end-diastole, and the software tracked the myocardium semi-automatically throughout the heart cycle. Manual adjustments, if needed, were performed to optimize the region of interest. Whenever that was not possible, the segments in question were excluded from the analysis and reported as “poor tracking quality” missing data, in order to assess the feasibility of the technique.

2.6. Formal aspects

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. The South Mediterranean V French Ethics Committee (2014-A00420–47) approved the study, which was registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT02893787). Informed consent was obtained from all parents or legal guardians.

2.7. Sample size and statistical analysis

The LV global longitudinal 2D strain (GLS) was defined as the primary outcome. To calculate the sample size, we hypothesized that the percentage of GLS would decrease by 1.4 points (7%), that is, from a mean normal value of −19% to a mean value of −17.6% in the anthracycline group (standard deviation, SD = 3) [38]. The value of 1.4 points was determined from our own pre-study, as no data was available in the literature at the time the study started. With a 90% power and a bilateral alpha risk of 5%, we planned to include 98 children treated with anthracyclines and 98 control subjects (1:1 case-control design). Each child with cancer was matched with a control subject according to age (± 1 year) and gender.

The characteristics of the children included in the study were described with proportions for categorical variables and with means and standard deviation (SD) values for continuous variables.

The comparisons of echocardiographic parameters between children treated with anthracyclines and control subjects were performed using

linear mixed models, with a pair-specific random intercept. In the anthracycline group, conventional and 2D strain echocardiographic values were expressed as Z-scores for age and gender, in order to evaluate the potential effect of anthracyclines according to the collected parameters, and regardless of differences in the scale and dispersion of these parameters. The Z-scores reference values were generated from the control group echocardiographic parameters, using a multivariate linear regression model. A Z-score < 2 was used to define abnormal values [11,21,24]. In children treated with anthracyclines, we compared children with abnormal and normal GLS values, using the Student's *t*-test or Mann-Whitney *U* test for quantitative variables, and using the Chi2 test for qualitative variables.

We applied Pearson correlation coefficients to assess the association between the cumulative dose of anthracyclines and/or radiotherapy use and strain measurements.

From a total of 40 subjects ($\approx 25\%$ of the cohort) randomly selected from the anonymized electronic case report form (e-CRF), we evaluated the reproducibility of the GLS (primary outcome), by calculating intra class correlation coefficients (ICC), in accordance with recommendations published in Shrout and Fleiss [39]. ICC of type $(2,1)$ was used to assess inter- and intra-observer reliability. ICC values under 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and above 0.90 were indicative of poor, moderate, good, and excellent reliability, respectively [40].

The statistical significance was set at 0.05, and analyses were performed using SAS version 9 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Population

The total expected number of 196 children was included in the study, with 98 children treated with anthracyclines (mean age 10.8 ± 3.6 years; 51% female) and 98 age- and gender-matched healthy control subjects (mean age 10.8 ± 3.5 years; 51% female).

The two groups were similar in terms of anthropometric parameters (weight, height, body mass index), however, in the anthracycline group, the heart rate was significantly higher (80.7 ± 13.2 vs. 76.2 ± 11.7 beats/min, $P = 0.006$), and the systolic blood pressure was lower (105.3 ± 12.4 vs. 108.3 ± 11.5 mmHg, $P = 0.04$). Acute lymphoblastic leukaemia was the main type of cancer (62%).

In the anthracycline group, no anthracycline-induced acute cardiotoxicity was reported during or immediately after chemotherapy infusion. Cardiac biomarkers (troponin, NT-proBNP) and haemoglobin were normal (Table 1). Doxorubicine was the most used anthracycline drug (82%), and the mean cumulative dose was 201.54 ± 109.1 mg/m². The relative cardiotoxicity of Idarubicine and Mitoxantrone to doxorubicin were 0.5 and 0.4, respectively. Adjuvant therapies included radiotherapy for 14% of patients and allogeneic or autologous hematopoietic stem cell transplant for 14% of patients. The median time interval between the end of chemotherapy and patient enrolment was 5.1 ± 3.2 years (Table 1). More than half of the patients (60.2%) were classified in the moderate cardiomyopathy risk group (Supplementary Table 1).

