# Using tissue Doppler imaging during exercise to assess ventricular function and wall motion in childhood survivors of acute lymphoblastic leukemia

by

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## ABSTRACT

**BACKGROUND:** Childhood survivors of Acute Lymphoblastic Leukemia (ALL) may be at risk of cardiotoxicity as a consequence of their treatment with anthracyclines. Stress echocardiography has been well established as a method to detect latent cardiac dysfunction, indicative of cardiotoxicity. Tissue Doppler Imaging (TDI) is a new echocardiographic technique that can be incorporated into current stress echocardiography protocols to potentially enhance our ability to detect early changes in cardiac function in ALL patients treated with anthracyclines. **PURPOSE:** To determine if ALL patients have abnormal wall motion responses to exercise. **METHODS:** Thirteen ALL patients (11 yrs; 9-14 yrs) and fourteen healthy children (10.5 yrs; 9-16 yrs) were studied. ALL patients were treated with a median cumulative anthracycline dose of 150 $mg/m^2$ (150-175 $mg/m^2$). TDI was performed during semi-supine cycle ergometry at rest, peak exercise, immediately post- and 3 minutes post-exercise. The parasternal long axis (posterior wall=POS) and apical 4-chamber (lateral wall=LAT, interventricular septum=SEP, and right ventricular wall=RV) views were used to obtain measurements. Tissue velocities (S', E', A'), strain ($\varepsilon_{sys}$), and tissue tracking (TT) were measured. TDI analyses were performed off-line. Oxygen capacity ($VO_2$) was measured concurrently. A Wilcoxon-Rank Sum test was used to determine whether there were differences between ALL patients and controls and between each stage. Data was analyzed using SPSS 12.0 Statistical Software (SPSS Inc., Chicago, IL). **RESULTS:** No significant differences were found between ALL patients and controls at rest, peak, immediately post-, and 3 minutes post-exercise for all TDI variables. S' and A' significantly increased in all walls, in both groups. E' significantly increased in the POS and RV, but not in the LAT and SEP. Strain did not increase with exercise in any of the segments evaluated. A significant increase in TT was only seen in the POS wall of the controls (p≤0.003);

however, values were approaching statistical significance in the POS of ALL patients (p=0.004). Peak $VO_2$ was similar between groups. **CONCLUSIONS:** I have shown that TDI variables and $VO_2$ peak are similar in ALL patients and controls. Further studies are needed to determine the clinical usefulness of TDI during stress echocardiography.

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# LIST OF ABBREVIATIONS

3' Post= Three minutes post-exercise

A=Velocity of blood flow during late filling or atrial contraction

A'=Late diastolic velocity obtained from the tissue velocity profile

ALL=Acute Lymphoblastic Leukemia

E=Velocity of blood flow during rapid early diastolic filling

E'=Early diastolic velocity obtained from the tissue velocity profile

$\varepsilon_{sys}$=Systolic strain representing myocardial deformation

ECG=Electrocardiogram

ESS=End-systolic wall stress

HR=Heart rate

Imm Post=Immediately post-exercise

LAT=Lateral wall, obtained from the apical 4-chamber view

LV=Left ventricle

LVED=Left ventricular end-diastolic dimension

LVES=Left ventricular end-systolic dimension

MVCFc=Rate-corrected mean velocity of circumferential fiber shortening

NS=Not statistically significant

POS=Left ventricular posterior wall, obtained from the parasternal long axis view

RER=Respiratory exchange ratio

RV=Right ventricular wall, obtained from the apical 4-chamber view

S'=Systolic velocity obtained from the tissue velocity profile

SEP=Interventricular septal wall, obtained from the apical 4-chamber view

SF=Shortening fraction

TDI=Tissue Doppler Imaging

TT=Tissue tracking, a measure of longitudinal systolic displacement

$V_E$=Minute ventilation

$VO_{2max}$=Maximum volume of oxygen consumed during exercise

$VO_{2peak}$=Volume of oxygen consumed at peak exercise

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed cancer among children, accounting for almost 20% of all new cancer diagnoses.[1] ALL is a cancer of the white blood cells which is characterized by an increased number of lymphoblasts (immature B and T cells) in the circulating blood. These lymphoblasts do not develop into functioning lymphocytes and thus cannot help the body fight infections. ALL tends to affect those under 20 years of age, and is primarily diagnosed between the ages of 2 to 5 years.[2,3] The survival rate for children and adolescents diagnosed with ALL has remarkably improved from almost always fatal before the mid 1960's to 80% in the late 1990's.[4] This dramatic improvement in survival has been partly attributed to the use of anthracyclines as chemotherapeutic agents.

Anthracyclines are a class of cytotoxic antibiotics that are highly effective against hematological and solid malignancies, and are considered the first-line agents in the management of various tumors.[5] Generally, anthracyclines are composed of a tetracycline ring with an attached sugar moiety. Their mechanism of action is to intercalate with certain DNA base-pairs in the cell nucleus to prevent RNA and DNA transcription and to inhibit protein synthesis, thus causing cell death.[6] Furthermore, the quinone and hydroquinone moieties on adjacent rings allow the anthracyclines to function as electron-accepting and electron-donating agents.[5] The conversion of the hydroquinone to a quinone form results in the production of free oxygen and hydroxyl radicals causing biochemical lesions such as DNA denaturation and mitochondrial peroxidation.[6] More specifically, anthracyclines inhibit topoisomerase II, an enzyme which is critical to DNA function.[6]

Free radicals, generated from the enzymatic conversion of the hydroquinone to quinone form, may also damage the myocardium as cardiac tissue contains lower levels of protective intracellular enzymes.[7] Various cellular changes have been noted as a result of anthracycline-induced cardiotoxicity. Ultrastructural studies in patients treated with anthracyclines have revealed that both single myocytes or clusters of myocytes may be affected as a result of treatment.[8] Two main types of myocyte injury occur: (1) myofibrillar loss within individual myocytes; and (2) vacuolar degeneration and coalescence of the swollen sarcotubular system.[8] Possible hypotheses for anthracycline-induced cardiotoxicity include: (1) vulnerability of sulfhydryl groups to anthracycline-catalyzed free-radical-mediated oxidation;[9] (2) accumulation of anthracyclines and metabolites within the heart, causing cellular toxicity;[10] (3) myocyte damage from calcium overload and disturbances in adrenergic function;[11,12] and (4) interference with normal cardiac growth.[13] These features tend to limit the therapeutic potential of anthracyclines.[14,15]

Among the most notable effects of cardiotoxicity are arrhythmias, cardiomyopathy, and congestive heart failure.[5] Cardiac abnormalities may present more than 1 year after cessation of chemotherapy and are indicative of late cardiotoxicity.[16,17] Increased risk of late cardiotoxic side effects has been reported in ALL survivors treated with high cumulative anthracycline doses.[17] Current treatment protocols have incorporated lower cumulative doses to try to reduce cardiovascular risk; however, functional cardiac abnormalities have still been reported in survivors treated with low doses.[18] This suggests that there may be no safe dose at which patients are immune from some degree of anthracycline-induced cardiotoxicity. Although most late anthracycline-induced cardiotoxicity is sub-clinical and does not warrant immediate treatment,

dysfunction may be progressive leading to potentially severe and fatal complications.[19] Thus, the need for sensitive monitoring methods for detecting and predicting long-term complications is imperative as it could facilitate earlier therapeutic strategies and may decrease the severity of symptoms in pediatric ALL survivors.[20] A comprehensive literature review of echocardiographic monitoring methods can be found in Appendix I.

The use of stress echocardiography has widely been suggested as a method for detecting sub-clinical cardiac dysfunction in pediatric cancer survivors who often appear clinically normal in resting conditions, but experience subtle cardiac abnormalities with exercise.[17,21-24] Tissue Doppler Imaging (TDI) is a relatively new echocardiographic technique that can be incorporated into standard stress echocardiography protocols to quantify global and regional ventricular function.[25] As opposed to the high velocity, low amplitude signals interrogated when measuring Doppler blood flow, low velocity and high amplitude signals of the myocardium are analyzed using TDI.[26] More specifically, TDI can be used to measure the velocity of various myocardial segments and other cardiac structures.[27] Tissue velocities can be measured during systole (S'), early diastole (E'), and late diastole (A'). Additional parameters including systolic strain ($\varepsilon_{sys}$) and tissue tracking (TT) can also be derived from TDI and used to further evaluate myocardial function. Strain is a parameter of regional myocardial function[28] and is defined as a dimensionless quantity that represents the percentage change in dimension from a resting state to one achieved following application of stress.[29] Although, strain is a load-dependent measure[30,31] and, therefore, not a perfect measure of contractility, it is less influenced by cardiac translation and motion due to tethering.[29] TT allows for the rapid assessment of systolic longitudinal displacement.[32] TDI may increase the sensitivity of stress echocardiography by revealing subtle changes in

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myocardial contractile function that may be indicative of myocardial damage.[27] This may facilitate the decision for cardiac treatment and possibly improve survival rates in cancer survivors.[16,33]

Semi-supine cycle ergometry stress echocardiography is a method that allows for echocardiography to be performed during exercise. This method can be used in conjunction with cardiopulmonary exercise testing to evaluate the integration of the cardiovascular, pulmonary, and skeletal muscle systems. Peak oxygen uptake ($VO_{2peak}$) is assessed during cardiopulmonary exercise testing and is an indicator of health status and a powerful predictor of mortality in both healthy and diseased individuals.[34,35] The response of tissue Doppler variables to exercise has not been documented in pediatric ALL survivors and may become an important tool for detecting sub-clinical myocardial impairment. The purpose of this study is to compare tissue Doppler indices of cardiac function and $VO_{2peak}$ in pediatric ALL survivors, treated with moderate doses of anthracyclines, and healthy children.

