Myocardial 2D Strain During Long-Term (>5 Years) Follow-Up of Childhood Survivors of Acute Lymphoblastic Leukemia Treated With Anthracyclines

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Anthracycline-induced cardiotoxicity can lead to clinical and subclinical heart failure. Decrease of global longitudinal strain is a predictor for heart failure. Early detection of subclinical cardiotoxicity is crucial for timely intervention and prevention of further progression. Cardiac function of 41 survivors of childhood acute lymphoblastic leukemia (ALL) was assessed. Values of cardiac troponin T, N-terminal-pro-brain natriuretic peptide, conventional and myocardial 2D strain echocardiography were measured before (T = 0), during (T = 1, cumulative dose of 120 mg/m^2), shortly after (T = 2) and long after anthracycline treatment (T = 3, ≥5 years after anthracycline exposure). Cardiac function of survivors at the latest follow up was compared with 70 healthy age-matched controls. None of the survivors showed clinical signs of cardiac failure at T = 3. Strain values decreased during anthracycline treatment and an ongoing reduction was seen at the latest follow-up (T = 3) with preserved cardiac function (normal ejection fraction and shortening fraction). At T = 1, a relative reduction in longitudinal strain (≥10% compared with baseline) was observed in 38% of the survivors, which increased to 54% at T=3. ALL survivors showed significantly lower conventional and myocardial 2D strain values, especially strain rate, compared with healthy age-matched controls. At T = 3, we did not find any abnormal cardiac troponin T levels. Six percent of the survivors showed abnormal N-terminal-pro-brain natriuretic peptide levels. This prospective study showed an ongoing reduction of 2D myocardial strain and strain rate, with preserved left ventricular ejection fraction (≤10% decrease compared with baseline) in asymptomatic ALL survivors at late follow-up. **(Am J Cardiol 2020;127:163−168)**

Survival of children with cancer has improved significantly over the last decades but has come with considerable late effects. Forty years after treatment with cardiotoxic chemotherapy, the estimated risk of symptomatic cardiac disease is 10.6%. This percentage increases to 27.8% if radiotherapy had been given.[1] Early detection of subclinical cardiotoxicity is crucial for timely intervention. Echocardiography is currently used for detection of cardiotoxicity.[2] However, left ventricular ejection fraction (LVEF) and shortening fraction (LVSF) lack sensitivity for detection of systolic dysfunction and a significant decrease may be a late finding in cardiotoxicity.[3,4] In the expert consensus for adult patients during and after cancer therapy, global longitudinal strain (GLS) has shown to be the single best parameter to predict anthracycline-induced cardiotoxicity, as a decrease of 10% to 15% of this parameter is often seen before a relevant reduction of LVEF is observed.[2,3] Cardiac biomarkers N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and cardiac troponin T (cTnT) are widely used for detection of cardiac injury (e.g. cardiac ischemia and heart failure) in both adults and children. In this study we investigate ongoing subclinical cardiotoxicity at late follow-up in previously reported patients with childhood acute lymphoblastic leukemia (ALL)[5] using conventional and myocardial strain echocardiographic parameters and measuring biomarkers. We compared cardiac function of ALL survivors at late follow-up to healthy age-matched controls.

Methods

Survivors of childhood ALL (included in our previous study[5]), were included in this pilot follow-up study when they visited our Late Effects outpatient clinic between March 2016 and June 2018. Focusing on subclinical

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cardiotoxicity, we used the following exclusion criteria: clinical heart failure (NYHA class II-IV), known cardiovascular disease or chronic renal disease. The control group consisted of 70 healthy age-matched controls (children as well as adults), routinely referred for echocardiographic evaluation of an asymptomatic, innocent heart murmur or for screening purposes. Their medical history, electrocardiogram, and echocardiogram were not indicative of cardiac disease. Data from our previous study were used to compare with the current data.[5] The study was approved by the local ethical committee (2016-2560) and informed consent was obtained from all included survivors (or their parents).

