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Original Article

Diastolic function in anthracycline-treated children

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Abstract *Background:* Anthracyclines are effective medications for childhood cancer. Their limitation is the risk of cardiomyopathy. Although diastolic dysfunction has been described in patients who received anthracyclines, cardiac monitoring has focused on systolic function, which is abnormal in up to 41% of the patients. We conducted a study to assess diastolic function utilising transmitral inflow Doppler velocities and tissue Doppler imaging in anthracycline-treated children 5 years post-therapy. *Methods:* This was a retrospective study on 63 anthracycline-treated patients. Echocardiographic parameters included peak early and late transmitral inflow Doppler velocities (E, A), E/A ratio, E deceleration time, and tissue Doppler imaging early and late diastolic mitral annulus velocities (E′, A′), E/E′ ratio, and E′/A′ ratio. *Results:* All indices of diastolic function that we measured were normal in the anthracycline-treated patients. *Conclusion:* We conclude that diastolic function assessed by transmitral inflow Doppler velocities and tissue Doppler imaging is normal in anthracycline-treated children 5 years after completion of treatment. Further longitudinal study is needed to determine whether diastolic function becomes abnormal with time in this patient population.

Keywords: Cardiomyopathy; echocardiogram; tissue Doppler imaging; paediatric cardiology

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ANTHRACYCLINES ARE VERY EFFECTIVE MEDICATIONS used in the treatment of multiple types of childhood cancer.[1,2] Their major limitation is the risk of cardiomyopathy that can occur many years after completion of treatment, is unpredictable, may increase with each dose, and becomes more prevalent with time.[3–7] Congestive heart failure secondary to cardiomyopathy is associated with a poor prognosis with a 2-year mortality rate of nearly 50%.[2,8]

Anthracycline-induced cardiomyopathy occurs after the loss of a critical number of myocardial cells with manifestations happening long after the therapy.[9,10] Anthracycline-induced cardiomyopathy can present clinically with heart failure and arrhythmias or subclinically with abnormal echocardiographic parameters in asymptomatic survivors of childhood cancer. The identification of subclinical abnormalities is important to develop a follow-up monitoring plan for such survivors.[9]

Subclinical diastolic dysfunction has been described in survivors of adult-onset malignancy after anthracycline treatment[11] and has been suggested to precede systolic dysfunction.[12] Abnormal diastolic function has been associated with increased risk for all-cause mortality in a general adult population, even in the presence of normal systolic function.[13] In an evaluation of 70 anthracycline-treated patients compared with 70 age- sex-, and body surface area-matched healthy

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controls at the mean interval from cancer diagnosis to evaluation of 14 years and mean cumulative anthracycline dose of 321.6 (range, 150–868 mg/m^2), Santin et al[9] found the mean early to late transmitral inflow Doppler velocities ratio (E/A) to be low normal in the anthracycline-treated patients compared with the normal group. Although there have been published reports[5,9,14] describing diastolic function in children who received anthracyclines, some had a wide range of cumulative anthracycline dose up to 868 mg/m^2,[9] whereas others had a short interval between the echocardiogram assessment and the last anthracycline dose received.[14] Early follow-up evaluation (<1 year) is not predictive of long-term anthracycline-induced cardiomyopathy,[15] and a very high cumulative anthracycline dose ⩾600 mg/m^2 has been associated with congestive heart failure in 18% of late survivors.[15] The cumulative anthracycline dose, thus, has been restricted to <550 mg/m^2.[15] Little has been written about diastolic function in anthracycline-treated survivors of childhood malignancies in the era of restricted cumulative anthracycline dose.