**Hypotheses**

(1) *Resting Hypothesis – Tissue Doppler indices*

$H_0$: At rest, there will be no difference in tissue velocities (S', E', A'), strain ($\varepsilon_{sys}$), and tissue tracking (TT) between ALL patients and healthy controls;

$H_1$: At rest, tissue velocities (S', E', A'), strain ($\varepsilon_{sys}$), and tissue tracking (TT) will be reduced by 15% in ALL patients.

(2) *Peak Exercise Hypothesis – Tissue Doppler indices*

$H_0$: At peak exercise, there will be no difference in tissue velocities (S', E', A'), strain ($\varepsilon_{sys}$), and tissue tracking (TT) between ALL patients and healthy controls;

$H_1$: At peak exercise, tissue velocities (S', E', A'), strain ($\varepsilon_{sys}$), and tissue tracking (TT) will be reduced by 25% in ALL patients.

(3) *Peak Exercise Hypothesis – VO$_{2peak}$*

$H_0$: At peak exercise, there will be no difference in $VO_{2peak}$ between ALL patients and healthy controls;

$H_1$: At peak exercise, $VO_{2peak}$ will be reduced by 25% in ALL patients.

**METHODS**

**Subjects**

A total of 13 ALL patients (7 males; 6 females), between the ages of 9 to 14 years, were recruited from a cohort of children previously diagnosed with ALL and followed regularly by the Pediatric Oncology Clinic at B.C. Children's Hospital. Twelve of the thirteen patients had been treated with a cumulative adriamycin dose of 150 mg/m$^2$, while the remaining patient received 175 mg/m$^2$ of adriamycin and daunamycin. These patients also received dexamethasone, prednisone, L-asparginase, vincristine, cyclophosphamide, cytosine arabinoside, 6-thioguanine, 6-mecaptopurine, and methotrexate as a part of their chemotherapy. Patients had completed their therapy 3 to 6 years prior, with no recurrent cancer, and had no chest radiation or undergone bone marrow transplantation. At the time of their last follow-up visit, these children all had normal cardiac anatomy and function when assessed by standard resting echocardiography. Standard echocardiographic parameters included: left ventricular

dimensions, shortening fraction, left ventricular posterior wall thickness, rate-corrected mean velocity of circumferential fiber shortening and wall stress. Fourteen healthy children (8 males; 6 females) were recruited from siblings and friends of the ALL patients and children or relatives of hospital employees. Six of thirteen (46%) ALL patients and six of fourteen (43%) controls participated in community recreational sports teams, but none were involved in regular aerobic training. Children with a history of congenital heart disease or respiratory disease were excluded from this study.

Informed consent was obtained from all subjects prior to participating in the study. Ethics approval was obtained from the University of British Columbia's Clinical Research Ethics Board and Children's and Women's Health Centre of British Columbia's Research Review Committee.

**Methods of Cardiac Evaluation**

Prior to stress echocardiography, a cardiac examination was performed by a pediatric cardiologist. Height and weight were taken, and a resting 12-lead electrocardiogram (ECG) was done (Case 8000 Stress System, GE Medical Systems, Milwaukee, WI).

*Stress Echocardiography*

All echocardiograms were obtained by the same echocardiographer, who was a registered diagnostic cardiac sonographer with more than 25 years of pediatric experience. The echocardiographer had specific training in stress echocardiography and TDI, and performed the stress echocardiogram using a commercially available cardiac ultrasound machine (System 7™, GE Vingmed Ultrasound, Horten, Norway). The frequency of the transducer used was dependent upon the size of the subject (M3S

or 5S, GE Vingmed Ultrasound, Horten, Norway). Exercise testing was performed on an Echo Cardiac Stress Table (Lode BV, Groningen, The Netherlands) with an electronically-braked cycle ergometer (Angio Ergometer, Lode BV, Groningen, The Netherlands). With the subject placed in a semi-supine position, the trunk was elevated to a 45° angle, with the heart being approximately 15 cm above the level of the crank axis of the ergometer. Echocardiographic images were taken at rest, 2 minutes into each stage of exercise, immediately post-exercise (Imm Post), and 3-minutes post-exercise (3' Post). Simultaneous blood pressure measurements were also taken. Systolic and diastolic cuff blood pressures were obtained in the right arm by auscultation. Diastolic pressure was defined by muffling (Phase V) of the Korotkoff sounds. Depending on the size of the subject, workloads were increased every three minutes by 20 or 30 Watts, until volitional fatigue was reached or the subject was unable to sustain a cadence of 60 rpm. The ECG was monitored continuously.

Total work was calculated using the following formula:

Total Work $(J \cdot kg^{-1})$ = $(Time_1 \times Work_1)/Weight + (Time_2 \times Work_2)/Weight + (Time_3 \times Work_3)/Weight + ...$

$\qquad$ Where $Time_1$ = Time at stage 1 (in sec)

$\qquad\qquad$ $Work_1$ = Work at stage (in Watts)

### Tissue Doppler Imaging

Images were digitized during consecutive cardiac cycles in cine-loop format for off-line analysis. Longitudinal and radial function was assessed using apical four-chamber and parasternal long axis views, respectively. From the apical view, images were taken from the lateral (LAT), septal (SEP), and right ventricular (RV) walls. Using the Vivid 7's tilt

function, care was taken to align the TDI sample volume along these walls to ensure that the ultrasound beam was parallel to the longitudinal direction of the wall motion. The parasternal long axis view was used to obtain images of the left ventricular posterior wall (POS). The TDI and the 2D images were coned down to achieve high frame rates (minimum 150 frames per second).

Tissue Doppler variables were measured during off-line analysis using proprietary software (Echopac™ 6.2; GE Medical Systems, Milwaukee, WI). Tissue velocities were measured during systole (S'), early diastole (E'), and late diastole (A'). Tissue tracking (TT) and strain ($\varepsilon_{sys}$) were measured during systole. Tissue velocities and TT were obtained from the basal segments of the walls, as previous studies have shown that the maximum velocity of displacement is at the base of the myocardium.[36] Strain was measured in the basal segment of the RV, but because systolic $\varepsilon$ is homogenous in the SEP and LAT walls, measurements in these walls were taken in the segment that was aligned nearest to the ultrasound beam to minimize angle-dependent measurement errors.[37] A positive strain indicated the lengthening or stretching of the wall, while a negative strain indicated shortening or compression. Each parameter was measured once. Examples of tissue velocity, strain, and tissue tracking tracings can be seen in Figures 1-3.