Survivors had been treated according to the DCOG-ALL-10 protocol and had been stratified in 3 treatment groups; standard-, medium-, and high-risk, largely based on treatment response.[6] Total treatment duration was 2 years, but shorter for HR patients who were eligible for stem cell transplantation. Results of cardiac assessment were reported at the following time points: timepoint 0 (T = 0): before start of anthracycline treatment, timepoint 1 (T = 1) after receiving a cumulative anthracycline dose of 120 mg/m^2, timepoint 2 (T = 2) at the end of anthracycline dosage in the protocol (1 year after start of treatment) and timepoint 3 (T = 3) at late follow-up (≥5 years after completion of anthracycline treatment). Cumulative anthracycline dosages are reported as the maximal anthracycline dosage at T = 2. None of the survivors received radiotherapy.

NT-pro-BNP (pg/ml) and cTnT (ng/ml) were measured using electrochemical luminescence immunoassay on a Modular E170 random access analyser (Roche Diagnostics, Mannheim, Germany). Reference values for NT-pro-BNP values for adults (male and female) were derived from a large population of healthy patients in a study by Fradley et al.[7] For normal values in children, we used age-dependent reference values published by Nir et al (cut off: 97.5th percentile).[8] A cTnT level of ≤0.01 ng/ml was defined as normal.

All subjects underwent a detailed transthoracic echocardiographic examination in left lateral position according to the recommendations of the American Society of Echocardiography.[9] Examinations were performed at rest. Images were obtained with a 3.0 MHz (S3) or a 5.0 MHz (S5) phased-array transducer, depending on age and weight of the patient, using a commercially available Vivid 7 echocardiographic scanner (GE, Vingmed Ultrasound, Horton, Norway). Quantification of cardiac chamber size, ventricular mass and LV function were measured in accordance with the American Society of Echocardiography's Guidelines and Standard Committee and the Chamber Quantification Writing Group.[9] Left ventricle dimensions were indexed for body surface area. Z-scores could not be used because of a mixed population of children and adults. Systolic function was determined using LVSF and LVEF. Left ventricular mass was calculated with the formula for estimation of left ventricular mass according to Devereux and Reichek.[10]

Two-dimensional multiframe B-mode (gray-scale) images were obtained in apical 4-chamber (4CH) for the longitudinal strain and in the parasternal mid-cavity short-axis view (at the level of the papillary muscle: SaxPM) for the circumferential strain. For an optimal 2D speckle tracking, a sector scan angle of 30 to 60 and a minimal frame rate of 60 Hz were chosen. Images from 3 cardiac cycles triggered by the R wave of the QRS complex were digitally saved in a cineloop format. Two observers (MP and MD) performed off-line speckle tracking analysis using software for echocardiographic quantification (EchoPAC version 113.1.3 GE Medical Systems, Horten, Norway). The EchoPAC software automatically divided the cross-sectional image into 6 segments, which were named and identified according to the cardiac imaging Committee of the Council of Clinical Cardiology of the American Heart Association.[11] Strain curves of 3 consecutive cardiac cycles and values of the manual timing were imported into a custom-made software package for estimation of final strain parameters after alignment and averaging of the curves, as described previously by our group.[12] Global longitudinal strain (GLS), global longitudinal strain rate (GLSr), global circumferential strain and global circumferential strain rate were calculated. We only used 4CH view to calculate longitudinal strain and not 2-chamber (2CH) and 3-chamber (3CH) view, to be able to compare the results with our previous data.[5] Interobserver and intraobserver variability scores have previously been described by our research group.[13]

In adults, a relative reduction of >15% in GLS (compared with baseline) is defined as subclinical cancer therapeutics related cardiac dysfunction (CTRCD).[2,3] We compared baseline values to T = 1 (acute CTRCD) and T = 3 (late CTRCD). In addition to this, in our study *in children*, we also calculated a relative reduction of 10% in GLS compared with baseline. CTRCD can be defined as a reduction of >10% in LVEF as mentioned in the expert consensus by Plana et al.[2]

Characteristics of the study population were summarized as median and range. Biomarkers and echocardiographic parameters were summarized as mean ± standard deviation. Characteristics of controls and ALL survivors were compared using independent sample *t* test (Mann-Whitney *U* test if not normally distributed). Changes in echocardiographic data over time in the survivor group were studied using linear mixed models (for continuous variables) to account for correlation between different time points. Statistical analysis was performed using Stata/IC, version 14.2. A 2-tailed p-value of less than 0.05 was considered to indicate statistical significance.

