Benefits of Cardiac Rehabilitation for Patients With Lymphoma Undergoing Hematopoietic Stem Cell Transplantation

BACKGROUND

Hematopoietic stem cell transplantation (HSCT) is standard treatment in recurrent lymphoma, with ~50 000 hematopoietic stem cell transplants performed annually worldwide.[1] The 5-yr cancer-specific survival continues to improve,[2] however, for many at high cost. At initial diagnosis, patients with lymphoma are treated with anthracycline-based chemotherapy protocols. With recurrence, HSCT is the only curative intervention involving peripheral stem cell collection, another high-dose chemotherapy, and then stem cell infusion. Stem cell engraftment requires prolonged recovery (4+ wk) during which patients are bedfast, critically ill with hemodynamic and major organ instability. In the short-term, decreased functional status and poor quality of life (QOL) are universal. In the longer-term, with organ toxicities, HSCT survivors develop cardiovascular risk factors at rates 7.0-15.9 times greater than their matched controls,[3,4] with subsequent 5.6 times greater risk of cardiovascular disease (CVD) events including myocardial infarction, heart failure, and stroke.

Aerobic exercise improves overall QOL and facilitates physical recovery in HSCT populations. However, this single intervention cannot adequately address multiple CVD risk factors, nor influence future events. A recent position statement from the American Heart Association recommends an approach based on the cardiac rehabilitation (CR) model[5] that has been beneficial in patients with early breast cancer.[6] In addition to clinical exercise physiologists, CR commonly involves multidisciplinary teams (MDTs) of dieticians, social workers, pharmacists, nurse practitioners, and cardiologists synergistically promoting heart-healthy lifestyle and reducing CVD risk. We have previously shown that CR improves multiple physical metrics in HSCT.[7] In brief, patients with recurrent lymphoma were sequentially referred to CR. Activity protocol testing was performed at three time points: before HSCT, 6 wk following HSCT, and 14 wk post-HSCT (Figure). After HSCT, CR was an 8-wk program of supervised moderate aerobic activities and light resistance training. At 14-wk testing, we observed significant improvements compared with baseline, concluding that with CR, HSCT survivors can meet or even surpass baseline functioning. However, in traditional CVD populations, participation in CR is often poor, influenced by multiple individual factors.[8] Accordingly, we studied perspectives of HSCT patients with recurrent lymphoma who participated in this CR program.

METHOD

Following ethical approval from Health Research Ethics Board of Alberta ID#: CC-16-0503, patients were mailed an invitation letter. Ten interviews were conducted in a private setting and using interpretive description, three key themes were identified.

All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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RESULTS

PERCEPTIONS OF CV RISK AND PRIORITIES

Participants reported the immediate issues associated with HSCT were their main priority, rather than theoretical future risk of CVD. However, some expressed CR as a means to convey their appreciation:

> I felt so committed to them, that was part of the reinforcement, part of the motivation. But it was a quid pro quo … [the nurse practitioner] especially was really committed to me … I would stand on my head for her and that team. Because they, well, they saved me.

Among those previously active, CR participation was a priority. In addition to exercise, patients could choose to attend via face-to-face interactions, written information, or group sessions. While some initially did not believe these sessions were useful, others reported benefits, especially where overlap of symptoms common to both CVD and HSCT occurred, such as energy conservation.

PERCEPTIONS OF CR ON HSCT RECOVERY

Much of participant reflections dealt with the debilitating treatment effects associated with HSCT. For many, returning to exercise exposed the marked decline from pre-HSCT status:

> One thing that shocked me with the transplant is how weak I got. Once I had the transplant, and crashed, if you tried to tell me to exercise, I would have told you to piss off.

Observing their strength improving as the CR program progressed provided patients a tangible motivation to continue.

CR AS A COPING MECHANISM

As HSCT was a long and difficult experience for most, coping and success during recovery were multifactorial processes influenced by goal setting, positive attitude, and the CR program itself:

> I had a goal for admitting one of my students to the bar the first week of July of that year. And so, I did everything humanly possible to get myself in shape … I had to be fit—mentally and physically fit.

Remaining positive and maintaining hope through recovery were seen as instrumental:

> As far as hope … [*sigh*] attitude going in, or during … the whole treatment and everything else, in my mind, makes a huge difference … just in terms of believing that you're gonna get out the other side.

Here, CR team members were especially important. Participants felt they had an additional team beyond the HSCT treatment team supporting them during recovery and coaching them to future health.

