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Endothelial Health in Childhood Acute Lymphoid Leukemia Survivors: Pilot Evaluation with Peripheral Artery Tonometry

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Abstract

Background—Childhood cancer survivors are a growing population at risk for poor cardiac outcomes. Acute lymphoid leukemia (ALL) survivors are among those at increased risk of cardiovascular complications. Early identification of impaired vascular health may allow for interventions to improve these outcomes. The purpose of this study is to evaluate vascular health using peripheral artery tonometry in ALL survivors and compare results to healthy siblings.

Procedure—Sixteen ALL survivor, healthy sibling pairs, ages 8-20, were evaluated for vascular health and cardiovascular risk factors (body mass index, central adiposity, blood pressure and fitness). One tailed paired T-test was used to compare the groups.

Results—Survivors were similar to siblings in cardiovascular risk measures but had poorer vascular health as measured by reactive hyperemia index (survivor RHI 1.54 vs sibling 1.77, p=0.0474).

Conclusion—This study reveals that even among survivors who are comparable to their healthy siblings in other traditional cardiovascular risks there is evidence of poorer vascular health.

Introduction

Improved cure rates for childhood cancer has led to a growing population of survivors who are at risk for long-term complications from their disease and treatment including high risk for accelerated atherosclerosis [1]. According to the Childhood Cancer Survivor Study, a landmark cohort study, childhood cancer survivors have more than 8 times increased mortality risk (Standardized Mortality Ratio [SMR]= 8.4; 95% CI 8.0 – 8.7) than the US general population of the same age, year and sex due, in large part, to pulmonary and cardiac complications [2].

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Leukemia is the most frequently diagnosed childhood cancer and acute lymphoid leukemia (ALL) is the most common form. Improved treatments have lead to an impressive five-year survival for childhood ALL of 88.5% [3] yet these survivors have a 4.2 SMR (95% CI 2.3-6.9) due to cardiac causes[2]. Treatment with cardio toxic chemotherapy and radiation in addition to the development of cardiovascular disease (CVD) risk factors after treatment are known to impact cardiac outcomes for cancer survivors[4-9].

Vascular endothelium plays a key role in the regulation of vascular health and based on findings in otherwise healthy children it is believed that impaired endothelial function in childhood may be the initial step in the pathogenesis of atherosclerosis[10-12]. The release of nitric oxide (NO) from the endothelium is a key factor in maintaining healthy vascular homeostatsis and measurement of NO response has become an important predictor of cardiovascular health[13-15] . Flow mediated dilatation (FMD) is used to assess endothelial health via NO release and subsequent dilation in response to shear stress caused by occlusion of blood flow. The response of blood vessels to this transient ischemia and the resulting reactive hyperemia state was first described by Celermajer et al (1992) as a method of identifying atherosclerosis risk in adults and children[16]. Initially FMD assessment required ultrasound measurement of intima-media thickness (IMT) at rest and during reactive hyperemia, this technique is highly operator dependent and technically challenging[17]. More recent developments in technology include the assessment of reactive hyperemic response via peripheral artery tonometry (PAT). PAT uses automated measurement of reactive hyperemic index with fingertip plethysmography and has been validated by correlation with brachial artery ultrasound [18] and conventional cardiovascular risk factors[19]. Pediatric studies including diabetic and healthy populations have shown PAT technology to be useful in evaluating endothelial health in younger populations[20,21]

To date research has focused predominantly on identifying risk factors associated with cardiovascular disease or changes in vascular health in adult survivors of childhood cancer. Recognition of early changes in vascular function in child cancer survivors may allow healthcare providers to identify and intervene earlier in children most at risk for poor cardiac outcomes. This study examines the vascular health of childhood ALL survivors earlier (while still in childhood) than previously reported in the literature and utilizes a sibling comparison group to control for potential environmental and genetic contributors to vascular health. The primary aim of this pilot study was to evaluate endothelial function using peripheral artery tonometry in childhood ALL survivors and compare them to healthy sibling controls.

