



UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Childhood cancer survivors: Evidence and care

Sieswerda, E.

Publication date
2013

[Link to publication](#)

Citation for published version (APA):

Sieswerda, E. (2013). *Childhood cancer survivors: Evidence and care*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

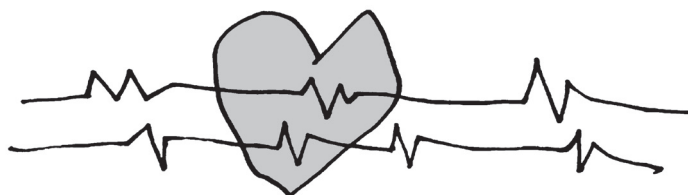
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

Chapter 6

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

Elske Sieswerda, Leontien C.M. Kremer, Suzanna Vidmar, Marie L. De Bruin, Elizabeth Smibert, Gunnar Sjöberg, Michael M.H. Cheung, Robert G. Weintraub

Pediatric Blood and Cancer. 2010 Apr;54(4):579-84



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.

Introduction

Many survivors of childhood cancer experience serious long-term complications related to their previous cancer therapy.^{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.³⁻⁵ It is estimated that 20 years after treatment, almost 10% of survivors treated with anthracycline doses of 300 mg/m² or more will have developed symptomatic cardiotoxicity, a condition that is often life-threatening.⁶⁻⁸ Additionally, asymptomatic cardiotoxicity is found in up to 57% of anthracycline-treated survivors.⁹ Since these abnormalities are often progressive, the general concern is that asymptomatic individuals are at increased risk of developing symptomatic cardiotoxicity.^{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.¹³⁻¹⁵

Established, evidence- and consensus-based guidelines from several cooperative groups recommend regular screening of anthracycline-induced cardiotoxicity in childhood cancer survivors.¹⁶⁻¹⁹ However, these guidelines acknowledge that there is no evidence what the best screening tool is for the detection of anthracycline-induced cardiotoxicity.^{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.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.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.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.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.²⁹ 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.³⁰ 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.²⁹ 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).³¹ LVEDD was converted to a z-score (LVEDDz) adjusting for BSA.³¹ RFS was converted to a z-score (RFSz) adjusting for age.³² 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 E1.²⁹

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

Table 1 Characteristics of the study cohort at E2

Characteristics	Study Cohort at E2 N=92	
	No. of patients	%
Sex		
Male	52	56.5
Female	40	43.5
Diagnosis		
<i>Haematological malignancies</i>		
ALL/NHL	42	45.7
AML	4	4.4
<i>Solid tumours</i>		
Ewing's sarcoma	16	17.4
Osteosarcoma	7	7.6
Wilm's tumour	10	10.9
Miscellaneous	13	14.1
Age at first anthracycline dose (years)		
< 2	10	10.9
2 – 4	35	38.0
5 – 9	24	26.1
10 – 14	21	22.8
≥ 15	2	2.2
Cumulative anthracycline dose (mg/m ²)		
75 – 199	15	16.3
200 – 299	21	22.8
300 – 399	28	30.4
400 – 540	28	30.4
Type of anthracycline		
Doxorubicin	50	54.4
Daunorubicin	17	18.5
Doxorubicin and Daunorubicin	25	27.2
Mode of administration of anthracycline		
Intravenous bolus	83	90.2
Intravenous infusion over 4 – 6 hours	9	9.8
Additional cyclophosphamide (mg/m ²)		
None	14	15.2
Any	78	84.8

Abbreviations: E2, second study evaluation between 2005 and 2006; ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin's disease; AML, acute myeloid leukaemia

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) 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

Parameter	E1 N=89		E2 N=89	
	N	%	N	%
RFSz	16	18	20	22
XFS	23	26	-	-
LVEDDz	2	2	7	8

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).

Table 3 Distribution of left ventricular echoparameters at E1 and E2, compared to the normal population ; Change of left ventricular echoparameters between E1 and E2

Parameter	E1 N=88			E2 N=88			Change between E2 and E1 N=88		
	Mean	95% CI	P ^a	Mean	95% CI	P ^a	Mean	95% CI	P
RFSz	-0.18	-0.58 to 0.21	0.36	-0.93	-1.27 to -0.58	<0.001	-0.74	-1.09 to -0.39	<0.001
LVEDDz	0.20	0.01 to 0.38	0.04	0.42	0.21 to 0.62	<0.001	0.22	0.04 to 0.40	0.02

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

^a Comparison with normative data

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)

Determinant	Univariate analyses			Multivariable analysis		
	B	95% CI	P	B	95% CI	P
Cumulative anthracycline dose (per 100 mg/m ²)	-0.56	-0.82 to -0.30	<0.001	-0.54	-0.82 to -0.27	<0.001
Age at start of treatment (years)	0.05	-0.03 to 0.13	0.25	0.06	-0.02 to 0.14	0.13
Time since start of treatment	-0.10	-0.20 to -0.00	0.05	-0.04	-0.13 to 0.06	0.45
Female gender	-0.08	-0.79 to 0.62	0.81	0.03	-0.62 to 0.67	0.93