DISCUSSION

Compared with all cancer survivors, those undergoing HSCT are likely the highest-risk group overall for concurrent and subsequent treatment-related cardiac events. A recent position statement from the American Heart Association recommends a risk-based cardio-oncology care delivery model based on CR programming.[5] Oncology guidelines recommend evaluation and management of risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity.[9] However, oncology teams are

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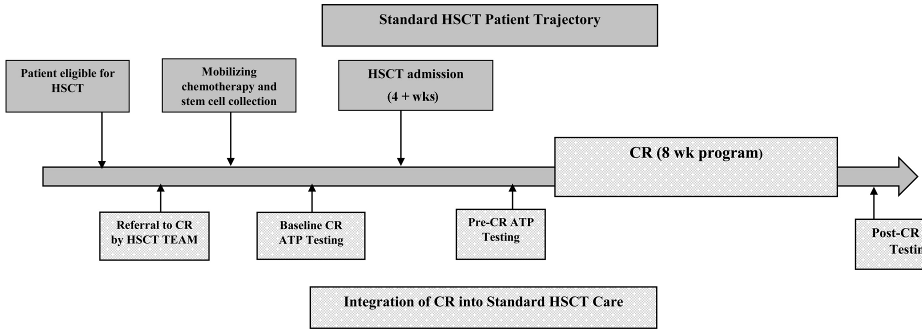

Figure. Integration of CR in HSCT trajectory. From Rothe et al.[7] Reproduced with permission. ATP indicates Activity Tolerance Protocol (exercise testing); CR, cardiac rehabilitation; HSCT, autologous hematopoietic stem cell transplant.

rarely sufficiently experienced to provide this specialized support. To our knowledge, we are the first to describe both physiological and psychological experiences of high-risk patients with cancer referred to CR. Cancer-specific rehabilitation centers are few and only in major urban centers. Thus, CR represents an optimal service model available in many settings, including telehealth, to address the complex needs of high-risk cancer populations.[5,9] A noteworthy finding was the powerful connection to both the HSCT oncology and CR MDTs. Both offered support during an extremely difficult time, aiding both emotional and physical recovery.

Approximately 18 million cancer survivors were expected in the United States by 2020,[10] struggling daily with persistent debilitating symptoms and exponential CVD risk. Cardio-oncology is a field in relative infancy but with great opportunity to reduce morbidity and mortality. As survivors have diverse needs associated with initial diagnosis and subsequent treatments, supportive CVD care should be personalized according to the degree of symptoms and accumulating risk. CR MDT care represents the future health promotion model for high-dose and high-risk cancer survivors with their extensive knowledge of proven approaches. Cancer and cardiovascular MDTs are key to patient coping and survivorship and could provide complementary efforts in effective CVD risk reduction before, after HSCT, and lifelong.

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A Strategy to Mitigate Airborne Particle Accumulation During Exercise in a Cardiac Rehabilitation Center

Exercise-based cardiac rehabilitation (CR) is a class 1 indication for patients with cardiovascular disease (CVD) and represents a mainstay of therapy to reduce CVD risk factors while reducing rehospitalization and mortality.[1] The coronavirus 2019 (COVID-19) pandemic resulted in closure of CR programs to in-person exercise training due to concerns for potential viral transmission.[2,3]

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Some programs have considered offering home-based CR[4,5] and instituting protective measures[6]; however, challenges remain. Exercise training, as conducted during CR, augments the generation of airborne respiratory droplets and aerosolized particles.[7] In addition, the utilization of face masks, while effective at capturing large droplets, has shown minimal efficacy in reducing small particulate accumulation during exercise.[7] Thus, there is an urgent need for guidance on alternative strategies that can be instituted by CR programs to mitigate the accumulation of airborne particles during exercise-based CR. In this study, we tested the efficacy of enclosed pods with continuous air filtration to mitigate the accumulation of airborne particles during exercise in a CR center setting.

METHODS

All experimental protocols were approved by the institutional review board at Mayo Clinic. Six healthy volunteers (three women; age: 31 ± 3 yr; body mass index: 25 ± 3 kg/m^2) free of any known CVD, pulmonary, or metabolic disease completed two 30-min moderate-intensity continuous training sessions with (MICT-F) and without air filtration (MICT-NF) and a single 30-min high-intensity interval training session with air filtration (HIIT-F) in the CR center at Mayo Clinic (Rochester, MN). Each MICT session consisted of treadmill running at a self-selected speed and grade to achieve a rating of perceived exertion (RPE) of 11-13. The HIIT-F session consisted of six high-intensity intervals (target RPE: 16-18; 2 min), each followed by a low-intensity interval (target RPE: 10-12; 3 min). All exercise sessions were preceded by a 5-min warm-up, followed by a 5-min cooldown. Face masks were not utilized during any of the exercise sessions. Heart rate was recorded during the final minute of exercise.