*Figure 1-Tissue velocity tracing taken from the basal segment of the lateral wall of the left ventricle. S' represents the velocity during systole, while E' and A' represents the velocities during early and late diastole, respectively.*
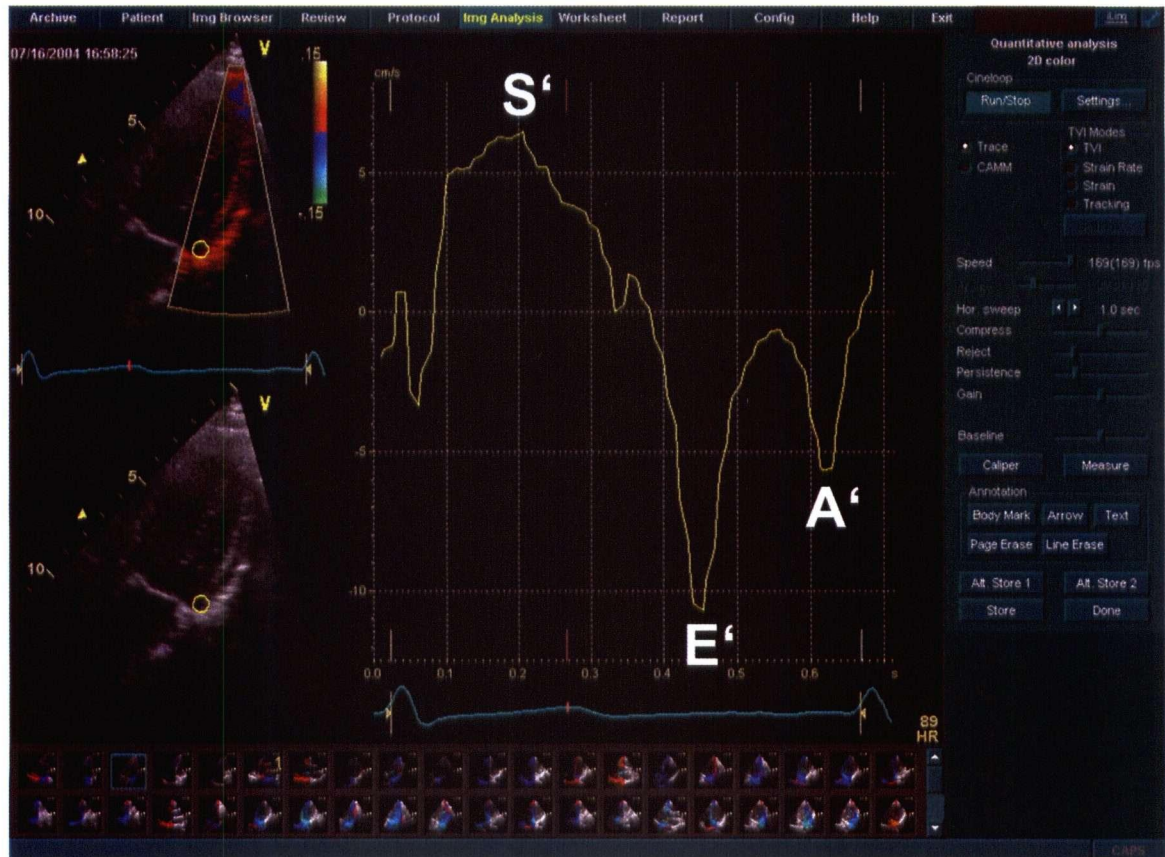
*Figure 2 – An example of a longitudinal strain ($\varepsilon_{sys}$) tracing taken from the lateral wall of the left ventricle.*
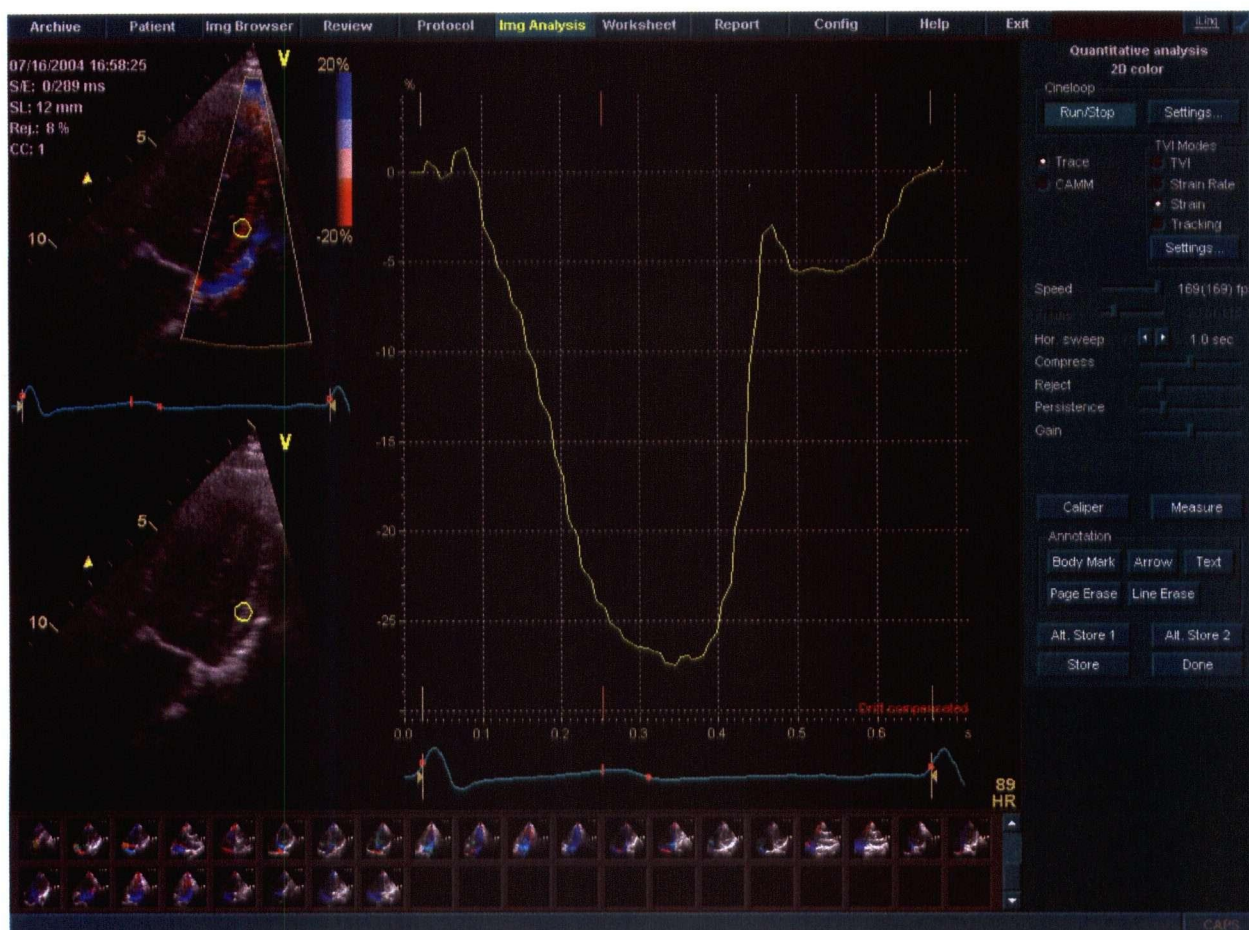
*Figure 3 - An example of a tissue tracking (TT) tracing taken from the basal segment of the lateral wall of the left ventricle.*
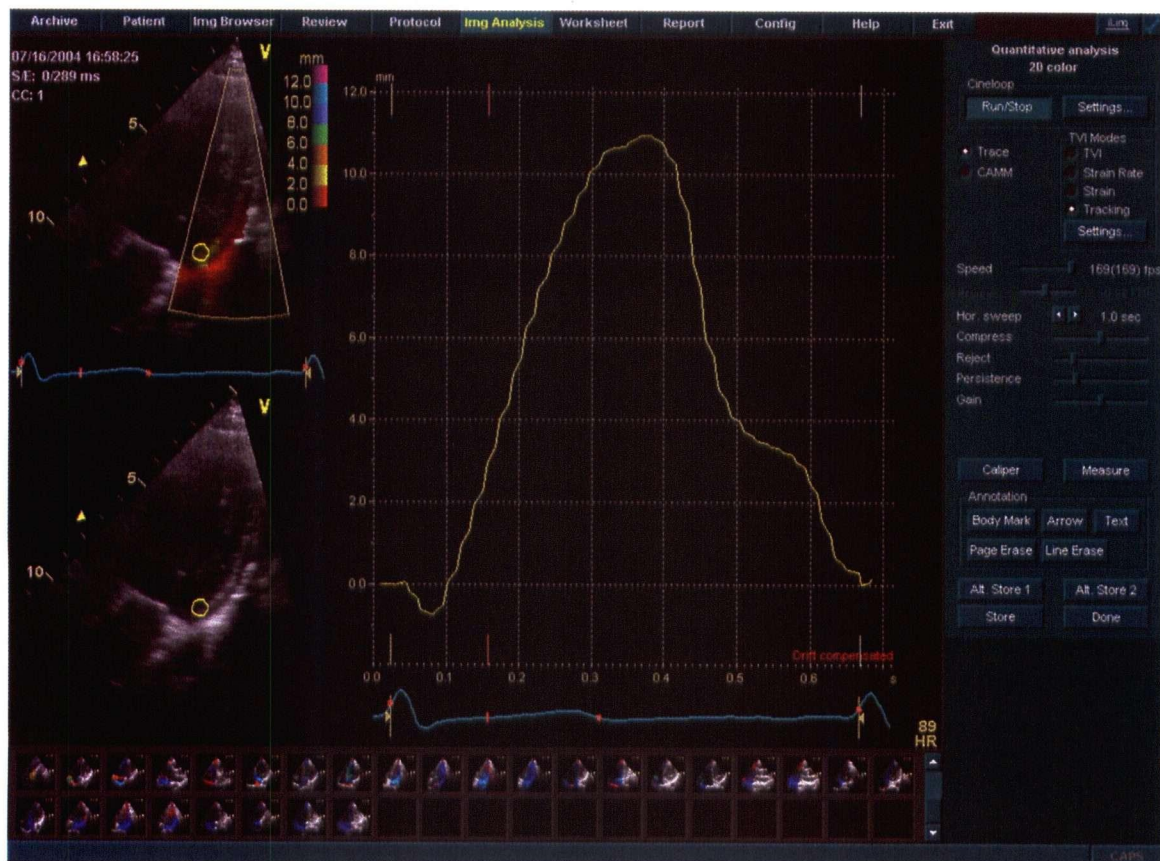


### Cardiopulmonary Exercise Testing

Open circuit spirometry was used to determine gas exchange variables during exercise and averaged over 15-second intervals. Subjects breathed through a Hans Rudolph valve (Hans Rudolph, Inc., Kansas City, MO). Using a MOXUS Modular $VO_2$ System (AEI Technologies, Inc, Pittsburgh, PA), expired gases were analyzed by oxygen and carbon dioxide analyzers (Model S-3A and CD-3A, respectively, AEI Technologies, Inc., Pittsburgh, PA). The system was calibrated before each test with standard gases of known oxygen (20.93% and 15.00%) and carbon dioxide (0.03% and 5.02%) concentrations   Volume was calibrated and verified using a 3-litre syringe (Hans Rudolph, Inc, Kansas City, MO).

## Daily Physical Activity

Patients and controls were asked to complete a written questionnaire (Appendix II) involving three questions: (1) How many days do you exercise per week?; (2) Approximately, how many hours do you participate in physical activity per week?; and (3) Describe the intensity of the exercise that you do?

## Data Analysis

Univariate analysis was used to analyze all continuous variables. Median values (ranges) are reported. Frequency tables were generated for all categorical data. Due to increased artifact and a high noise-to-signal ratio, data could not always be obtained at peak exercise; therefore, a repeated measures analysis of variance could not be performed. Values were not reported if less than 50% of data could be obtained. A Wilcoxon-Rank Sum test was used to determine whether there were differences in the median values between ALL patients and controls or between stages of the exercise test (ie. rest vs. peak, rest vs. 3' post, etc.) for respective groups. A Bonferroni correction was done to account for multiple comparisons, thus the level of significance was established at $p \leq 0.003$. Data was analyzed using SPSS 12.0 Statistical Software (SPSS Inc., Chicago, IL).

## RESULTS

On physical examination, all subjects had a normal pulse and precordium, normal heart sounds, no significant murmurs, and showed no signs of cardiac failure. Both the resting and exercise ECG was normal in all subjects.

Descriptive data are shown in Table 1. Age, height, weight, and body surface area (BSA) were similar between groups.

*Table 1 - Subject Demographics.*

|  | Patients (n=13) | Controls (n=14) |
|---|---|---|
| Age (years) | 11.0 (9-14) | 10.5 (9-16) |
| Height (cm) | 147.2 (131.4-181.8) | 145.9 (132.5-158.3) |
| Weight (kg) | 42.3 (29.5-66.6) | 41.2 (26.9-57.0) |
| BSA (m²) | 1.28 (1.07-1.83) | 1.30 (1.00-1.57) |
| Cumulative Anthracycline Dose (mg/m²) | 150 (150-175) | — |

*Table 2 – Responses to questionnaire assessing physical activity.*

|  | Patients | Controls |
|---|---|---|
| # of subjects exercising ≥3 times per week | 10/13 | 14/14 |
| # of subjects exercising ≥5 hours per week | 9/13 | 9/14 |
| # of subjects working at a moderate-high intensity | 8/13 | 8/14 |

**Tissue Doppler Imaging**

There were no significant differences in S', E', A', $\varepsilon_{sys}$, and TT between ALL patients and controls at rest, peak exercise, immediately post-exercise or three minutes post-exercise (p>0.003). Similarly, there were no significant differences in peak exercise and immediate post-exercise values between groups for the POS, LAT, SEP, and RV walls.

