# Dynamic Myocardial Response to Exercise in Childhood Cancer Survivors Treated with Anthracyclines

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*Background:* Anthracycline cardiotoxicity can cause significant long-term morbidity in childhood cancer survivors (CCS), but many CCS do not manifest clinical symptoms until adulthood. The aims of this study were to characterize the dynamic myocardial response to exercise of CCS at long-term follow-up by combining semisupine bicycle exercise stress echocardiography with myocardial imaging techniques and to establish whether semisupine bicycle exercise stress echocardiography could identify CCS with abnormal exercise response.

*Methods:* This was a single-center prospective cross-sectional study. One hundred CCS and 51 control subjects underwent semisupine bicycle exercise stress echocardiography. Color Doppler tissue imaging peak systolic (s′) and diastolic (e′) velocities, myocardial acceleration during isovolumic contraction, and longitudinal strain were measured at rest and at incremental heart rates in the left ventricular (LV) lateral wall, basal septum, and right ventricle. The relationship with increasing heart rate was evaluated for each parameter by plotting the values against heart rate at each stage of exercise. Kernel density estimate was used to establish the normality of the individual CCS exercise responses.

*Results:* At rest, no significant differences were found for LV lateral wall, right ventricular (RV), and basal septal systolic and diastolic velocities between CCS and control subjects. Only septal e′ was lower in CCS. LV longitudinal strain was similar between groups, while RV longitudinal strain was lower in CCS. At peak exercise, LV lateral wall, RV, and septal s′ were not different between groups, while e′ were significantly lower in CCS. LV lateral wall and septal isovolumic acceleration were also reduced in CCS. LV longitudinal strain was different between groups, while RV longitudinal strain was similar. The dynamic response of Doppler tissue imaging velocities, isovolumic acceleration, and strain was similar between CCS and control subjects. Kernel density estimate analysis confirmed that most CCS responses were within the normal range.

*Conclusions:* At 10-year follow-up, anthracycline-treated CCS with normal baseline ejection fractions have LV and RV systolic and diastolic myocardial exercise response comparable with that of control subjects. Minor differences were observed between CCS and control subjects at rest and at peak exercise, but the dynamic response is within the normal range. (J Am Soc Echocardiogr 2018;■:■-■.)

*Keywords:* Anthracycline cardiotoxicity, Stress echocardiography, Children, Strain echocardiography

The long-term effect of anthracyclines on cardiac function is an ongoing concern in the treatment of childhood cancer. Cardiac disease is the third leading cause of premature death (after cancer recurrence and secondary cancers) in childhood cancer survivors (CCS), with a sevenfold increased risk for premature cardiac death compared with the general population.[1,2] Echocardiographic surveillance for potential long-term cardiotoxic effects of anthracyclines is an important component in the follow-up of CCS. One of the challenges is

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Drs. Cifra and Chen contributed equally to this work.

Conflicts of Interest: None.

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| Abbreviations |
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| **CCS** = Childhood cancer survivor(s) |
| **DTI** = Doppler tissue imaging |
| **EF** = Ejection fraction |
| **HR** = Heart rate |
| **IVA** = Isovolumic acceleration |
| **KDE** = Kernel density estimate |
| **LV** = Left ventricular |
| **RV** = Right ventricular |
| **RVFW** = Right ventricular free wall |

the early identification of cardiac dysfunction in patients at risk for developing late cardiomyopathy.[3] Changes in ejection fraction (EF) typically become evident only in the more advanced stages of myocardial disease.[4] In the acute treatment phase, Doppler tissue and myocardial strain imaging have been described to detect early changes in myocardial function before a decrease in EF.[5] In a large adult cohort of CCS with preserved EFs late after treatment, left ventricular (LV) global longitudinal strain was lower compared with normal control subjects.[6] In the present study, we aimed to study the dynamic myocardial response to exercise in pediatric CCS with preserved EF at rest. We hypothesized that exercise stress echocardiography combined with myocardial imaging techniques such as color Doppler tissue imaging (DTI) and speckle-tracking echocardiography may unveil subclinical myocardial dysfunction in this population and may be helpful in identifying patients at risk.

