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Original Article

Left ventricular strain and strain rates are decreased in children with normal fractional shortening after exposure to anthracycline chemotherapy

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Abstract *Background:* Anthracycline chemotherapeutic agents carry the well-recognised risk of cardiotoxicity. Previous methods to evaluate cardiac function are useful, but have significant limitations. We sought to determine the left ventricular strain and strain rate of paediatric cancer patients with normal fractional shortening treated with anthracyclines using the latest ultrasound feature-tracking technology. *Patients and methods:* Echocardiograms on cancer patients before anthracycline exposure and following completion of treatment were retrospectively analysed using Velocity Vector Imaging software in the circumferential and longitudinal planes. The same analysis was performed on matched controls. Only patients with a fractional shortening $\geq$28% were included. *Results:* In all, 71 patients were identified with an age at diagnosis of 10.5 ± 4.7 years. The time from diagnosis to follow-up was 3.9 ± 4.0 years and the cumulative anthracycline dose was $356 \pm 106\,mg/m^2$. Following anthracycline exposure, paediatric cancer patients had a higher heart rate and a lower longitudinal strain, longitudinal diastolic strain rate, circumferential strain, and circumferential systolic and diastolic strain rate when compared with controls. Diastolic strain rate showed the greatest percent difference following anthracycline exposure versus controls. *Conclusion:* Despite having a normal fractional shortening, children exposed to anthracyclines have subclinical derangement of their left ventricular deformation as measured by decreases in strain and strain rate in both the circumferential and longitudinal axis. In particular, there was a profound decrease in diastolic strain rate following anthracycline exposure compared with controls. Whether the decline of strain or strain rate can predict future risk of developing cardiomyopathy requires further investigation.

Keywords: Echocardiography; Velocity Vector Imaging; anthracycline; left ventricular function; paediatric

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The use of anthracycline chemotherapeutic agents in the treatment of childhood cancers has significantly improved the long-term survival of these patients.[1–3] Unfortunately, these agents have long been recognised as causing both clinical and subclinical cardiotoxicity, which is dose related.[2,4–10] Owing to this well-recognised cardiotoxic effect, cardiac function is monitored using serial echocardiograms.[11] For many years, left ventricular function after exposure has been estimated by calculating the fractional shortening, which is readily obtained from M-mode echocardiography.[11–13] Although only a fraction of cancer survivors treated with anthracyclines ultimately develop a significant decline in fractional shortening, subclinical changes in cardiac function do occur after even relatively low doses of anthracyclines.[10,14–16] For this reason, investigators have sought to find more sensitive tools with which to analyse left ventricular function in an effort to better characterise the significance of subtle changes after anthracycline treatment.

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The concept of deformation analysis as a means to better understand and quantify myocardial mechanics has been popularised over the past several years. Tagged magnetic resonance imaging and tissue Doppler imaging, although both useful modalities to investigate deformation, have limitations. Newer ultrasound technology based on grey-scale imaging can now track individual speckle patterns within the myocardium along with endocardial border detection throughout the cardiac cycle.[17] The combination of these techniques is termed "feature-tracking". This new technology is angle-independent, which eliminates the necessity for a precise beam angle and is more available than magnetic resonance imaging. Strain and strain rate as calculated using feature-tracking software has been validated by numerous studies.[18–22] Overall, this method has reasonable inter- and intraobserver variability and has good overall correlation with sonomicrometry and magnetic resonance imaging.[17,19,23–25]

A few studies have recently investigated this topic, but unfortunately there is a relative paucity of information on the ventricular function of children after anthracycline treatment specifically using feature-tracking technology.[26,27] The primary purpose of this investigation is to characterise changes in strain and strain rate after anthracycline therapy. Our hypothesis is that subclinical abnormalities in cardiac mechanics exist and can be identified by using the latest feature-tracking software in children exposed to anthracycline who have a normal fractional shortening.

Materials and methods

Study group and patient variables

The standard practice at our institution is to obtain a two-dimensional echocardiogram before the initiation of anthracycline-based treatment and periodically thereafter according to the recommended Children's Oncology Group guidelines.[11] We retrospectively analysed echocardiograms of patients following completion of therapy. We targeted four specific diagnoses whose treatment protocol calls for high cumulative doses of anthrcyclines: acute myeloblastic leukaemia, Burkitt's lymphoma, Ewing's sarcoma, and osteosarcoma. By cross-referencing the oncology and echocardiography databases at Children's Hospital Colorado, we identified a total of 81 patients with one of the designated forms of cancer and had at least one echocardiogram between 1 June, 2006 and 31 December, 2009. 1 June, 2006 was chosen as the study start date as this was when all echocardiograms at our institution were digitally stored in standard DICOM format.

Several patient variables were recorded including the age of the patient at diagnosis, age of the patient upon completion of treatment, specific cancer diagnosis, gender, type of anthracycline, and cumulative dose of anthracycline. Given that the various anthracyclines have different potency, the cumulative anthracycline dose was derived using a previously published method and expressed in mg/m^2.[11] At the time of each echocardiogram, several other variables were recorded including patient weight, height, and calculated body surface area.

Patients were only included in the study if they were older than 1 year of age at the time of diagnosis, had one of the four forms of cancer mentioned above, and had a known cumulative anthracycline dose. Patients with any genetic syndrome, that is, trisomy 21, were excluded from the study. All of the patients at the time of their follow-up study were asymptomatic from a cardiovascular standpoint and were not on cardiac medications. This project was granted institutional review board approval in accordance with the rules as dictated by the State of Colorado.

