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Original Article

Impact of rest interval duration on muscle performance in Hodgkin's Lymphoma survivors

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Abstract
Objective: This study aimed to compare the acute effects of three different rest intervals on peak torque (PT) and total work (TW) between Hodgkin's lymphoma survivors and age- and sex-matched healthy subjects. **Methods:** Fourteen Hodgkin's lymphoma survivors (34.4 ± 10.1 years) and 14 healthy subjects (34.1 ± 10.7 years) participated in three distinct strength training protocols on separate days. Each protocol consisted of three sets of 10 maximal unilateral isokinetic extensions of the right knee at 60 °/s, with rest intervals (RI) between sets of 1,2, and 3 min. PT and TW were measured during each set of all training protocols. **Results:** The results revealed no significant interaction between groups in terms of the effect of rest intervals and sets on PT ($p = 0.70$) and TW ($p = 0.34$). However, both groups exhibited a smaller decrease in PT and TW with 2- and 3-min rest intervals compared to 1 min one ($p < 0.01$). Notably, only in the Hodgkin's lymphoma survivors' group, PT was significantly greater in the third set with a 3-min rest interval (169.2 ± 51.2) compared to the same set with 1 min (146.2 ± 45.9) and 2 min (157.7 ± 47.3) of rest ($p < 0.05$). **Conclusion:** The results of this study suggest that Hodgkin's lymphoma survivors benefit from at least 2 min of rest intervals to maintain muscle performance during an ST session. This finding implies that exercise professionals working with this population can implement extended rest intervals (beyond 120 s) to ensure proper recovery between sets and optimize ST.
Key words: Strength Training; Cancer survivors; Lymphoma survivors; Rest interval; Fatigue.

Introduction

Strength training (ST) has been widely used to improve muscular performance and physical function in health and disease and is involved in increasing protein synthesis, reducing body fat, and improving muscle strength and power, even in unhealthy individuals, such as sarcopenics, diabetics, people with kidney disease and patients with cancer (Kraemer et al., 2002; Battaglini et al., 2014; Rosa et al., 2021). Therefore, ST plays an important role in preventing muscle loss and preserving muscle function in cancer survivors like Hodgkin's lymphoma (Yildiz Kabak et al., 2019; Cavalheri et al., 2017), despite the disease-related cachexia and fatigue (Saultier et al., 2021).

Hodgkin's lymphoma (HL) has a well-established treatment and a high prevalence of survivorship. However, the pathology and the treatment induce several side effects after the end of therapy (Gotte et al., 2022). Such side effects induced by cancer and its medical treatments are known to cause significant decrease in functional capacity due to negative metabolic, endocrine, physical, functional, and mental alterations, which significantly affect the health-related quality of life and functional capacity (Gaser et al., 2022). Cancer-related fatigue (CRF) is the most commonly reported side effect in cancer patients. It is a multifactorial process that involves negative alterations in different physiological systems (Andrade de Brito et al., 2020). This debilitating fatigue is often accompanied by reductions in overall physical activity that can lead to decrements on physical function (ie, loss of skeletal muscle tissue), cognitive impairment, depression, pain, among other negative effects (de Lima et al., 2018).

Although most cancer survivors do not meet physical activity guidelines, even though several studies have shown the benefits and safety of ST programs for this population, during and after treatment (Battaglini et

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al., 2014; Santos et al., 2017; Hanson, Wagoner, Anderson, & Battaglini, 2016). In this sense, considering the severe fatigue, muscle loss and muscle weakness induced by metabolic, inflammatory, and neuroendocrine disorders in cancer survivors (Saligan et al., 2015; Antwi et al., 2019), a ST program is able to reduce this cancer-related fatigue, prevent cancer-related cachexia and recover the muscle function (Santos et al., 2017; Hanson et al., 2016). However, in order to fulfill its goals, a ST program must be prescribed considering the effect of cancer on the acute training variables, such as volume, rest interval (RI) between sets and intensity. The training volume performed during a resistance exercise session demonstrates a strong connection with muscle adaptations (Peterson, Rhea, & Alvar, 2004) and relies on RI.

