EVALUATION OF TRADITIONAL AND NOVEL MEASURES OF CARDIAC FUCNTION TO DETECT ANTHRACYCLINE INDUCED CARDIOTOXICITY IN SURVIVORS OF CHILDHOOD CANCER

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Abstract

Background: Cardiovascular disease is the leading non-cancer cause of death among survivors of childhood cancer. Ejection fraction (EF) and fractional shortening (FS) are common echocardiographic measures of cardiac function. Newer analysis modalities, including radial displacement, may provide additional information about pre-clinical disease such as regional myocardial dysfunction. **Methods:** We compared mean radial displacement, EF, and FS among adult survivors of childhood cancer exposed to ≥ 250 mg/m^2 of anthracyclines to age, sex-matched healthy controls. Survivors with a history of cardiac directed radiation, diabetes, or heart disease were excluded. **Results:** There were no differences in gender (35% male vs. 35% male, p=1.0) or current age (28.4 years (range18-50) vs. 28.7 years (range 18-50), p=0.94) between survivors and controls, respectively. Among survivors mean age at diagnosis was 12.5 (range 1-20) years, mean survival time 16 (range 5-30) years, and mean anthracycline exposure was 420 (range 300-645) mg/m^2. FS (35.5% vs. 39.6%, $p < 0.01$) and radial displacement (5.6 mm vs. 6.7 mm, $p = 0.02$) were significantly lower in cancer survivors as compared to controls. EF showed a trend towards being lower in survivors versus controls (55.4% vs. 59.7%, $p = 0.057$). All echocardiographic measures were inversely related with dose of anthracyclines, though radial displacement was no longer significantly correlated with antrhacycline dose after controlling for survival time ($p = 0.07$) while EF remained correlated ($p = 0.003$). **Conclusions:** Novel and traditional measures of radial displacement, FS, and EF are lower in childhood cancer survivors in long-term follow-up compared to controls. Novel measures may add new information, but the potential clinical utility remains undetermined and requires further longitudinal study.

Table of Contents

List of Tables

Page

List of Figures

Page

Background

Survivorship

The history of pediatric oncology is remarkably compelling. In the early 20th century most of childhood cancer diagnoses resulted in death. In the 1940's development of Nitrogen Mustard as the first chemotherapeutic agent[1] occurred as 5-year survival was around 20%.[2] By 1970 multimodal therapy improved survival to 50%.[3] Currently multiple studies report upwards of 80% survival for all patients presenting with a pediatric malignancy as a result of large cooperative group efforts, advanced therapeutic protocols and novel treatment agents.[3-7]

With more patients surviving childhood cancer for the last half century, the ever decreasing mortality, and a concomitant rise in new cancer diagnoses,[8] thousands of children and young adults each year join hundreds of thousands of survivors of childhood cancer in the United States.[5, 7] Surviving 5 years from diagnosis is considered a benchmark for cure by many patients, families and providers.[6] Pediatric oncologists more often refer to remission than cure, perhaps because of knowledge of recent epidemiologic history, or perhaps because of recognition that death from the primary disease is still the main cause of premature mortality in the survivor population beyond 20-years post-diagnosis when primary disease mortality finally plateaus.[5, 6]

This increasing survivor population has given rise to a new field of study and recognition of the adverse effects resulting from diagnosis of and treatment for a pediatric malignancy. Nearly 2/3 of childhood cancer survivors report a chronic medical condition with over 1/4 considered severe or life-threatening.[9] Premature morbidity and mortality of survivors compared to sibling controls and compared to the general population is well described with primary and secondary causes being recurrence of the original cancer and developing a second malignant neoplasm.[5, 6, 10-12] The leading non-cancer cause of death is premature cardiovascular disease (CVD), which is nearly 5 to 10 times that of either sibling controls or the general population.[4, 10, 11, 13]

Cardiac Toxicity

The most well studied cancer treatments associated with CVD are cardiac directed radiation therapy and anthracycline chemotherapy. Despite limitations due to cardiac toxicity, anthracyclines remain one of the most potent anti-neoplastic classes of agents in oncology and are used in nearly half to two thirds of all pediatric oncology patients.[3, 14] While there are many reviews addressing cardiac toxicity following cancer therapy, many questions regarding pathophysiology, screening and management continue to remain unanswered.[3, 15-18]

