Chapter 6

Exercise echocardiography in asymptomatic survivors of childhood cancer treated with anthracyclines: A prospective follow-up study

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**Abstract**

**Background**
Exercise echocardiography reveals abnormalities in asymptomatic childhood cancer survivors who previously have been treated with anthracyclines. We determined the added value of monitoring childhood cancer survivors with exercise echocardiography compared to monitoring with resting echocardiography alone to predict anthracycline-induced cardiotoxicity. Secondary aims were to evaluate change in resting cardiac function over 10 years and to determine risk factors for late cardiotoxicity.

**Procedure**
We invited a cohort of 110 originally asymptomatic anthracycline-treated childhood cancer survivors, who had undergone cardiac tests including exercise echocardiography 10.5 years earlier, for new cardiac evaluation. Each subject underwent a resting echocardiogram at both evaluations. At first evaluation a repeat echocardiogram was performed following peak exercise. Resting echocardiographic parameters were converted to z-scores.

**Results**
92 of 110 survivors (mean anthracycline dose 307 mg/m², mean follow-up time from start of treatment 8.2 years at first and 18.8 years at second evaluation) were evaluated prospectively. Mean resting fractional shortening z-score (RFSz) decreased from -0.18 to -0.93. Higher cumulative anthracycline dose was a risk factor for a lower RFSz at late follow-up (p=0.0002). Adding exercise fractional shortening (XFS) to a model containing RFSz did not improve prediction of abnormal RFSz at late follow-up.

**Conclusions**
Monitoring with exercise echocardiography has no added value to monitoring with resting echocardiography alone in predicting late anthracycline-induced cardiotoxicity in childhood cancer survivors. RFSz deteriorates over time, even in originally asymptomatic patients. Previous treatment with higher cumulative anthracycline dose is the main risk factor for a lower RFSz at late follow-up.
Exercise echocardiography after anthracyclines in children

Introduction

Many survivors of childhood cancer experience serious long-term complications related to their previous cancer therapy.\textsuperscript{1,2} Anthracycline-induced cardiotoxicity is one of the most important of these health problems, which can occur not only during, but also years after therapy.\textsuperscript{3-5} It is estimated that 20 years after treatment, almost 10% of survivors treated with anthracycline doses of 300 mg/m\textsuperscript{2} or more will have developed symptomatic cardiotoxicity, a condition that is often life-threatening.\textsuperscript{6-8} Additionally, asymptomatic cardiotoxicity is found in up to 57% of anthracycline-treated survivors.\textsuperscript{9} Since these abnormalities are often progressive, the general concern is that asymptomatic individuals are at increased risk of developing symptomatic cardiotoxicity.\textsuperscript{7,10-12} Early detection of cardiotoxicity is important, in order to counsel the patient about lifestyle recommendations and to consider interventions that could prevent further deterioration of cardiac function.\textsuperscript{13-15}

Established, evidence- and consensus-based guidelines from several cooperative groups recommend regular screening of anthracycline-induced cardiotoxicity in childhood cancer survivors.\textsuperscript{16-19} However, these guidelines acknowledge that there is no evidence what the best screening tool is for the detection of anthracycline-induced cardiotoxicity.\textsuperscript{16,20} Assessment of resting cardiac function by conventional echocardiography has been the generally recommended method to evaluate cardiac performance in anthracycline-treated childhood cancer survivors. This recommendation is primarily based on consensus of involved health care specialist, supported by the fact that resting echocardiography is a non-invasive and widely available tool to evaluate cardiac function and has been used most in studies on anthracycline-induced cardiotoxicity in childhood cancer survivors. However, no prospective studies have been performed that have evaluated what the best screening tool is to detect or predict (clinically relevant) anthracycline-induced cardiotoxicity in childhood cancer survivors.\textsuperscript{19,21}