Echocardiographic data

Only patients with "normal" left ventricular systolic function, defined as a fractional shortening $\geq 28\%$, were included in this study. Patients with congenital or structural heart disease were excluded from this study, but those with trivial valve disease – that is, trace tricuspid valve regurgitation – and those with a small patent foramen ovale with an insignificant shunt were included. In most instances, the oncology patients had multiple echocardiograms performed for the purposes of periodic functional evaluation during the study dates, but only the most recent study was used for the analysis.

The two-dimensional echocardiograms were performed using commercially available systems (Vivid 7; GE Healthcare, Milwaukee, Wisconsin, United States of America; and iE33; Philips Healthcare, Andover, Massachusetts, United States of America). The standard apical four-chamber view and parasternal short-axis view at the mid-ventricular – mid-papillary muscle – level were stored in the standard digital cine loop format for one cardiac cycle and selected for analysis. The specific transducer used at the time of the study was determined at the discretion of the sonographer performing the study. Only those studies that had an acceptable frame rate (>50 frames/second) were included owing to concern that a low frame rate would not accurately capture the peak strain and strain rate. Our institution intentionally stores images as raw DICOM files, which preserves the intrinsic frame rate of the particular study and does not reduce it to the standard 30 frames/second typical of regular DICOM images.

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M-mode imaging of the left ventricle was performed from the standard parasternal short-axis view. Recorded M-mode data included left ventricular septal wall thickness at end-systole and end-diastole, left ventricular free wall thickness at end-systole and end-diastole, and left ventricular internal diameter at end-systole and end-diastole. From the M-mode data, the left ventricular fractional shortening was calculated. Ejection fraction was inconsistently reported in these studies and therefore could not be included in the analysis.

Strain and strain rate data acquisition

To determine strain and strain rate data, Syngo® Velocity Vector Imaging™ software by Siemens (Siemens Medical Solutions, Mountain View, California, United States of America) was used. This program was ideal in that analysis of the study was possible regardless of the sonographic system used to obtain the images so long as the data were in DICOM format. Syngo® Velocity Vector Imaging has been validated using various vendors and the analysis does not significantly vary depending on which system was used to collect the echocardiographic data. Siemens is in the process of publishing this validation. The left ventricular endocardial border was manually traced at end-systole in both the short-axis and four-chamber views. The software tracks this endocardial layer throughout the cardiac cycle using the feature-tracking algorithm that incorporates both speckle-tracking and border detection. In those instances when there was poor tracking of the endocardial border, the trace was readjusted in an effort to obtain better tracking. This process was repeated until the endocardial border was optimally tracked. A study was excluded from the analysis if the border could not be traced accurately after three attempts. In each view, the software automatically subdivided the endocardial border into six separate regions. The peak circumferential strain along with the peak circumferential systolic and early diastolic strain rate for each of the six segments of the short-axis of the left ventricle was calculated by the software. Similarly, the peak longitudinal strain along with the peak longitudinal systolic and early diastolic strain rate for each of the six segments of the long axis of the left ventricle was also calculated. These six peak regional values were then averaged to obtain the overall global peak circumferential and longitudinal strain and strain rate. In addition, the time to peak strain and time to peak strain rate for systole and early diastole were calculated and averaged in the same manner. Late diastolic strain rate was not investigated in this study, and thus any reference to diastolic strain rate indicates early diastolic strain rate.

A typical output from the Syngo® software is shown below in the short-axis and four-chamber view, respectively (Figs 1 and 2). The upper plot in each of the figures is the strain curve versus time, whereas the lower plot represents the strain rate curve versus time. The vertical coloured lines – pink in the strain curve and red in the strain rate curve – demarcate the beginning and end of the cardiac cycle. The initial portion of the plot indicates the contraction, or systolic, phase of the cardiac cycle, whereas the latter portion of the plot indicates the relaxation, or diastolic, phase. The strain and strain rate in each of the six segments previously described are plotted versus time using a different colour with the black curve representing the average strain or strain rate. The software calculates the peak strain and the peak systolic and peak early diastolic strain rate along with the time to these peak events. Note that in the diastolic portion of the strain rate curves there are two separate peaks. The initial crest reflects the peak early diastolic strain rate, which reflects early ventricular relaxation. The second crest is the effect seen from atrial contraction, which occurs in late ventricular diastole.

The R-wave to R-wave interval for each study was determined by the software, and thus the heart rate was known. By convention, lengthening is assigned a positive value, whereas shortening is assigned a negative value. As strain is defined as the deformation of an object divided by its original length, the standard expression of strain is a percentage of the original object length. Strain rate is the temporal derivative of strain, otherwise known as the speed at which strain occurs, and is usually expressed as percent per second.