Results

In our longitudinal study, 60 patients were included at T = 0. At late follow-up, 7 survivors were lost to follow-up, 8 died due to their (noncardiac) disease and 4 relapsed. Current analysis was therefore done in the remaining 41 survivors. None of the survivors were excluded because of cardiovascular−or chronic renal disease.

None of the survivors showed clinical symptoms of late onset anthracycline-induced cardiotoxicity. Demographic characteristics of the 41 survivors and the 70 controls are shown in Table 1.

In Table 2, the results of the cardiac biomarkers, obtained in 33 from 41 survivors, are shown. Survivors of

Table 1
Characteristics of study population

Variable	Patients (n = 41)	Controls (n = 70)	p-Value*
Male	27 (66%)	45 (64%)	0.7
Age at diagnosis (years)	5.1 (2.2-16.9)		-
Age at follow-up (years)	15.1 (11.1-28.2)	15.1 (8-26.5)	0.625
Follow up duration after diagnosis (years)	9.7 (7.9-12.6)		-
Body surface area (m^2)	1.72 (1.12-2.18)	1.68 (0.93-2.40)	0.494
Body mass index (kg/m^2)	20.1 (14.7-36.6)	19.9 (14.6-28.8)	0.248
Heartrate (bpm)	67 (53-113)	68 (47-116)	0.985
Mean arterial pressure (mm Hg)	86 (68-115)	86 (70-99)	0.795
Cumulative anthracycline dose	300 (120-300)		
Risk stratification			
Standard risk	16		
Medium risk	23		
High risk	2		

Values are expressed as median and range.
* Mann-Whitney *U* test.

Table 2
Cardiac biomarkers in ALL survivors during and after treatment with anthracyclines

	T = 0	T = 1	T = 2	T = 3
Number of patients	41	41	41	41
Number of biomarker samples	29	26	33	33
Abnormal cardiac Troponin T (%) [N]	0	18.5 [5]	3.0 [1]	0
Cardiac Troponin T (ng/ml)	0.01 (0.01-0.01)	0.01 (0.01-0.04)	0.01 (0.01-0.02)	0.01 (0.01-0.01)
Abnormal N-terminal-pro-brain natriuretic peptide (%) [N]	20.7 [6]	11.5 [3]	15.2 [5]	6.1 [2]
N-terminal-pro-brain natriuretic peptide (pg/ml)	109.9 (16.9-685.0)	93.0 (8.5-380.6)	84.6 (8.5-575.1)	36 (0-300)

Values are expressed as median and range.

ALL showed no abnormal cTnT, and only 2 survivors showed an abnormal NT-pro-BNP.

Conventional echocardiographic and strain parameters are shown in Table 3. In this study, the feasibility was similar to our previous study.[5] No major missing data was seen in our dataset. LVSF and LVEF decreased significantly during treatment but stabilized at late follow-up. Only 1 survivor had a LVSF <30% (26%) at late follow-up (T = 3). This survivor received a cumulative anthracycline dose of 300 mg/m^2. Although LVSF and LVEF remained stable from T = 1 to T = 3, all myocardial strain parameters decreased during anthracycline treatment and at late follow-up (T = 3).

In 38% of our survivors, an early relative reduction ≥10% in GLS was seen (comparing T = 1 to T = 0). At late follow-up (comparing T = 3 to T = 0), this percentage increased to 54% (≥15% reduction in 40%). Although a reduction of at least 10% in GLS was seen, all survivors had a preserved LVEF (≤10% decrease). There was no correlation between strain (rate) values or biomarker levels and follow-up duration (data not shown).