All sessions were performed in a custom-manufactured exercise pod housed inside the CR center. The pod was an enclosed structure with a single doorway and internal dimensions of 124 × 124 × 144 inches (1281 ft).[3] An OptiClean Dual-Mode (Carrier) air scrubber and negative air machine was incorporated into the pod and provided 99.97% high-efficiency particulate air filtration of particles ≥0.3 μM at 713 ft^3/min (~33 air exchanges/hr). Airborne particles were measured inside the pod and at a centralized location within the CR center using a light-scattering 985 Particle Counter (Fluke) capable of quantifying airborne particles between 0.3-10 μM. Particle counters were positioned opposite the air filtration system inside the pod and near the middle of the CR center ~15 ft from the pod doorway. Air samples were taken every 10 sec at baseline (>10 min) and during each exercise session. The accumulation of aerosols (0.3-0.5 μM),[8] droplets (0.5-1.0 μM),[8] and cumulative particle counts (0.3-10 μM) was calculated as changes from baseline and time averaged into 5-min bins to determine peak particle accumulation for each condition.

Data are presented as mean ± SD, and statistical significance was set at $P < .05$. Nonparametric distribution of measurements was assumed. A Friedman test was used to detect differences in peak particle accumulation among exercise conditions. If significant, Wilcoxon signed rank tests with Bonferroni correction applied ($\alpha = .025$) were used to compare both MICT-F and HIIT-F with MICT-NF.

RESULTS

The Table shows baseline particle densities as well as peak particle accumulation in the CR center and exercise pod during all exercise sessions. The greatest increase in cumulative particle density in the CR center was only ~10% above baseline levels and occurred during HIIT-F (Table). No differences in peak aerosol ($P = .25$), droplet ($P = .57$), or cumulative particle accumulation ($P = .43$) were detected in the CR center among exercise conditions. Aerosol particle accumulation inside the exercise pod was significantly less during both MICT-F and HIIT-F than during MICT-NF ($P = .016$ and $P = .028$, respectively; Table). Aerosol droplet particle accumulation inside the exercise pod was significantly less during both MICT-F and HIIT-F than during MICT-NF ($P = .032$ and $P = .046$, respectively; Table). Similarly, droplet particle accumulation inside the exercise pod was significantly less during both MICT-F and HIIT-F than during MICT-NF ($P = .041$ and $P = .047$,

Table

Baseline Particle Densities and Peak Particle Accumulation in the CR Center and Exercise Pod[a]

Baseline Particle Density	Aerosols (particles/L)	Droplets (particles/L)	Cumulative (particles/L)
CR center	13 976 ± 14 520	498 ± 379	14 554 ± 14 929
Exercise pod	14 460 ± 14 929	595 ± 496	15 211 ± 15 518
Peak Particle Accumulation	**MICT-NF**	**MICT-F**	**HIIT-F**
CR center			
ΔAerosols, particles/L	571 ± 960	−59 ± 474	1 431 ± 2 519
ΔDroplets, particles/L	31 ± 50	−5 ± 16	92 ± 213
ΔCumulative, particles/L	606 ± 1 002	−61 ± 466	1 519 ± 2 714
Exercise pod			
ΔAerosols, particles/L	30 217 ± 13 001	225 ± 1 879[b]	2 915 ± 2 523[b]
ΔDroplets, particles/L	9 197 ± 4 066	361 ± 204[b]	754 ± 365[b]
ΔCumulative, particles/L	42 492 ± 18 042	751 ± 2 034[b]	3 914 ± 2 780[b]

Abbreviations: CR, cardiac Rehabilitation; HIIT-F, high-intensity interval training session with air filtration; MICT-F, moderate-intensity continuous training sessions with air filtration; MICT-NF, moderate-intensity continuous training sessions without air filtration.

[a]Data are presented as mean ± SD. ΔAerosols, 0.3-0.5 μM; ΔDroplets, 0.5-1.0 μM; ΔCumulative, 0.3-10 μM. Data were analyzed using a nonparametric Friedman test; when a significant overall effect was detected, Wilcoxon signed rank tests with Bonferroni correction applied ($\alpha = .025$) were used to compare both MICT-F and HIIT-F with MICT-NF.

[b]Significantly less than MICT-NF ($P < .05$).

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respectively; Table). Cumulative particle accumulation inside the exercise pod was also significantly less during both MICT-F and HIIT-F than during MICT-NF (P = .026 and P = .043, respectively; Table). Finally, heart rate tended to be higher at end of the exercise during HIIT-F (162 ± 23 bpm; P = .07) than at MICT-NF (147 ± 25 bpm) and MICT-F (149 ± 17 bpm).