*Tissue Velocities*

<u>Systolic Velocity (S')</u>

Systolic velocity data is shown in Table 3. The peak and immediate-post exercise S' were significantly higher than resting values in both patients and controls in all 4 walls. At three minutes post-exercise, S' was no different than resting values in the LAT, SEP, and RV walls. S' remained significantly elevated in the POS wall of the controls (p≤0.003) and was approaching statistical significance (p<0.004) in the patients.

*Table 3 – Comparison of systolic velocity (S') measured in cm/s between the two groups for each of the ventricular walls that were measured.*

|  | REST | PEAK | IMM POST | 3' POST |
|---|---|---|---|---|
| **PATIENTS** | | | | |
| **POS** | 4.0 (2.9-4.9) | 6.3* (4.3-9.2) | 6.7* (5.3-9.2) | 5.0 (3.8-6.1) |
| **LAT** | 5.2 (3.3-6.9) | 10.1* (5.7-13.2) | 9.1* (6.0-12.6) | 5.2 (4.1-7.6) |
| **SEP** | 5.7 (4.6-7.5) | 7.9* (6.2-11.8) | 7.8* (5.2-9.7) | 5.7 (3.8-8.2) |
| **RV** | 8.4 (7.2-13.0) | 13.8* (10.4-15.1) | 12.8* (10.4-15.1) | 10.0 (8.5-13.4) |
| **CONTROLS** | | | | |
| **POS** | 3.1 (2.1-5.1) | 7.4* (5.3-9.3) | 6.6* (4.7-9.1) | 4.9* (3.9-7.1) |
| **LAT** | 4.7 (3.6-6.1) | 8.8* (4.9-11.6) | 9.6* (7.0-13.0) | 5.1 (3.8-8.2) |
| **SEP** | 6.2 (4.4-7.2) | 8.7* (6.5-12.6) | 8.5* (6.3-11.3) | 6.7 (4.7-11.2) |
| **RV** | 9.5 (7.2-13.6) | 11.9* (10.1-14.3) | 12.7* (9.5-14.7) | 10.2 (7.7-15.3) |

*$p \leq 0.003$ compared with the value at rest

<u>Early Diastolic Velocity (E')</u>

'Values for early diastolic velocity are shown in Table 4. E' was difficult to obtain in the LAT, SEP, and RV walls at peak exercise due to increased artifact and a high noise-to-signal ratio. Values are not reported because we could only obtain data in less than 50% of the patients and controls. Data acquisition greatly improved immediately post-exercise. There was a significant increase in E' in both the POS and RV walls with

exercise. At three minutes post-exercise, E' was similar to resting values in the POS, LAT, and RV, but remained significantly higher in the SEP wall of the controls.

Table 4 – Comparison of early diastolic velocity (E') measured in cm/s between the two groups for each of the ventricular walls that were measured.

| | REST | PEAK | IMM POST | 3' POST |
|---|---|---|---|---|
| **PATIENTS** | | | | |
| **POS** | -4.3 (-2.5- -7.8) | -9.7* (-6.1- -14.3) | -10.2* (-5.4- -13.9) | -6.2 (-3.3- -8.5) |
| **LAT** | -13.6 (-8.8- -15.3) | ⎯ | -14.3 (-9.7- -15.3) | -13.5 (-8.0- -15.2) |
| **SEP** | -11.5 (-9.8- -15.2) | ⎯ | -14.1 (-10.4- -15.1) | -12.6 (-9.8- -15.2) |
| **RV** | -11.8 (-9.3- -13.6) | ⎯ | -13.7* (-11.7- -15.4) | -12.3 (-9.5- -15.2) |
| **CONTROLS** | | | | |
| **POS** | -4.5 (-3.2- -9.9) | -10.8* (-7.7- -15.2) | -9.4* (-7.6--15.1) | -6.8 (-4.0- -10.7) |
| **LAT** | -13.0 (-8.3- -15.3) | ⎯ | -13.9 (-12.0- -15.2) | -13.7 (-9.7- -15.2) |
| **SEP** | -11.7 (-7.4- -15.0) | ⎯ | -13.8 (-10.2- -15.4) | -13.7* (-12.4- -15.4) |
| **RV** | -12.7 (-8.5- -15.4) | ⎯ | 14.8* (-13.5- -15.2) | -13.9 (-10.8- -15.4) |

*p≤0.003 compared with the value at rest

## Late Diastolic Velocity (A')

Late diastolic velocity data is presented in Table 5. As with E', values for A' in the LAT, SEP, and RV walls are not reported at peak exercise. All late diastolic velocities (A') were significantly higher than resting values immediately post-exercise. During the three

minute recovery period, A' remained elevated in the POS and RV walls for both groups (p≤0.003 and p≤0.003, respectively). In addition, LAT A' was significantly higher in the controls during recovery (p≤0.003).

Table 5 – Comparison of late diastolic velocity (A') measured in cm/s between the two groups for each of the ventricular walls that were measured.

| | REST | PEAK | IMM POST | 3' POST |
|---|---|---|---|---|
| **PATIENTS** | | | | |
| **POS** | -1.6 (-0.7- -2.7) | -7.1* (-2.1- -11.5) | -6.4* (-5.4- -8.2) | -6.2* (-3.3- -8.5) |
| **LAT** | -3.2 (-1.7- -6.7) | — | -7.7* (-6.2- -10.3) | -4.7 (-3.0- -8.1) |
| **SEP** | -3.7 (-2.2- -6.3) | — | -7.2* (-3.7- -9.8) | -4.5 (-3.6- -7.7) |
| **RV** | -4.9 (-2.5- -9.5) | — | -10.1* (-8.3- -12.5) | -9.0* (-6.3- -10.8) |
| **CONTROLS** | | | | |
| **POS** | -1.6 (-0.7- -5.5) | -6.0* (-3.5- -12.4) | -6.6* (-4.7- -9.1) | -4.4* (-1.5- -9.6) |
| **LAT** | -3.2 (-1.4- -5.6) | — | -5.8* (-2.8- -10.3) | -4.8* (-2.9- -6.8) |
| **SEP** | -4.1 (-2.0- -6.0) | — | -7.5* (-4.8- -10.6) | -6.3 (-2.9- -9.6) |
| **RV** | -5.0 (-2.4- -7.4) | — | -11.7* (-8.2- -13.0) | -8.8* (-2.8- -12.3) |

*p≤0.003 compared with the value at rest

## Strain

Strain did not significantly change with exercise in any of the 4 walls that were measured (Table 6).

*Table 6 – Comparison of strain (ε) measured as a % between the two groups for each of the ventricular walls that were measured.*

|  | REST | PEAK | IMM POST | 3' POST |
|---|---|---|---|---|
| *PATIENTS* | | | | |
| POS | 44 (31-60) | 36 (23-43) | 46 (27-70) | 37 (19-60) |
| LAT | -32 (-21- -40) | -34 (-25- -38) | -31 (-20- -38) | -29 (-24- -38) |
| SEP | -28 (-23- -38) | -31 (-25- -37) | -31 (-26- -37) | -32 (-24- -37) |
| RV | -36 (-29- -47) | -38 (-24- -50) | -39 (-28- -48) | -40 (-29- -52) |
| *CONTROLS* | | | | |
| POS | 39 (25-48) | 41 (22-66) | 44 (26-66) | 37 (22-66) |
| LAT | -31 (-19- -40) | -27 (-23- -42) | -30 (-24- -34) | -32 (-27- -36) |
| SEP | -30 (-25- -39) | -32 (-22- -37) | -33 (-26- -37) | -32 (-22- -37) |
| RV | -35 (-30- -48) | -39 (-27- -49) | -38 (-30- -54) | -37 (-30- -49) |

## Tissue Tracking

Tissue tracking data are shown in Table 7. TT significantly increased with exercise in the POS wall of the controls and approached statistical significance in the patients (p<0.004). There were no significant changes in the LAT, SEP or RV walls.

*Table 7 – Comparison of tissue tracking (TT) measured in mm between the two groups for each of the walls that were measured.*

|  | REST | PEAK | IMM POST | 3' POST |
|---|---|---|---|---|
| **PATIENTS** | | | | |
| **POS** | 6.9 (4.7-8.4) | 9.5 (6.3-12.6) | 9.1 (6.2-12.9) | 6.1 (3.2-8.8) |
| **LAT** | 10.8 (6.7-15.5) | 12.9 (6.4-18.6) | 12.9 (7.6-15.0) | 12.9 (7.2-18.3) |
| **SEP** | 12.3 (10.7-16.0) | 13.6 (11.9-17.6) | 12.5 (10.5-18.1) | 12.3 (8.3-17.9) |
| **RV** | 17.8 (14.5-20.5) | 17.8 (12.7-20.6) | 21.4 (13.4-25.5) | 19.3 (14.6-23.2) |
| **CONTROLS** | | | | |
| **POS** | 5.9 (3.7-8.0) | 9.4* (6.0-15.0) | 7.5* (5.2-14.7) | 7.0 (3.4-10.3) |
| **LAT** | 10.1 (7.7-14.5) | 12.6 (9.6-16.7) | 12.0 (8.2-16.5) | 11.1 (7.6-15.1) |
| **SEP** | 13.1 (9.6-15.0) | 14.5 (11.2-18.0) | 13.4 (10.5-17.9) | 13.9 (10.8-17.0) |
| **RV** | 16.7 (10.7-21.8) | 15.9 (11.4-21.5) | 18.5 (13.6-24.2) | 18.6 (13.4-25.0) |

*$p \leq 0.003$ compared with the value at rest

**Exercise Testing**

At rest, there was no difference in $V_E$, $VO_2$, HR, and RER. Similarly, at peak exercise, no significant differences were found. Peak exercise data are shown in Table 8. Both ALL patients and controls reached 62% of their predicted $VO_{2max}$. Only 10/27 subjects reached an RER $\geq$ 1.1 during exercise and, as a result, ventilatory thresholds were not determined. During the test, patients reached 83% of their predicted HR, while controls reached 86% of their predicted HR (p=NS). Total work achieved during the test was

lower in patients (957 J/kg) when compared to controls (1125 J/kg), although this difference did not reach statistical significance ($p \leq 0.02$). Patients and controls exhibited a similar systolic blood pressure response to increasing workload (Appendix III) and a similar heart response with increasing $VO_2$ (Appendix IV). Regression lines appeared parallel and slopes were similar.

