Myocardial Dysfunction Late After Low-Dose Anthracycline Treatment in Asymptomatic Pediatric Patients

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**Background:** The occurrence of chronic anthracycline cardiotoxicity leading to heart failure and even death is a major concern in the treatment of childhood malignancies. Currently, most treatment protocols use reduced anthracycline doses compared with historical exposure. The long-term effect of these reduced doses on myocardial function has not been well studied.

**Methods:** We examined 56 asymptomatic patients. They all had been treated with anthracyclines at a cumulative dose less than 300 mg/m² 5.2 (range: 2.0-15.2) years before the current evaluation. In all patients, standard two-dimensional, Doppler echocardiographic measurements, end-systolic wall stress calculation, and color Doppler myocardial imaging data were obtained. From the color Doppler myocardial imaging data, peak systolic myocardial velocities, peak systolic strain rate, and peak systolic strain \( e \) were computed. The myocardial acceleration during isovolumetric contraction was measured at the basal left ventricular (LV) lateral and right ventricular free wall. Data were compared with 32 age-matched normal controls.

**Results:** In asymptomatic patients previously exposed to low-dose anthracycline treatment, several changes in cardiac function were noted: 1. LV diastolic function was abnormal with a prolonged isovolumetric relaxation time and abnormal pulmonary venous flow patterns. 2. End-systolic wall stress was increased. 3. LV annular motion was reduced. 4. Systolic myocardial deformation was reduced with a significant decrease in both radial and longitudinal peak systolic strain rate and \( e \).

**Conclusions:** Changes in systolic and diastolic function are noted in asymptomatic patients with normal ejection fraction late after low-dose anthracycline treatment. This confirms that subclinical LV dysfunction is present in patients after low-dose anthracycline treatment during childhood. The long-term significance of these findings warrants further follow-up. (J Am Soc Echocardiogr 2007;20:1351-1358.)

Anthracyclines are effective drugs widely used in pediatric cancer treatment. Unfortunately, they affect cardiac function and their use is associated with acute and chronic cardiotoxicity. Because the cardiotoxic effect is partially dose-dependent, this has brought the oncologist to decrease the cumulative dose in most protocols; however, this does not prevent cardiac damage because histologic myocardial changes can be detected even after exposure to low doses. Lipshultz et al. also demonstrated that previous exposure to lower doses of anthracyclines (<300 mg/m²) induces a progressive decrease in cardiac function during long-term follow-up.

Left ventricular (LV) systolic function after anthracycline therapy is generally assessed using M-mode and two-dimensional echocardiography. On the basis of dimensional changes and volume calculations, fractional shortening and ejection fraction are calculated. These measurements have several limitations. First, only global LV function is quantified, and regional myocardial function is not evaluated. This could be important as regional dysfunction can precede global LV dysfunction. Second, fractional shortening and ejection fraction are load-dependent measurements that are influenced by changes in preload and/or afterload. To overcome the load-dependency, Colan et al. introduced calculation of the stress-velocity relationship. This method is an M-mode based methodology that requires the estimation of LV end-systolic pressure. Therefore, a phonographic recording of the carotid pulse with
some off-line processing is to be performed. This is probably one of the reasons why this method has not gained widespread use in the routine echocardiographic assessment of patients after anthracycline treatment.

During the last decade, new echocardiographic techniques for evaluating myocardial function have been introduced. Myocardial velocity and deformation imaging, namely, strain (ε) and strain rate (SR) imaging, have been demonstrated to have potential value for the quantification of global and regional systolic and diastolic myocardial function. Only limited data are currently available on the usefulness of these new techniques when evaluating patients exposed to anthracyclines. Kapusta et al. reported the use of myocardial velocities to quantify the effect of previous anthracycline exposure. They found that neither peak systolic nor early diastolic myocardial velocities were reduced in long-term survivors of childhood cancer. They also demonstrated a reduced transmyocardial velocity gradient (endocardium to epicardium) in the interventricular septum and inferolateral wall both during systole and early diastole could be observed in the patients exposed to anthracyclines. This reflects a reduced SR.