3.2. Conventional echocardiography

All conventional echocardiographic parameters were normal in both groups and for both ventricles (Table 2). No relevant pattern of cardiomyopathy was observed, as LVEF and LV diastolic diameter were strictly normal in terms of Z-scores and not significantly different between groups. The early to late diastolic filling ratio (E/A ratio) and the VCFc were the only two LV parameters significantly lower in the anthracycline group. RV conventional variables were not significantly different between groups.

Table 1
Children treated with anthracyclines: population characteristics.

Qualitative variables		N	%
Gender	Male	48	49
	Female	50	51
Type of cancer	Acute lymphoblastic leukaemia	61	62
	Acute myeloblastic leukaemia	8	8
	Burkitt lymphoma	3	3
	Hodgkin lymphoma	8	8
	Lymphoblastic lymphoma	2	2
	Ewing's sarcoma	6	6
	Rhabdomyosarcoma	1	1
	Neuroblastoma	3	3
	Wilms' tumour	4	4
	Other	2	2
Type of anthracyclines	Doxorubicine	80	81.6
	Daunorubicine	58	59.2
	Mitoxantrone	12	12.2
	Other	6	6.1
Radiotherapy		14	14.3
Bone marrow transplant		14	14.3
Quantitative variables		Mean \pm SD	
Age at study enrolment (year)		10.8 \pm 3.6	
Weight at study enrolment (kg)		40.3 \pm 16.2	
Height at study enrolment (cm)		143.8 \pm 19.4	
BMI at study enrolment (kg/m ²)		18.6 \pm 3.7	
Age at initiation of chemotherapy (year)		5.8 \pm 3.6	
Age at end of chemotherapy (year)		6.2 \pm 3.6	
Doxorubicin equivalent value (mg/m ²)		201.54 \pm 109.1	
Time interval between end of chemotherapy and study enrolment (years)		5.1 \pm 3.2	
Troponin at study enrolment (ng/mL)		4.0 \pm 1.6	
NT-ProBNP at study enrolment (ng/mL)		69.2 \pm 57.6	
Haemoglobin at study enrolment (g/dL)		13.2 \pm 1	

BMI: Body mass index. Quantitative variables are expressed as mean \pm standard deviation.

3.3. Speckle tracking echocardiography (STE) analysis

The GLS was significantly worse in the anthracycline group than in healthy matched controls ($-19.1\% \pm 4.2\%$ vs. $-21.5\% \pm 2.7\%$, $P < 0.0001$, respectively), with a mean absolute decrease of 2.4% (Table 3).

Table 2
Conventional echocardiographic parameters.

Variables		Anthracycline group (N = 98)		Control group (N = 98)		Adjusted difference between groups*	
		Mean \pm SD	Z-score \pm SD	Mean \pm SD		Coefficient	[95% CI] P-value†
Left ventricle	LVEF (%)	62.9 \pm 5.2	0.19 \pm 1.16	63.8 \pm 4.6		-0.87	[-2.30; 0.56] 0.23
	LVIDd (mm)	41.1 \pm 5.2	0.16 \pm 1.16	41.5 \pm 4.9		-0.51	[-1.46; 0.43] 0.27
	E/A ratio	1.9 \pm 0.7	0.48 \pm 1.08	2.2 \pm 0.6		-0.28	[-0.45; 0.11] 0.001
	E deceleration time (ms)	165.6 \pm 46.2	0.16 \pm 1.22	170.8 \pm 38.5		-5.21	[-16.61; 6.17] 0.36
	E/E'	5.5 \pm 1.3	-0.06 \pm 1.20	5.4 \pm 1.1		0.05	[-0.26; 0.38] 0.71
	Wall stress (g/cm ²)	43.9 \pm 13.1	-0.17 \pm 1.01	41.8 \pm 13.9		2.12	[-2.22; 6.46] 0.33
	VCFc (s ⁻¹)	1.1 \pm 0.3	0.37 \pm 1.14	1.2 \pm 0.3		-0.09	[-0.18; -0.01] 0.02
Right ventricle	TAPSE (mm)	20.6 \pm 3.6	0.28 \pm 1.05	21.5 \pm 3.6		-0.91	[-1.91; 0.08] 0.07
	TEI index (TDI)	0.38 \pm 0.14	-0.04 \pm 1.22	0.37 \pm 0.12		0.01	[-0.02; 0.05] 0.64
	IVC %	68 \pm 11.1	-0.22 \pm 0.95	65.2 \pm 15.5		2.64	[-1.36; 6.63] 0.19

