Exercise training in childhood cancer survivors with subclinical cardiomyopathy who were treated with anthracyclines

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Abstract

Childhood cancer survivors (CCS) treated with anthracyclines are at risk for cardiomyopathy. This case series evaluated the response of anthracycline exposed CCS with subclinical cardiomyopathy to aerobic and strength training. Body composition, strength and cardiopulmonary fitness were evaluated before and after the 12-week intervention. All equipment and materials were provided to five 10+ year CCS (3 males, mean age 38.0±3.3 years) for a guideline-based home exercise program. All five completed the study with no adverse events. Compliance with exercise was 86%. These results suggest that exercise training may improve exercise capacity of CCS with subclinical cardiomyopathy.

Keywords

childhood cancer survivor; exercise training; strength training; anthracyclines; cardiomyopathy

Introduction

There are over 360,000 childhood cancer survivors (CCS) in the United States [1], 70% will experience at least one chronic health condition within 30 years of diagnosis [2]. CCS have an elevated risk for cardiovascular disease [2,3], including 15-fold increased risk for congestive heart failure and a 10-fold increased risk of coronary heart disease, compared to siblings with no cancer history [3]. Anthracycline antibiotics, such as doxorubicin and daunorubicin, used in the treatment of approximately 45% of children diagnosed with cancer [4], are strongly associated with impaired cardiovascular function [5]. The risk of anthracycline-induced cardiomyopathy is dose dependent, and may manifest either during treatment or much later, with declines in cardiac function appearing as late as 10 or more years after completion of therapy [6-9].

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The Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers suggest that anthracycline-treated CCS undergo cardiac function monitoring and avoid intensive isometric exercise and heavy resistance training [10]. Previous research in non-cancer patients at risk for, or who have, subclinical cardiomyopathy indicates that exercise programs, that include aerobic and resistance training, are safe and that training improves peak oxygen consumption and exercise tolerance [11,12]. The responses to exercise training among CCS with anthracycline-induced cardiomyopathy have not been evaluated.

This case series was designed to evaluate response of anthracycline-treated CCS diagnosed with subclinical cardiomyopathy to a 12-week exercise training program.

Methods

Participants were members of the St. Jude Lifetime Cohort (SJLIFE), a study of adult survivors of childhood cancer treated at St. Jude Children's Research Hospital (SJCRH) between 1962 and 2003 [13]. Potential participants were at least 18 years old, 10 or more years from diagnosis of childhood cancer, treated with doxorubicin and/or daunorubicin, sedentary (less than 150 minutes of moderate intensity physical activity per week), not currently receiving pharmacotherapy for cardiomyopathy, and who had an ejection fraction between 40% and 55%. Patients who had received chest radiation therapy were not eligible.

Demographic information was obtained from self-report questionnaires and data on prior cancer treatment were collected from medical records by trained abstractors.

Functional assessments were performed at baseline and 12 weeks. Body fat was assessed via dual-energy x-ray absorptiometry using Hologic Model QDR 4500 fanarray scanner (Bedford, MA, USA). Blood pressure was evaluated manually in a sitting position, following a five minute rest period. Height and weight were measured with a wall mounted stadiometer (centimeters [cm]) and electronic scale (kilograms [kg]), respectively. Knee extension peak torque in Newton meters was measured at 60 degrees per second using a Biodex System III pro (Biodex International, Shirley, NY). The average of both legs was used for analysis, except in the case of lower extremity amputation, where peak torque from the unaffected limb was reported. Three-dimensional echocardiography was performed with the GE Vivid E9 cardiovascular ultrasound system (GE Healthcare, Buckinghamshire, UK) and interpreted by a board certified cardiologist. Ejection fraction (%) was reported for each participant. Cardiopulmonary exercise testing (CPET) employed a modified Bruce protocol or a 10 watt per minute arm ergometer protocol. Electrocardiogram (ECG), blood pressure, and gas collection were recorded and monitored continuously until volitional fatigue using the Ultima Cardio2 gas exchange and ECG system (MGC diagnostics, St. Paul, MN). As a surrogate for stroke volume and arteriovenous oxygen differences, peak oxygen pulse (mL/beat) was calculated from CPET as peak oxygen consumption (ml/min) divided by the corresponding heart rate (bpm).