In a recent study at our institution, 63 patients who received anthracyclines were studied. Although cardiac dysfunction, identified as the presence of abnormal shortening fraction, rate-corrected velocity of circumferential fibre shortening, end-systolic wall stress, or the relationship of rate-corrected velocity of circumferential fibre shortening to end-systolic wall stress (stress velocity index) was found in 26 (41%) of 63 patients, the diastolic parameter of transmitral inflow Doppler velocities: early (E), late (A), and (E/A) ratio were normal in all patients.[16] It has been shown previously that this measure of diastolic function can be falsely normal (pseudonormalisation).[17] Tissue Doppler imaging has been shown to be superior to transmitral inflow velocities in identifying diastolic dysfunction, as it is not subject to pseudonormalisation.[17–19]

In this study, we evaluated diastolic function assessed by transmitral inflow Doppler velocities and tissue Doppler imaging of patients who were enroled in the above-mentioned study using more accurate measures of diastolic function. The aim of the study was to determine whether diastolic dysfunction as tested by these methods was present in children after treatment with anthracyclines.

Materials and methods

This was a retrospective study conducted at Children's Hospital of Michigan. Waiver of consent was approved by the institutional review committee at Wayne State University School of Medicine. The echocardiographic data were reviewed from the recently concluded study on anthracycline-treated children. The inclusion criteria in the original study were patients of either gender who had completed anthracycline chemotherapy at least a year before echocardiogram assessment. Patients with CHD, cardiomyopathy before initiation of chemotherapy, chromosomal defects, pregnant patients, smokers, or patients who had received mediastinal radiation were excluded.

The echocardiograms were obtained using a Phillips Sonos 5500 ultrasound machine. From the apical four-chamber view, transmitral inflow Doppler velocities: early (E), late (A), and (E/A) ratio, and E deceleration time were obtained.[17,20] Using tissue Doppler imaging, early and late diastolic mitral annulus velocities were measured (E′, A′, respectively) from both the lateral mitral valve annulus (lateral) and the interventricular septum (septal).[17] Each measurement was obtained from three cardiac cycles and an average of these measurements was recorded.[18] The E/A, E/E′ (lateral), the E/E′ (septal), E′/A′ (lateral), and E′/A′ (septal) ratios were calculated.

Diastolic function was considered abnormal if E was <62.5 cm/second, A was <21.9 cm/second, E/A ratio was <0.86:1, and/or E deceleration time was more than 0.195 seconds.[21,22] Tissue Doppler imaging-derived measurements were considered abnormal if lateral E′ was <12.8 cm/second, lateral A′ was <2.8 cm/second, lateral E/E′ was more than 7.5:1, septal E′ was <9.3 cm/second, septal A′ was <1.5 cm/second, septal E/E′ was more than 9.4:1,[21] lateral E′/A′ was <1.2:1,[14] and/or septal E′/A′was <1:1.[14]

Statistical considerations

All data were summarised using descriptive statistics such as mean and standard deviation. To compare the sub-groups: analysis of variance and Bonferroni post hoc tests were used. All statistical comparisons in the study were considered significant at a p-value ⩽0.05. The statistical analyses were performed using SPSS (version 13) software.

Results

A total of 63 patients who received anthracyclines were included. The mean age at the time of echocardiographic evaluation was 13.7 ± 4.5 years, and the mean interval since the last dose of anthracycline was 5.3 ± 4 years (range, 1.1–17.5 years). Of the patients, 37 (59%) were male, 53 (84%) were Caucasian, and 7 (11%) were African American.

The clinical diagnoses included acute lymphocytic leukaemia in 29 (46%), osteosarcoma in 12 (19%), Wilms tumour in 12 (19%), and lymphoma in 10 patients (16%). The median cumulative dose of anthracycline received was 165 mg/m^2 (range, 45–520; mean 160 mg/m^2). The cumulative anthracycline dose

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received was <150 mg/m^2 in 29 (46%) patients, between 150 and 300 mg/m^2 in 20 (32%), and >300 mg/m^2 in 14 (22%) patients. No patient received more than 550 mg/m^2. Whereas 9 (14.3%) of 63 patients had abnormal shortening fraction (range, 23–28; median 26%; mean 26%), only five patients were on cardiac medications such as angiotensin-converting enzyme inhibitors and Digoxin. Of those five patients, only three were symptomatic with heart failure.