Several studies have suggested that echocardiography performed just after exercise could be a tool to detect asymptomatic anthracycline-induced cardiotoxicity at an earlier stage compared to resting echocardiography.\textsuperscript{22-28} In a previous study performed in the Royal Children’s Hospital in Melbourne between 1994 and 1997, it was found that asymptomatic, anthracycline-treated childhood cancer survivors had a lower FS after exercise (XFS) as well as a smaller increase in FS after exercise when compared to a group of normal controls, while mean resting FS (RFS) in this group was normal.\textsuperscript{29} Previous treatment with higher cumulative anthracycline dose was associated with the abnormalities after exercise in this group. We therefore hypothesized that exercise echocardiography is a better tool to predict future cardiotoxicity than resting echocardiography. Several other studies have also shown impaired myocardial response to the physiological stress of exercise in asymptomatic anthracycline-treated survivors.\textsuperscript{22-28} However, no prospective studies have been performed to evaluate the predictive value of this finding.
We assessed current, resting cardiac function in a previously studied cohort of asymptomatic childhood cancer survivors, approximately 10 years after the first evaluation. The primary purpose of this study was to determine if monitoring of survivors with exercise echocardiography has added value compared to monitoring with conventional resting echocardiography alone in predicting late anthracycline-induced cardiotoxicity. Secondary objectives of this study were to evaluate the change in resting cardiac measurements between both evaluations and to define determinants of late cardiotoxicity in this cohort of childhood cancer survivors who were initially asymptomatic.

Methods

Study population
We determined current cardiac function in 92 long-term childhood cancer survivors in 2005 and 2006 (evaluation 2: E2). These 92 subjects were part of a cohort of 110 childhood cancer survivors who had been tested between 1994 and 1997 (Evaluation 1: E1). Details of original inclusion criteria have been described previously. In summary, at E1, patients were consecutively selected at the paediatric oncology outpatient clinic of the Royal Children’s Hospital in Melbourne. They had all been treated with anthracyclines for childhood cancer, were in continuous remission for at least 12 months and did not have cardiac symptoms or known pre-existing cardiac abnormalities. At the time, none of the subjects were treated with mediastinal radiotherapy or had undergone prior bone marrow transplant. At E2, all subjects had stayed in continuous remission during the period of follow-up. Ethics approval for his study was obtained from the Human Research Ethics Committee.

Cardiac evaluation
Subjects underwent resting echocardiography at both E1 and E2. We performed a routine echocardiogram, including M-mode measurements, two-dimensional echocardiography and Doppler interrogation to confirm normal cardiac anatomy, to rule out significant valvular problems and to identify wall motion abnormalities. We determined left ventricular (LV) cavity dimension (left ventricular end diastolic dimension, LVEDD) and LV (resting) fractional shortening (RFS). At E1, we had additionally performed an exercise echocardiogram by repeating the echocardiographic measurements within 90 seconds of peak exercise and determined exercise FS (XFS). The methodology and results from the initial study have been described previously. At E2, echocardiograms were executed by one of three sonographers. A single, experienced paediatric cardiologist (M.C.) interpreted and reported all echocardiographic studies. All were unaware of any clinical information related to the study subjects or any previous echocardiographic findings. Follow-up exercise tests
were not performed, as the primary objective of the present study was to determine the predictive value of the original exercise echocardiograms on late resting cardiac function.

**Statistical analysis**

Echocardiographic parameters for patients of different ages and body surface areas (BSA) were compared by firstly converting them to standard deviation scores (z-scores). These calculations were based on echocardiographic data of the normal population previously described for children up to 20 years old and data from subjects of 20 to 40 years (unpublished data of the same study). LVEDD was converted to a z-score (LVEDDz) adjusting for BSA. RFS was converted to a z-score (RFSz) adjusting for age. An abnormal echocardiographic parameter was defined as a z-score less than $-2.00$ (RFSz) or more than $+2.00$ (LVEDDz). Abnormal XFS was defined as less than 36% as this was the -2SD value of the group of normal controls that underwent exercise echocardiography at E1.

We performed one sample t-tests on RFSz and LVEDDz at E1 and E2 to compare their means against those of a normal population. Analysis of change in RFSz and LVEDDz between the two evaluations was done using paired t-tests. Determinants (cumulative anthracycline dose, gender, age at start of treatment and time since start of treatment) of the standardised echocardiographic parameters were assessed by linear regression.