Intraclass correlations at timepoint 3 for intra-observer and inter-observer were calculated for 10 patients and ranged from 0.81 to 0.95 and 0.62 to 0.94, respectively.

The echocardiographic data of the survivors at T = 3 compared with healthy controls are shown in Table 4.

Discussion

This study addresses the role of strain echocardiography in evaluating subclinical cardiotoxicity in childhood cancer survivors (CCS) by providing prospective longitudinal echocardiographic assessment from start of therapy to late follow-up, including strain. It is unique because of its prospective follow-up of the same patient group.

We showed that cardiac function of asymptomatic ALL survivors decreased further over time, even long after anthracycline exposure, as measured by conventional and myocardial 2D strain echocardiography. The cardiac function of these survivors at the latest follow-up was also significantly less compared with healthy controls.

The effect of the decrease in the conventional echocardiographic parameters, from T = 2 to T = 3 might be partially explained by the significant increase in body surface area because of a longer time interval from T = 2 to T = 3. Nevertheless, these conventional parameters remained significantly lower compared with healthy controls, possibly related to myocardial fibrosis due to anthracycline-induced cardiotoxicity. The latter is reported in previous literature.[14]

In current screening guidelines for childhood cancer survivors, only conventional echocardiographic parameters, such as LVSF and LVEF are recommended for screening for late onset cardiotoxicity.[15,16] As previously reported,

Table 3
Clinical, echocardiographic and strain parameters in ALL patients during and after anthracyclines treatment

					p-Value*	
	T = 0	T = 1	T = 2	T = 3	T0-T2	T2-T3
Clinical parameters						
Body surface area, BSA (m^2)	0.92 ± 0.36	0.95 ± 0.36	1.01 ± 0.38	1.69 ± 0.29	***0.005***	***<0.001***
Conventional parameters						
Diastolic intraventricular septum (cm)	0.50 ± 0.11	0.51 ± 0.10	0.48 ± 0.13	0.62 ± 0.16	0.315	***<0.001***
Diastolic intraventricular septum/BSA (cm/m^2)	0.56 ± 0.12	0.58 ± 0.13	0.50 ± 0.14	0.37 ± 0.07	***0.003***	***<0.001***
Diastolic left ventricular posterior wall (cm)	0.57 ± 0.13	0.55 ± 0.12	0.54 ± 0.17	0.67 ± 0.18	0.137	***<0.001***
Diastolic left ventricular posterior wall/BSA (cm/m^2)	0.64 ± 0.15	0.64 ± 0.17	0.54 ± 0.15	0.40 ± 0.08	***<0.001***	***<0.001***
Diastolic left ventricle internal diameter (cm)	3.63 ± 0.66	3.85 ± 0.46	3.96 ± 0.57	4.84 ± 0.45	***<0.001***	***<0.001***
Diastolic left ventricle internal diameter/BSA (cm/m^2)	4.17 ± 0.80	4.45 ± 0.93	4.15 ± 0.90	2.92 ± 0.43	0.907	***<0.001***
Systolic left ventricle internal diameter (cm)	2.18 ± 0.44	2.46 ± 0.35	2.56 ± 0.36	3.13 ± 0.36	***<0.001***	***<0.001***
Systolic left ventricle internal diameter/BSA (cm/m^2)	2.51 ± 0.52	2.84 ± 0.60	2.70 ± 0.63	1.89 ± 0.26	***0.003***	***<0.001***
Left ventricular shortening fraction (%)	40 ± 4	35 ± 0.03	35 ± 3	35 ± 5	***<0.001***	0.941
Left ventricular ejection fraction (%)	71 ± 5	65 ± 0.04	65 ± 4	65 ± 5	***<0.001***	0.836
Intraventricular relaxation time (ms)	68.8 ± 12.3	55.4 ± 12.5	62.6 ± 12.0	60.2 ± 19.0	0.56	0.673
Ratio early and late diastolic filling mitral valve	1.81 ± 0.57	1.73 ± 0.38	1.80 ± 0.59	2.11 ± 0.90	0.99	***0.009***
Strain (rate) parameters						
Global longitudinal strain (%)	−19.3 ± 2.72	−18.4 ± 2.58	−18.6 ± 3.3	−17.4 ± 2.2	0.29	0.066
Global longitudinal strain rate (1/s)	−1.39 ± 0.16	−1.33 ± 0.25	−1.24 ± 0.22	−1.08 ± 0.19	***0.002***	***<0.001***
Global circumferential strain (%)	−19.2±3.56	−18.0 ± 2.76	−18.6 ± 2.52	−18.7 ± 2.0	0.724	0.981
Global circumferential strain rate (1/s)	−1.76±0.38	−1.76 ± 0.32	−1.82 ± 0.34	−1.49 ± 0.29	0.412	***<0.001***