LVEF: left ventricle ejection fraction (Simpson biplane); LVIDd: left ventricle internal diastolic diameter; TDI: Tissue Doppler imaging; VCFc: contraction velocity corrected by cardiac frequency; TAPSE: tricuspid annular plane systolic excursion; TEI: myocardial performance index; IVC %: inferior vena cava collapse index.

* Difference between groups adjusted for age.

† Difference between groups is significantly different from 0 when P-value < 0.05 (significant P-values < 0.05 are marked in bold).

The proportion of children with an abnormal GLS was significantly higher in the anthracycline group with a Z-score < 2 in 18.6% of them vs. 1.0% in the healthy population ($P < 0.0001$). In the anthracycline group, the GLS was more frequently abnormal in female than in male patients (Z-scores < 2 in 77.8% vs. 22.2%, $P = 0.01$, respectively). No association was found between abnormal GLS and treatment (age, type, time since end of treatment, cumulative dose of treatment) or biological markers (troponin, NT-proBNP, haemoglobin). Moreover, the level of GLS alteration was not correlated with the cardiomyopathy risk stratification (Supplementary Table 2).

The global radial LV strain was significantly better in the anthracycline group than in healthy matched controls ($+51.4\% \pm 17.1\%$ vs. $+35.9\% \pm 16.7\%$, $P < 0.0001$), with a mean absolute increase of 15.6% (Table 3).

The global circumferential LV strain was significantly worse in the anthracycline group than in healthy matched controls ($-16.8\% \pm 3.7\%$ vs. $-19.4\% \pm 3.2\%$, $P < 0.0001$), with a mean absolute decrease of 2.6% (Table 3).

In the anthracycline group, segmental LV longitudinal 2D strain values were significantly worse in the mid-anterior and apical segments, and segmental LV circumferential 2D strain values were significantly worse in the 3 inferior wall segments. However, segmental LV radial strain values were significantly better in all 6 segments (Fig. 1).

The RV free wall longitudinal strain analyses were not significantly different between children treated with anthracyclines and control subjects, except for a significantly better value in the anthracycline basal segment on the apical 4-chamber view (Supplemental Table 3).

In children treated with anthracyclines, the global strain rate values were significantly worse in LV longitudinal 4-chamber view and radial analyses, and significantly better in RV free wall apical 4-chamber view.

3.4. Feasibility and reproducibility of STE analysis

In terms of tracking quality, missing data per segment were indicated in Table 3 and supplemental Table 3. After removal of poorly detected segments from the analysis, the global longitudinal, radial, and circumferential LV strain analyses could be calculated in nearly all subjects: in the anthracycline group we reported missing data for only one subject (1%) for all three displacements; in the control group, we reported missing data for only one subject (1%) in the global longitudinal analysis, and for four subjects (4%) in radial and circumferential strain analyses. A suboptimal tracking quality was observed for RV strain analysis, with poorly detected segments for 19.4% patients in the anthracycline group and 25.5% in the control group.

The reproducibility of the GLS was good, with an ICC of 0.85 (95% confidence interval [0.73–0.92]) for the intra-observer variability, and an ICC of 0.78 (95% confidence interval [0.62–0.88]) for the inter-

Table 3

Left ventricle longitudinal, radial and circumferential 2D strain.