We assessed the added value of exercise echocardiography in predicting future cardiotoxicity compared to resting echocardiography alone by using the likelihood ratio test and by creating receiver operating (ROC) curves of two predictive models and comparing their areas under the ROC curve (AUC). Late cardiotoxicity was defined as abnormal RFSz at E2. Two logistic regression models, both containing RFSz at E1 as an explanatory variable but only the second model containing XFS at E1, were compared. Both predictive models were adjusted for cumulative anthracycline dose, gender, age at start of treatment and time since start of treatment. Statistical analyses were performed using Stata software (Stata Corporation, College Station, TX, Version 9).

**Results**

**Study population**

Of the original cohort of 110 childhood cancer survivors, we were not able to perform clinical follow-up in 18 patients (16%): 8 patients were lost to follow-up, 6 patients were living remotely (abroad or interstate), 3 patients were unable to visit our clinic for personal reasons and 1 patient had died from a motor vehicle accident. We contacted all 9 patients who live remotely or were unable to visit our clinic and none had cardiac symptoms.

We found no differences in patient characteristics or cardiac function at E1 between the cohort evaluated at E1 and the cohort at E2 (data not shown). Mean (SD) age at start of
treatment of the cohort studied at E2 was 6.4 (4.2) years. The mean (SD) cumulative dose of anthracyclines was 307 (123) mg/m². Evaluation at E1 and E2 was done after a mean follow-up time of 8.2 years (range 1.8 to 17.4 years) and 18.8 years (range 11.3 to 29.0 years).
years) respectively since the start of anthracycline treatment. Mean (SD) age of survivors at E1 and E2 was 14.6 (5.0) years and 25.2 (5.2) years respectively and E2 was a mean of 10.5 years after E1 (range 8.9 to 12.4 years). Other patient characteristics of the cohort evaluated at E2 are shown in Table 1.

Cardiac evaluation
In the group of survivors examined, 1 patient (1%) had developed clinical heart failure NYHA stage III between E1 and E2 and is receiving extensive medical therapy. Three subjects had structural echocardiographic abnormalities at E2: thickening of mitral valve leaflets (1 patient), bicuspid aortic valve and dilated aortic sinus (1 patient) and dilated aortic root (1 patient). Another three patients had abnormal septal motion and therefore unreliable echocardiographic outcomes. We excluded the echocardiographic data of the three patients with abnormal septal motion from further statistical analyses. In addition, the patient who had developed clinical heart failure was excluded from the t-tests and linear regression analyses. This patient was included in the analysis where a dichotomous endpoint was studied. Table 2 shows the numbers of patients with abnormal values at both evaluations. At latest follow-up, 22% of subjects had a depressed fractional shortening Z score. All patients with abnormal RFSz at E2 had received anthracycline doses of 210 mg/m² or more.

Table 2 Number of survivors with abnormal echocardiographic parameters at E1 and E2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>E1 N=89</th>
<th></th>
<th>E2 N=89</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>RFSz</td>
<td>16</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>XFS</td>
<td>23</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>LVEDDz</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: E1, first study evaluation between 1994 and 1997; E2, second study evaluation between 2005 and 2006; RFSz, resting fractional shortening z score; XFS, exercise fractional shortening; LVEDDz, left ventricular end diastolic dimension z score

Echocardiographic values at E1 and E2
Mean z-score values of resting echocardiographic parameters at each evaluation and the mean difference between the two evaluations are shown in Table 3. There was no evidence of a difference in RFSz at E1 compared to the normal population (-0.18; 95%CI -0.58 to 0.21; p=0.36) but very strong evidence of a difference compared to the normal population at E2 (-0.93, 95%CI -1.27 to -0.58, p<0.001). Mean LVEDDz of the left ventricle in our cohort was slightly dilated in diastole at E1 compared to the normal population (0.20, 95%CI 0.01, 0.38, p=0.04). This difference in LVEDDz had increased at E2 (0.42, 95%CI 0.21, 0.62, p<0.001).
**Determinants of cardiotoxicity**

Table 4 shows the demographic and clinical characteristics that were examined as determinants for late cardiotoxicity (RFSz at E2). Univariate analysis identified increasing cumulative anthracycline dose and a longer time since start of treatment to be associated with lower RFSz at E2 (p=0.0001 and p=0.05, respectively). When all these characteristics were examined in a multivariable model, only cumulative anthracycline dose was found to be associated with a lower RFSz at E2 (p=0.0002). None of the assessed determinants were found to be associated with LVEDDz (data not shown).