Abbreviations: RFSz, resting fractional shortening z score; E2, second study evaluation between 2005 and 2006; B, coefficient of regression line; CI, confidence interval; P, probability

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)

Determinant	Model 1: including RFSz at E1 ^a			Model 2: Including XFS and RFSz at E1 ^b		
	OR	95% CI	P	OR	95% CI	P
Cumulative anthracycline dose (per 100 mg/m ²)	2.11	1.06 to 4.20	0.03	2.10	1.03 to 4.29	0.04
Age at start of treatment (years)	0.87	0.74 to 1.02	0.08	0.87	0.74 to 1.02	0.08
Time since start of treatment	1.14	0.92 to 1.40	0.24	1.13	0.91 to 1.42	0.27
Female gender	1.41	0.40 to 4.98	0.59	1.39	0.35 to 5.48	0.63
XFS				1.00	0.86 to 1.15	0.97
RFSz	0.45	0.27 to 0.73	0.001	0.45	0.26 to 0.78	0.005

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

^a -2 Log Likelihood of model with RFSz only: 64.683 (4df)

^b -2 Log Likelihood of model with both XFS and RFSz: 64.681 (5 df)

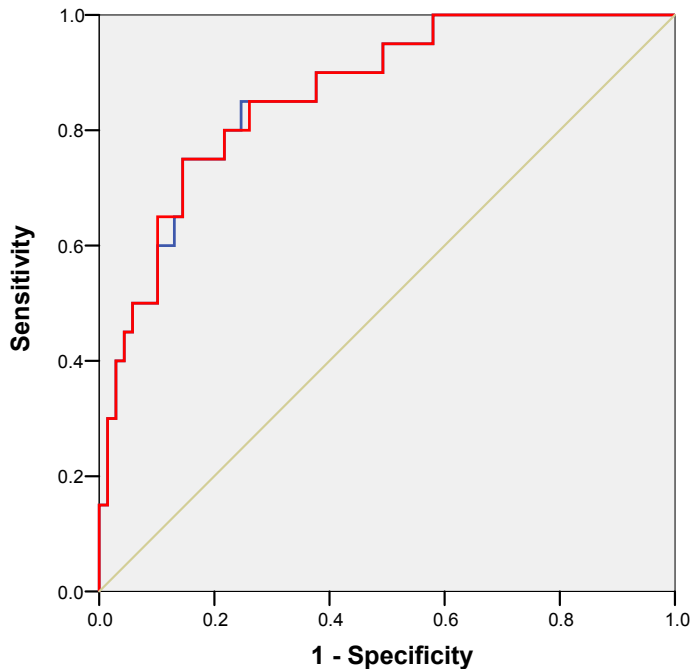


Figure 1 ROC curves of model 1 and model 2. Model 1 including RFSz at E1 (blue), model 2 including RFSz and XFS at E1 (red), both adjusted for cumulative anthracycline dose, age at treatment, years since start of treatment, gender.

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.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.²²⁻²⁸ Alternatively, some studies have evaluated cardiac function after pharmacologically-induced stress, such as with dobutamine infusion.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.^{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.³⁹ Other load independent parameters of cardiac function have been used, such as systolic wall stress and the stress-velocity index.⁹ 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.⁹⁻¹¹ 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.^{40,41} 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

We would like to thank Steven D. Colan, MD, for providing normative echocardiographic data. This research project was supported by the Department of Cardiology at the Royal Children's Hospital, Melbourne, the Tom Voûte Foundation (previously the Foundation of Paediatric Cancer Research, SKK) and by student grants from the Dutch Heart Foundation (NHS) and the Queen Wilhelmina Cancer Foundation (KWF).