Values are expressed as mean±SD.
* p-value was calculated using linear mixed models.

we found that LVSF and LVEF decreased mostly after the first induction therapy (cumulative anthracycline dose of 120 mg/m^2) and stabilized at end of therapy (T = 2), also previously reported by other authors.[17] We did not find a further decrease at the latest follow-up (T = 3). This finding is also supported by Aznar et al, where echocardiography was done at diagnosis, end of treatment and at 10 years follow-up.[18] Although we cannot exclude that the first decrease in LVSF (T = 0 to T1) might also be attributed to the hyperdynamic state of the heart at baseline (anemia and hyperhydration), LVSF and LVEF values were consistently lower compared with controls, both 1 and 5 years after diagnosis.

In contrast to LVSF and LVEF, we showed that global myocardial strain and strain rate parameters decreased significantly not only during, but also long after (≥5 years) anthracycline treatment in childhood. This suggests that myocardial strain might be superior to LVSF and LVEF in detection of subclinical cardiac dysfunction. Armstrong et al showed in 1,820 adult childhood cancer survivors that

Table 4
Echocardiographic conventional and myocardial strain parameters in survivors at T=3 compared with healthy controls

	Patients (n = 41)	Controls (n = 70)	p-Value*
Conventional parameters			
Diastolic intraventricular septum (cm)	0.62 ± 0.16	0.68 ± 0.18	0.068
Diastolic intraventricular septum/BSA (cm/m^2)	0.37 ± 0.07	0.42 ± 0.09	***0.002***
Diastolic left ventricular posterior wall (cm)	0.67 ± 0.18	0.74±0.17	***0.041***
Diastolic left ventricular posterior wall/BSA (cm/m2)	0.40 ± 0.08	0.45 ± 0.08	***<0.001***
Diastolic left ventricle internal diameter (cm)	4.84 ± 0.45	4.86 ± 0.62	0.808
Diastolic left ventricle internal diameter/BSA (cm/m^2)	2.92 ± 0.43	3.05 ± 0.43	0.153
Systolic left ventricle internal diameter (cm)	0.87 ± 0.18	1.07 ± 0.29	0.253
Systolic left ventricle internal diameter/BSA (cm/m^2)	1.89 ± 0.26	1.88 ± 0.30	0.915
Left ventricular shortening fraction (%)	35 ± 5	38 ± 5	***0.004***
Left ventricular ejection fraction (%)	65 (5)	67 (7)	0.196
Left ventricular mass (g/m^2)	60.34 ± 13.23	68.55 ± 18.65	***0.014***
Ratio early and late diastolic filling mitral valve	2.11 ± 0.90	2.25 ± 0.89	0.517
Strain (rate) parameters			
GLS (%)	−17.4 ± 2.19	−19.3 ± 2.43	***<0.001***
GLSr (1/s)	−1.08 ± 0.19	−1.17 ± 0.17	***0.008***
GCS (%)	−18.7 ± 1.95	−19.7 ± 2.86	0.060
GCSr (1/s)	−1.49 ± 0.29	−1.50 ± 0.27	0.861

Values are expressed as mean±SD.
* p-values were calculated by using independent sample *t* test.

only 5.8% of survivors had an abnormal 3D LVEF <50%. However, 28% of the survivors with a normal 3D LVEF had cardiac dysfunction measured by global longitudinal strain.[19] A recent review by Tuzovic et al (based on the results of 7 studies) also reported a decrease in strain parameters, comparing the pretreatment- to early posttreatment values (<1 year after anthracycline dose).[20] Yet, prospective studies with a long follow-up duration of the same patients are scarce.