Comparison to controls

There were two sets of echocardiograms on patients in the anthracycline group; the baseline studies before anthracycline exposure and the follow-up studies following completion of treatment. About 50% of the patients identified in the study group had both an adequate baseline and follow-up study. The remaining patients either had a baseline study only, as they had not yet finished their treatment regimen, or they had a follow-up study only, as their baseline study pre-dated the study start date and was not stored in DICOM format. Of those study patients with both a baseline and follow-up study, there was only a short period of time between studies, on the order of 1 year. As such, a longitudinal analysis comparing a patient's pre-anthracycline study to their corresponding post-anthracycline study would have consisted of relatively few patients and would

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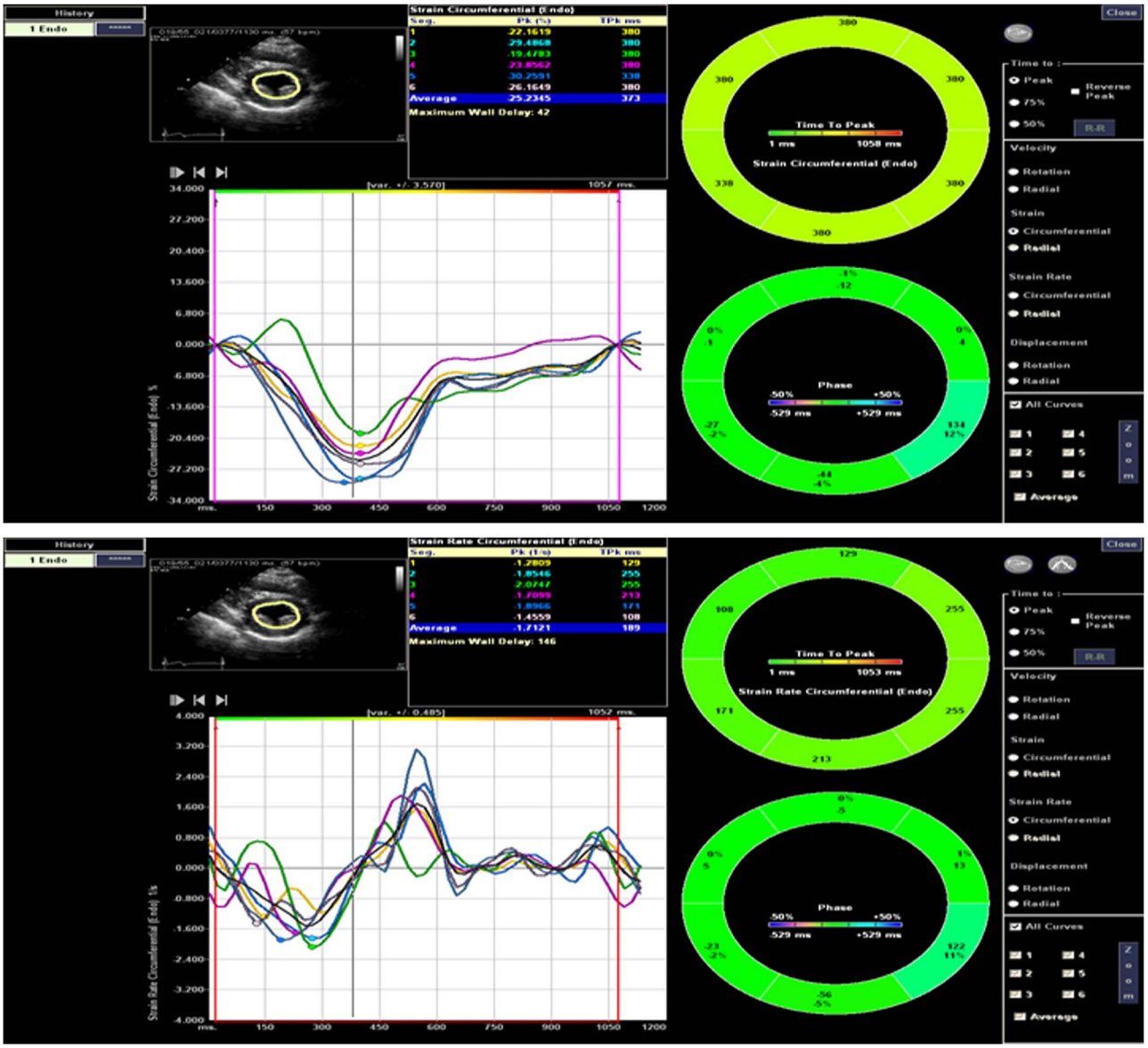

Figure 1.
Example of circumferential strain (top) and strain rate (bottom) curves versus time.

not take into account the effect of time since completion of therapy on ventricular function. To overcome this, the before and after treatment groups were compared indirectly by comparing each group to a group of normal control patients. For each echocardiogram analysed in the anthracycline group at baseline, an echocardiogram of a normal age- and gender-matched control was identified. Similarly, for each echocardiogram analysed in the anthracycline group at follow-up, an echocardiogram of a normal age- and gender-matched control was also identified. The same analysis was then performed on the control group. The values obtained from the analysis on the anthracycline group at baseline and follow-up were then compared with their respective control group.

Statistical analysis

The results from the anthracycline and control groups are presented as mean ± standard deviation. The statistical analysis was based on the paired Student's t-test. All statistical analysis was performed using JMP software version 8.0 (SAS, Cary, North Carolina, United States of America). A p-value of <0.05 was considered statistically significant.