2D strain and strain rate variables			Anthracycline group			Control group		Adjusted difference between groups*		
			n/N	Mean \pm SD	Z-score \pm SD	n/N	Mean \pm SD	Coefficient	[95% CI]	P-value [†]
Longitudinal 2D strain (%)	Global		97/ 98	-19.1 \pm 4.3	-0.96 \pm 1.83	97/ 98	-21.5 \pm 2.7	2.38	[1.38; 3.39]	<0.0001
	Segment 1	Basal anterior	95/ 98	-18.7 \pm 3.9	-0.08 \pm 1.04	95/ 98	-19 \pm 4.1	0.26	[-0.78; 1.30]	0.62
	Segment 2	Basal anteroseptal	98/ 98	-19.4 \pm 3.3	0.26 \pm 1.20	97/ 98	-18.7 \pm 2.9	-0.73	[-1.60; 0.14]	0.09
	Segment 3	Basal inferoseptal	96/ 98	-21.2 \pm 5	-0.03 \pm 1.44	96/ 98	-21.4 \pm 3.6	0.11	[-1.13; 1.36]	0.86
	Segment 4	Basal inferior	93/ 98	-17 \pm 7.7	-0.16 \pm 1.11	96/ 98	-18.1 \pm 7.5	1.07	[-1.09; 3.23]	0.32
	Segment 5	Basal inferolateral	92/ 98	-17.9 \pm 7.7	0.25 \pm 1.42	94/ 98	-16.5 \pm 6.5	-1.45	[-3.54; 0.64]	0.17
	Segment 6	Basal anterolateral	93/ 98	-21.5 \pm 4.7	0.05 \pm 0.94	96/ 98	-21.3 \pm 5.3	-0.19	[-1.57; 1.19]	0.78
	Segment 7	Mid anterior	89/ 98	-21.3 \pm 3.9	-0.31 \pm 0.96	95/ 98	-22.6 \pm 4.2	1.29	[0.23; 2.35]	0.01
	Segment 8	Mid anteroseptal	98/ 98	-21.4 \pm 2.9	-0.21 \pm 1.15	97/ 98	-22 \pm 2.5	0.52	[-0.20; 1.25]	0.16
	Segment 9	Mid inferoseptal	97/ 98	-22 \pm 4.2	-0.28 \pm 1.34	96/ 98	-22.9 \pm 3.3	0.93	[-0.14; 2.01]	0.08
	Segment 10	Mid inferior	95/ 98	-18.9 \pm 3.3	-0.07 \pm 0.85	97/ 98	-19.3 \pm 4.2	0.31	[-0.77; 1.40]	0.56
	Segment 11	Mid inferolateral	96/ 98	-18.9 \pm 3.8	-0.09 \pm 0.83	97/ 98	-19.4 \pm 4.8	0.47	[-0.76; 1.70]	0.45
	Segment 12	Mid anterolateral	92/ 98	-20.8 \pm 3.9	-0.12 \pm 0.84	96/ 98	-21.3 \pm 4.5	0.58	[-0.58; 1.75]	0.32
	Segment 13	Apical anterior	85/ 98	-21.6 \pm 5.2	-0.40 \pm 0.90	92/ 98	-23.9 \pm 5.8	2.36	[0.73; 3.99]	0.005
	Segment 14	Apical septal	87/ 98	-23.6 \pm 3.9	-0.48 \pm 1.00	94/ 98	-25.6 \pm 4.1	1.94	[0.79; 3.08]	0.001
	Segment 15	Apical inferior	92/ 98	-23.1 \pm 4.5	-0.50 \pm 1.19	97/ 98	-25 \pm 4	1.99	[0.76; 3.22]	0.001
	Segment 16	Apical lateral	89/ 98	-22.2 \pm 3.6	-0.38 \pm 0.91	97/ 98	-23.7 \pm 4.2	1.58	[0.46; 2.71]	0.006