Our aim was to further explore these findings and evaluate whether regional changes in peak systolic SR and ε could be detected in patients after treatment with anthracyclines. Moreover, global cardiac systolic function was evaluated by measuring the myocardial velocity acceleration during the isovolumic contraction period (IVA) in the basal segments of the LV lateral and right ventricular (RV) walls. This measurement has been shown to be a relatively preload- and afterload-independent parameter that correlates well with invasive indices of global cardiac systolic function.

**METHODS**

**Study Group**

We cross-sectionally studied 56 patients (median age: 12.7 years, range: 4-28), 27 males and 34 females, followed at the Pediatric Hemato-Oncology Department of the University Hospitals Leuven, Belgium. They all had received anthracycline treatment (doxorubicin, daunorubicin, or idarubicin) as part of a chemotherapeutic treatment for acute lymphoblastic leukemia (n = 35), lymphoma (n = 9), solid tumors (n = 9), or acute myeloblastic leukemia (n = 3). They had been given a median cumulative dose of 240 mg/m²; range: 90-300 mg/m². Patients who had received a cumulative dose greater than 300 mg/m² were excluded from the study. They were studied at a median of 5.2 years (range: 2.0-15.2 years) after the last dose of anthracyclines. None of the patients had cardiovascular symptoms or were on cardiac medication at the time of evaluation. All were in sinus rhythm at the time of evaluation. As a control group, 32 age-matched normal subjects also underwent the same echocardiographic examination. Informed consent was obtained from the patients and/or the parents in accordance with institutional regulations.

**Echocardiographic Data Acquisition**

Standard transthoracic echocardiograms including gray scale and blood pool Doppler and the two-dimensional color Doppler myocardial imaging (CDMI) studies were performed using a commercially available system (System 5 or Vivid 5, GE Vingmed Ultrasound, Horten, Norway) equipped with a 2.5-MHz transducer. In each patient, standard parasternal and apical views were recorded.

**Systolic Function Assessed Using Standard Methods**

LV end-diastolic, end-systolic, and septal and inferolateral end-diastolic and end-systolic wall thicknesses were all measured using the standard M-mode approach from parasternal LV short-axis views. LV fractional shortening, LV mass, and rate-corrected mean velocity of circumferential fiber shortening were calculated using validated formulae. End-systolic wall stress (ESWS) was calculated as ESWS = 0.534 × SBP × ESD/ESWT(1 + ESWT/ESD), where SBP is peak systolic blood pressure measured with a cuff, ESWT is end-systolic wall thickness of the inferolateral wall, and ESD is end-systolic diameter of the LV. The relation between the rate-corrected mean velocity of circumferential fiber shortening and the end-systolic wall stress was plotted. The modified Simpson’s method was used for the determination of LV ejection fraction. To assess global longitudinal function, atrioventricular ring displacement was measured at the lateral mitral ring and the lateral tricuspid ring using M-mode. The percentage of systolic wall thickening was calculated in the inferolateral wall as: (end-systolic wall thickness – end-diastolic wall thickness)/end-diastolic wall thickness × 100. As an index of global myocardial function, the myocardial performance index was calculated according to published formulae from the mitral and aortic flows.

**Diastolic Function Assessed Using Standard Methods**

Pulsed Doppler recording of transmitral flow velocities was performed by positioning the sample volume at the tips of the mitral leaflets from apical four-chamber views. The peak velocities of early and late filling waves, the deceleration time of early filling, and the early-to-late filling ratio were measured from the transmitral flow velocities. The isovolumic relaxation time was measured using a continuous-wave Doppler beam intersecting the LV outflow and inflow tract. The pulmonary venous flow was recorded from apical four-chamber views. The peak systolic, peak diastolic, peak velocity, and duration of the reversal wave during atrial contraction were measured.
Color Doppler Myocardial Imaging

Real-time two-dimensional CDMI data were recorded to evaluate longitudinal function from the interventricular septum, LV lateral, and RV free walls using standard apical four-chamber views. To evaluate radial function in the LV inferolateral wall, CDMI data were recorded from the parasternal short-axis view. All data were acquired at a high frame rate of 155 ± 30 frames/s using the narrowest image sector angle possible (usually 30 degrees) and the optimal depth of imaging to increase temporal resolution. Allowing was eliminated from the CDMI data sets by setting appropriate pulse repetition frequency values (range 14-28 cm/sec). For longitudinal views, care was taken to keep each wall in the center of the ultrasound sector in an attempt to align the ultrasonic beam as near zero degrees as possible with longitudinal motion. Three cardiac cycles were stored for subsequent postprocessing.