The RI aims to reduce physical fatigue and promote muscle recovery, consequently improving work capacity (Bottaro et al., 2010; Pincivero, & Campy, 2004). Furthermore, the training volume and RI, including the intensity, are directly associated with mechanical stress induced by strength training. The influence of mechanical stress was primarily suggested by Goldberg et al. (1975), disturbing the integrity of skeletal muscle tissue, causing molecular signaling and cellular responses, such as satellite cell recruitment and protein synthesis stimulation (Toigo, & Boutellier, 2006; Schoenfeld, 2013).

According to Schoenfeld, (2010), the RI is often classified as short (less than 60 seconds), moderate (between 60 and 120 seconds) and long (more than 120 seconds) and it depends on training goals, physical conditions, and individual characteristics. Several studies have analyzed the effects of different RI in healthy adults, children, and elderly (Bottaro et al., 2010; Pincivero, & Campy, 2004; Stossel et al., 2020; Nielsen et al., 2020). However, to the best of our knowledge, only one study analyzed the acute effect of different RI in muscle performance of cancer survivors (Vieira et al., 2015). This study showed that breast cancer survivors may need a longer RI (longer than 2 minutes) to sustain muscle performance during three sets of isokinetic knee extension. Such a requirement may be justified by inflammatory imbalance, metabolic impairments, and/or hormonal dysfunctions often reported by breast cancer survivors (Saligan et al., 2015; Antwi et al., 2019).

Although Vieira et al. have studied the effect of different RI in breast cancer survivors, it is not possible to generalize these findings to Hodgkin's lymphoma survivors (HLS). The median age at diagnosis of Hodgkin's lymphoma is 39 years, with higher prevalence in the age group of 20 to 34 years (Howlader et al., 2016). These characteristics are different from breast cancer survivors studied by Vieira et al. (post-menopausal women aged between 44 and 65 years), which may suggest different arrangements of ST acute variables. Moreover, HLS suffers a greater impairment in physical function than other cancer types, due to an aggressive chemotherapy (Malysse et al., 2021). Otherwise, despite persistent and more aggressive late side effects than other cancers, Hodgkin's lymphoma shows 75 to 90% remission rate and a greater survivorship (Miltényi, Magyari, Simon, & Illés, 2010). According to the World Health Organization, the growing population of survivors requires specialized follow-up and care, to reduce the incidence and severity of the late side effects of the disease and treatment process. (McGuire, 2016).

Thus, the purpose of this study was to investigate the acute effect of three different RI between sets of isokinetic knee extension on strength (peak torque) and work capacity of Hodgkin's lymphoma survivors. The hypothesis postulated that HLS individuals would require longer rest intervals compared to healthy control subjects, due to greater fatigue levels (de Lima et al., 2018).

Material and Methods

Participants

Hodgkin's lymphoma survivors were recruited from public and private hospitals. Healthy subjects were recruited from the university community, by word-of-mouth and advertisements on the Internet. All participants were informed about the purpose, procedures, and risks of the study design prior to signing an informed consent. All procedures were approved by the University Institutional Ethics Committee and were conducted according to Harriss, MacSween, & Atkinson, 2019. The patients were included in the HLS group if they were aged between 18 and 45 years and had completed anti-cancer treatments at least six months before experimental procedures. Healthy subjects were included in the control group individually based on matched age and gender of the HLS group. Patients were excluded if diagnosed with hypertension, cardiovascular, metabolic and/or neuroendocrine disease, and/or any orthopedic limitation. Fourteen Hodgkin's lymphoma survivors (six men and eight women; 34.4 ± 10.1 years) composed the HLS group, while 14 control healthy subjects (six men and eight women; 34.1 ± 10.7 years) composed the CNT group.

Instruments

The International Physical Activity Questionnaire - IPAQ (Matsudo et al., 2001) was used to evaluate the level of physical activity. Total body mass was measured in a scale to the nearest 0.50 g. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The body fat percentage was measured using Dual Energy X-Ray Absorptiometry (DXA), using a General Electric GE Healthcare® bone densitometer, model Lunar Prodigy ProTM (GE Lunar, Madison, WI). The individual was positioned on the equipment in the supine position, with legs extended and arms extended close to the body. Data were analyzed using GE Medical Systems LunarTM software and the sample healthy questionnaire.