Anthracycline-induced cardiotoxicity can typically present in 3 ways: 1.) Acute toxicity within hours or days of exposure, 2.) Early-onset toxicity within the first year off treatment, and/or 3.) Late-onset toxicity a year or more off treatment. Late-onset

cardiotoxicity is often a progression from a dilated cardiomyopathy to a restrictive cardiomyopathy with abnormal diastolic dysfunction and elevated left ventricular (LV) filling pressures.[3, 16]

Late-onset cardotoxicity often results in overt congestive heart failure (CHF). The diagnosis is objectively made by traditional echocardiographic monitoring measures of global cardiac function, including Ejection Fraction (EF) and Fractional Shortening (FS). Additionally, patients experience cardiac related symptoms of CHF including fatigue, dyspnea with exertion, orthopnea, and peripheral edema, accompanied by significant changes in echocardiographic measures of systolic function in up to 26% of those exposed to current recommended doses as late as 20 years after therapy.[3, 10, 19] Unfortunately those who present with class III or IV New York Heart Association CHF have 50% mortality at 2 years.[4] Furthermore, a significant proportion of those patients presenting with clinically symptomatic CHF will ultimately progress to cardiac transplantation or premature death despite current therapies. As an example, currently available heart failure treatment with afterload reduction through an angiotensin converting enzyme (ACE) inhibitor did not prevent but rather shifted the progression of left ventricular dysfunction out 6 to 10 years.[20]

CHF associated with anthracyclines has a number of mitigating factors including total cumulative lifetime dose, individual dosing, duration of dose infusion, use of liposomal formulations, use of cardioprotective agents, gender, race, cardiac directed radiation exposure, age of exposure, time since treatment, genetic predisposition, and exposure to

other cardiovascular risk factors such as smoking, alcohol, diet, lack of exercise and health screening.[3, 4, 6, 7, 10, 14-18, 21] Some of these factors are well described while others remain in question with many of these studies reporting conflicting results. Still others are only at the early stages of investigation such as the polygenic influence of functional candidate genes in the anthracycline metabolic and oxidative stress pathways.[22-24]

One of the most important cardiotoxicity factors is cumulative lifetime anthracycline exposure as recognized in the 1970's,[25, 26] and consistently falling out in subsequent studies as an independent risk factor. The threshold dose for toxicity continues to be debated, but has steadily decreased since the 1970's where initial limits were set over 500 mg/m^2 to a point where no dose is currently considered safe.[3] While overt cardiotoxicity is virtually guaranteed at doses over 800 mg/m^2, toxicity continues to manifest in up to 11% of patients at doses lower than 400 mg/m^2,[27] and doses as low as 200 mg/m^2 have necessitated cardiac transplantation in some patients.[28] Cumulative incidence is only increasing with time showing no plateau,[10] and the full extent of this problem is not yet known.[3]

The proposed mechanisms of anthracycline induced cardiotoxicity are multiple, varied and debated. They include: generation of free radicals both enzymatically and non-enzymatically that damage cardiac myocytes; anthracycline-iron complexes leading to lipid peroxidation and DNA damage; formation of toxic metabolites; inhibition of nucleic acid and protein synthesis; release of vasoactive amines; decreased expression of specific genes; impairment of mitochondrial membrane binding, assembly and creatinine kinase

activity; induction of apoptosis; disturbance of intracellular calcium homeostasis; alterations in transcriptional respiratory proteins; induction of nitric oxide synthetase; increased cytochrome C release from mitochondria; and accumulation of mitochondrial DNA and respiratory chain defects.[29-39] There are many areas of continued investigation.

Screening

Findings of cardiotoxicity are based on clinical symptoms or changes in traditional echocardiography measures, including EF and FS. Echocardiographic imaging came into routine use in the late 1970's.[27] Confirming early findings of declining EF and FS with increasing follow-up,[25, 26] recent studies have documented that earlier in follow-up both EF and FS remain normal but significantly lower compared to controls and the general population. EF and FS have since been validated as surrogates for CHF and death.[2, 40]

Although EF and FS are the current mainstays of screening guidelines,[4] there continues to be a lack of precise cardiovascular definitions and standardized evaluations.[3] Other problems in the evaluation of patients include bias from inter and intra-observer reliability and the variety of different manufacturers of echocardiographic equipment and processing software that is built upon varying algorithms. Additionally, changes in EF and FS are often detected late in the clinical course and may reflect advanced myocardial dysfunction.[19]

While traditional echocardiography exists as a diagnostic test, questions remain concerning its utility in population screening. In 1968 the World Health Organization published basic principles of screening[41] that continue to have important implications for clinical care:

1.) The condition should be an important health problem.

2.) There should be a treatment for the condition.

3.) Facilities for diagnosis and treatment should be available.