All transmittal inflow Doppler measurements were normal in the anthracycline-treated patients. The mean E-wave Doppler (cm/second) was 99 ± 15, mean A-wave Doppler (cm/second) was 50 ± 9, and the mean ratio of E/A was 2.1 ± 0.43. The mean E deceleration time (second) was 0.17 ± 0.03 seconds.

To ensure that normally appearing transmittal inflow Doppler velocities E, A, and E/A were not due to pseudonormalisation, tissue Doppler imaging-derived assessment was performed. All tissue Doppler imaging-derived measurements were within normal range. The mean lateral E′ (cm/second) was 18.3 ± 3, mean lateral A′ (cm/second) was 6.6 ± 1.7, mean septal E′ (cm/second) was 14.4 ± 2.3, mean septal A′ (cm/second) was 7.2 ± 2, mean lateral E/E′ was 5.5 ± 1.2, mean septal E/E′ was 7.1 ± 1.5, mean lateral E′/A′ was 2.9 ± 0.8, and mean septal E′/A′ was 2.11 ± 0.56.

The anthracycline-treated patients were stratified by cumulative anthracycline dose received and the groups were compared with each other. There was no difference seen among the three anthracycline subgroups. All diastolic measures assessed by transmitral inflow Doppler velocities and tissue Doppler imaging were within the normal range, as shown in Tables 1 and 2.

Comparison of the diastolic function in those with abnormal versus normal shortening fraction is shown in Tables 3 and 4. In 9 (14.3%) of the 63 patients who had abnormal shortening fraction compared with those with normal shortening, the A wave was significantly reduced and closer to abnormal, the septal E′/A′ was significantly increased but closer to normal. All other indices tested were not significantly different. Although the isolated differences in A wave and septal E′/A′ is statistically significant, the fact

Table 1. Transmitral inflow Doppler measurements of the anthracycline group stratified by cumulative anthracycline dose.

	<150 mg/m^2 (n = 29)	150–300 mg/m^2 (n = 20)	>300 mg/m^2 (n = 14)
E wave (cm/second)	102 ± 15	99.5 ± 15	92 ± 15
A wave (cm/second)	50 ± 10	48 ± 10	48 ± 9
Ratio of E/A	2.1 ± 0.5	2.1 ± 0.4	1.9 ± 0.3
DT (second)	0.17 ± 0.03	0.18 ± 0.03	0.17 ± 0.04

E: mean early transmitral inflow Doppler-wave velocity; A: mean late transmitral inflow Doppler-wave velocity; DT: E deceleration time
Unless noted the p-value was insignificant (>0.05)
Data are displayed as mean ± standard deviation

Table 2. Tissue Doppler imaging measurements of the anthracycline group stratified by cumulative anthracycline dose.

	<150 mg/m^2 (n = 29)	150–300 mg/m^2 (n = 20)	>300 mg/m^2 (n = 14)
Lateral E′ (cm/second)	18.3 ± 3.2	19 ± 2.8	17.4 ± 2.7
Lateral A′ (cm/second)	6.6 ± 1.4	6.6 ± 1.9	6.4 ± 2
Lateral E/E′	5.7 ± 1.2	5.4 ± 1.3	5.3 ± 0.8
Lateral E′/A′	2.9 ± 0.7	3.1 ± 1	2.9 ± 0.9
Septal E′ (cm/second)	14.2 ± 2.4	14.7 ± 1.9	14.5 ± 2.7
Septal A′ (cm/second)	6.8 ± 2	7.4 ± 1.5	7.6 ± 2
Septal E/E′	7.4 ± 1.6	7 ± 1.4	6.7 ± 1.3
Septal E′/A′	2.2 ± 0.6	2.1 ± 0.5	2 ± 0.5