Color Doppler Myocardial Imaging Data Analysis

All data were digitally transferred from the ultrasound machine and postprocessed on an off-line workstation. The CDMI data sets were analyzed using dedicated software (Software Package For Echocardiographic Quantification Leuven, Specle 4, Catholic University of Leuven, Belgium). This allows the computation of regional myocardial velocities, natural SR, and ε values. Longitudinal peak systolic SR and ε were estimated for the basal, mid, and apical segments of each wall by measuring the spatial velocity gradient over a computation area of 10 mm. A computation area of 5 mm was used for the calculation of peak systolic radial SR and ε. A manual M-mode–based tracking algorithm was applied to maintain the sample volume within the region of interest throughout the cardiac cycle. To determine the duration of ejection, the aortic valve opening and closure clicks were introduced and aligned from blood pool pulsed-wave Doppler tracings recorded from cycles with a comparable R-R interval.

Table 1 Intraobserver and interobserver variability of regional deformation data

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<th>Intraobserver</th>
<th>Interobserver</th>
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<tr>
<td></td>
<td>Mean difference</td>
<td>95% CI</td>
</tr>
<tr>
<td>Longitudinal SR</td>
<td>0.11</td>
<td>0.12</td>
</tr>
<tr>
<td>Longitudinal ε</td>
<td>2.56</td>
<td>3.72</td>
</tr>
<tr>
<td>Radial SR</td>
<td>0.51</td>
<td>0.47</td>
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<tr>
<td>Radial ε</td>
<td>2.79</td>
<td>2.91</td>
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CI, Confidence interval; SR, strain rate; ε, strain.

In each myocardial segment peak systolic myocardial velocities were measured. In the basal septal, basalar lateral, and basal RV free wall myocardial segments, peak early diastolic (E) and late diastolic (A) myocardial velocities were also measured. The myocardial isovolumic relaxation time was measured in the LV basal septal segment and was defined as the time interval between the end of the myocardial systolic velocity wave and the beginning of the myocardial early diastolic wave. The ratio of the early mitral diastolic blood flow over the early diastolic septal myocardial velocity (E/E') was calculated as a parameter for LV filling pressures. The IVA was measured in the basal LV lateral and basal RV free wall, as previously reported.

Statistical Analysis

Statistical analysis was performed using the Statistica data analysis software system (Stat Soft, Inc. 2001, version 6.0). Normally distributed continuous data are reported as mean value ± standard deviation. Not normally distrib-
28% (Figure 1). The myocardial performance index was significantly prolonged in patients compared with controls ($P < .01$).

On the basis of the CDMI velocity data, LV radial myocardial systolic function was studied. The results are summarized in Figure 2. There was no significant difference in the peak systolic myocardial velocities, but peak systolic SR and $\varepsilon$ values were significantly lower in the anthracycline group compared with the control group. Also, LV longitudinal function was analyzed (Figure 3). Peak systolic myocardial velocities were unchanged in the septal segments and even higher in patients compared with normal controls in the LV lateral wall. Peak systolic SR and $\varepsilon$ were significantly reduced in the six myocardial segments analyzed in patients compared with controls.

Peak systolic myocardial velocity, peak systolic SR, and peak systolic $\varepsilon$ derived from the three RV free wall segments are shown in Table 3. There was only a significant reduction in peak systolic $\varepsilon$ in the basal RV free wall in the patients’ group.

### Myocardial Velocity Acceleration During the Isovolumic Contraction Period

The IVA was significantly reduced in the basal lateral LV segment ($P < .05$) in patients compared with controls. No difference in IVA was found in the basal RV free wall (Table 4).