Results

From the original 81 patients identified, four were excluded. There were three patients who were <1 year old at diagnosis and one patient was found to have a patent ductus arteriosus. No patients had a

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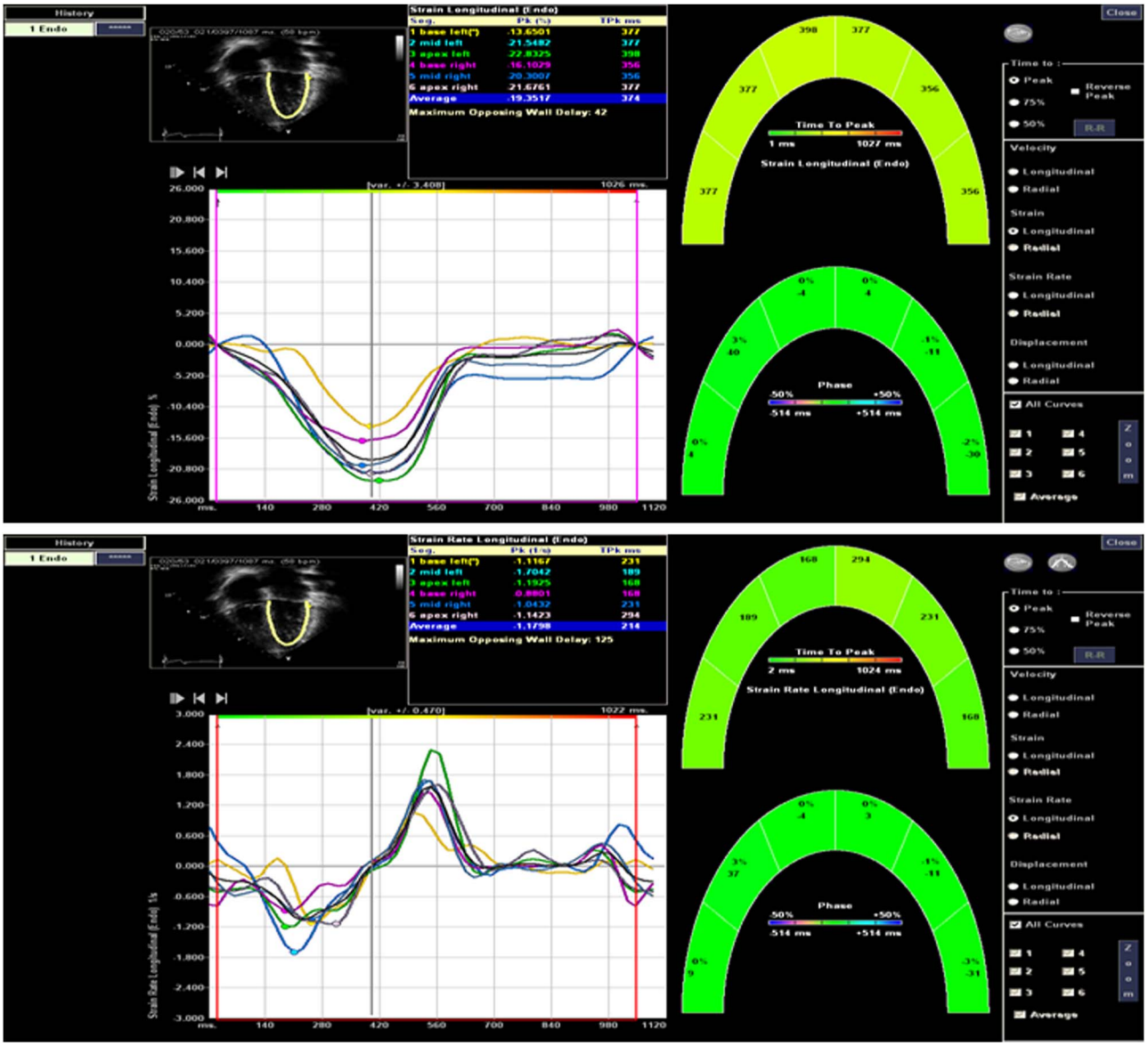

Figure 2.
Example of longitudinal strain (top) and strain rate (bottom) curves versus time.

genetic syndrome. From the remaining 77 patients, an additional six studies (8%) were excluded for a fractional shortening <28%. Therefore, after applying all the inclusion and exclusion criteria, a total of 71 post-anthracycline studies were deemed suitable for analysis. Of these patients 30 had Ewing's sarcoma, 20 had acute myeloblastic leukaemia, 12 had osteosarcoma, and nine had Burkitt's lymphoma. Of the 71 patients, 37 were male (52%). The average cumulative anthracycline dose was $356 \pm 106\ mg/m^2$. A breakdown of cumulative anthracycline dose showed that 21 patients (30%) received $300\ mg/m^2$ or less, 33 patients (46%) received between 300 and $450\ mg/m^2$, and 17 patients (24%) received more than $450\ mg/m^2$. The average age at diagnosis was 10.5 ± 4.7 years and the average time from diagnosis to follow-up was 3.9 ± 4.0 years. The anthracycline agents used in our patient population were doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone. There were no significant differences between the study group and controls with respect to age, gender, weight, height, and body surface area (Table 1).

Strain and strain rate comparison

As is typical in retrospective studies, not all of the 71 echocardiograms were able to be successfully analysed using the Syngo® software. In the short axis, 55 of the original 71 studies (77%) were successfully analysed. There were six studies that

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Table 1. Demographic comparison between anthracycline groups and controls.