*Table 8 – Comparison of metabolic measurements at peak exercise.*

|  | Patients (n=13) | Controls (n=14) |
|---|---|---|
| $VO_2$ (mL/min/kg) | 30.5 (18.3-40.3) | 31.8 (23.1-66.4) |
| $V_E$ (L/min) | 42.7 (29.1-64.4) | 48.3 (30.9-66.4) |
| RER | 1.04 (0.75-1.12) | 1.03 (0.93-1.17) |
| HR (bpm) | 173 (162-196) | 183 (151-203) |
| Work (J/kg) | 957 (595-1277) | 1125 (700-1934) |

## DISCUSSION

Long-term survivors of cancer represent one of the largest and ever increasing groups of patients at risk from premature cardiovascular disease as a result of cardiomyopathy.[20] As the number of children surviving cancer increases, the need for sensitive methods to monitor the negative consequences of their therapy are necessary as the effects of these drugs may only become evident years later.[38] We have evaluated a unique method of stress echocardiography that allows for TDI to be measured during a cardiopulmonary exercise test.

### Tissue Doppler Imaging

#### Tissue Velocities

The analysis of regional ventricular function using tissue velocities is of particular importance as it may show local abnormalities prior to any changes in global function.[39] In our study, median tissue velocities (S', E', A') obtained in both longitudinal (LAT, SEP, RV) and radial (POS) views were similar in our patients and controls at rest, peak, immediately post-, and 3 minutes post-exercise. Previous resting studies, in pediatric oncology patients, have indicated that regional diastolic wall motion abnormalities are common (60%) during anthracycline therapy.[33] These changes appear to decrease (20%) during follow-up of late survivors treated with a mean cumulative anthracycline dose of 241 mg/m$^2$ (range: 50-950 mg/m$^2$).[16] Abnormalities are represented as paradoxical myocardial movements involving mainly the basal and mid segment of the LAT wall and could be detected by visual inspection. None of our patients exhibited this abnormal tissue velocity pattern.

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Many studies have been conducted to establish normal resting myocardial velocities in healthy children. Our resting tissue velocities appear marginally lower than those previously described.[36,39-42] The differences in our results are likely due to the use of different modes of TDI. Studies in children, thus far, have used spectral pulsed-wave Doppler which obtains tissue velocities during the echocardiogram (online analysis). In contrast, we used color TDI and measured myocardial velocities off-line. Spectral pulsed-wave Doppler measures peak tissue velocities, while color TDI measures mean velocities.[27,43] The age of our subjects did not contribute to the differences in our findings, as the subjects in our study had a narrow age range and comparisons of our subjects were made with similarly aged cohorts reported by Eidem et al and Mori et al.[40,42] Additional factors such as, gender, weight, height, body surface area, heart rate, or any of the conventional echo Doppler parameters (left ventricular dimensions, wall thickness, shortening fraction, mitral and tricuspid E and A waves) should not have affected our resting findings as they have been shown to have no relationship with TDI velocities.[39]

Tissue velocities have been measured during exercise in adults,[43,44] but have not been studied during exercise in children. We have shown a significant increase in S' in both the circumferential (POS) and longitudinal fibers (LAT, SEP, RV) at peak exercise. This linear increase in S' during cycle ergometry has also been described in adults.[44,45] At peak exercise, Saha et al. showed a significant increase in S' in both the LAT and SEP walls. Quintana et al. described the changes in left ventricular S' during exercise and found a linear increase in the longitudinal fibers, while in the circumferential fibers, S' remained fairly constant at low workloads and then increased linearly at moderate-to-high workloads.[44] This finding may be explained by the differences in the role of the

longitudinally and circumferentially oriented fibers of the left ventricle. In the non-exercising heart, longitudinal fiber contraction precedes circumferential fiber contraction.[46] Similarly, during exercise the initial contribution of the left ventricle to meet the physiological demands of the heart comes from the sub-endocardial longitudinal fibers of the heart. With increasing metabolic demand the left ventricle brings the circumferential fibers into the contractile process in order to increase the stroke volume.[44]

A strong correlation between S' and heart rate (r=0.92) has also been noted emphasizing the fact that the achieved peak heart rate must be taken into account when interpreting stress echocardiography.[44] No statistical difference was noted in the heart rates of our patients and controls at peak exercise; however, the inability of some subjects to achieve high peak heart rates during semi-recumbent exercise may have affected the results of our study.[44] No study has investigated the effect of body position on tissue velocities.

Diastolic velocities that reflect longitudinal fiber function were more difficult to obtain during peak dynamic exercise than those reflecting radial function. Because of the difficulty in measuring diastolic velocities at peak exercise, we were unable to visualize the fusion of E' and A'. Similar to the Doppler spectrum of transmitral flow, diastolic E' and A' waves tend to merge during tachycardia.[27] Our ability to measure diastolic velocities greatly improved immediately post-exercise. E' was significantly higher in the POS wall at peak and immediately post-exercise. E' was also significantly elevated in the RV wall immediately post-exercise, but was not statistically different in the LAT and SEP walls. A previous study in healthy elderly subjects showed that E' significantly

increased in response to exercise in both longitudinal and circumferential fibers.[44] While our findings show a similar increase in the circumferential fibers (POS), we did not show a significant increase in the longitudinal fibers (LAT, SEP, RV) of the left ventricle. This is a surprising finding as we expected to see a significant increase in E' during exercise in all walls, as early diastole is an active process which, presumably, should result in increased tissue velocity. Abnormalities of early diastole (ie. active relaxation) normally precede systolic abnormalities; thus, this unexpected finding is counterintuitive to our understanding of these physiological mechanisms. The variability in our data may account for our inability to detect statistical changes in E'. Late diastolic velocities (A') were significantly higher in all walls for both patients and controls ($p \leq 0.003$). This finding has also been noted in the POS and LAT walls of elderly subjects.[44]

### Strain

Strain and strain-rate imaging techniques have yet to be evaluated in childhood survivors of ALL. These methods have been thought to potentially enhance the value of TDI by reducing the dependency of velocity measurements on the imaging angle, overall heart motion, cardiac rotation, and contraction in adjacent segments.[47] Furthermore, these techniques can be used to diagnose early cardiomyopathy by detecting subtle transient changes in deformation patterns and regional myocardial function before global impairment occurs.[28] In this study we only measured $\varepsilon_{sys}$, as strain-rate is difficult to obtain at peak work rates due to the presence of high signal noise and cardiac and respiratory artifacts.[48]

Systolic strain reflects myocardial deformation and is the result of the complex interaction of intrinsic contractile force and extrinsic loading conditions applied to a

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tissue with variable elastic properties.[47] Consequently, changes in preload (blood returning to the heart) and afterload (myocardial stiffness) are important determinants of the pattern and the magnitude of myocardial deformation.[47] Reduced $\varepsilon_{sys}$ has been reported in patients with hypertrophic cardiomyopathy (LAT $\varepsilon_{sys}$=-9%) and severe pulmonary stenosis (RV $\varepsilon_{sys}$=-14%). Our ALL patients did not demonstrate a reduction in $\varepsilon_{sys}$ and had comparable values to our controls at rest, peak, immediately post-, and three minutes post-exercise. Our control values are similar to resting values previously established in a group of 33 healthy children.[37]

Changes in $\varepsilon_{sys}$ with the administration of dobutamine or exercise have been shown to parallel changes in stroke volume.[30,48] Weidemann et al. have described the relationship of $\varepsilon_{sys}$ and stroke volume with dobutamine infusion in pigs and have shown a biphasic response, increasing with low dobutamine doses and decreasing with high dobutamine doses.[30] Davidavicus et al. have demonstrated a similar $\varepsilon_{sys}$ response for both radial and longitudinal deformation during exercise in humans. They suggest that during exercise, the increase in stroke volume is limited by an increasing heart rate which shortens diastolic filling time, leading to a progressive decrease in preload and, eventually, a decrease in stroke volume after an initial rise.[48] Previous work in healthy children has shown that maximal stroke volumes are significantly elevated above resting values.[49,50] An initial increase in stroke volume occurs from rest to moderate intensity exercise before reaching a plateau or, in some cases, slightly falling during high intensity exercise.[49,50] Since changes in $\varepsilon_{sys}$ parallel changes in stroke volume, any increase in $\varepsilon_{sys}$ would likely have occurred during the early stages of exercise, and it might be expected that $\varepsilon_{sys}$ would remain significantly elevated above resting values. However, the lack of a significant increase at peak exercise may be related to the fact

that $\varepsilon_{sys}$, which is derived from TDI, is a relative measure of deformation calculated from the change in velocity between two points of a fixed length.