4.) There should be a latent stage of the disease.

5.) There should be a test or examination for the condition.

6.) The test should be acceptable to the population.

7.) The natural history of the disease should be adequately understood.

8.) There should be an agreed policy on whom to treat.

9.) The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.

10.) Case-finding should be a continuous process, not just a "once and for all" project.

Despite the rapid advancement in recognition of anthracycline-induced cardiotoxicity, there is still a great deal unknown about the underlying pathophysiology, or if the ability exists to identify early toxicity at a point when intervention might slow or abate the progression of cardiac dysfunction.[3] With these uncertainties, current guidelines do not actually meet all of the WHO principles of screening. As anthracycline induced cardiotoxicity remains an important health problem, there are now facilities for diagosis

and treatment, a latent stage of this disease has been identified, acceptable testing can be performed on the population at risk, and the natural history of this disease is better characterized. However, within the bounds of current detection methods we do not have a successful treatment for this condition, there is no consensus on which patients meet criteria for treatment, and the cost to benefit ratio is not favorable without action to take.

In an attempt to answer some of these important questions, newer echocardiographic technologies have been applied to anthracycline-induced cardiotoxicity. Tissue Doppler imaging (TDI) is a more sensitive technique for assessing regional wall-motion abnormalities and diastolic dysfunction and may identify changes earlier than either EF or FS. A number of studies have now demonstrated these changes in both early and late ventricular filling ratios (E/A) as well as tissue Doppler velocities (E/E') and myocardial performance index (MPI or Tei) in survivors of childhood cancer exposed to anthracyclines.[42-47] Interestingly many of these same studies also demonstrated significantly lower FS in survivors compared to controls, although still falling within a normal range. The 50-80% of exposed survivors exhibiting changes suggestive of cardiac dysfunction in these studies approaches the 85% reported in exposed survivors that historically have exhibited changes based on endocardial biopsy or post-mortem pathology.[48, 49] All of these technologies still remain somewhat operator and platform dependent, and problems around the influence of respiration and nearby motion on detection of velocities as well as load dependency need to be addressed.[42, 45]

Stress echocardiography[50] and non-imaging diagnostics including serum markers of N-terminal pro-beta natriuretic peptide, cardiac troponins and antioxidant capacity[51-53] have similarly been investigated. While some show promise, there are few data to date that support their regular use in the evaluation of anthracycline-induced cardiotoxity.

More recent advancements have been further developments of echocardiographic imaging with strain and strain rate. This modality is able to differentiate between active and passive movement of myocardial segments, to quantify intraventricular dyssynchrony, and to evaluate regional components of myocardial function. There are two modes, one analyzed through TDI and one analyzed through 2-dimensional speckle tracking. It provides further information about regional myocardial function by measuring local stretching or deformation.[54] Normal values have been established for all 3 cardiac orientations: radial, circumferential, and longitudinal.[55] Strain and strain rate imaging already has clinical utility in ischemic heart disease, valvular heart disease, diastolic dysfunction, hypertension with and without diastolic dysfunction, hypertrophic cardiomyopathies, monitoring of cardiac resynchronization therapy, assessing RV function, monitoring therapies, and in the transplanted heart for graft rejection.[56] As well, there is ongoing research into its use for congenital heart disease.[57]

These measures have been studied in adults exposed to anthracyclines[58, 59] and children during anthracycline infusions and in short-term follow-up.[57, 60-62] Despite not reaching abnormal levels in these studies, a decrease in EF, FS and some TDI measurements were

reported. These observations were more noticeable as the study population was further from exposure.[53]

This novel strain and strain rate technology also has its own inter and intra-observer reliability issues similar to, and in some cases worse than, traditional technology.[19, 54, 55] Challenges that currently exist include load dependency,[63] time-consuming off-line processing,[47, 54] substantial operator education,[19, 54] dependency on high-quality images that can be difficult to obtain in survivors,[53, 54] sensitivity to acoustic artifacts from calculations that amplify any noise component,[54, 56] the use of rapidly changing technology with different algorithms in different platforms that may not allow for comparable values, and heart rate variability that can be more pronounced in children.[54] The additional advantages and disadvantages of this technology have not been fully established.