Procedures and Data Collection

Before the tests, all participants performed a familiarization of 2 sets of 5 submaximal isokinetic knee extensions at 60º.s-1, with one minute of RI. The isokinetic exercise sessions test consisted of 3 sets of 10 maximal unilateral isokinetic extensions of the right knee at 60º.s^{-1}, with three different RI (1, 2 and 3 minutes). Exercise sessions were conducted on 3 separate days, with a minimum of 72 hours and a maximum of seven days between each session. Participants performed the sessions in a randomized order of RI, designed through the method of *randomly permuted blocks*.

The resting periods and the number of sets were selected following the guidelines for exercise prescription designed by the American College of Sports Medicine (Kraemer et al., 2002; American College of Sports Medicine, 2009; American College of Sports Medicine, 2013). Training volume and velocity were adopted based on a previous study conducted with breast cancer survivors (Vieira et al. 2015). All evaluations and tests were performed by the same researcher at the same time of the day. Individual measurements such as seat and dynamometer height, backrest inclination and lever arm length were recorded and standardized as a test position for the exercise sessions.

Isokinetic peak torque (PT) and total work (TW) were measured during each exercise session using the Biodex System III Isokinetic Dynamometer (Biodex Medical, Inc., Shirley NY, USA). The subjects were positioned on the dynamometer seat with velcro belts fastened to the trunk, pelvis, and thigh to minimize body movements that could affect results.

The lateral epicondyle of the femur was used to align the knee rotation axis and the dynamometer rotation axis, allowing the free knee extension and flexion from 80º flexion up to full extension. Gravity correction was obtained by measuring the torque exerted by the lever arm and the leg of the subject. The values of the isokinetic variables were automatically adjusted for gravity using software Biodex Advantage (Biodex Medical Systems, Inc., New York, USA). The calibration of the dynamometer was carried out according to the manufacturer specifications. For the test, participants were asked to cross their arms across the chest. The same researcher carried out the test procedures for all subjects and provided verbal encouragement to guarantee maximal effort.

Statistical Analysis

Descriptive data is presented as mean ± standard deviation. Data normality was verified by the Shapiro-Wilk test. Sample characteristics were compared between groups by an independent t-test. A two-way repeated measures ANOVA [Group (HLS and CNT) versus RI (1, 2 and 3 minutes) versus set (1^{st}, 2^{nd} and 3^{rd})] was used to evaluate PT and TW measurements. Bonferroni adjustment was used as a post hoc test. The analyses were performed in the statistical software SPSS version 21.0, and $p \leq 0.05$ was adopted as the level of statistical significance.

Results

Fourteen Hodgkin's lymphoma survivors (six men and eight women; 34.4 ± 10.1 years) composed the HLS group, while 14 control healthy subjects (six men and eight women; 34.1 ± 10.7 years) composed the CNT group. All participants of HLS had completed their treatment at least six months prior to the experimental procedures. The descriptive characteristics of the sample are presented in Table 1. There was no significant difference between groups in terms of age, height, weight, body mass index, body fat percentage and level of physical activity (p>0.05).

Table 1. Sample characteristics.

	HLS (n = 14) Mean ± SD	**CNT (n = 14)** Mean ± SD
Age (years)	34.4 ± 10.1	34.1 ± 10.7
Height (cm)	169.4 ± 7.8	167.2 ± 8.9
Weight (kg)	71.6 ± 11.5	69.3 ± 13.2
BMI ($kg.m^2$)	24.9 ± 3.1	24.6 ± 2.8
Body Fat (%)	37.7 ± 10.8	33.2 ± 7.8
Level of Physical Activity		
Low levels	2 (14.3%)	4 (28.6%)
Moderate levels	8 (57.1%)	7 (50%)
High levels	4 (28.6%)	3 (21.4%)

BMI: Body Mass Index.

Table 2 shows PT and TW results in HLS and CNT at different rest intervals (1, 2 and 3 minutes).

Table 2. Peak Torque (PT) and Total Work (TW) in Hodgkin's Lymphoma survivors and control group expressed in mean ± standard deviation.