The exercise prescription was 12 weeks in length and included both aerobic and resistance training. Aerobic training was prescribed according to American Cardiology/American

Heart Association guidelines to gradually achieve workloads of 40% to 70% of heart rate reserve [(maximal heart rate-resting heart rate)*intensity+ resting heart rate] for 20 to 45 minutes three to five times per week [14,15]. Resistance training was prescribed according to the American Association of Cardiovascular and Pulmonary Rehabilitation and included one set of 12 to 15 repetitions on eight to ten exercises two to three days per week [15,16]. Exercise training was completed by participants at home; all equipment was provided. Following baseline testing, an exercise physiologist reviewed and demonstrated each component of the exercise training program and the suggested progression of intensity and repetitions for each participant. Weekly phone calls between the exercise physiologist and survivor were completed to track progress, adjust progression of workouts, and promote compliance. Compliance, evaluated using workout logs and self-report during weekly phone calls, was calculated as the number of sessions completed divided by the number of sessions prescribed. This research project was reviewed and approved by the SJCRH Institutional Review Board and all subjects gave written, informed consent to participate.

Results

Five survivors (3 males; mean age 38 ± 3.3 years) completed the training program with no adverse events (Table 1). Compliance with the prescribed exercise was 86%. Participants lost an average of 1.3 kg (percent change; -2.0%) of bodyweight, and 1.1% body fat (-3.9%) over 12 weeks. Peak oxygen consumption and ejection fraction improved, on average, 10.6% and 12.6%, respectively. Maximal heart rate responses (-4.6%) and respiratory exchange ratios (0.0%) remained relatively stable. Oxygen pulse improved increased by a mean of 13.6%. Results for each participant are reported in Table 2.

Discussion

This case series evaluated the efficacy of prescribed aerobic and resistance training among five CCS with subclinical cardiomyopathy. No participant had a significant cardiovascular event during CPET or exercise training. Additionally, no participant was removed from exercise testing or training. These findings are consistent with previous reports documenting the responses to exercise training programs in non-cancer populations with dilated cardiomyopathy and congestive heart failure [11,12,17,18].

This preliminary work indicates that CCS can respond to training like other populations of patients with dilated cardiomyopathy (DCM) or congestive heart failure (CHF) [17,18]. Our training program included both aerobic and resistance exercises, which stimulate adaptation in both central (i.e cardiac) and peripheral (i.e. muscle, and vascular) structures. Previous literature regarding patients with DCM and CHF report that improvements in exercise tolerance are primarily related to increased function in peripheral structures, including increased numbers of and function among mitochondria, and an increase in capillary density [19,20]. Improvements in left ventricular function, particularly improved filling in those with abnormal diastolic filling patterns, are also possible [17]. Although not directly measured in our patients, it appears that improvement in left ventricular function, when oxygen pulse was used to represent stroke volume, is one potential contributor to increased exercise capacity. Additionally, because increases in oxygen pulse were not always

proportional to increases in exercise capacity in our case series, it is likely that peripheral adaptation also contributed to improved function.

Clinical trials are needed to definitively evaluate the efficacy and safety of aerobic and resistance exercise training programs in CCS treated with anthracyclines. Childhood cancer survivors with other diagnoses and those on medications for DCM should be included in these studies and evaluated for their responses. Additionally, research is needed to determine the independent contributions of exercise induced muscular, vascular, and cardiac adaptation with respect to increased aerobic capacity in CCS with DCM. This case series demonstrates that carefully prescribed exercise training including aerobic and resistance training can be effectively administered as a home-based intervention in CCS with DCM.