	Segment 17	Apex	89/ 98	-22.5 \pm 3.8	-0.55 \pm 1.08	86/ 98	-24.7 \pm 3.8	2.19	[1.04; 3.35]	<0.001
Longitudinal global strain rate (s ⁻¹)	4-chamber		98/ 98	-1.9 \pm 0.4	0.59 \pm 1.18	98/ 98	-1.7 \pm 0.3	-0.19	[0.28; 0.09]	<0.001
	3-chamber		97/ 98	-2 \pm 0.5	0.28 \pm 1.15	95/ 98	-1.9 \pm 0.5	-0.12	[-0.24; 0.01]	0.06
Radial 2D strain (%)	Global		97/ 98	51.4 \pm 17.1	-0.98 \pm 1.19	94/ 98	35.9 \pm 16.7	15.55	[10.71; 20.39]	<0.0001
	Segment 7	Mid anterior	97/ 98	46.1 \pm 19.2	-0.89 \pm 1.24	93/ 98	30.9 \pm 17.9	15.17	[9.80; 20.53]	<0.0001
	Segment 8	Mid anteroseptal	97/ 98	47.6 \pm 18.9	-0.92 \pm 1.27	94/ 98	30.7 \pm 20.9	16.91	[11.22; 22.65]	<0.0001
	Segment 9	Mid inferoseptal	97/ 98	54.5 \pm 21.1	-0.82 \pm 1.18	93/ 98	38 \pm 21.3	16.49	[10.41; -22.57]	<0.0001
	Segment 10	Mid inferior	97/ 98	57.1 \pm 21.8	-0.37 \pm 1.10	93/ 98	49.6 \pm 20.7	7.52	[1.41; 13.63]	0.01
	Segment 11	Mid inferolateral	97/ 98	54.7 \pm 21.5	-0.86 \pm 1.08	92/ 98	36.5 \pm 21.2	18.20	[12.01; 24.39]	<0.0001
	Segment 12	Mid anterolateral	96/ 98	50.5 \pm 20.5	-1.13 \pm 1.16	93/ 98	28.9 \pm 20.5	21.65	[15.72; 27.59]	<0.0001
Radial strain rate (peak systolic, s-1)			97/ 98	2.6 \pm 0.7	0.29 \pm 0.62	94/ 98	2.9 \pm 1.2	-0.33	[-0.59; 0.07]	0.01
Circumferential 2D strain (%)	Global		97/ 98	-16.8 \pm 3.7	-0.86 \pm 1.29	94/ 98	-19.4 \pm 3.2	2.61	[1.68; 3.55]	<0.0001
	Segment 7	Mid anterior	97/ 98	-21 \pm 6.4	-0.13 \pm 0.99	93/ 98	-22 \pm 6.8	1.00	[-0.82; 2.83]	0.2
	Segment 8	Mid anteroseptal	97/ 98	-25.7 \pm 4.6	0.12 \pm 0.87	94/ 98	-25.1 \pm 5.3	-0.61	[-1.99; 0.77]	0.3
	Segment 9	Mid inferoseptal	97/ 98	-17.8 \pm 5	-0.56 \pm 0.96	93/ 98	-21.2 \pm 6	3.36	[1.88; 4.84]	<0.0001
	Segment 10	Mid inferior	97/ 98	-9.9 \pm 6.9	-0.64 \pm 0.97	93/ 98	-14.7 \pm 7.9	4.87	[2.79; 9.97]	<0.0001
	Segment 11	Mid inferolateral	97/ 98	-11.6 \pm 6.4	-0.48 \pm 0.87	92/ 98	-15.1 \pm 7.5	3.57	[1.70; 5.43]	<0.01
	Segment 12	Mid anterolateral	96/ 98	-16.6 \pm 5.1	-0.17 \pm 0.90	93/ 98	-17.7 \pm 6.6	1.08	[-0.58; 2.75]	0.2
Circumferential strain rate (peak systolic, s-1)			97/ 98	-2.1 \pm 0.5	0.03 \pm 1.12	94/ 98	-2.1 \pm 0.6	-0.01	[-0.15; -0.14]	0.8