### Tissue Tracking

Tissue tracking allows for a more complete estimation of global systolic function[51] by providing a rapid assessment of systolic longitudinal myocardial displacement.[52,53] There are no published normal values for TT in children. In adults, Pan et al. have determined that a displacement of less than 4.8 mm in the lateral wall is predictive of a severe reduction in ejection fraction.[32] Tissue displacement in our subjects is well above this value. Although studies have shown decreasing longitudinal contraction with age[51,52] our resting values are similar to those established in the basal segments of the LAT and SEP of adults in the supine position (age range: 18-76 years).[51] Systolic blood pressure was also found to influence the longitudinal contraction of the left ventricle suggesting that tissue tracking may be dependent on left ventricular afterload.[52]

A significant increase in TT was only seen in the POS of the control group at peak exercise, although values were approaching statistical significance in the ALL group (p=0.004). We expected an increase in both short-axis and long-axis displacement as Quintana et al. have shown significant increases during sub-maximal exercise.[44] These authors have shown that, in the long-axis, displacement occurred mostly in the initial phase of exercise and then leveled off while, in the short-axis, it steadily increased throughout the exercise duration. In addition, they noted that the lack of further displacement during later stages of exercise is not a pathological phenomenon, but lends support to the observations of radial thickening (ie. circumferential fiber function) and a continuous decrease in LV cavity size at peak stress. It is possible that in our

subjects, displacement in the longitudinal walls (ie. longitudinal fiber function) occurred in the early stages of exercise and then leveled off at peak exercise. Studies measuring these variables during staged exercise may help to answer this question. In addition, our large range in TT values may have led to our inability to detect statistical differences.

**Aerobic Capacity**

The evaluation of aerobic capacity during cardiopulmonary exercise testing has been suggested as a useful method to quantify potential sub-clinical cardiotoxicity as it measures the individual's response to the metabolic demand of exercise.[54] Not only does a reduction in aerobic capacity reflect potential cardiovascular risk,[34] it may also significantly affect the quality of life of these patients. Outdoor physical activities involving cardiorespiratory work of moderate intensity are an essential part of the daily routine of children;[55] thus, there is a need to determine if functional capacity, as assessed by $VO_{2peak}$ measurement, is impaired. In adult cancer patients and survivors, $VO_{2peak}$ is reported to be considerably lower than predicted (~50%);[55] however, studies that have looked at childhood cancer survivors have produced conflicting results.[38,56-59] The majority of studies are confounded by different treatment regimens, diverse diagnoses and wide age ranges in study populations. While many of these studies have indicated that anthracycline-treated cancer survivors have reduced $VO_{2peak}$ compared to controls,[38,59-61] others have suggested that $VO_{2peak}$ is normal in many of these patients.[56,57] Van Brussel et al. conducted a meta-analysis of studies that specifically looked at $VO_{2peak}$ in ALL patients and found a reduction of 6 mL/kg/ min or 13% when compared to non-cancer patients. This may be a clinically significant finding as a

decrease of 3.5 mL/kg/min has been associated with a 12% decrease in survival rates in elderly males with cardiovascular disease.[35]

In our study, we looked at a fairly homogeneously treated subset of ALL patients and found a comparable $VO_{2peak}$ to healthy controls. Both Black et al. and Hauser et al. have reported a normal $VO_{2peak}$ in 75% of ALL patients.[56,57] Previously published $VO_{2peak}$ values are considerably higher than those obtained in our study. Only one study used a semi-recumbent cycle ergometer for cardiopulmonary evaluation, but this study did not publish $VO_{2peak}$ values.[56] Hauser et al. used the Bruce treadmill protocol and measured a $VO_{2peak}$ of 49.5±10.9 mL/min/kg in ALL patients with a normal stress echocardiogram and 50.2±12.6 mL/min/kg in healthy controls.[57] Matthys et al. used the James protocol on a cycle ergometer and reported a similar $VO_{2peak}$ in male patients and controls (41±4 mL/min/kg vs. 44±5 mL/min/kg, respectively).[58] The difference between $VO_{2peak}$ values obtained on a treadmill and cycle ergometer has been well documented and is largely attributed to blood pooling in the lower extremities during cycling.[62] In addition, differences in $VO_{2peak}$ and heart rate have been noted between upright and supine cycling,[63] and may partially explain the lower values obtained by our subjects.

The semi-recumbent position may also limit our subjects' ability to achieve a true $VO_{2peak}$. Often subjects complained of local muscle fatigue in their legs rather than central fatigue as their reason for termination of the test. This is reflected by our patients and controls only reaching 83% and 86% of their predicted maximum heart rate, respectively, and 62% of their predicted $VO_2$. In addition, only 10/27 of our subjects achieved an RER>1.1. The young age of our cohort may have also influenced our results. Exercise performance is noted to be effort-dependent relating to motivation and

tolerance of the individual to the anaerobic state, and is specific to age, musculoskeletal and pubertal development of the subjects.[54]

### Reproducibility of Tissue Doppler Studies

The high variability in our data may have affected our ability to detect statistically significant changes. Coefficients of variation (CV) were established in a pilot study and are presented at rest and at peak exercise in Appendix V. CV was generally higher for A' than any of the other TDI indices and for the POS when compared to the other walls measured. At rest, CV ranged from 13-53% depending on the index and wall, while at peak exercise, CV ranged from 5-43%.

### Clinical Impression

Despite the high variability in our TDI results and our difficulty in obtaining a true $VO_{2peak}$, it appears that the cardiac function of our ALL patients is normal. At the time of their last follow-up visit ALL patients had a normal resting echocardiogram. The cardiopulmonary exercise test showed that patients and controls had almost identical $VO_{2peak}$ values. In addition, patients exhibited a comparable heart rate response to the controls, as indicated by the similar slopes and parallel regression lines obtained when $VO_2$ vs. heart rate was plotted. The regression lines obtained from the plot of systolic blood pressure vs. work also yielded similar slopes and the patients showed no signs of any ECG abnormalities during the exercise test further suggesting that the exercise response of the ALL patients is normal. The long-term follow-up of these patients with exercise testing will help to determine if these patients continue to have a normal response to exercise.

**Limitations**

Stress echocardiography with cardiopulmonary testing is a technically difficult test. In order for this test to be performed accurately, an experienced echocardiographer was needed. Despite the care taken to align the ultrasound beam in a parallel position with the interrogated direction of myocardial motion, the variability of this procedure was higher than expected and TDI data acquisition was not always possible during exercise. High frame rates (>150 frames per second) were used to try and ensure clear tracings; however, at peak exercise there was increased artifact in our tissue velocity data making it difficult to obtain diastolic velocities in any wall. Due to missing data, we were unable to use a repeated measures analysis of variance to analyze our data; thereby, reducing our statistical power. In a post-hoc power analysis (Appendix VI), we have shown that with the minimal group differences in our TDI data we would have required 1,200 subjects to power our study at 90%. More advanced 3-D imaging techniques were not available for clinical use at the time of this study. This new technology may help to eliminate some of the problems we encountered with data acquisition at peak exercise and may also reduce the angle dependency errors that are associated with current TDI technology.

In addition, it was difficult to ascertain whether our subjects truly reached their $VO_{2peak}$ during this test. Because children often do not meet the "adult" criteria for $VO_{2max}$ (ie. a plateau in $VO_2$; RER>1.1; and HR within 10 beats of age-predicted maximum) the reasons for termination of the exercise test were primarily volitional fatigue and their inability to sustain a cadence of 60 rpm. Subjects often noted that leg fatigue was the reason for termination, as is often the case with upright or semi-recumbent cycle ergometry. Our results were obtained with subjects exercising in a semi-recumbent

position and, therefore, may not be representative of supine or upright exercise. In addition, some of our controls were good friends of the ALL patients. They may have shared a similar lifestyle, interests, and activity patterns which may help to explain the lack of differences in exercise parameters found between the groups. Finally, due to the nature of this study, researchers were not blinded to the classification of subjects.

## Future Directions

We have studied a group of ALL patients with no known cardiac dysfunction at rest. Cancer patients with known resting cardiac dysfunction should also be studied using our suggested method to determine if TDI is sensitive enough to detect changes due to cardiotoxicity. As anthracycline-induced cardiotoxicity may not present for several years, a repeat study in 5-10 years or a study of patients 10-15 years post-treatment may be warranted. Newer TDI techniques should also be studied to determine if we could reduce the variability in our data. In addition, it would be interesting to determine the relationship of these TDI variables with other standard exercise echocardiography parameters (ie. stroke volume, cardiac output, shortening fraction, mean velocity of circumferential fiber shortening, wall stress, etc.). A study examining all of these parameters during staged exercise might help to clarify this.

## CONCLUSIONS

In this study, we have shown that ALL patients previously treated with moderate doses of anthracyclines have similar tissue Doppler indices and exercise capacity as their healthy counterparts. This might be because the patients were normal or, as described above, the test was insensitive. We have also shown that with our current technology, TDI variables were similar at peak and immediately post-exercise, and easier to obtain

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immediately post-exercise. For each of our hypotheses, the null hypothesis was confirmed: (1) resting tissue velocities (S', E', A'), strain ($\epsilon_{sys}$), and tissue tracking (TT) were similar between ALL patients and healthy controls; (2) exercise tissue velocities, strain, and tissue tracking were similar between ALL patients and healthy controls; and (3) $VO_{2peak}$ was similar between ALL patients and healthy controls. Further research is needed to determine whether TDI can be used to detect group differences in cohorts of patients with and without overt myocardial dysfunction or whether it is a sensitive enough test to monitor subtle changes in myocardial function of individual patients over time.

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# APPENDIX I

## "Assessing Cardiac Function in Children in Remission from Cancer: Reviewing the Utility of Exercise Echocardiography"

### 1. Introduction

With increased cure rates and longer disease-free survival, the long-term consequences of anthracycline treatment are a concern in the management of pediatric cancer survivors. Cardiotoxicity is a possible side effect of anthracycline therapy and may lead to the development of myocardial dysfunction years after treatment.[16,17] Late development of myocardial damage is thought to be dependent upon the cumulative dose received, with patients treated with higher cumulative doses being more susceptible to cardiac dysfunction.[17,64,65] There also appears to be an individual sensitivity to the drugs whereby some patients experience cardiotoxic side effects even when treated with low cumulative doses.[17] Resting echocardiography is the most widely used method to monitor cardiotoxicity; however, studies have indicated that these measurements may be inadequate in detecting subtle myocardial changes.[21] Improvements in the sensitivity of standard echocardiography can be achieved by performing echocardiography with exercise.[66] The focus of this review is to examine the detection of late anthracycline-induced cardiotoxicity, by echocardiography, in pediatric cancer survivors both at rest and with exercise.