### DISCUSSION

This study showed that several subtle abnormalities in myocardial function could be detected in asymptomatic pediatric patients who had been exposed to low to moderate doses of anthracyclines approximately 5 years after treatment. The changes we observed were as follows: (1) abnormalities in LV diastolic function with an increased isovolumic relaxation time and a reduced systolic pulmonary venous flow; (2) an increased end-systolic wall stress; (3) a reduction in LV systolic ring displacement and LV systolic wall thickening; (4) a reduction in myocardial systolic deformation in the radial and longitudinal direction. Significant reductions in peak systolic SR and peak systolic $\varepsilon$ were noted in the inferolateral wall and in the basal, mid, and apical segments of the interventricular septum and the LV lateral wall; and (5) abnormalities in parameters of global LV cardiac function, such as myocardial performance index and IVA.
All of these findings were observed in patients who were described to have normal LV systolic function when assessed using M-mode and two-dimensional echocardiography. Therefore, one may conclude that either the more commonly used methods to evaluate global systolic function are not sensitive enough to detect subtle changes in LV function or that the abnormalities reported in the present study reflect “unimportant” changes in LV function. The real answer to this question will be given by the long-term outcome of the current patient group, but we believe the observed changes to be relevant for a number of reasons. In a recent study on the long-term outcome of patients exposed to anthracyclines, Lipshultz et al. demonstrated a progressive deterioration in LV function 10 to 15 years after completion of the treatment. They showed a progressive decline in fractional shortening and stress-velocity index. The authors observed an early reduction in contractility months after the administration of anthracyclines; this was followed by an improvement in function. However, 6 years after completion of treatment, a progressive functional deterioration was observed. They observed equivalent changes in high-dose (>400 mg/m²) and low-dose (<300 mg/m²) groups. Our patients can be considered as patients from the low-dose group and were studied approximately 5 years after completion of chemotherapy. In the study by Lipshultz and colleagues, this is the moment when the functional parameters were still within normal ranges but started to deteriorate. Our findings are consistent with this, because different parameters of cardiac performance, such as ejection fraction, fractional shortening, and stress-velocity measurements, were still within normal range in most of our patients. Nevertheless, some of the changes observed seem to reflect early subtle changes in cardiac function that might be the first signs of deterioration in myocardial function.

Subtle abnormalities in diastolic function could be observed in the patient group. These could be observed on the mitral inflow (prolonged isovolumic relaxation times), pulmonary venous flows.

Figure 2 Peak systolic radial function of the inferolateral wall.

Figure 3 Peak systolic indices of longitudinal function at the basal, mid, and apical segments of the interventricular septum and left ventricular lateral wall.
(decreased systolic flow), and diastolic tissue Doppler data (increased myocardial isovolumic relaxation time and peak E' velocity). A prolonged isovolumic relaxation time has been reported in patients after anthracycline administration.\textsuperscript{21,22} It suggests changes in early relaxation. The decreased systolic pulmonary flow suggests a decreased LV longitudinal systolic performance and reduced atrial compliance.\textsuperscript{23} The increase in early diastolic myocardial velocities is difficult to explain, because this seems to indicate an increased diastolic performance at rest. Remarkably, also systolic myocardial velocities were higher in the basal myocardial segments. The preserved E/E' ratio suggests normal filling pressures in the patient group. This would be expected in view of the subtle diastolic changes.

Regional LV systolic myocardial deformation was significantly reduced in patients compared with controls. Consistent with a reduction in longitudinal myocardial deformation in the different myocardial segments of the LV lateral wall and interventricular septum, the annular motion or ring displacement in both septal and lateral mitral annuli were reduced. These data suggest a reduction in longitudinal LV function. In other studies a reduction in longitudinal function has been found to be an early indicator of LV dysfunction, preceding a reduction in radial function.\textsuperscript{24,25} Also in the inferolateral wall, peak systolic SR and $\varepsilon$ were significantly reduced. This indicates a reduced radial myocardial function in this particular segment. Despite the reduction in radial deformation in the inferolateral wall, global radial cardiac performance as assessed by fractional shortening remained normal. This could be due to the fact that the changes are small and localized to certain myocardial segments and did not yet result in changes in global ejection parameters.