Both traditional and novel screening methods lack in at least one major area: establishing long-term longitudinal data within each patient. While early descriptive studies accomplished this with FS,[27] it has not been consistently replicated for the other types of technology. While most are time consuming, costly, and difficult to perform, longitudinal studies are the only way to transition from the "snapshot in time" to a "life-course perspective" that has been suggested due to the undulating cardiovascular phenotype observed in this population.[3]

As progress often comes at a price and as cancer therapies continue to advance, there has been subsequent understanding regarding the costs of these therapies on the growing minds and bodies of children. Knowledge about anthracycline-induced cardiotoxicity has grown rapidly, but current clinical guidelines do not meet international standards for effective population screening. As proposed in this study, a better test that is able to define patients who should and could be effectively treated might allow progress toward meeting those standards.

Methods

Participants

This study was approved by the University of Minnesota Institutional Review Board and conducted in accordance with good clinical practice as described in the Declaration of Helsinki. All participants signed appropriate informed consent prior to enrollment and study procedures.

The survivor population was identified and recruited through the Long-Term Follow-Up Clinic at the University of Minnesota, Minneapolis, MN. Survivors were invited to participate by letter or in person by a study investigator. Inclusion criteria included: age ≤ 21 years at the time of cancer diagnosis, ≥ 18 years old at the time of study entry, in cancer remission and surviving ≥ 5 years from diagnosis, cumulative anthracycline exposure ≥ 250 mg/m^2, and ability to give informed consent. Cumulative anthracycline exposure was defined as doxorubicin dose + 0.833 * daunorubicin dose, according to the COG Long-Term Follow-Up Guidelines.[64] Exclusion criteria included: ongoing myelosuppressive therapy, history of cardiac directed radiation therapy, and history of known cardiovascular disease or clinically diagnosed diabetes mellitus.

The age and gender matched comparison group was recruited from healthy volunteers in the community. Inclusion criteria included: ≥ 18 years old at the time of study entry and the ability to give informed consent. Exclusion criteria included: myelosuppressive

therapy, history of cardiac directed radiation therapy, and history of known cardiovascular disease or clinically diagnosed diabetes mellitus.

Echocardiography

Studies were performed in the University of Minnesota Medical Center, Fairview Echocardiography Laboratory by a trained echosonographer with analysis performed by a trained cardiologist, both of whom were blinded to treatment status. Participants underwent 2-dimensional, pulse wave, continuous wave, and color flow Doppler transthoracic echo, as well as tissue Doppler imaging (TDI) and strain imaging using a Philips iE33 Ultrasound Machine (Philips Healthcare, Andover, MA, USA) with a variable transducer. Offline image analysis was performed using QLAB (Philips Healthcare, Andover, MA, USA).

The peak velocity of early (E) and late (A) ventricular filling and the E/A ratio were measured by using pulsed wave Doppler techniques. Deceleration time was measured as the interval from the peak of the E velocity extrapolated to baseline. Early and late diastolic tissue motions (E' and A') were measured with spectral TDI imaging. Load-independent mitral E'/A' and E/E' ratios were calculated for each subject. Left ventricular myocardial performance index (MPI), also known as Tei index, was measured by using the isovolumic contraction time (IVCT) + isovolumic relaxation time (IVRT) divided by ejection time (ET).

Two-dimensional gray-scale, short-axis, parasternal images were obtained at the level of the papillary muscle to evaluate radial function of the left ventricle. Cine-loops of 3 cardiac cycles triggered by the R wave of the QRS complex were saved digitally. Myocardial velocity data were analyzed on an off-line workstation using the dedicated QLAB quantification software (Philips Healthcare, Andover, MA). To evaluate left ventricular radial function peak systolic strain, early and late peak diastolic strain rate, and radial displacement were determined using a standard 6-segment regional analysis from the short-axis view. High levels of data variability in strain and strain rate capture and post-processing with considerably less variability in radial displacement resulted in the use of radial displacement as a surrogate for strain.

All traditional and TDI measures were generated by a single cardiologist. All strain imaging was processed with measures generated by a single investigator. The same single investigator repeated a smaller subset of 20 studies (10 survivors and 10 controls) to obtain intra-observer reliability. A second investigator then processed the same smaller subset of studies independently to obtain inter-observer reliability.

Statistical Analysis

The study was powered to detect a 1.0 standard deviation difference in radial displacement between cases and age and gender-matched controls at the 0.05 level of significance, using a 2-sided t-test test with 80% power. A standard deviation of ± 2.2 mm in healthy adult subjects was estimated from the literature.[61]

Descriptive statistics including means, standard deviations, and ranges were calculated for participant characteristics as well as echocardiographic measures. Means were compared between survivors and controls using unpaired two-sample t-tests. Linear regression was performed to compare correlation between continuous variables, with adjustment for additional modifying variables such as survival time. Adjustments were limited to one additional variable so as to maintain adequate power during the analysis. Results were considered significant at an alpha level of 0.05 or less. Statistics were performed in Microsoft Excel X for Mac (Microsoft Corporation, Redmond, WA, USA) and SAS 9.2 (SAS Institute Inc., Cary, ND, USA).