## 2. Resting Echocardiography

### 2.1. Systolic Function

Standard resting echocardiography studies have primarily examined systolic function to determine if there are late cardiotoxic side effects after treatment with anthracyclines. Johnson et al. showed that patients who had received cumulative anthracycline doses ranging from 76 to 500 mg/m$^2$, and who had not received therapy for at least 2 years, had normal resting systolic parameters including: shortening fraction (SF), left ventricular wall thickness, left ventricular end-diastolic (LVED) and end-systolic (LVES) dimensions, and rate-corrected mean velocity of circumferential fiber shortening (MVCFc).[59] Similarly, Turner-Gomes et al. showed that SF, LVED, and end-systolic wall stress (ESS) were within the normal range for all patients that had received both low and high cumulative doses of anthracyclines.[67] Interestingly, although SF was within acceptable limits, patients receiving high doses of anthracyclines had a significantly lower SF than those in the low dose group (32.6% vs. 39.0%; p<0.05).

In contrast, Kapusta et al. found that LVED (45.8 vs 42.5 mm; p<0.01) and LVES (30.9 vs 27.4 mm; p<0.001) were significantly bigger in anthracycline-treated patients.[16] It is unclear whether these dimensions are in fact abnormal because of the diverse age range (5-18 years) of the patients and controls. Since these dimensions are dependent on age and body surface area and the median age of the patients (13.5 years) was higher than the controls (10.8 years), it is reasonable to expect that the patients would have higher left ventricular dimensions. SF was also significantly lower in this group (33 vs. 36%; p<0.001), but only 4 patients had a SF out of the normal range (<28%). These survivors had received a median cumulative anthracycline dose of 241 mg/m$^2$.[16] Using a smaller age range of patients (11-18 years), Bossi et al. found that 15% of cancer

survivors treated with moderate doses of anthracyclines (mean: 214±103 mg/m$^2$) had an increased LVED and LVES, reduced SF, reduced septum thickness, and a thinner posterior wall in diastole.[68] Although statistical differences were found in these studies, the clinical significance of these findings remained in question as little was known about whether there was a progressive decline in these parameters.

Sorensen et al. recently published a longitudinal study that looked at the effect of moderate anthracycline doses (mean: 180 mg/m$^2$; range: 90-270 mg/m$^2$) in a group of Acute Lymphoblastic Leukemia (ALL) survivors. Patients were assessed 5 years and 10 years after treatment. After 10 years, ALL survivors had enlarged and thinner-walled ventricles in systole, reduced SF and MVCFc, and higher ESS (p<0.05). There was no deterioration, from 5 years to 10 years post-treatment, in LV wall thickness, cavity size, SF, stress-velocity index or ESS, although MVCFc showed slight improvement. Overall, 15% of the ALL survivors had cardiac abnormalities as defined as reduced contractility and increased wall stress.[69]

## 2.2. Diastolic Function

Resting diastolic function has also been shown to be impaired in anthracycline-treated patients. There are three major phases in diastole: isovolumic relaxation, rapid filling, and late filling of the ventricle. Isovolumic relaxation occurs after systole and prior to the opening of the mitral valve, where there is no change in left ventricular volume. Lengthening of the isovolumic relaxation time is indicative of diastolic dysfunction and has been observed in pediatric cancer survivors treated with a mean cumulative dose of 250 mg/m$^2$.[64] Velocities during rapid filling (E) are reported to be normal in these patients; however, differences in velocities during late filling or atrial contraction (A)

have been noted.[21,67] Sung et al. showed that patients had higher A velocities compared with the controls (53.8 vs. 47.2; $p<0.05$). Turner-Gomes et al. also reported increased A velocities in 13/18 (73%) patients treated with anthracyclines. The ratio of E/A is another indicator of diastolic function. Turner-Gomes found this ratio to be normal in those patients that increased A, but abnormal in those that decreased A. In addition, there was no statistical difference in E/A ratios between those receiving low dose vs. high dose anthracyclines.[67] Weesner et al. and Sung et al. found significantly lower E/A ratios in anthracycline-treated patients.[21,66] Further research is needed to clarify whether anthracycline treatment impairs resting diastolic function over time.

## 2.3. Hemodynamic Function

Resting hemodynamic findings of patients treated with anthracyclines are highly variable. This may be the result of using different testing protocols or may be due to the diversity of the patient groups tested. Some authors have found that heart rate is comparable between patients and healthy controls,[24,59] but higher resting heart rates have also been observed.[21] All three of these studies reported similar resting systolic and diastolic blood pressures between groups. Differences in resting cardiac index have also been reported. Weesner et al. found a mean resting cardiac index of 5.6 ± 1.6 $L/min/m^2$, whereas, Johnson et al. observed a cardiac index of 2.6 ± 0.7 $L/min/m^2$.[59,66] The mean age of the patient groups and the method of estimating cardiac index (echocardiography-Doppler) were similar in both studies.

## 2.4. Tissue Doppler Echocardiography

Tissue Doppler Imaging (TDI) is a relatively new and promising tool for the assessment of myocardial function.[64] This echocardiographic method interrogates the low velocity

and high amplitude signals of the myocardium to measure tissue velocities.[26] Using spectral pulsed-wave TDI, circumferential peak myocardial velocities were measured in the posterior wall (POS), while longitudinal peak myocardial velocities were measured in the right ventricular wall (RV), the interventricular septum (SEP), and the left ventricular wall (LAT). Velocities were obtained during systole (S'), early (E') and late (A') diastole and within the basal, mid, and apical segments of the RV, SEP, and LAT. Wall motion abnormalities were reported in 25% of patients. Abnormal left ventricular relaxation patterns were present in 19% of patients and akinesis of the SEP was found in 5% of patients. Peak myocardial velocities obtained from the POS revealed that late diastolic velocities were significantly decreased in the patient group (p<0.01).[16] It was also shown that using TDI with conventional methods improved the ability to detect cardiac dysfunction.[70] These findings indicate that investigating tissue velocities may be an important component in the early detection of local myocardial abnormalities in children treated with anthracyclines.

Developments in TDI have also led to the ability to assess regional myocardial deformation. Strain (the amount of deformation) can be measured during off-line analysis and has been used clinically to detect early cardiomyopathy and to differentiate physiologic and pathologic myocardial hypertrophy.[28] Tissue tracking is another parameter that can be obtained from TDI and is used to measure myocardial displacement.[53] To date, there have been no studies that have examined strain or tissue tracking at rest in anthracycline-treated patients. In addition, there have been no studies that have looked at tissue velocities, strain, and tissue tracking at peak exercise in pediatric cancer survivors.

# 3. Exercise Echocardiography

## 3.1. Systolic Function

The detection of latent cardiac dysfunction in pediatric cancer survivors may be enhanced by the use of exercise echocardiography.[24] Studies have typically compared pre- and post-exercise echocardiograms to determine if there are any signs of dysfunction. At peak exercise, patients treated with anthracyclines had lower SF (38 vs. 52%; $p<0.005$), lower MVCFc (1.5 vs. 1.8 circ/s; $p=0.05$), and a lower peak aortic velocity (72 vs. 124 cm/s; $p=0.01$) compared to non-anthracycline treated patients.[66] Findings by Sung et al. are in agreement with this study.[21] In addition, Yeung et al. showed that not only were anthracycline-treated patients unable to increase their SF to the same extent as the non-anthracycline group, but some patients actually showed a reduction in SF after exercise.[23] This observation has also been noted by others.[49,61] Lang et al. found normal mean values for SF and MVCFc at rest; however, immediately following exercise both SF and MVCFc were significantly below the expected range for the normal population.[71] These patients had received a mean cumulative anthracyclines dose of 129 mg/m$^2$. Hauser et al. also observed a reduction in SF during exercise in 26% (10/38) of ALL patients treated with moderate cumulative doses of anthracycline.[57] These findings are contrary to those of Smibert et al. which showed that all patients treated with anthracyclines increased their SF during exercise.[24]

## 3.2 Hemodynamic Function

Johnson et al. documented the impaired hemodynamic responses to sub-maximal exercise in pediatric cancer patients.[59] While there was a significant increase in cardiac index from rest to immediate post-exercise in both patients and controls, patients exhibited smaller relative increases. From rest to 33% VO$_{2max}$, patients increased their

cardiac index by 73%; while controls showed a relative increase of 116%. At 66% $VO_{2max}$, the relative increase was 115% for patients compared to 192% for controls. Because the heart rate response was normal in this patient group, differences in cardiac index were a reflection of an impaired stroke index response. Stroke index significantly increased from rest to 33% of $VO_{2max}$ in both groups with no further significant increases at 66% of $VO_{2max}$. Similar to the cardiac index response, relative increases were greater in control subjects than in patients. At 33% $VO_{2max}$, controls were able to increase their stroke index by 54%, whereas, patients exhibited a 33% increase. At moderate intensities (66% $VO_{2max}$), the controls were able to increase their stroke index by 69%, while the patients were still only able to exhibit a relative increase of 33%.[59] Contrary to these findings, stroke volume has been shown to decrease by 15% from resting values immediately following supine exercise, while cardiac output increased by 30%.[71] This decrease in stroke volume was attributed to a lack of increase in preload and an inability to increase contractility.