CI: confidence interval; n: patients with good tracking quality; N: overall number of patients in each group, representing the expected number of segments for each STE analysis (N-n = “poor tracking quality” missing data).

* Difference between groups adjusted for age.

† Difference between groups is significantly different from 0 when P-value <0.05 (significant P-values <0.05 are marked in bold).

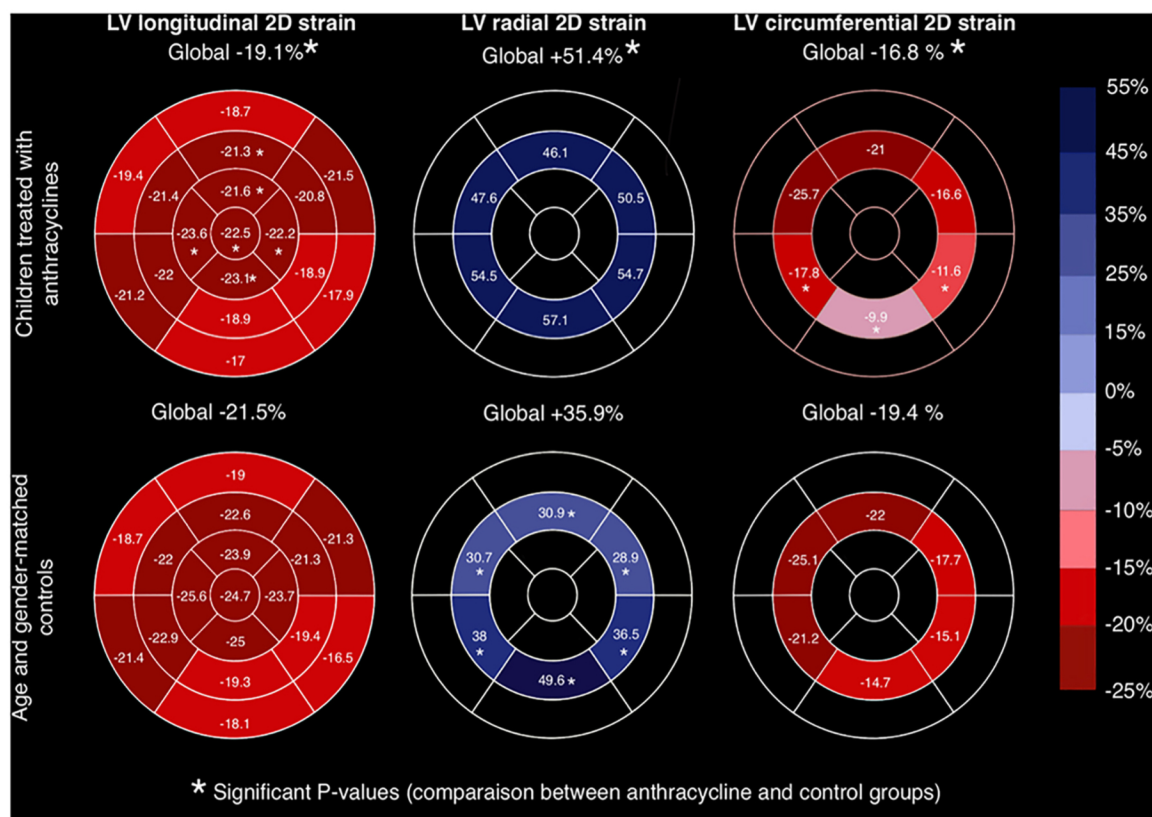


Fig. 1. Left ventricle global and segmental 2D strain in children treated with anthracyclines and control subjects.

Legend: These 6 figures represent, for each group, the longitudinal, radial and circumferential 2D strain, using the classical blue (positive displacement) and red (negative displacement) color-coded bull's eye plot. The anthracycline group is represented on the top 3 figures and the controls on the 3 bottom ones. In each strain segment of the anthracycline group, an asterisk indicates the existence of a significant difference with the corresponding segment of the control group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

observer variability.