References

1. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572-1582.
2. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007;297:2705-2715.
3. Lefrak EA, Pitha J, Rosenheim S, et al. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer* 1973;32:302-314.
4. Von Hoff DD, Rozenzweig M, Layard M, et al. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. *Am J Med* 1977;62:200-208.
5. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996;125:47-58.
6. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6-19 years after anthracycline therapy: A series of 15 patients. *Med Pediatr Oncol* 1995;24:352-361.
7. Nysom K, Colan SD, Lipshultz SE. Late cardiotoxicity following anthracycline therapy for childhood cancer. *Progress in Pediatric Cardiology* 1998;8:121-138.
8. van Dalen EC, van der Pal HJ, Kok WE, et al. Clinical heart failure in a cohort of children treated with anthracyclines: A long-term follow-up study. *Eur J Cancer* 2006;42:3191-3198.
9. Kremer LC, van der Pal HJ, Offringa M, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: A systematic review. *Ann Oncol* 2002;13:819-829.
10. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol* 2005;23:2629-2636.
11. Sorensen K, Levitt GA, Bull C, et al. Late anthracycline cardiotoxicity after childhood cancer: A prospective longitudinal study. *Cancer* 2003;97:1991-1998.
12. Poutanen T, Tikanoja T, Riikonen P, et al. Long-term prospective follow-up study of cardiac function after cardiotoxic therapy for malignancy in children. *J Clin Oncol* 2003;21:2349-2356.
13. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol* 2004;22:820-828.
14. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. *J Clin Oncol* 2002;20:4517-4522.
15. van Dalen EC, van der Pal HJ, van den Bos C, et al. Treatment for asymptomatic anthracycline-induced cardiac dysfunction in childhood cancer survivors: The need for evidence. *J Clin Oncol* 2003;21:3377; author reply 3377-3378.
16. Scottish Intercollegiate Guidelines Network (SIGN). Long-term follow up care of survivors of childhood cancer. 2004: Guideline no. 76: Available at: www.sign.ac.uk/pdf/sign76.pdf.
17. Skinner R, Wallace WH, Levitt G, et al. Therapy based long term follow up: A practice statement (second edition). United Kingdom Children's Cancer Study Group, Late Effects Group. 2005: Available at: www.ukccsg.org.
18. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers, version 3.0. Arcadia, CA. October 2006: Available on-line: www.survivorshipguidelines.org.
19. Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: Report from the cardiovascular disease task force of the children's oncology group. *Pediatrics* 2008;121:e387-396.

20. Landier W, Wallace WH, Hudson MM. Long-term follow-up of pediatric cancer survivors: Education, surveillance, and screening. *Pediatr Blood Cancer* 2006;46:149-158.
21. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: The children's oncology group long-term follow-up guidelines from the children's oncology group late effects committee and nursing discipline. *J Clin Oncol* 2004;22:4979-4990.
22. Yeung ST, Yoong C, Spink J, et al. Functional myocardial impairment in children treated with anthracyclines for cancer. *Lancet* 1991;337:816-818.
23. Weesner KM, Bledsoe M, Chauvenet A, et al. Exercise echocardiography in the detection of anthracycline cardiotoxicity. *Cancer* 1991;68:435-438.
24. Lang D, Hilger F, Binswanger J, et al. Late effects of anthracycline therapy in childhood in relation to the function of the heart at rest and under physical stress. *Eur J Pediatr* 1995;154:340-345.
25. Hauser M, Gibson BS, Wilson N. Diagnosis of anthracycline-induced late cardiomyopathy by exercise-spiroergometry and stress-echocardiography. *Eur J Pediatr* 2001;160:607-610.
26. De Souza AM, Potts JE, Potts MT, et al. A stress echocardiography study of cardiac function during progressive exercise in pediatric oncology patients treated with anthracyclines. *Pediatr Blood Cancer* 2007;49:56-64.
27. Jarfelt M, Kujacic V, Holmgren D, et al. Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2007;49:835-840.
28. Guimaraes-Filho F, Tan D, Braga J, et al. Ventricular systolic reserve in asymptomatic children previously treated with low doses of anthracyclines. *Am J Cardiol* 2007;100:1303-1306.
29. Smibert E, Carlin JB, Vidmar S, et al. Exercise echocardiography reflects cumulative anthracycline exposure during childhood. *Pediatr Blood Cancer* 2004;42:556-562.
30. Sahn DJ, Demaria A, Kisslo J, et al. Recommendations regarding quantitation in m-mode echocardiography - results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-1083.
31. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol* 2005;99:445-457.
32. Colan SD, Parness IA, Spevak PJ, et al. Developmental modulation of myocardial mechanics: Age- and growth-related alterations in afterload and contractility. *J Am Coll Cardiol* 1992;19:619-629.
33. Klewer SE, Goldberg SJ, Donnerstein RL, et al. Dobutamine stress echocardiography: A sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. *J Am Coll Cardiol* 1992;19:394-401.
34. De Wolf D, Suys B, Verhaaren H, et al. Low-dose dobutamine stress echocardiography in children and young adults. *Am J Cardiol* 1998;81:895-901.
35. Cottin Y, L'Huillier I, Casasnovas O, et al. Dobutamine stress echocardiography identifies anthracycline cardiotoxicity. *Eur J Echocardiogr* 2000;1:180-183.
36. Lanzarini L, Bossi G, Laudisa ML, et al. Lack of clinically significant cardiac dysfunction during intermediate dobutamine doses in long-term childhood cancer survivors exposed to anthracyclines. *Am Heart J* 2000;140:315-323.
37. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. *Semin Oncol* 1998;25:72-85.

38. Hudson MM, Rai SN, Nunez C, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. *J Clin Oncol* 2007;25:3635-3643.
39. Colan SD. Assesment of ventricular and myocardial performance. In: Fyler DC. *Nadas' pediatric cardiology*. Philadelphia: Hanley and Belfus; 1992. p 225-248.
40. Wang TJ, Evans JC, Benjamin EJ, et al. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;108:977-982.
41. Devereux RB, Roman MJ, Palmieri V, et al. Prognostic implications of ejection fraction from linear echocardiographic dimensions: The strong heart study. *Am Heart J* 2003;146:527-534.