Materials and Methods

A convenience sample of ALL survivors and healthy siblings (control group) were recruited from an established survivorship program via flyers mailed or distributed to parents during routine follow-up visits. Inclusion for survivors included age 8-20 years, and at least 1 year and not more than 10 years off therapy. The lower age was chosen due to availability of valid measures and upper age to include National Institutes of Health definition of child as persons under the age of 21. One year off therapy was chosen to allow for recovery from acute toxicity and not more than 10 years was chosen to limit the co-morbid conditions not

related to cancer diagnosis and treatment. Exclusions included history of bone marrow transplantation or inability to ambulate. Control group inclusion included full or half biological siblings, living in the same household, with no uncontrolled medical conditions, ages 8-20 years and able to ambulate. If more than one sibling met the inclusion criteria the closest in age to the ALL survivor was chosen. Sixteen survivor/sibling pairs were enrolled over an 18 month period. IRB approval was obtained for the study and all participants signed informed consent.

All participants underwent anthropometric measures which were chosen based on cardiovascular risk potential including body mass index (BMI), blood pressure and waist to height ratio (marker of central adiposity). Survivor medical characteristics such as history of cranial radiation and anthracycline exposure were gathered from the medical records. Height to the nearest 0.1cm measured with a stadiometer, weight to the nearest 0.1 kg on a calibrated digital scale and waist circumference to the nearest 0.1cm with a tape measure at the top of the iliac crest. Anthropometric values were used to obtain BMI percentile for age and sex matched data from the Center for Disease Control and to calculate waist to height ratio (WHR). Blood pressure was measured 3 times at 2 minute intervals in the right arm after 5 minutes of quiet sitting using a Dinamap automated sphygmomanometer. A mean systolic and diastolic reading was calculated from the 3 readings. Mean blood pressures were compared to age and height matched data from the National Heart, Lung and Blood Institute to calculate the systolic and diastolic percentile.

The Six Minute Walk Test (SMWT) was used to assess physical fitness on all subjects. In childhood populations the concurrent validity of the SMWT has been determined by correlation with maximum oxygen uptake measured during treadmill testing and reliability with test/retest intraclass correlation coefficient 0.94 (95% CI 0.89-0.96)[22]. Subjects were asked to walk as many times as possible in six minutes, between two cones placed 20 meters apart, they were instructed to walk as quickly as comfortable without jogging or running. The results of the SMWT were recorded as the number of feet covered.

Endothelial function was measured with non-invasive technology using peripheral artery tonometry (PAT). The PAT device captures a beat-to-beat plethysmographic recording of the finger arterial pulse wave amplitude with pneumatic probes. The ENDOPAT 2000 (Itamar Medical, Caesarea, Israel) is a PAT device that has been used to measure vascular health in children and adolescents including healthy, sickle cell anemia, obese and diabetic populations[21,23-27]. Endothelial health was measured with the PAT on all subjects in the morning after overnight fasting per manufacturer recommendation. One finger probe is placed on the index finger of the hand which undergoes five minutes of ischemia, induced by a blood pressure cuff which is inflated to suprasystolic levels. A second probe is placed on the contralateral index finger. A hyperemic condition is created upon release of the blood pressure cuff. Patients must lie quietly during the testing which takes approximately 15 minutes to complete. A PAT hyperemia ratio is defined as the ratio of the average pulse wave amplitude during the 1-minute period beginning after 60 seconds of hyperemia compared with the average pulse wave amplitude during a 210-second preocclusion baseline period. This ratio us normalized to the concurrent signal form the contralateral, nonischemic hand and reported as a reactive hyperemia index (RHI), lower RHI indicates poorer

endothelial function[18,28,29]. The PAT was successful on most participants and was well tolerated. Results from the PAT were not valid on one survivor, who was 8 years old, due to the inability to lie quietly.

Initially descriptive statistics were used to summarize participant characteristics. Paired t-test was used to compare RHI between survivors/siblings and anthropometric variables (BP, BMI percentiles, WHR) and SMWT. A p value <0.05 was used to determine statistical significance. STATA 10.0 software was used to conduct the analysis.