	Baseline SA – ATC (n = 53)	Baseline SA – control (n = 53)	p-value	Baseline 4C – ATC (n = 43)	Baseline 4C – control (n = 43)	p-value
Male (%)	54.72	54.72		60.47	60.47	
Age (years)	11.35 ± 4.78	11.28 ± 4.67	0.94	11.25 ± 5.38	11.10 ± 5.18	0.89
Ht (cm)	146.99 ± 26.00	145.14 ± 28.12	0.73	144.9.3 ± 27.93	143.53 ± 30.17	0.82
Wt (kg)	46.72 ± 24.04	45.95 ± 22.22	0.87	45.08 ± 23.77	46.04 ± 24.59	0.85
BSA (m^2)	1.35 ± 0.46	1.34 ± 0.45	0.88	1.32 ± 0.47	1.33 ± 0.50	0.89
	Follow-up SA – ATC (n = 55)	**Follow-up SA – control (n = 55)**	**p-value**	**Follow-up 4C – ATC (n = 60)**	**Follow-up 4C – control (n = 60)**	**p-value**
Male (%)	49.09	49.09		50.00	50.00	
Age (years)	14.80 ± 4.87	14.45 ± 4.43	0.69	14.79 ± 5.17	14.35 ± 4.59	0.63
Ht (cm)	151.50 ± 29.23	156.18 ± 22.20	0.35	151.43 ± 28.95	155.95 ± 22.63	0.34
Wt (kg)	55.86 ± 24.82	54.56 ± 19.26	0.76	53.62 ± 22.84	53.63 ± 19.13	0.99
BSA (m^2)	1.52 ± 0.43	1.52 ± 0.38	0.98	1.49 ± 0.41	1.51 ± 0.38	0.82
Time to F/U (years)	3.59 ± 3.89			3.96 ± 4.27		
Dose (mg/m^2)	351.02 ± 105.34			354.97 ± 108.60		

ATC = anthracycline group; BSA = body surface area; F/U = follow-up; Ht = height; SA = short axis; Wt = weight; 4C = four chamber

had insufficient frame rates and 10 studies had prohibitively poor image quality or the desired view was absent entirely. In the four-chamber view, 60 of the 71 studies (85%) were able to be evaluated, with seven of those studies having inadequate frame rates and four having poor or absent images. Of those studies successfully analysed, several interesting findings were noted when comparing the strain and strain rate between the anthracycline and control groups (Table 2). Notably, nearly every measurement of the left ventricular strain and strain rate were significantly depressed when compared with normal controls. The largest difference between the anthracycline group and the control group, in either the longitudinal or circumferential plane, is the diastolic strain rate.

A sub-analysis was performed to inspect the impact of cumulative dose. Specifically, the strain and strain rate findings were compared between those individuals who received a low cumulative dose (300 mg/m^2 or less), medium dose (between 300 and 450 mg/m^2), and high dose (more than 450 mg/m^2) (Table 3). In this analysis, the low dose group was statistically different from the medium and high dose groups for circumferential strain and circumferential systolic strain rate.

Heart rate and timing comparison

Before any chemotherapy treatment, the patients with cancer had a significantly higher heart rate (~30% faster) when compared with the control group (Table 4). Following treatment, those treated with anthracycline continued to have a higher heart rate, but the difference compared with controls was relatively less than the difference before treatment (~13% faster). Given these differences in heart rate, the time to peak events – time to peak strain, time to peak systolic strain rate, and time to peak early diastolic strain rate – were all normalised to heart rate and expressed as a percent of cycle length. At baseline, the time to peak events occurred relatively later in the cardiac cycle in the anthracycline group. In the follow-up echocardiograms, the anthracycline group continued to show relative overall delays in the time to peak events when compared with controls, although the distinction is less striking. However, as mentioned above, although the average heart rate is still higher in the anthracycline group, the difference in average heart rate between the anthracycline group and control group is lower following anthracycline exposure.

Short-axis M-mode comparison

Comparison of the short-axis M-mode data showed several notable findings (Table 5). Before anthracycline treatment, the average fractional shortening in the anthracycline group was significantly higher than the control group. Following anthracycline exposure, however, the anthracycline group had a lower fractional shortening versus the control group, although still within normal limits per the study design. In addition, the left ventricular posterior wall following anthracycline exposure was thinner than in the unexposed control group. No other measure of left ventricular wall thickness or cavity dimension was statistically different.

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Table 2. Strain and strain rate comparison between Anthracycline groups and controls.

	Baseline SA – ATC (n = 53)	% Difference	Baseline SA – control (n = 53)	p-value		Baseline 4C – ATC (n = 43)	% Difference	Baseline 4C – control (n = 43)	p-value
CS (%)	−26.84 ± 5.61		−26.69 ± 3.50	0.86	LS (%)	−19.26 ± 3.78	−8.6	−21.06 ± 3.43	0.023*
CSSR (%/second)	−2.36 ± 0.54		−2.23 ± 0.43	0.2	LSSR (%/second)	−1.58 ± 0.44		−1.46 ± 0.34	0.17
CDSR (%/second)	2.85 ± 0.74		2.77 ± 0.61	0.55	LDSR (%/second)	2.10 ± 0.58		2.22 ± 0.59	0.32
	Follow-up SA – ATC (n = 55)	**% Difference**	**Follow-up SA – control (n = 55)**	**p-value**		**Follow-up 4C – ATC (n = 60)**	**% Difference**	**Follow-up 4C – control (n = 60)**	**p-value**
CS (%)	−24.21 ± 3.74	−8.6	−26.48 ± 4.00	0.003*	LS (%)	−18.27 ± 3.35	−7.4	−19.74 ± 3.63	0.02*
CSSR (%/second)	−1.96 ± 0.41	−8.5	−2.15 ± 0.44	0.03*	LSSR (%/second)	−1.25 ± 0.33		−1.31 ± 0.32	0.3
CDSR (%/second)	2.33 ± 0.56	−14.0	2.71 ± 0.77	0.004*	LDSR (%/second)	1.70 ± 0.63	−12.1	1.94 ± 0.57	0.03*

ATC = anthracycline group; CS = circumferential strain; CSSR = circumferential systolic strain rate; CDSR = circumferential diastolic strain rate; LDSR = longitudinal diastolic strain rate; LS = longitudinal strain; LSSR = longitudinal systolic strain rate; SA = short axis; 4C = four chamber
A negative % Difference represents when the ATC value is less than the control. Only significant % Difference values are listed
*Statistically significant