DISCUSSION

This study provides clear evidence in support of using enclosed pods with air filtration to contain and mitigate airborne particles generated during exercise in a center-based CR setting. Considering respiratory droplets and aerosolized particles are key pathways for viral transmission,[9-11] identifying strategies to mitigate the accumulation of airborne particles is a critical step in safely reopening and maintaining normal operations of CR programs to in-person patient care while minimizing the risk of COVID-19 transmission. The enclosed exercise pod used in this study effectively contained airborne particles generated during exercise. Moreover, incorporating air filtration successfully mitigated the accumulation of airborne particles inside the pod. These findings provide a potential strategy for safely reestablishing outpatient exercise-based CR, which is critical for reducing risk factors, rehospitalization, and mortality in patients with CVD.[1]

A potential limitation of this study is the use of young, healthy volunteers. The self-selected exercise intensities in which our participants engaged are likely much greater than patients in a CR program. Therefore, the tidal volume, respiratory rate, overall minute ventilation, expiratory pressure, and, presumably, generation of airborne particulate matter are likely much greater in this study than would be expected by older patients with CVD engaging in CR. In addition, face masks were not worn during the exercise sessions conducted in this study; however, currently available data suggest masking does not negatively impact the physiologic response to exercise and may be appropriate in CR settings.[12]

In conclusion, airborne particles generated during exercise in a CR center can be successfully contained by enclosed exercise pods. Furthermore, incorporating air filtration systems effectively mitigates the accumulation of respiratory droplets and aerosols.

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Cardiopulmonary Responses During Exergame in Cardiac Rehabilitation Patients

The combination of exercise and video games, known as exergames, allows for the interaction between individuals and the game by performing standardized movements that can be modulated to involve different skills and energy expenditure. These devices seem to be fun and engaging, with the potential for increasing treatment adherence in home-based cardiac rehabilitation (CR) programs.[1] However, few studies have investigated the cardiovascular physiological response, safety, and aerobic exercise intensity in patients with cardiovascular disease (CVD), which are often done using a cardiopulmonary exercise test (CPX), the gold standard for functional assessment of CVD patients.

Therefore, the aim of this study was to compare electrocardiographic, hemodynamic, and CPX variables obtained during exergame session with those during a maximal CPX.

METHODS

Participants were adult men and women, with a previous diagnosis of CVD, on optimal medical therapy and clinically stable. This study was conducted from October 2018

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to January 2019, and the study protocol was approved by the Research Ethics Committee of our institution (CAAE: 04684918.1.0000.5440). The exclusion criteria were as follows: hypertrophic or Chagas cardiomyopathy; cardiac valve disease; acute or unstable CVD; inflammatory or other connective tissue diseases; myocardial ischemia in low workload (<3 metabolic equivalents [METs]); and orthopedic, neurological, or cognitive impairment that could limit physical activity.

A ramp protocol for continuous dynamic physical effort on a treadmill was used until exhaustion or limiting signal/symptoms. Respiratory variables were measured using a Vmax Encore 29 ergospirometric system for gas analysis (SensorMedics). Continuous 12-lead electrogram with a CardioSoft Exercise Stress Testing system (GE Medical Systems Information Technologies GmbH) was monitored to assess heart rate (HR), arrythmias, and ST-segment alterations. Blood pressure was assessed over the entire test every 2 min. Ischemic threshold was determined by the HR at the start of >1-mm ST-segment depression and/or a plateau in the O_2-pulse increment, indicating failure to augment the stroke volume–$CavO_2$ ($CaO_2 - CvO_2$) product throughout exercise. Ratings of perceived exertion were acquired at peak of the test.

Exergame session was performed for 48-72 hr at the same period of the day after CPX by using XBOX 360 with Kinect, and the game used was Kinect Adventures with Reflex Ridge modality. The three first stages of basic level were chosen to reach moderate to high exercise intensity. First, patients were submitted to training how to use the exergame and allow better familiarization with this modality. On the next day, a 20-min exergame protocol was applied and respiratory variables were measured using the same system for CPX. Continuous 12-lead electrogram was also acquired as well as the blood pressure after each three stages. The exergame protocol was preceded by 3 min at rest and 3 min more for recovery (26 min in total). Ratings of perceived exertion were acquired before the recovery.

The Shapiro-Wilk normality test was applied to determine whether the variables studied presented normal distribution. The Student paired *t* test (for variables following normal distribution) or the Wilcoxon matched pairs test (non-normal distribution) was used to compare the variables. The level of significance was 5% ($P < .05$), two-tailed, in all analysis.