Results

Participant characteristics are presented in Table I. Survivor/sibling pairs were primarily Caucasian (13/16, 81%) and one pair each African American, Asian and Hispanic. There were no statistical differences between survivors and siblings for gender, age, SMWT, anthropometric measures or blood pressure on paired t tests. Using BMI percentile cut offs of ≥ 85, 44% (7/16) of the survivor group were considered overweight or obese compared to 31% (5/16) of the sibling group. Using WH ratio of > 0.50 as a threshold, 31% (5/16) of the survivor group and 25% (4/16) of the sibling group had central adiposity. All but one survivor had treatment with anthracyclines with a mean cumulative dose of 148 mg/m^2 (sd 85mg/m^2) and nearly one third had cranial radiation. The mean (sd) RHI and the p-value for the paired t-test comparing survivors and siblings are presented in Table II. The spaghetti plot, Figure 1, of each survivor/sibling pair illustrates that only 3/15 (20%) of survivors had higher RHI than their healthy sibling.

Discussion

To the best of our knowledge this is the first study to use PAT technology to evaluate vascular health in child and adolescent ALL survivors. While cardiovascular implications of cancer chemotherapy during childhood have recently been identified in the literature, available research on impaired vascular function among childhood ALL survivors has primarily focused on adult survivors of childhood cancer [30-33]. In addition, the use of PAT has only been reported in one study, to evaluate vascular health in survivors and found childhood Hodgkin lymphoma survivors who received mediastinal radiation had significantly lower RHI scores than those without radiation (RHI 1.67 vs. 2.03, p <0.01)[34]. We found that our ALL survivors shared similar cardiovascular health parameters with their healthy siblings in terms of BMI, blood pressure, WH ratio and the marker of fitness (SMWT), although more survivors than siblings were considered overweight or obese (44% vs. 31%). Despite the similarities with their siblings, survivors had statistically significant lower RHI which is indicative of poorer endothelial health. This finding suggests a possible mechanism other that commonly identified cardiovascular risks may be implicated in survivors. To minimize participant burden we did not measure lipid profiles in the study sample. Previous researchers have suggested that abnormal lipid profiles, especially triglycerides, contribute to endothelial dysfunction, which was further hypothesized for adult survivors of childhood ALL (Dengel et al., 2008) and might have helped explain the differences in RHI for survivors and siblings.

Due to the homogeneity of anthracycline treatment we were not able to analyze possible associations of this known cardio toxic drug and endothelial function. Two previous studies have suggested that childhood cancer survivors treated with anthracyclines have impaired endothelial function[33,35]. Our study makes two unique contributions to the evidence of impaired endothelial function, first the use of healthy sibling controls which, unlike other potential comparison groups, helps control for confounding environmental and genetic factors. Second our study demonstrates the utility of PAT for evaluation endothelial function in survivors. PAT has been validated with brachial artery ultrasound with significant correlation ($r=0.55$, $P < 0.0001$) between RHI and flow mediated dilatation, but unlike other non-invasive methods for assessing endothelial health, PAT does not require extensive training and is not highly operator dependent [18]. The successful use of PAT could be valuable in both the research and clinical setting for identifying risk factors and monitoring response to interventions.

In conclusion, the growing number of childhood cancer survivors at risk for poor cardiac outcomes is a challenge to healthcare providers. The ability to identify survivors at greatest risk for cardiovascular disease would allow us to provide aggressive management of risk factors and appropriate lifestyle interventions, ultimately improving the cardiac mortality seen in this population. Our study reveals that even among survivors who are comparable to their healthy siblings in other traditional cardiovascular risks there is evidence of poorer endothelial function. Interventions aimed at improving cardiovascular health in childhood cancer survivors should consider adding the assessment of endothelial function to their outcomes as similar measures have noted improvement of endothelial health after treatment of obstructive apnea [36]. Longitudinal studies will also help us determine the course of vascular health in this population and better identify associations and etiologies.