Discussion

Comparisons of the strain and strain rate in cancer patients before anthracycline treatment when compared with controls show that only longitudinal strain was significantly lower. All other measurements of strain and strain rate were similar at baseline. Our findings indicate that after anthracycline exposure, nearly every measure of strain and strain rate in children with a normal fractional shortening are depressed when compared with normal age-matched controls. These findings are consistent with the results of other recently published studies.[16,26,27] Our analysis is unique in that the present study is the first to use Velocity Vector Imaging for the analysis. As opposed to other studies, changes in diastolic strain rate following anthracycline exposure in children were noted in this investigation, and these changes might help shed light on the abnormal diastolic function, which is well recognised in post-anthracycline patients but not well understood. This study also suggests that circumferential strain and strain rate show more differences versus controls than its longitudinal counterpart. Namely, the longitudinal strain in the anthracycline group was about 8% below the longitudinal strain of the control group both at baseline and at follow-up, making this difference less meaningful. In addition, there was no statistical difference between the anthracycline group and control in the longitudinal systolic strain rate at either baseline or follow-up. On the other hand, there were statistical differences in all measures of circumferential strain and strain rate at follow-up where none were noted at baseline. Of the various parameters compared between groups, the diastolic strain rate showed the largest percent decline when compared with controls, suggesting that diastolic dysfunction might play a larger role than systolic dysfunction.

This study also describes heart rate changes in paediatric cancer patients both before and after anthracycline. Importantly, the recent studies by Cheung et al[26] and Mavinkurve-Groothuis et al[27] did not include heart rate as a study variable and may account for some of the changes seen. Specifically, it was interesting that, before any treatment, patients with cancer had a resting heart rate ~30% higher than controls. Following treatment, the heart rate remained elevated but was only about 13% higher. A combination of factors such as mild dehydration from a poor appetite, anaemia, pain or discomfort, and anxiety could reasonably account for the increase in heart rate at baseline. Following treatment with anthracycline, the average heart rate continued to be elevated in the anthracycline group, but there were

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Table 3. Strain and strain rate comparison between low-, medium-, and high-dose groups.

	Low dose (n = 19)	Medium dose (n = 26)	High dose (n = 15)
CS (%)*	−26.87 ± 0.78	−22.78 ± 0.67	−23.15 ± 0.91
CSSR (%/second)*	−2.23 ± 0.09	−1.83 ± 0.08	−1.84 ± 0.10
CDSR (%/second)	2.54 ± 0.13	2.17 ± 0.11	2.32 ± 0.15
	(n = 18)	(n = 24)	(n = 13)
LS (%)	−18.9 ± 0.77	−18.43 ± 0.65	−17.21 ± 0.86
LSSR (%/second)	−1.21 ± 0.08	−1.29 ± 0.07	−1.23 ± 0.09
LDSR (%/second)	1.81 ± 0.14	1.74 ± 0.12	1.5 ± 0.16

CDSR = circumferential diastolic strain rate; CS = circumferential strain; CSSR = circumferential systolic strain rate; LDSR = longitudinal diastolic strain rate; LS = longitudinal strain; LSSR = longitudinal systolic strain rate
*Indicates the low-dose group was statistically different ($p < 0.01$) from either the medium- or high-dose group, but the medium- and high-dose groups were not statistically different from one another

significant declines in nearly every measure of strain and strain rate. This finding is significant as Boettler et al[28] previously described the effect of heart rate on longitudinal strain and strain rate using tissue Doppler imaging in healthy children. That study showed the time in systole decreased linearly with increasing heart rate, but there was an exponential decrease in the time in early diastole. In addition, Boettler found that systolic longitudinal strain rate did not show significant differences with heart rate, whereas longitudinal strain significantly decreased with increasing heart rate. Our results were consistent with those observations, suggesting that the noted heart rate differences might account for these differences in longitudinal strain and strain rate. However, given the limitations of tissue Doppler, that study was only able to analyse longitudinal strain and strain rate changes and could not assess circumferential findings.

Another significant revelation in this investigation was the difference in the timing of peak events. Not only were there alterations in the peak strain and strain rate as a result of anthracycline but there were also shifts in the time during the cardiac cycle in which these events took place. With an elevated heart rate and fractional shortening before treatment, it is reasonable to presume that the patients with cancer were in an elevated adrenergic state. In this state, it was interesting that the time to peak strain and the time to peak systolic and early diastolic strain rate occurred relatively later in the cardiac cycle when compared with controls. Owing to the fact that the baseline data were recorded before anthracycline exposure, the faster heart rate likely explains much of this phenomenon. In the follow-up group after exposure to anthracycline, there remained relative delays in the timing of the peak events.

This study also reinforces other previously reported findings after anthracycline treatment of a decline in fractional shortening along with a decrease in the left ventricular wall thickness as measured by standard short-axis M-mode.[3,7,10,13,15,29] Of note, our study found that the fractional shortening of paediatric cancer patients before treatment was significantly higher compared with controls. In other words, before treatment, patients with cancer had an elevated heart rate and fractional shortening, but following treatment with anthracycline, although the heart rate remained elevated, the fractional shortening was lower than controls. This finding is significant for two reasons. First, it would be incorrect to use the baseline fractional shortening as the reference for all subsequent echocardiographic studies, as this value is artificially elevated for the reasons stated above. Second, even though this study does show that the follow-up fractional shortening is statistically below age- and gender-matched controls, it still remains in the normal range and the presumption might be that a normal fractional shortening indicates no deleterious effects from anthracycline treatment.