By definition, deformation parameters are load-dependent, with an increased afterload resulting in a reduction in peak systolic $\varepsilon$ and SR for the same contractility.\textsuperscript{26} In contrast, IVA has been described to be a load-independent parameter for cardiac function.\textsuperscript{14} We found an increase in end-systolic wall stress consistent with increased afterload in our patients. So part of the abnormalities in systolic deformation could be related to changes in loading conditions. The observation that also IVA was reduced in the LV favors the hypothesis that LV contractile function is affected. This indicates that at least part of the changes in deformation may be secondary to subtle reductions in contractility. However, an influence of the increased afterload on deformation parameters cannot be entirely excluded.

Our data indicate that the right ventricle is affected to a lesser extent than the left ventricle. Whether this truly demonstrates a lower susceptibility of the RV myocytes to anthracycline-induced cardiotoxicity or purely expresses the incapacity of the detection techniques to uncover dysfunction on this side of the heart needs to be further addressed with a follow-up study. It may well be that the combination of the higher pressure development with an associated higher myocardial oxygen consumption in the left compared with the right ventricle may contribute to the development of the process.\textsuperscript{27} Previous studies with radionuclide angiography have shown normal RV function late after anthracycline administration.\textsuperscript{28}

There is concern about the variability of deformation data. However, the changes detected exceeded the 95% confidence interval of the intraobserver and interobserver variability. This suggests that the reduction in deformation seen in patients treated with anthracycline is likely the effect of the drugs.

**Table 3** Longitudinal systolic function of the right ventricular free wall

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<thead>
<tr>
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<th>Anthracycline</th>
<th>Controls</th>
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<tbody>
<tr>
<td>RV basal</td>
<td>9.1 ± 1.8</td>
<td>8.5 ± 2.1</td>
</tr>
<tr>
<td>RV mid</td>
<td>7.4 ± 1.8</td>
<td>7.0 ± 2.0</td>
</tr>
<tr>
<td>RV apical</td>
<td>4.9 ± 2.1</td>
<td>4.8 ± 1.8</td>
</tr>
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*RV, Right ventricle. *P < .05 versus controls.

**Table 4** Myocardial velocity acceleration during isovolumic contraction period

<table>
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<tr>
<th></th>
<th>Anthracycline (n = 56)</th>
<th>Control (n = 32)</th>
</tr>
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<tbody>
<tr>
<td>IVA LV</td>
<td>98.4 ± 51.1*</td>
<td>122.2 ± 38.5</td>
</tr>
<tr>
<td>IVA RV</td>
<td>172.4 ± 54.3</td>
<td>177.0 ± 42.9</td>
</tr>
</tbody>
</table>

*IVA, Myocardial velocity acceleration during isovolumic contraction period; LV, left ventricle; RV, right ventricle. *P < .05 versus controls.

**POTENTIAL CLINICAL IMPLICATIONS**

Our findings suggest that the measurement of global LV function by either fractional shortening or ejection fraction may not be sufficiently sensitive to detect cardiac involvement at an early stage. On the other hand, SR/$\varepsilon$ imaging and measurement of IVA can detect impaired myocardial function at an early stage. It seems that regional dysfunction can be
detected earlier than global dysfunction especially in the longitudinal direction. This might provide the rationale to start treatment early in asymptomatic patients with angiotensin-converting enzyme inhibitors, beta-blockers, or erythropoietin as recently suggested. 29,30 Furthermore, deformation parameters might well be used to monitor and evaluate the long-term effects of different treatments on cardiac function.

In any case, a continued surveillance of ventricular function is warranted even years after receiving a low-to-moderate cumulative dose of anthracyclines. Follow-up studies are needed to define the best predictive parameters for those patients at risk of developing LV dysfunction who might benefit the most from an early start of treatment.

CONCLUSIONS

We investigated cardiac function in patients who had received a low dose of anthracyclines during childhood using several echocardiographic parameters of systolic and diastolic function. Some subtle abnormalities were found; reduced longitudinal myocardial function and diastolic dysfunction were especially noted.

The predictive value of these findings needs to be further studied. In the meantime, close follow-up of survivors of low-dose anthracycline treatment will be necessary for many years for a better understanding of the process and for an improvement in the prediction of the outcome.

REFERENCES