4. Discussion

This single-centre prospective controlled study of 196 children demonstrated that the GLS in children treated with anthracyclines in malignancy remission was significantly different in the three displacements than in healthy age-matched children, despite the absence of any relevant pattern of cardiomyopathy using conventional echocardiography. The expected number of 98 children treated with anthracyclines and 98 healthy matched control subjects were included in the study. A significant difference in the primary outcome was observed, with a mean GLS decrease of 2.4% in children treated with anthracyclines, after a mean time interval of 5 years after the end of chemotherapy. Overall, nearly 19% of children treated with anthracyclines in this study had an abnormal GLS with Z-score values <2. Furthermore, a mean decrease of 2.6% was observed for the global circumferential LV strain. Interestingly, a mean increase of 15.6% was observed for the global radial LV strain, in the anthracycline group. However, no significant RV strain anomalies after anthracycline therapy were observed in this study. The GLS decrease observed in this study is in line with previous research on long-term follow-up after anthracycline therapy in the paediatric population. A 1.6% GLS decrease, using three-dimensional STE, has been reported in 15 years-old adolescents six years after anthracycline therapy [38]. Similarly, Ganame et al. found a significant GLS decrease,

using velocity vector imaging-strain, in 12-year-old children five years after anthracycline therapy [41]. In adult patients with breast cancer, GLS has been considered as a reproducible indicator of early anthracycline-related myocardial dysfunction and future reduction in LVEF [42]. A recent meta-analysis concluded that early 2D strain decrease after anthracycline therapy may precede LVEF decrease and reflect early onset of heart failure [43]. The latest expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy stated that a relative decrease in GLS > 15% was considered pathological and predictive of future LV systolic dysfunction [12]. However, longitudinal on-going studies need to confirm that GLS can be used as a predictor of late-onset anthracycline-induced cardiomyopathy [44].

Interestingly, we found that abnormal GLS in the anthracycline group was 4 times more frequent in female than in male patients. Female subjects, especially before puberty and adolescence, or after menopause, seem to be more at increased risk of anthracycline-induced cardiotoxicity. Indeed, sex hormones can modulate oxidative stress and apoptosis in anthracyclines heart damage [45].

Classically, “there is no safe dose of anthracycline” in terms of cardiotoxicity and late-onset anthracycline-induced cardiomyopathy rely on administration mode of anthracyclines, adjuvant drugs, and individual susceptibility factors [46]. Indeed, in our study, GLS changes were also observed after low and moderate doses of anthracyclines in this young population. Nevertheless, no significant association was

found between LV 2D strain change and anthracycline cumulative dose, as in a previous pilot study using similar dose ranges [24]. Moreover, the absence of association between strain values and several relevant clinical data may reflect the absence of significant on-going cardiac lesions in this young population treated with anthracyclines, suggesting the early subclinical nature of the lesions detected by STE in paediatrics.

In terms of LV segmental strain results, the main longitudinal strain changes in the anthracycline group were observed in the mid-anterior and apical segments. Similar findings have been reported in older patients treated with anthracyclines, such as 3D-strain anomalies in mid and apical segments [47], reduced apical rotation and apical untwisting rate [48], or apical LV longitudinal strain correlations with LVEF change [25].

Our study also showed a significant decrease regarding LV circumferential global peak systolic strain in young patients exposed to anthracycline therapy compared to age-matched controls. Especially, mid-inferoseptal, mid-inferior and mid-inferolateral segments decreased in the regional analysis. Cheung et al. demonstrated a similar and major decrease (-2.9%) in LV circumferential global peak systolic strain in the anthracycline group, with a concordant impairment in mid-inferoseptal, mid-inferior and mid anterior segments. Therefore, they proposed LV circumferential strain as a more sensitive marker as LV longitudinal strain to detect early myocardial dysfunction [38].