RESULTS

Eight CVD patients (aged 52.5 ± 14.3 yr) with left ventricular ejection fraction 38 ± 15% were evaluated. The CPX was considered maximum (respiratory exchange ratio >1.1) in six (75%) patients. The two remaining patients had the tests terminated because of chest pain and an O_2-pulse plateau. A third patient who reached maximum showed >1-mm ST-segment depression concomitant with O_2-pulse plateau without symptoms. During the exergame, these three patients kept HR values below the ischemic threshold. The results of the CPX and the exergame are presented in the Table.

DISCUSSION

The mean oxygen uptake ($\dot{V}O_2$) during the exergame play was comparable with the $\dot{V}O_2$ at the anaerobic threshold and corresponded to 54% of $\dot{V}O_{2peak}$ by the CPX. Moreover, the exergame HR mean was slightly above the anaerobic threshold ($P = .14$), reaching 78% of HR_{peak} observed in the CPX. These intensities are in accordance with the recommendations from the main guidelines for CR of individuals with CVD.[2,3]

Table

Cardiopulmonary Exercise Test and Exergame Variables[a]

Variables	CPX	Exergame	*P* Value
Resting HR, bpm	56.6 ± 6.5	60 ± 4.9	.01
Resting systolic BP, mm Hg	105 ± 16.3	103.7 ± 13.0	.56
Resting diastolic BP, mm Hg	65 ± 12.2	68.7 ± 10.3	.12
$\dot{V}O_2$@AT, mL·kg^{-1}·min^{-1}	11.7 ± 1.2	…	…
$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	20.1 ± 4.9	14.9 ± 2.4	.04
$\dot{V}O_2$, mL·kg^{-1}·min^{-1}	…	10.9 ± 1.4	…
HR@AT, bpm	81.7 ± 9.3	…	…
HR_{peak}, bpm	111.6 ± 18.7	97 ± 8.9	.01
HR, bpm	…	87.2 ± 7.8	…
$\dot{V}E/\dot{V}CO_2$ slope	29.1 ± 2.8	…	…
RER_{peak}	1.2 ± 0.1	1.0 ± 0.1	.01
Systolic BP_{peak}, mm Hg	137.5 ± 17.5	122.5 ± 11	.08
Diastolic BP_{peak}, mm Hg	71.3 ± 8.8	71.6 ± 11.5	.94
RPP_{peak}	15 410 ± 3 516	11 841 ± 1 061	.02
RPE_{peak} (0-10 scale)	7.9 ± 1.5	3.5 ± 1.2	.01

Abbreviations: BP, blood pressure; CPX, cardiopulmonary exercise test; HR, heart hate; HR@AT, heart rate at anaerobic threshold; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; RPP, rate pressure product; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_2$@AT, oxygen uptake at anaerobic threshold.
[a]All data are presented as mean ± SD.

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Interestingly, the peak systolic blood pressure during the exergame was similar to that observed on CPX. These similar values may be explained by the amount of muscle groups involved in each exercise type. Although the CPX has reached a greater intensity of effort, the exergame involves upper- and lower-limb muscles simultaneously, demanding greater muscle perfusion at a given intensity of effort. However, myocardial $\dot{V}O_2$, given by rate-pressure product, was smaller than CPX because of HR response.

The game and the modality used in our study have previously been shown to be feasible and safe in individuals with Parkinson disease.[4] However, authors themselves pointed out, as a limitation of the study, the lack of monitoring of cardiac performance during the sessions. The safety was assessed by reports of adverse events during the intervention, such as orthopedic injuries, in the same way that has been evaluated in studies with individuals with CVD.[5,6] In this sense, our study presents relevant data regarding the cardiovascular stress caused by this modality, thus offering a safe game option for prescription in CR programs.

Previous studies also investigated the cardiac impact during the exergame in patients with CVD[7,8]; however, only the HR response was assessed. Studies using respiratory gas analysis during the exergame have been conducted in different health conditions such as cystic fibrosis[9] and type 2 diabetes.[10] Corroborating our findings, these studies concluded that the exercise intensity reached during the exergame meets the recommended intensity according to the physical training guidelines for those health conditions.

Finally, given the lack of consensus regarding the use of the exergame in CR, the present study shows that specific exergame exercise protocols can provide a safe cardiac stress response with adequate intensity, potentially associated with benefits in improving the aerobic capacity.

The small sample size prevents the generalization of the results; however, by using multiple assessment methods and the comparison with the CPX, this study offers the reasoning for larger randomized clinical trials to confirm the findings.

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