E′: mean early diastolic mitral annulus velocity obtained from the lateral mitral valve annulus (lateral) and the interventricular septum (septal); A′: mean late diastolic mitral annulus velocity obtained from the lateral mitral valve annulus (lateral) and the interventricular septum (septal); E/E′: ratio of early transmitral valve inflow Doppler-wave velocity (E) to E′; E′/A′: ratio of early to late diastolic mitral annulus velocities
Unless noted the p-value was insignificant (>0.05)
Data are displayed as mean ± standard deviation

Table 3. Transmitral inflow Doppler measurements of the anthracycline group stratified by normal or abnormal shortening fraction.

	Abnormal shortening fraction (n = 9)	Normal shortening fraction (n = 54)	p-value
E wave (cm/second)	97 ± 12.4	99.3 ± 15.6	1
A wave (cm/second)	40.1 ± 5.9	50.6 ± 9.1	0.02
Ratio of E/A	2.4 ± 0.38	2.0 ± 0.41	0.06
DT (second)	0.16 ± 0.04	0.18 ± 0.03	0.07

E: mean early transmitral inflow Doppler-wave velocity; A: mean late transmitral inflow Doppler-wave velocity; DT: E deceleration time
Data are displayed as mean ± standard deviation

Table 4. Tissue Doppler imaging measurements of the anthracycline group stratified by normal or abnormal shortening fraction.

	Abnormal shortening fraction (n = 9)	Normal shortening fraction (n = 54)	p-value
Lateral E′ (cm/second)	19.9 ± 4	18 ± 2.7	0.13
Lateral A′ (cm/second)	6 ± 1.8	6.7 ± 1.7	0.6
Lateral E/E′	5.2 ± 1.4	5.6 ± 1.1	1
Lateral E′/A′	3.5 ± 0.9	2.9 ± 0.8	0.12
Septal E′ (cm/second)	14 ± 2.5	14.5 ± 2.3	1
Septal A′ (cm/second)	6.2 ± 1.9	7.4 ± 1.8	0.07
Septal E/E′	7.2 ± 1.3	7 ± 1.5	1
Septal E′/A′	2.4 ± 0.53	2.06 ± 0.6	0.05

E′: mean early diastolic mitral annulus velocity obtained from the lateral mitral valve annulus (lateral) and the interventricular septum (septal); A′: mean late diastolic mitral annulus velocity obtained from the lateral mitral valve annulus (lateral) and the interventricular septum (septal); E/E′: ratio of early transmitral valve inflow Doppler-wave velocity (E) to E′; E′/A′: ratio of early to late diastolic mitral annulus velocities
Data are displayed as mean ± standard deviation

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that there is an overlap and that the velocities fall within the normal range suggests that this is not of any clinical significance.

Discussion

In this report of anthracycline-treated cancer survivors, all measures of diastolic function that we measured were normal, despite our previous observation that 41% had abnormalities of systolic function, including abnormal shortening fraction, rate-corrected velocity of circumferential fibre shortening, end-systolic wall stress, and/or stress velocity index.[16]

Although clinically apparent anthracycline-induced cardiomyopathy (heart failure) can affect 5–20% of long-term childhood malignancy survivors,[15,23] subclinical anthracycline-induced cardiomyopathy, detected by echocardiogram only, can be seen in up to 57% of survivors, with elevated end-systolic wall stress as the most common abnormality.[6,10,16,23] These reports of subclinical anthracycline-induced cardiomyopathy concentrated on the systolic and afterload functions. More recently, the diastolic function in cancer survivors has been reported. Subclinical diastolic dysfunction was seen in all anthracycline-treated survivors of adult-onset malignancy.[11] This is confounded by the presence of diastolic dysfunction in 35–40% of the older population without any anthracycline treatment.[24,25] In survivors of childhood malignancy, conflicting reports assessing the presence and the pattern of diastolic function exist with some indicating normal diastolic function like our study, whereas others showing abnormal diastolic function – delayed ventricular relaxation or restrictive physiology.[5,9,14,26] This is complicated by the wide range of intervals between echocardiogram assessment and last anthracycline dose received, the inclusion of patients who received very high cumulative anthracycline dose (up to 868 mg/m^2), and the sole use of transmitral inflow Doppler measures, which are preload-dependent.[9,27] By utilising a superior echocardiographic modality (tissue Doppler imaging), our report provides an insight into the late-term – 5 years since the last anthracycline dose – diastolic function assessed by transmitral inflow Doppler velocities and tissue Doppler imaging of survivors of childhood cancer who had received a restricted cumulative anthracycline dose.