Results

Participant Characteristics

Demographics for survivors and controls are shown in Table 1. Consistent with the study design there were no differences in gender ($p = 1.00$) or age ($p = 0.94$). The study population was overall predominantly female and in the young adult age group. Survivors had most often been diagnosed with a sarcoma, and had on average survived over a decade from diagnosis. This placed them in the chronic cardiotoxicitity risk category. Anthracycline exposure was in the moderate to high dose range. All survivors had their medical records abstracted and none had experienced acute or early-onset cardiac toxicity. One survivor was being treated for hypertension with lisinopril and was also incidentally noted to have a bicuspid aortic value. One control subject was incidentally noted to have a dilated aortic root. All abnormal echocardiographic findings were communicated to study participants to allow for appropriate follow-up.

Traditional Echocardiographic Measures

Survivors had statistically significantly lower Fractional Shortening (FS) and Ejection Fraction (EF) compared to controls (Table 2). However, these variables were still within normal limits on both scales with FS ≥ 28% and EF ≥ 55% considered normal. Two controls and 4 survivors fell below the normal threshold of EF. No controls and 1

survivor fell below the normal threshold for FS. FS and EF were reasonably well correlated with each other ($r = 0.33$, $p = 0.056$).

In the control population there was no correlation between age and EF ($r = 0.03$, $p = 0.9$) or FS ($r = 0.28$, $p = 0.27$). In the survivor group there was no correlation between age and FS ($r = -0.02$, $p=0.95$), however there was a statistically significant decline in EF associated with advancing age ($r = -0.64$, $p = 0.006$). Figure 1 shows the difference in trends for EF versus age between the two groups. EF declined with increased survival time ($r = -0.48$, $p = 0.05$) and increasing anthracycline doses ($r = -0.61$, $p = 0.009$), but not with earlier age at diagnosis ($r = -0.32$, $p = 0.22$). EF did however decline with age at diagnosis once controlling for survival time ($r = -0.64$, $p = 0.03$). FS declined with increasing anthracycline doses ($r = -0.56$, $p = 0.02$), but not with earlier age at diagnosis ($r = 0.12$, $p = 0.66$), or increased survival time ($r = -0.11$, $p = 0.69$). Figure 2a shows the effect of anthracycline dose on EF and FS respectively.

Also shown in Table 2, pulse wave Doppler E/A ratios of ventricular filling did not show any statistical differences between survivor and controls.

Novel Echocardiographic Measures

TDI measures of E/E' ratios at the medial and lateral aspects of the mitral valve as well as the left ventricular Tei index (MPI) revealed no differences between the survivor and control groups (Table 2).

Radial displacement was statistically significantly lower in survivors compared to controls (Table 2). There was 1 survivor for whom radial displacement was obtained but the data were lost before analysis. Normal ranges are not well established; however, decline in radial displacement is associated with decreased cardiac function. Radial displacement increased with advancing age in the control population ($r = 0.56$, $p = 0.02$), but not in survivors ($r = 0.06$, $p = 0.82$). Radial displacement declined with increasing anthracycline dose ($r = -0.57$, $p = 0.02$) as shown in Figure 2b, but was not correlated with age at diagnosis ($r = 0.2$, $p = 0.46$) or survival time ($r = -0.07$, $p = 0.8$).

Traditional Versus Novel Echocardiographic Measures

Radial displacement is significantly correlated with both FS ($r = 0.52$, $p = 0.002$) and EF ($r = 0.35$, $p = 0.04$), as shown in Figure 3. Despite all three measures being associated with each other, the significant difference in radial displacement between survivors and controls remains even when controlling for FS ($p = 0.004$) or EF ($p = 0.03$).

After adjusting for survival time, there was still a significant association between EF and anthracycline dose ($p = 0.003$) but there is no longer a significant association between radial displacement and anthracycline dose ($p = 0.07$). The association did remain significant if controlling for survival time with respect to FS instead of EF ($p = 0.03$).