With the advent of tissue Doppler imaging and feature-tracking ultrasound technology, our understanding of ventricular function has been greatly expanded. Researchers have looked at adult women with breast cancer treated with anthracyclines and trastuzumab and demonstrated that changes in left ventricular strain were predictive of outcomes and occurred before declines in ejection fraction.[30,31] With regard to children, several studies using tissue Doppler have investigated ventricular function of various diseased states. Ganame et al[16] studied children after low-dose anthracycline treatment and demonstrated reduced longitudinal myocardial function and diastolic dysfunction despite no significant difference in fractional shortening when compared with age-matched controls. Mertens et al[32] were able to show that children with Duchenne muscular dystrophy had significant decreases in radial and

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Table 4. Heart and time to peak strain and strain rate comparison between Anthracycline groups and controls.

	Baseline SA – ATC (n = 53)	% Difference	Baseline SA – control (n = 53)	p-value		Baseline 4C – ATC (n = 43)	% Difference	Baseline 4C – control (n = 43)	p-value
HR (beats/minute)	97.13 ± 22.87	30.5	74.41 ± 15.20	<0.001*	HR (beats/minute)	98.21 ± 20.04	30.4	75.31 ± 16.76	<0.001*
TTP CS (% of RRI)	0.48 ± 0.07	17.1	0.41 ± 0.08	<0.001*	TTP LS (% of RRI)	0.52 ± 0.07	20.9	0.43 ± 0.08	<0.001*
TTP CSSR (% of RRI)	0.26 ± 0.07		0.24 ± 0.07	0.09	TTP LSSR (% of RRI)	0.27 ± 0.08	12.5	0.24 ± 0.08	0.048*
TTP CDSR (% of RRI)	0.64 ± 0.10	12.3	0.57 ± 0.10	0.003*	TTP LDSR (% of RRI)	0.70 ± 0.09	16.7	0.60 ± 0.10	<0.001*
	Follow-up SA – ATC (n = 55)	**% Difference**	**Follow-up SA – control (n = 55)**	**p-value**		**Follow-up 4C – ATC (n = 60)**	**% Difference**	**Follow-up 4C – control (n = 60)**	**p-value**
HR (beats/minute)	81.24 ± 18.70	12.6	72.15 ± 15.04	0.006*	HR (beats/minute)	80.62 ± 19.86	13.6	70.95 ± 13.99	0.003*
TTP CS (% of RRI)	0.45 ± 0.07	9.8	0.41 ± 0.08	0.008*	TTP LS (% of RRI)	0.47 ± 0.07	11.9	0.42 ± 0.06	<0.001*
TTP CSSR (% of RRI)	0.24 ± 0.06		0.24 ± 0.08	0.7	TTP LSSR (% of RRI)	0.23 ± 0.05		0.25 ± 0.09	0.34
TTP CDSR (% of RRI)	0.62 ± 0.10	10.7	0.56 ± 0.11	0.012*	TTP LDSR (% of RRI)	0.63 ± 0.11	8.6	0.58 ± 0.09	0.025*

ATC = anthracycline group; CS = circumferential strain; CSSR = circumferential systolic strain rate; CDSR = circumferential diastolic strain rate; HR = heart rate; LDSR = longitudinal diastolic strain rate; LS = longitudinal strain; LSSR = longitudinal systolic strain rate; RRI = R wave to R wave interval; SA = short axis; TTP = time to peak; 4C = four chamber
A positive % Difference represents when the ATC value is greater than the control and vice versa. Only significant % Difference values are listed
*Statistically significant

longitudinal strain and strain rate despite a normal fractional shortening and that these changes progressed over time. Of course, both of those studies were conducted using tissue Doppler imaging, which has limitations as previously discussed. Migrino et al[33] were able to show using speckle-tracking technology in rats that following radial strain was useful in the early detection of doxorubicin-induced cardiac injury and the reduction in radial strain was associated with histologic markers of doxorubicin cardiomyopathy. Of particular note, a decline in radial strain was noted significantly earlier than a decline in fractional shortening. That study highlights how following serial echocardiograms for changes in mechanics might have predictive value and is superior to fractional shortening as a global measure of function.

The improved long-term survival of paediatric cancer patients represents a major success in modern medicine. With such improvements being realised, focus has shifted towards not only a decrease in mortality but a decrease in morbidity as well. More attention is being given to the long-term sequelae of paediatric cancer treatment, specifically as it pertains to the heart. At present, many paediatric cancer centres rely on fractional shortening as a surrogate for global cardiac function. However, the results of our study suggest that a "normal" fractional shortening should not necessarily be interpreted as freedom from the harmful effects of anthracycline for reasons mentioned previously. Fortunately, the vast majority of long-term cancer survivors treated with anthracycline do not develop clinical cardiomyopathy, but serial monitoring of these patients remains crucial. Cardiovascular outcomes can potentially be improved if subclinical abnormalities in cardiac function identified with feature-tracking technology provide an early warning sign of evolving cardiomyopathy. This would allow for early initiation of cardiac medications to hopefully attenuate remodelling and preserve cardiac function. With the advent of newer echocardiographic technologies such as feature tracking, this goal of early identification of at-risk patients is possible. Similar to any new technology, additional work is needed to identify the most sensitive indicators of declining function. Normal values to allow for appropriate comparison also need to be defined for each available software package as different algorithms might yield different values for strain and strain rate.