Our results on decreased myocardial strain at late follow-up, compared with healthy controls, are supported by our own results in a different group of CCS[12] as well as in others.[21,22] However, whereas most studies are cohort studies with cardiac evaluation at 1 time point, we showed in this prospective study an ongoing reduction of global myocardial strain parameters over a longer period of time in the same study population. Early cardiotoxicity is a strong predictor for late overt cardiotoxicity.[23] In the review by Thavendiranathan et al, an early reduction of 10% to 15% in GLS was stated as the best predictor of late cardiotoxicity (expressed as a decrease in LVEF or clinical heart failure).[3] According to the expert consensus statement for *adult* cancer survivors,[2] a relative percentage reduction of GLS <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal. Other studies use a cut-off value of 10% relative decrease (compared with baseline) in GLS as a predictor for cardiotoxicity.[24,25]

In our group of 41 ALL survivors, early relative reduction of 10% in GLS increased from 38% to 54% of our survivors at late follow-up, implicating an ongoing subclinical deterioration of cardiac function. We propose using a cut-off of ≥10% reduction of GLS to be more cautious in *childhood* cancer survivors, since they have a long life expectancy after their cancer diagnosis and therefore careful monitoring might be even more crucial for timely intervention.

Strain rate is a marker of (maximal) cardiac contractility.[26,27] Two interesting findings in our study are the significant decrease in all strain rate parameters in survivors over time (rather than only GLS) and significantly lower strain rate values of survivors compared with healthy controls. These 2 findings suggest strain rate as potential marker for early detection of subclinical anthracycline induced cardiotoxicity.

An interesting and relatively new imaging modality for early detection of subclinical cardiotoxicity is cardiac magnetic resonance (CMR), also able to demonstrate reduced cardiac function when LVEF is still normal.[28] The advantage of CMR is the ability to detect even more subtle changes for subclinical cardiotoxicity. However, not all Late effect Clinics have CMR readily available, making it difficult to implement in national protocols.

Another interesting novel method that might be interesting in predicting cardiotoxicity in patients is comprehensive genomic variations analysis. This method has been studied in CCS in the past and is of interest in current studies.[29]

Biomarker results at late follow-up were in line with our previous study.[12] A recent review concluded that the diagnostic value of NT-pro-BNP in LV dysfunction in CCS is limited and there is no role for Troponins.[30]

There were a number of limitations of this study. First, this is a study with a small number of survivors (n=41). Nevertheless, significant ongoing reduction in cardiac function over time was seen in the remaining survivors. The clinical implications of these findings have yet to be studied in long-term follow-up studies in a larger population. Second, due to inter-vendor variability of strain and strain rate values, the results of this study apply only to survivors who are screened and followed with the technology used in this study. Third, myocardial strain measurements are nowadays performed in 3 apical views. We used strain measurements only in apical 4CH view, since we had to compare them with measurements at previous time points when 2CH and 3CH views were not part of the protocol. Fourth, because there were no cardiac events in this small population, we were unable to determine a predictive value for our cut-off limits.

In conclusion, in this study, asymptomatic ALL survivors showed an ongoing subclinical decrease of their cardiac function over time (from early to late follow-up), even long after anthracycline exposure. This was mainly expressed by further reduction of strain and in particular strain rate parameters, with preserved LVEF and LVSF (≤10% decrease compared with baseline). Strain has shown to be an important tool in assessment of subclinical cardiac dysfunction in childhood survivors of ALL. Further research is needed to assess the clinical implications and predictive value of our findings.

Disclosures

The authors have no conflicts of interest to disclose.

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