Reliability Measures

Using the Phillips system there was an excessive amount of variability with over 11% of all values measured in both survivors and controls having fallen out of normal physiologic ranges. Radial displacement, which is related through temporal integration of velocity and spatial integration of strain, is much less variable and can act as a surrogate for radial strain.[54, 56, 61] Less than 1% of all radial strain data fell out of normal physiologic range and was more reliable in this study. Inter-observer reliability showed an average difference of 16% between 2 readers with a correlation of 0.65 ($p = 0.002$). Intra-observer reliability showed an average difference of 12% with a correlation of 0.74 ($p = 0.0002$).

Discussion

Novel cardiac imaging techniques are rapidly changing. In addition to TDI and the use of strain and strain rate with 2D speckle tracking, more advanced methods including 3D and 4D strain techniques[65] and strain imaging with Magnetic Resonance Imaging (MRI)[66] are being investigated. With these new technologies, areas of improvement in the field of anthracycline-induced cardiotoxicity are being investigated, including earlier detection and improved understanding of the underlying pathophysiology.

Given how well correlated EF, FS and radial displacement were in this study, it raises the question as to whether any additional prognostic information can be generated by these novel measurements. Many studies have made the claim for earlier, preclinical detection.[42-47, 50-53, 57-62, 67] In this study both EF and radial displacement were significantly correlated with anthracycline dose. EF remained significantly correlated with anthracycline dose even when controlling for survival time, however radial displacement lost its association. This change in association is an example of additional information radial displacement is able to provide. Whether this translates to true preclinical detection is not yet determined, and will only be so with longitudinal studies of larger sample size.

The time course of cardiotoxicity from anthracyclines is primarily derived from meta-analysis of single time-point studies. However, within the chronic progressive decline that has been described, there is also a temporary recovery phase after the initial insult

with chemotherapy exposure.[20, 68] How each of these new measures in turn change throughout the course of initial damage, recovery, and subsequent progression from subclinical to clinical disease has not been shown within individual patients.

Information about the pathophysiology of this process is varied and specific mechanisms are debated.[16] The human heart is quite complex and the mechanism of action consists of increased rates of contraction and relaxation with increased twisting and untwisting motion of the LV.[50] Though this study did not directly address the question of pathophysiology, others have used novel technology such as regional deformational changes of strain and strain rate imaging to hypothesize further into this area. Issues about how involved the septum versus the lateral wall[62] or various layers of the myocardium from the epicardium to the endocardium[59] may provide more insight into some of the twisting and untwisting that needs to occur.

An additional consideration is the timeframe over which anthracycline-induced cardiotoxicity occurs, which can often be over many decades.[3, 10] While slow to change, the differences in individual FS and EF may yet yield much of the screening information pediatric oncologists desire with additional information to be added from TDI and strain imaging in more acute evaluation. Currently these newer modalities are more often used to diagnose and track acute changes in cardiac status including ischemic heart disease, monitoring of cardiac resynchronization therapy, and in the transplanted heart for graft rejection.[56] There are also no validated studies to suggest that in the long-term these

novel measures accurately predict morbidity and mortality in this disease, mostly because of a lack of longitudinal studies.

Limitations to this study included problems with quality data acquisition, significant time post-processing data offline, and moderate inter-observer and intra-observer reliability. Data quality in strain and strain rate imaging forced the use of a surrogate marker in radial displacement that while mathematically related, does not yield exactly the same information. The exposed survivor population is over the cardiac risk stratification of 300 mg/m^2 and far enough out in their follow-up at a mean of 16 years, but still under a mean 30 years of age. It might be expected that more pronounced results will occur as these patients age into their fifth and sixth decades. In fact, the patient with the most pronounced cardiac findings was the oldest, furthest out in follow-up and had been exposed to the highest cumulative anthracycline dose of 645 mg/m^2. The small size of this study also prevented further subgroup analysis and multiple variable regression analysis.

Strengths of this study included the use of an age and gender-matched healthy control population rather than comparing to a reported normal population, examination of a group of survivors later into their follow-up period than reported by most prior studies, and the simultaneous inclusion of traditional measures, TDI measures and novel radial displacement as the surrogate for strain.

In conclusion, both traditional and novel measures of cardiac function are reduced in anthracycline exposed cancer survivors compared to age & gender-matched healthy controls. All of these measures significantly decrease as expected with increasing anthracyline dose. Radial displacement may be an additional monitoring technique for anthracycline induced cardiotoxicity, but the clinical advantage of novel compared to traditional measures requires further study, specifically in a longitudinal fashion.