## METHODS

This was a single-center, prospective, cross-sectional study approved by the institutional research ethics board. Eligible participants included children and adolescents (<18 years of age) who had been treated with anthracyclines and completed cancer treatment ≥5 years before enrollment. Exclusion criteria were congenital heart disease, history of cardiotoxicity or dilated cardiomyopathy, known abnormal LVEF (<55%) on the last echocardiogram, and inability to perform bicycle exercise testing. Patients were recruited from the long-term survivor cohort included in the prospective study Preventing Cardiac Sequelae in Pediatric Cancer Survivors (ClinicalTrials.gov identifier NCT01805778) described by Skitch *et al.*[7] Only patients followed in Toronto were included from the multicenter cohort. Before semisupine bicycle exercise stress echocardiography, patients underwent resting functional echocardiography, including DTI and strain imaging. All measurements were performed in accordance with the American Society of Echocardiography pediatric guidelines.[8] Healthy control subjects were recruited from pediatric patients referred for heart murmur assessment who had normal results on echocardiography, physical examination, and electrocardiography and from a group of healthy volunteers.[9]

### Clinical Data

The age, gender, height, and weight of all participants were recorded. Body surface area was calculated using the Mosteller formula. Baseline physical examination measurements included resting heart rate (HR) and blood pressure. Participants' medical charts were reviewed to obtain information on their cancer diagnoses, age at diagnosis, cumulative anthracycline dose, and history of radiotherapy to the thorax. The range of follow-up time since the completion of cancer treatment was 5 to 17.5 years. CCS were stratified into two groups: "low risk" (<300 mg/m$^2$ of doxorubicin-equivalent cumulative anthracyclines without radiotherapy involving the heart) and "high risk" (≥300 mg/m$^2$ of doxorubicin-equivalent cumulative anthracyclines or any anthracycline dose in addition to cardiac radiation exposure).[10]

### Semisupine Bicycle Exercise Stress Echocardiography Protocol

All stress examinations followed a standardized Bruce exercise protocol, using 3-min stages with a target speed of 60 rpm. Workload was increased in 20-W increments every 3 min for children up to 14 years of age and 25-W increments above this age. A semisupine bicycle (Lode B.V., Groningen, The Netherlands) was used. The target HR was 85% of the maximal HR, calculated as 220 − age. Early termination was determined by patient fatigue, the occurrence of predefined adverse events (arrhythmia, ischemia, chest pain, clinical signs of circulatory compromise, progressive fall in systolic blood pressure >10%, or severe hypertension) or decline in image quality related to moving or breathing at the more intense phases of exercise. Patients were monitored with continuous 12-lead electrocardiography. Sphygmomanometry blood pressure measurements were obtained during the last 30 sec of each stage (Dinamap; GE Medical Systems, Milwaukee, WI).

### Echocardiographic Acquisition and Analysis

Images were obtained using a Vivid E9 ultrasound system (GE Medical Systems) during the last 2 min of each stage using the Smart Stress application. The stress protocol included acquisition of color DTI velocities and storage of raw Digital Imaging and Communications in Medicine grayscale images that can be analyzed using two-dimensional speckle-tracking echocardiography. Echocardiographic images were acquired at each stage of exercise and during recovery, and image loops of ≥10 beats were captured to ensure a sufficient number of heart cycles for offline analysis. The stress protocol included a parasternal long-axis view, a parasternal short-axis view at the papillary muscle level, and two apical four-chamber view optimized for offline two-dimensional speckle-tracking echocardiographic analysis each focused on the left ventricle and right ventricle (frame rate >80 frames/sec), spectral pulsed-wave Doppler of mitral inflow, and high–frame rate narrow-sector color DTI of the LV lateral wall and the interventricular septum and of the right ventricular (RV) free wall (RVFW), in the apical three- and two-chamber views.

Resting and exercise echocardiographic parameters were analyzed offline using EchoPAC software (GE Medical Systems). All conventional systolic and diastolic parameters were measured according to published guidelines.[11] Fractional shortening was measured from the parasternal short-axis view by M-mode imaging. LVEF was determined using the biplane Simpson method. Color DTI was performed using a 5-mm sample volume placed in the middle of the myocardium at the basal third of the left ventricle and RVFW and basal septum. Peak systolic and early diastolic DTI velocities were measured at each stage of exercise. Fusion of the e′ and a′ waves was frequently seen during exercise and this fused wave was measured as e′. Velocity measurements were recorded as the average value from three consecutive cardiac cycles. Isovolumic acceleration (IVA) was obtained as described previously.[12] At each stage of exercise, three measurements of IVA were made, and an average was recorded. LV and RV longitudinal strain measurements during exercise were performed using two-dimensional speckle-tracking echocardiography from the apical four-chamber view. LV longitudinal strain was defined as the mean value of segmental longitudinal strain indices obtained in the six LV segments. RVFW longitudinal strain was calculated on the basis of three segments.

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