Interestingly, we found a significant increase of LV radial strain values in the anthracycline group compared to healthy subjects. Previous studies have found a radial strain decrease in adolescents treated with anthracyclines, whereas no significant change in radial strain has been observed one year after the end of anthracycline therapy in 6 year-old children [38,41,49]. Radial strain improvement has been related to myocardial remodelling, as observed in cardiac rehabilitation after acute myocardial injuries [50]. Therefore, the radial strain increase observed in our study may reflect a low-dose anthracycline-related myocardial remodelling. Indeed, multidirectional strain reflects damage across the different myocardial layers, with longitudinal strain being predominantly affected by the subendocardial fiber damage and the circumferential strain being predominantly affected by the mid-myocardial fiber damage. The change in radial strain may be a myocardial adaptation to longitudinal and circumferential alterations in order to maintain contractile LV efficiency in the early stages of cardiac anthracycline toxicity. In line with this hypothesis, our group has recently observed similar transient segmental strain improvement in preclinical rodent toxicity studies [27].

This study was performed in children after anthracyclines treatment with no evidence of significant cardiomyopathy, e.g. no relevant symptoms of heart failure and no systolic dysfunction using conventional echocardiography. Thus, the main result of this study, that is, a lower LV global longitudinal strain despite a normal ejection fraction, represents an important perspective for future paediatric drug trials in anthracycline-related cardiomyopathy prevention (dexrazoxane, for example; NCT01790152). Indeed, reliable and non-invasive biomarkers are necessary for paediatric cardiology trials. Our study showed that speckle tracking analysis in children was feasible, with an excellent tracking quality and a good reproducibility.

5. Study limitation

The control group was screened from the outpatient paediatric cardiology consultation; however, strict criteria were applied to select healthy subjects, as in our previous similar studies [8,29].

A single ultrasound system and its dedicated 2D-STE software were used, despite the existence of other ultrasound systems, STE vendors, vendor-independent software, and more advanced techniques such as 3D-STE.

Our results suggest that STE could be used as a non-invasive outcome in future clinical trials for children treated with anthracyclines. However, further studies will have to demonstrate that 2D strain represents a

reliable surrogate endpoint for heart failure in this population and a prognosis biomarker for cardiomyopathy.

6. Conclusion

In children treated with anthracyclines, and after an average delay of 5 years after the end of chemotherapy, the GLS was significantly decreased in longitudinal and circumferential displacements, without any pattern of cardiomyopathy using conventional echocardiography. The main segmental strain changes were observed in the mid-anterior, inferior, and apical segments. Overall, nearly 19% of children treated with anthracyclines had an abnormal GLS. Interestingly, the global LV radial strain was significantly increased, suggesting an adaptive myocardial remodelling, as observed after acute myocardial infarction.

The existence of a LV strain change after anthracycline treatment in young cancer survivors despite normal clinical, biological and conventional echocardiographic status, suggests the interest of using STE in routine cardiac monitoring from paediatric age. Further prospective cohort studies will need to confirm that GLS measured during childhood represents a reliable surrogate outcome for heart failure and a predictor of future cardiomyopathy in childhood cancer survivors. It would therefore represent an important perspective for future paediatric drug trials in anthracycline-induced cardiomyopathy prevention.

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Authors statements

All authors made substantial contributions to all of the following: the conception and design of the study (Pascal Amedro, Marie Vincenti, Karine Lopez-Perrin, Hamouda Abassi) the acquisition of data (Nicolas Lanot, Gregoire De La Villeon, Stephany Haoouy, Alain Lacampagne), or analysis and interpretation of data (Sophie Guillaumont, Lucie Gamon, Thibault Mura, Olivier Cazorla, Laurence Vergely), drafting the article or revising it critically (Pascal Amedro, Anne Sirvent, Martina Avesani, Nicolas Sirvent) for important intellectual content and final approval of the version to be submitted (Pascal Amedro, Martina Avesani, Laure Saumet).

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

Declaration of Competing Interest

None.

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