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Appendix of Tables and Figures

Table 1: Patient Characteristics (n=34)

	Survivors (n = 17)	**Controls (n = 17)**
Gender (male)	35 %	35 %
Current mean age and range (years)	28.4 (18-50)	28.7 (18-50)
Mean age at diagnosis and range (years)	12.5 (1-20)	n/a
Mean survival time and age (years)	16 (5-30)	n/a
Diagnosis (#)	17	n/a
Osteosarcoma	10	
Rhabdomyosarcoma	3	
Ewing Sarcoma	1	
Synovial Sarcoma	1	
Lymphoma	1	
Wilm's Tumor	1	
Mean anthracycline dose and range (mg/m^2)	420 (300-645)	n/a

Table 2: Echocardiographic Measures

	Survivors	**Controls**	**p-value**
Ejection Fraction (%)	55.4 ± 6.7	59.7 ± 6.2	0.057
Fractional Shortening (%)	35.5 ± 3.8	39.6 ± 4.7	0.009
E/A Ratio	1.65 ± 0.53	1.78 ± 0.53	0.49
Medial E/E' Ratio	7.33 ± 2.09	6.6 ± 2.02	0.32
Lateral E/E' Ratio	5.35 ± 1.73	4.84 ± 1.47	0.37
Tei Index	0.4 ± 0.14	0.39 ± 0.09	0.26
Radial Displacement (mm)	5.61 ± 1.16	6.73 ± 1.52	0.025

All values expressed as mean ± standard deviation

Figure 1: Correlation of Ejection Fraction versus Age

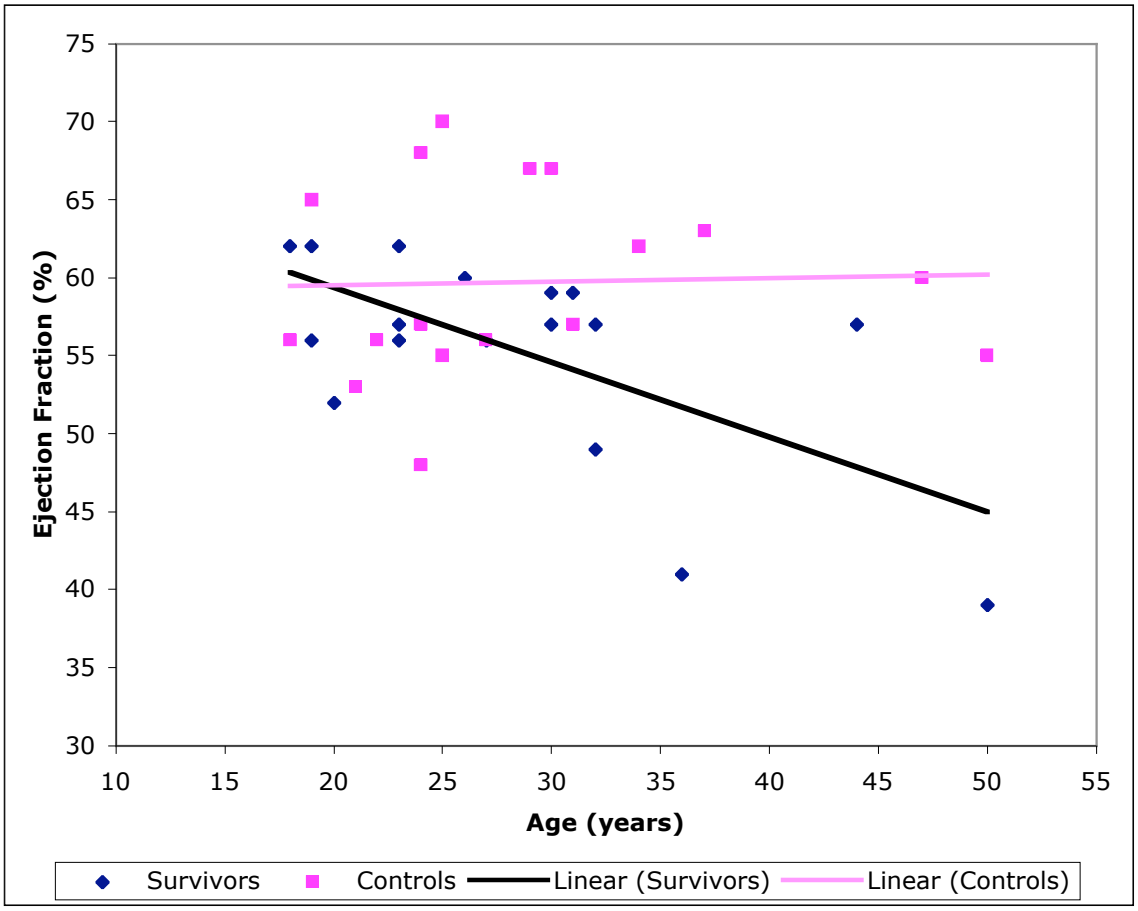
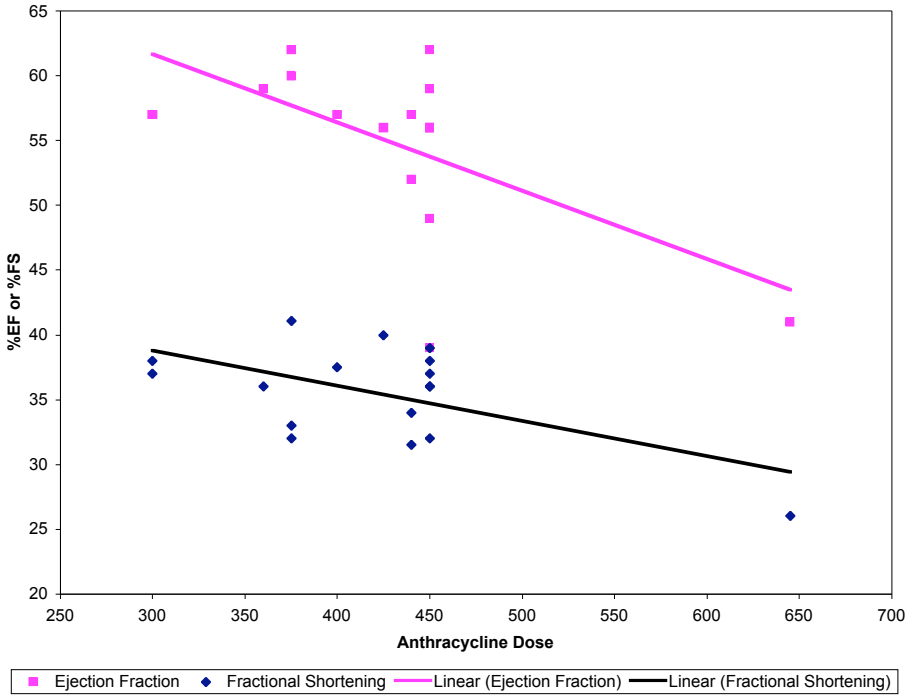