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Table 1

Patient characteristics

Patient	Age at baseline (years)	Sex	Race	Primary diagnosis	Age at diagnosis (years)	Surgery	Treatment	
							Chemotherapy agent	Cumulative dose (mg/m ²)
1	33	male	black	osteosarcoma (humerus)	3	forequarter amputation	Cisplatin	356
							Doxorubicin	298
							Ifosfamide	64,000
2	38	male	white	Ewing sarcoma (metatarsal)	13	amputation fourth toe	Cyclophosphamide	1048
							Cyclophosphamide (oral)	10,993
							Dactinomycin	5
							Doxorubicin	367
3	40	female	black	osteosarcoma (femur)	13	above the knee amputation	Bleomycin	90
							Cisplatin	300
							Cyclophosphamide	5,700
							Dactinomycin	6
							Doxorubicin	380
4	40	male	white	osteosarcoma (femur)	14	above the knee amputation	High-dose Methotrexate	120,000
							Bleomycin	135
							Cisplatin	400
							Cyclophosphamide	5,400
							Dactinomycin	6
							Dexamethasone	33
5	41	female	white	osteosarcoma (tibia)	15	above the knee amputation	Doxorubicin	330
							High-dose Methotrexate	144,000
							Bleomycin	150
							Cisplatin	400
							Cyclophosphamide	6,000
							Dactinomycin	6
							Doxorubicin	380
							High-dose Methotrexate	144,000

Table 2

Response to exercise training in Childhood Cancer Survivors with Cardiomyopathy

Patient	Height (cm)	Weight (kg)	Body fat (%)	RHR (bpm)	SBP (mmHg)	DBP (mmHg)	EF (%)	VO ₂ (ml/kg/min)	O ₂ Pulse (ml per beat)	MHR (bpm)	RER	Leg strength (n·m)	
1	Baseline	189.5	102.4	28.1	76	126	90	40	30.2	14.7	211	1.2	273.5
	12 Weeks		97.2	24.1	80	126	90	51	35.4	16.5	208	1.27	353.0
	% change		-5.1%	14.2%	5.3%	0.0%	0.0%	27.5%	17.2%	12.2%	-1.4%	5.8%	29.1%
2	Baseline	163.8	58.9	29.2	88	123	84	45	27.5	7.9	205	1.23	143.1
	12 Weeks		54.8	27.6	86	118	81	47	30.9	8.4	202	1.3	144.9
	% change		-7.0%	-5.5%	-2.3%	-4.1%	-3.6%	4.4%	12.4%	6.3%	-1.5%	5.7%	1.3%
3	Baseline	168.3	48.2	34.7	87	124	74	42	10.9	2.9	181	1.4	102.5
	12 Weeks		48.1	34.6	94	124	70	46	17.1	4.6	178	1.33	123.5
	% change		-0.1%	-0.3%	8.0%	0.0%	-5.4%	9.5%	56.9%	58.6%	-1.7%	-5.0%	20.5%
4	Baseline	171.4	66.9	18.5	79	125	82	42	26.3	9.7	182	1.23	254.7
	12 Weeks		67.8	16.8	79	133	87	43	28.3	12.2	157	1.19	277.4
	% change		1.3%	-9.2%	0.0%	6.4%	6.1%	2.4%	7.6%	25.8%	-13.7%	-3.3%	8.9%
5	Baseline	169.9	52.5	30	68	104	66	50	13.1	3.8	180	1.12	87.5
	12 Weeks		54.7	32.1	74	105	58	60	18.1	5.8	171	1.12	95.4
	% change		4.2%	7.0%	8.8%	1.0%	-12.1%	20.0%	38.2%	52.6%	-5.0%	0.0%	90.0%

RHR: Resting heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; EF: ejection fraction; VO₂: volume oxygen consumed; MHR: maximal heart rate; RER: respiratory exchange ratio