Limitations

Owing to the retrospective nature of this study, several limitations are noted. Only one cardiac cycle was analysed, which might increase variability in

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Table 5. Short-axis m-mode measurement comparison between Anthracycline group and controls.

	Baseline SA – ATC (n = 53)	% Difference	Baseline SA – control (n = 53)	p-value	Baseline 4C – ATC (n = 43)	% Difference	Baseline 4C – control (n = 43)	p-value
IVSd (mm)	6.41 ± 1.63		6.39 ± 1.59	0.96	6.43 ± 1.77		6.33 ± 6.33	0.78
IVSs (mm)	9.62 ± 2.40		9.89 ± 2.14	0.54	9.68 ± 2.54		9.83 ± 2.30	0.78
LVPWd (mm)	6.37 ± 1.50		6.16 ± 1.40	0.47	6.23 ± 1.59		6.28 ± 1.62	0.88
LVPWs (mm)	12.04 ± 4.43		10.73 ± 2.19	0.06	12.02 ± 4.83		10.70 ± 2.50	0.12
LVIDd (mm)	42.75 ± 6.60		42.87 ± 6.99	0.93	42.63 ± 6.28		43.12 ± 7.75	0.75
LVIDs (mm)	25.83 ± 4.48		26.63 ± 5.05	0.39	25.67 ± 4.32		26.93 ± 5.61	0.25
FS (%)	39.66 ± 5.10	5.5	37.60 ± 4.60	0.033*	39.92 ± 4.72	6.9	37.33 ± 4.33	0.01*
	Follow-up SA – ATC (n = 55)	**% Difference**	**Follow-up SA – control (n = 55)**	**p-value**	**Follow-up 4C – ATC (n = 60)**	**% Difference**	**Follow-up 4C – control (n = 60)**	**p-value**
IVSd (mm)	6.61 ± 1.41		7.44 ± 5.06	0.25	6.68 ± 1.45		7.41 ± 4.85	0.27
IVSs (mm)	9.61 ± 1.91		10.61 ± 3.36	0.06	9.60 ± 1.88		10.47 ± 3.32	0.08
LVPWd (mm)	6.36 ± 1.52		6.61 ± 1.60	0.4	6.40 ± 1.73		6.55 ± 1.53	0.63
LVPWs (mm)	10.64 ± 2.24	−8.4	11.62 ± 2.39	0.03*	10.59 ± 2.38	−8.2	11.54 ± 2.50	0.04*
LVIDd (mm)	44.30 ± 5.71		44.87 ± 7.79	0.66	43.54 ± 5.25		44.50 ± 7.73	0.43
LVIDs (mm)	28.77 ± 4.18		27.93 ± 4.98	0.34	28.35 ± 3.87		27.85 ± 4.92	0.53
FS (%)	34.90 ± 4.26	−5.5	36.94 ± 6.00	0.042*	34.73 ± 4.21	−5.2	36.63 ± 5.83	0.043*

ATC = anthracycline group; FS = fractional shortening; IVSd = interventricular septum thickness at diastole; IVSs = interventricular septum thickness at systole; LVIDd = left ventricular internal diameter at diastole; LVIDs = left ventricular internal diameter at systole; LVPWd = left ventricular posterior wall thickness at diastole; LVPWs = left ventricular posterior wall thickness at systole; SA = short axis; 4C = four chamber

A positive % Difference represents when the ATC value is greater than the control and vice versa. Only significant % Difference values are listed

*Statistically significant

the results. Several studies could not be successfully analysed for strain and strain rate. The most common reasons for unsuccessful analysis were lack of the desired view on the echocardiogram, poor image quality making for a poor endocardial border trace, and inadequate frame rate of the desired image. It has been shown that lower frame rates result in unstable speckle patterns.[34] In an attempt to minimise these limitations, where there was a lack of desired image, an unacceptably low frame rate, or poor image quality, a patient's previous echocardiogram was utilised when available and adequate. Similar to any study using speckle-tracking technology, good image quality is necessary and can be better controlled for when moving forward and applied in a prospective manner. If care is given during image acquisition to optimise image quality and frame rate along with parallel gains being realised in improved ultrasound equipment, the vast majority of studies can be successfully analysed. Normal values for paediatric strain and strain rate have not widely been established. For this reason, it is difficult to determine the significance of the changes noted in our study. Our study had a reasonable number of study patients, but this became less so when performing the sub-analysis into the groups who received low, medium, and high cumulative anthracycline doses. Perhaps additional findings could be discovered with a larger sample size. Investigation into the reproducibility of the data was not performed, but several studies have previously demonstrated strain and strain rate as determined using automated myocardial-tracking ultrasound technology to be highly reproducible with only minimal intraobserver and interobserver variability.[18,20,35]

Conclusions

Our results demonstrate that despite a normal fractional shortening children exposed to anthracyclines have subclinical derangement of their left ventricular deformation as measured by decreases in strain and strain rate in both the circumferential and longitudinal axis. In particular, there was a profound decrease in diastolic strain rate following anthracycline exposure compared with controls, which can, in part, be explained by a relatively higher heart rate. As further research becomes available, the importance of peak global strain and strain rate will become more apparent as will the impact of heart rate. The ultimate future goal will be to accurately identify those asymptomatic patients with subtle echocardiographic evidence of declining function. Additional studies are necessary to determine whether early initiation of heart failure therapies in this subset of anthracycline-treated patients can result in improved long-term outcomes for this vulnerable population.

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