Figure 2: Effect of Anthracycline Dose

2a: Ejection Fraction and Fractional Shortening



2b: Radial Displacement

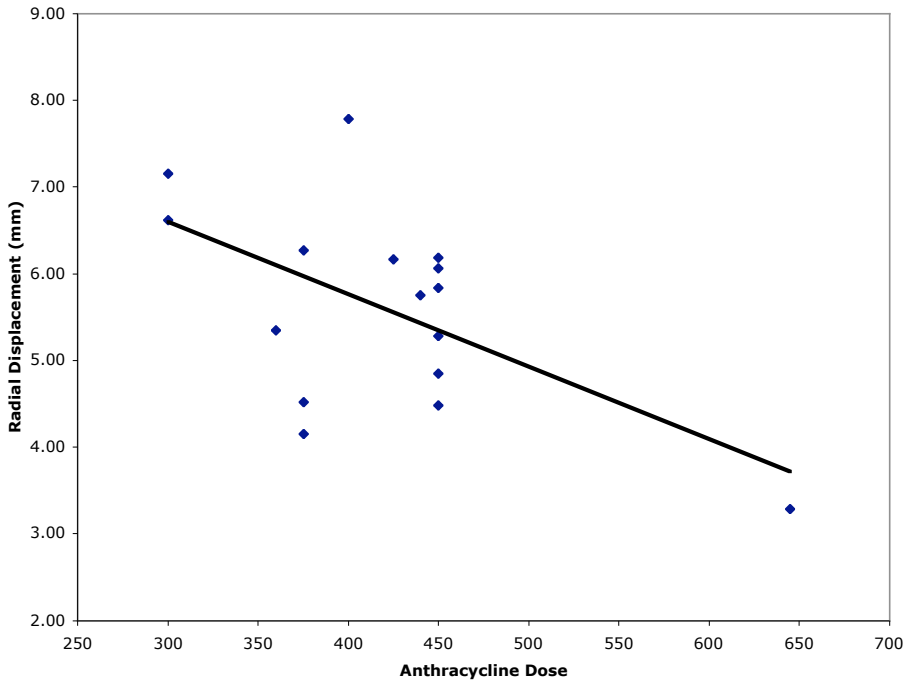


Figure 3: Correlation of Novel versus Traditional Measures