**Table 4.** Univariate and multivariable linear regression analyses of determinants of distribution of RFSz at E2 (n=88)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Univariate analyses</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cumulative anthracycline dose</td>
<td>-0.56</td>
<td>-0.82 to -0.30</td>
</tr>
<tr>
<td>(per 100 mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of treatment (years)</td>
<td>0.05</td>
<td>-0.03 to 0.13</td>
</tr>
<tr>
<td>Time since start of treatment</td>
<td>-0.10</td>
<td>-0.20 to -0.00</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.08</td>
<td>-0.79 to 0.62</td>
</tr>
</tbody>
</table>

**Added value exercise echocardiography**

Adding XFS at E1 to a multivariable model containing RFSz at E1, cumulative anthracycline dose, age at start of treatment, time since start of treatment and gender, did not improve model fit (likelihood ratio test, p=0.97, Table 5). In addition, the ROC curve of the second model with XFS and RFSz at E1 (AUC 0.864, standard error 0.04) did not differ from the ROC curve of the first model with RFSz at E1 only (AUC 0.863, standard error 0.04) (Figure 1).
Table 5 Multivariable logistic regression analysis on RFSz at E2, comparing two models that include RFSz at E1 and RFSz as well as XFS at E1 (n=89)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Model 1: including RFSz at E1</th>
<th></th>
<th>Model 2: Including XFS and RFSz at E1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
</tr>
<tr>
<td>Cumulative anthracycline dose (per 100 mg/m²)</td>
<td>2.11</td>
<td>1.06 to 4.20</td>
<td>0.03</td>
<td>2.10</td>
</tr>
<tr>
<td>Age at start of treatment (years)</td>
<td>0.87</td>
<td>0.74 to 1.02</td>
<td>0.08</td>
<td>0.87</td>
</tr>
<tr>
<td>Time since start of treatment</td>
<td>1.14</td>
<td>0.92 to 1.40</td>
<td>0.24</td>
<td>1.13</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.41</td>
<td>0.40 to 4.98</td>
<td>0.59</td>
<td>1.39</td>
</tr>
<tr>
<td>XFS</td>
<td>1.00</td>
<td>0.86 to 1.15</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>RFSz</td>
<td>0.45</td>
<td>0.27 to 0.73</td>
<td>0.001</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Abbreviations: RFSz, resting fractional shortening z score; E2, second study evaluation between 2005 and 2006; E1, first study evaluation between 1994 and 1997; XFS, exercise fractional shortening

-2 Log Likelihood of model with RFSz only: 64.683 (4df)
-2 Log Likelihood of model with both XFS and RFSz: 64.681 (5 df)

Figure 1 ROC curves of model 1 and model 2. Model 1 including RFSz at E1 (blue), model 2 including RFSz and XFS at E1 (red), both adjusted for cumulative anthracycline dose, age at treatment, years since start of treatment, gender.

Abbreviations: RFSz, resting fractional shortening z score; E1, first study evaluation between 1994 and 1997; XFS, exercise fractional shortening
Discussion

Many studies have shown an impaired cardiac function after exercise in anthracycline-treated children, but no long-term follow-up study has been done previously to evaluate the predictive value of this finding.\textsuperscript{22-28} In our prospective follow-up study we found no added value of exercise echocardiography to resting echocardiography in predicting the occurrence of cardiotoxicity in originally asymptomatic childhood cancer survivors. We therefore cannot confirm the hypothesis that exercise echocardiography should be added to the conventional monitoring of these patients with repeat resting echocardiograms in order to predict future cardiotoxicity in anthracycline-treated childhood cancer survivors.