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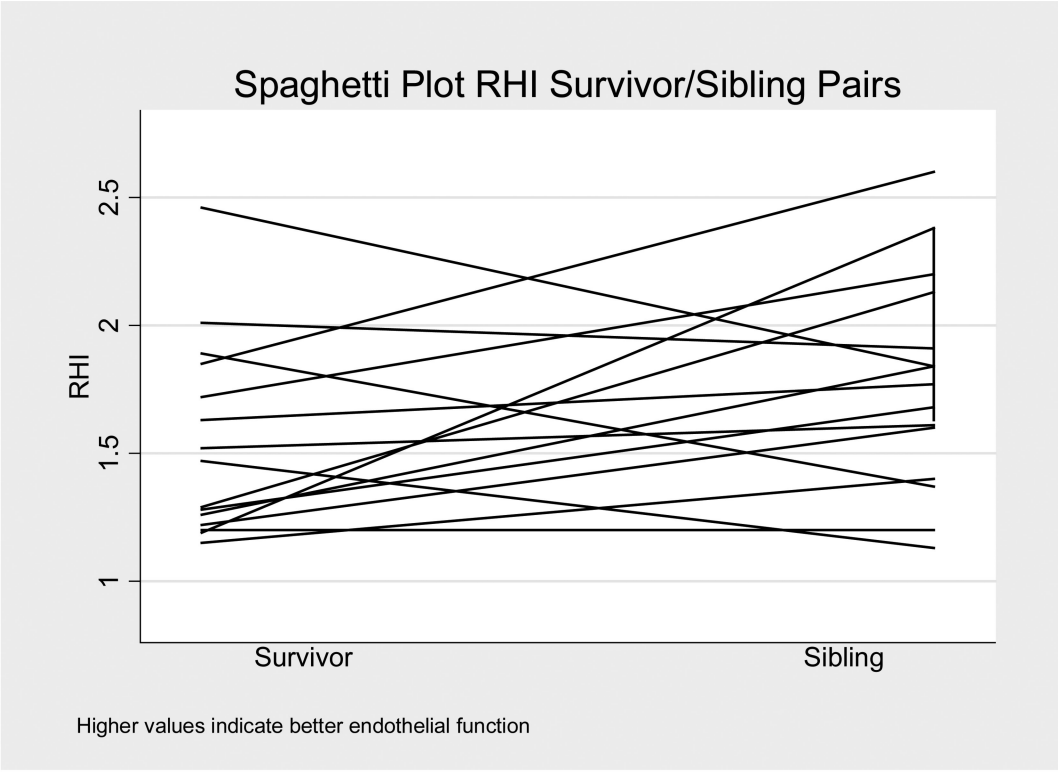

RHI- reactive hyperemia index

FIGURE 1.
Spaghetti plot RHI survivor/sibling pairs. RHI indicates reactive hyperemia index.

Table I

Participant Characteristics (N=32)

Characteristics	Survivor (n=16)	Sibling (n=16)
Male (%)	50%	38%
Age in years (mean/sd)	12.9/0.9	13.8 /0.9
Waist Height Ratio in cm(mean/sd)	0.49/0.02	0.46/0.01
BMI percentile (mean/sd)	68.1/7.1	63.3/7.2
Diastolic percentile (mean/sd)	54.0/5.5	54.4/6.1
Systolic percentile (mean/sd)	41.1/6.4	54.5/6.5
SMWT in feet (mean/sd)	1825/222	1947/265
Anthracycline treated (%)	94%	N/A
Cumulative anthracycline dose mg/m2 (mean/sd)	148/85	N/A
Years out from therapy (mean/sd)	3.6/2.3	N/A
Cranial radiation (%)	31%	N/A

BMI-Body Mass Index

SMWT-Six Minute Walk Test

Table II

One tailed paired T test for differences in RHI between Survivors and Siblings

RHI	Survivor (n=15)	Sibling(n=15)	p-value
RHI			
Mean(SD)	1.54 (0.38)	1.77 (0.41)	0.0474

RHI- reactive hyperemia index