### 3.2 Exercise Capacity

Exercise intolerance has been well documented in studies with pediatric cancer survivors.[22,38,57,59,72] Prestor et al. showed that 48% of ALL survivors had impaired exercise tolerance.[72] Turner-Gomes et al. indicated that 12 patients treated with anthracyclines attained a maximal exercise capacity of 93 watts which represented 68% of the predicted value.[67] Johnson et al. found that anthracycline-treated patients achieved significantly lower maximal workloads than controls (700 vs. 1108 kpm; $p<0.01$) and had a lower $VO_{2max}$ compared to controls (32.0 vs. 41.3 ml/min/kg; $p<0.01$).[59] Hauser et al. stratified their patients to those with normal and abnormal echocardiograms. $VO_{2max}$ for ALL patients with a normal stress echocardiogram were

comparable to controls (49.5 vs. 50.2 ml/min/kg), while patients with abnormal stress echocardiograms had lower values (35.4 ml/min/kg; $p<0.01$).[57] Patients in this study were younger than those studied by Johnson et al. resulting in higher relative $VO_{2max}$ values.

## 4. Summary

Echocardiographic studies involving patients with cancer who have been treated with anthracyclines have produced variable findings and these studies have been confounded by diverse patient groups treated with a large range of cumulative anthracycline doses. Although differences in cardiac function have been reported, the clinical significance of these findings has not been fully explained. Few studies have examined TDI in pediatric cancer survivors at rest and there have been no studies that have incorporated TDI during exercise testing. Investigation of TDI at rest and with exercise will provide additional information about the cardiac function of anthracycline-treated patients and may help to guide their clinical treatment.

# APPENDIX II

## - Physical Exam Sheet -

| Name: | Study ID: |
|-------|-----------|
| Hospital ID: | Date of Test: |
| Date of Birth: | Height: |
| Weight: | BSA: |

Date Tx Started: _____ Date Tx Ended: _____

Total Cumulative Anthracycline Dose: _____ mg/m$^2$

## Cardiac Examination

Resting BP: _____      Resting HR: _____

Pulse:      Normal      Abnormal_____

Precordium: Normal      Abnormal_____

Heart Sounds: Normal      Abnormal_____

Murmurs:      No      Yes_____

Cardiac Failure:      No      Yes_____

## Physical Activity Level (Circle the answer that best applies)

How many **days** do you exercise per week?

     **None**      **1-2**      **3-4**      **>5**

Approximately, how many **hours** do you participate in physical activity per week?

     **None**      **1-2**      **3-4**      **>5**
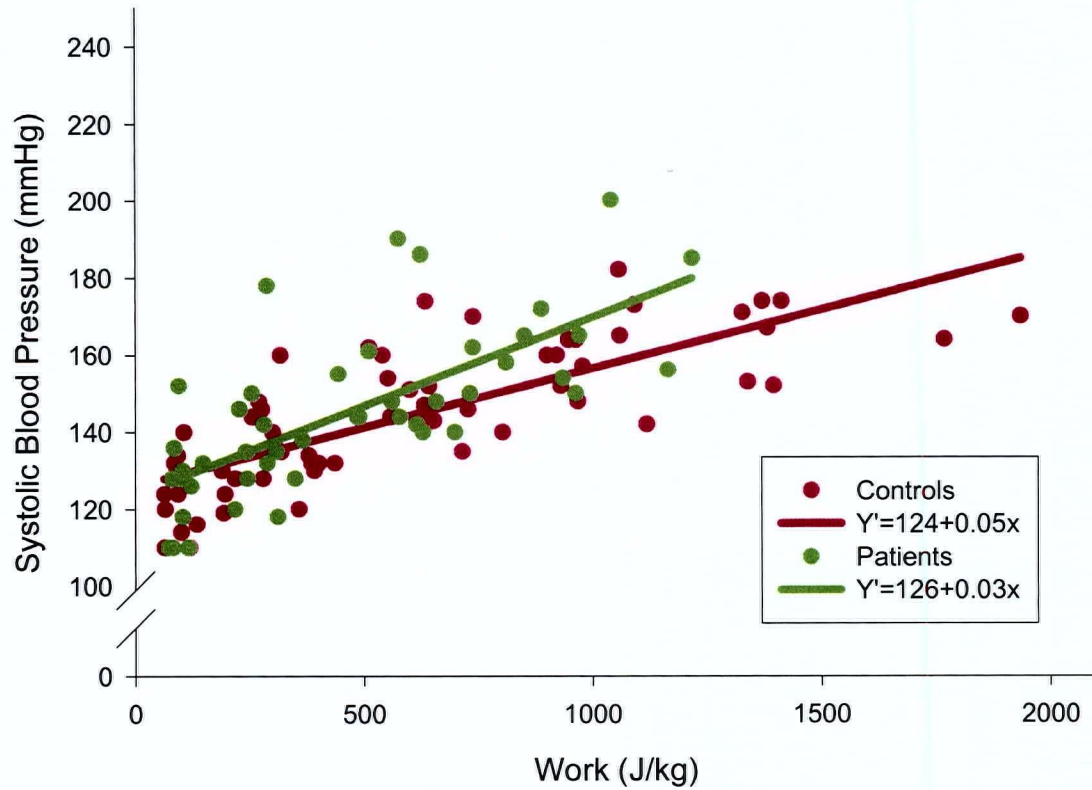
Describe the **intensity** of the exercise that you do?

     **Low**    **Low-Moderate**      **Moderate-High**      **High**

Briefly comment on the types of activity you do? (ie. PE class, organized sports
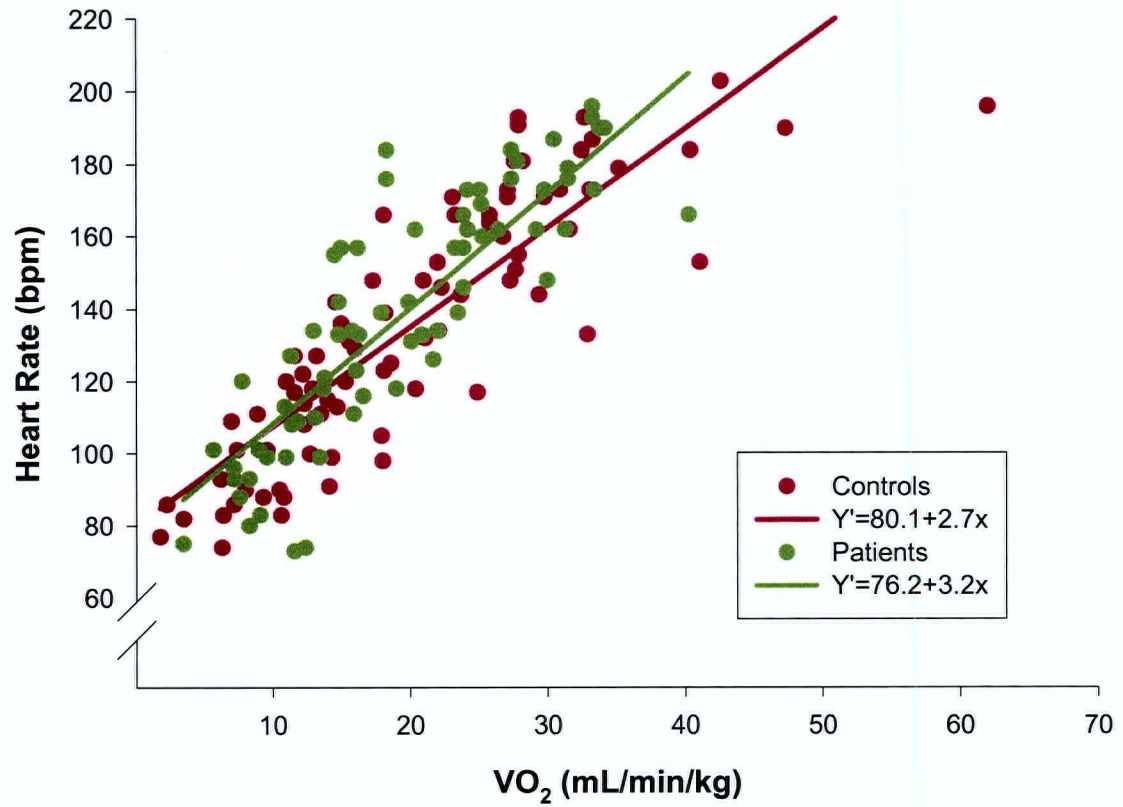
etc.)_____

# APPENDIX III

## Systolic Blood Pressure Response to Exercise in ALL Patients and Controls



Legend:
- Controls — $Y'=124+0.05x$
- Patients — $Y'=126+0.03x$

(x-axis: Work (J/kg); y-axis: Systolic Blood Pressure (mmHg))

# APPENDIX IV

## Heart Rate Response to Increasing VO$_2$ in ALL Patients and Controls



Legend:
- Controls — Y'=80.1+2.7x
- Patients — Y'=76.2+3.2x

X-axis: VO$_2$ (mL/min/kg)
Y-axis: Heart Rate (bpm)

# APPENDIX V

## - Coefficients of Variation -

## Coefficients of variation for TDI variables at rest

|     | POS | LAT | SEP | RV  |
| --- | --- | --- | --- | --- |
| S'  | 29% | 18% | 15% | 15% |
| E'  | 27% | 25% | 13% | 19% |
| A'  | 53% | 27% | 38% | 42% |
| ε   | 27% | 22% | 18% | 20% |
| TT  | 29% | 24% | 20% | 15% |

## Coefficients of variation for TDI variables at peak exercise

|     | POS | LAT | SEP | RV  |
| --- | --- | --- | --- | --- |
| S'  | 38% | 18% | 21% | 5%  |
| E'  | 31% | 11% | 9%  | 8%  |
| A'  | 22% | 25% | 43% | 24% |
| ε   | 33% | 23% | 14% | 22% |
| TT  | 33% | 17% | 24% | 23% |

# APPENDIX VI

## - Post-Hoc Power Analysis -

The following results were found from our post-hoc power analysis using E', at peak exercise, as our outcome variable with an $\alpha=0.05$, difference=0.28, and a standard deviation=1.46

| N (# pairs) | Power (1-$\beta$) |
|---|---|
| 13 | 7.3% |
| 30 | 11% |
| 50 | 15% |
| 100 | 27% |
| 200 | 48% |
| 300 | 65% |
| 400 | 77% |
| 500 | 86% |
| 600 | 91% |