Our finding of normal ventricular diastolic function is in agreement with previous reports assessing cardiac function in anthracycline-treated childhood cancer survivors. Although Santin et al, compared with normal controls, showed an increased E deceleration time, more towards abnormal, at a mean follow-up interval of 14 years, all measures of diastolic function, including the E deceleration time, were within the normal range.[9] Karakurt et al[5] reported a slightly reduced but within the normal range E′ in anthracycline-treated survivors of childhood malignancy compared with a normal group at a mean follow-up period of 2.2 years.

Our report failed to show a difference in diastolic function assessed by transmitral inflow Doppler velocities and tissue Doppler imaging among the different cumulative anthracycline dose. Although others have suggested that there may be no safe dosage of anthracycline and that all patients receiving anthracyclines should have lifetime cardiac monitoring, irrespective of the cumulative anthracycline dose received, one cannot conclude that from our current data.[14,16,28]

Although this paper focused on the diastolic function as assessed by transmitral inflow Doppler velocities and tissue Doppler imaging, one cannot emphasise enough the value of systolic ventricular function assessment in this population. Previous reports have shown the presence of abnormal systolic function, irrespective of the cumulative anthracyclines dose.[16,29]

Although cardiac dysfunction, identified as the presence of abnormal shortening fraction, rate-corrected velocity of circumferential fibre shortening, end-systolic wall stress, and/or the stress velocity index, was found in 26 (41%) of the 63 patients[16], none had abnormal diastolic function as assessed by transmitral inflow Doppler velocities and tissue Doppler imaging. This is in contrast with previous reports suggesting that abnormal diastolic function precedes systolic dysfunction.[12] The lack of diastolic dysfunction in this report could be related to only including patients whose last anthracycline therapy was more than a year from the echocardiogram assessment, only including patients whose maximum cumulative anthracycline therapy was $\leqslant$520 mg/m^2, only including transmitral inflow Doppler velocities and tissue Doppler imaging as diastolic function assessment tools, and/or not including a control group.

It has been suggested that anthracycline-treated survivors of childhood cancer should undergo serial monitoring of the E/A ratio as a measure of diastolic function.[2] In this report, E/A ratio and all tissue Doppler imaging-derived measures were normal. Further studies are needed to serially evaluate diastolic function in this manner as well as to assess the appropriateness of the tissue Doppler imaging-derived measurements' use in the regular assessment of anthracycline-treated survivors of childhood cancer.

Limitations

This was a single-centre study, with echocardiograms obtained at one point in time, precluding assessment of progression of diastolic dysfunction. The echocardiogram parameters used relied on transmitral

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inflow Doppler velocities and tissue Doppler imaging. Other measures of diastolic function – example left atrial size and pulmonary venous Doppler – were not assessed. It has been suggested that strain imaging and strain rate imaging are more sensitive in assessing the subendocardial region of the myocardium, which is affected first in anthracycline-treated children.[30–32] Further studies utilising strain imaging might be needed. This was a case series of anthracycline-treated children 5 years post-therapy. Normal values for diastolic function are age-dependent. Future case–control studies in the restricted anthracycline era might be needed.

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Conflicts of Interest

The authors report no conflicts of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional review committee at Wayne State University.

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