The underlying idea of performing an exercise echocardiogram in asymptomatic anthracycline-treated childhood cancer survivors was that the heart that is affected by a chemotherapeutic agent and performs acceptable during rest, might not be able to cope with a higher demand on its function such as during exercise. Several cross-sectional studies as well as the first evaluation in our longitudinal study seemed to confirm this idea.\textsuperscript{22-28} Alternatively, some studies have evaluated cardiac function after pharmacologically-induced stress, such as with dobutamine infusion.\textsuperscript{33-36} Often similar findings have been described in these studies, but also no long-term follow-up studies have been performed to evaluate the predictive value of this stress test. In the present study we evaluated the predictive value of exercise echocardiography in a clinically relevant setting, by taking into account also the resting echocardiogram as well as the most important risk factors for anthracycline-induced cardiotoxicity in our predictive model. We showed that performing exercise echocardiography late after anthracycline administration, does not improve the prediction of future cardiac dysfunction, when compared to resting echocardiography. Therefore, based on our data, performing an additional echocardiogram after exercise for monitoring asymptomatic survivors does not give the care-giver extra, clinically relevant information. Interestingly, although this wasn’t the original purpose of the study, our data do suggest that resting fractional shortening Z scores in asymptomatic survivors correlate well with resting fractional shortening Z scores more than a decade later. This indicates that monitoring with resting echocardiography is appropriate in childhood cancer survivors and that a lower fractional shortening implies an increased risk for late cardiac dysfunction.

Notable features of this study are the longitudinal character with 10.5 years of follow-up after the exercise echocardiogram and a high percentage of the cohort that was contacted or that returned for late follow-up, indicating that there is no reason for concern about follow-up bias. Also, we confirmed findings of other studies that resting left ventricular function deteriorates over time in anthracycline-treated survivors and that cumulative dose is the most important risk factor for an abnormal resting fractional shortening Z score many years after treatment.\textsuperscript{10,37,38} It should be noted that because we selected only survivors for this longitudinal study who were asymptomatic at the first evaluation, incidences
of abnormalities in this cohort will underestimate the incidence of cardiotoxicity in all anthracycline treated subjects. However, even in patients who were asymptomatic 1 to 15 years after anthracyclines treatment, 22% had a depressed fractional shortening Z score 11 to 25 years after treatment. The high number of abnormalities at late follow-up as well as the decline in left ventricular parameters over time found in our study reinforces the necessity of regular cardiac follow-up in anthracycline treated childhood cancer survivors and the need for further studies on prevention and treatment of anthracycline-induced cardiotoxicity in childhood cancer survivors.

Limitations of our study are that our outcomes are subclinical parameters. Ideally, we would have taken clinical outcome parameters. However, even in a larger cohort with longer follow-up, the number of patients with clinical heart failure would likely be too low in a cohort that was originally asymptomatic, in order to be able to use it as an outcome parameter. Another limitation of our study is that the use of fractional shortening as a measure of cardiac function has disadvantages. It is influenced by preloading conditions of the heart as well as afterload. Other load independent parameters of cardiac function have been used, such as systolic wall stress and the stress-velocity index. However, fractional shortening has been widely reported in this field and is therefore a clinically relevant measurement in assessing cardiac function in anthracycline-treated childhood cancer survivors. Moreover, several studies in adults have shown that the ejection fraction, a parameter similar to fractional shortening, is strongly related to the prognosis of the patient with regards to symptomatic heart failure and even mortality. Therefore, and for the purpose of longitudinal evaluation, we used fractional shortening Z score as the main parameter of left ventricular function. Last, exercise echocardiography performed sooner after completion of anthracycline administration may have been more highly predictive of late resting left ventricular function. This seems unlikely as resting fractional shortening Z scores continued to decline during the course of the study.

We conclude that exercise echocardiography with measurement of fractional shortening, has no role in the routine monitoring for anthracycline-induced cardiotoxicity occurring in the first two decades after treatment in asymptomatic childhood cancer survivors. Resting fractional shortening Z scores deteriorate over time in originally asymptomatic patients, with cumulative anthracycline dose as the main risk factor for cardiotoxicity at late follow-up. To improve cardiac follow-up of survivors, research in this field should include efforts to define the most optimal diagnostic method to detect late anthracycline-induced cardiotoxicity at an early stage.
Acknowledgement

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References