	HLS (n = 14)			CNT (n = 14)		
	1st set	2nd set	3rd set	1st set	2nd set	3rd set
PT (N.m)						
1 min	182.8 ± 58.8	166.0 ± 51.9*	146.2 ± 45.9*#	191.8 ± 72.2	174.2 ± 61.7*	153.9 ± 44.1*#
2 min	174.8 ± 46.2	166.2 ± 46.2*	157.7 ± 47.3*#†	184.8 ± 55.9	180.5 ± 57.5	170.0 ± 52.6*#†
3 min	181.6 ± 53.9	178.8 ± 53.0†§	169.2 ± 51.2#†§	190.4 ± 66.9	183.2 ± 56.3	171.3 ± 44.0*#†
TW (J)						
1 min	1572.1 ± 514.5	1436.2 ± 442.7*	1222.1 ± 389.2*#	1666.9 ± 651.8	1425.4 ± 492.5*	1202.4 ± 328.8*#
2 min	1515.0 ± 467.3	1440.5 ± 438.8	1342.7 ± 413.8*#	1551.1 ± 511.9	1526.9 ± 554.9†	1380.7 ± 485.6*#†
3 min	1568.0 ± 529.7	1511.4 ± 491.9	1408.7 ± 433.3#†	1626.8 ± 650.4	1531.7 ± 539.9†	1426.6 ± 447.9*#†

(*) $P \leq .05$, lower than 1st set
(#) $P \leq .05$, lower than 2nd set
(†) $P \leq .05$, higher than 1 min RI
(§) $P \leq .05$, higher than 2 min RI

There were no significant differences between groups in terms of PT and TW (p > 0.05). In the HLS group the PT decreased significantly in the second and third sets of 1 and 2 minutes RI compared to the first set (p < 0.05). However, under a 3-minute RI, a notable reduction was observed in the PT during the third series in comparison to the second set (*p* = 0.04). No disparity in PT was detected between the protocols within the initial set (p > 0.05). Additionally, the peak torque (PT) exhibited a higher value in the second and third sets of 3 minutes RI when compared to 1 and 2 minutes (p < 0.05). In the control group, PT decreased significantly during the second and third sets of 1-minute RI (p < 0.01). However, in 2- and 3-minutes RI, PT decreased significantly only in the third set (p < 0.05). There was no difference observed in PT between protocols in the first and second sets (*p* > 0.05). Furthermore, PT was greater in the third set of 3 minutes RI compared to 1 and 2 minutes (*p* < 0.05). There were no differences between groups regarding all rest intervals (*p* > 0.05). In both HLS and CON groups, the PT reduction was smaller with 2 and 3 minutes RI compared to 1 minute (*p* ≤ 0.01). Both groups showed similar PT decreases during 2- and 3-minutes RI (*p* > 0.05). However, only in the Hodgkin's Lymphoma survivors' group, PT was greater in the third set of 3 minutes rest interval (169.2 ± 51.2) than 1 (146.2 ± 45.9) and 2 (157.7 ± 47.3) minutes intervals (*p* < 0.05).

Regarding TW, in the HLS group, it decreased in the second set of 1-minute RI (*p* ≤ 0.05). However, in the 2 and 3 minutes RI, TW only decreased in the third set *(p* < 0.05). Also, TW was greater in the third set of 3-minute RI compared to the intervals of 1 and 2 minutes (*P* < .05). In the control group, TW decreased in the second set of 1-minute RI (p < 0.05). Similarly, within the 2- and 3-minute RI, TW decreased only in the third set (*p* < 0.01). Moreover, TW was greater in the second and third sets of 2- and 3-minute RI compared to the 1-minute interval (*p* < 0.05). This contrast was not observed in the HLS group.Finally, TW reduction was smaller in the 2- and 3-minute RI compared to the 1-minute interval in both groups (*p* < 0.05). Both groups showed similar TW reductions during 2 and 3 minutes of RI (*p* > 0.05).

Discussion

The aim of this study was to compare the acute effect of 3 different rest intervals on peak torque (PT) and total work (TW) between Hodgkin's lymphoma survivors and control healthy subjects matched by sex and age. The main result revealed no significant differences between groups across all sets and RI schemes. However, only participants from the HLS group presented a greater PT in the second and third sets of 3-minute RI compared to intervals of one and two minutes. Such a result was not evident in the control group. On the other hand, only the control group showed a significantly greater TW in the second and third sets of 2 and 3 minutes RI when compared to 1 minute of RI. In this sense, even without significant differences between groups, it can be assumed that Hodgkin's lymphoma survivors require longer rest intervals than healthy control subjects to sustain muscle performance.

Although several studies have already shown the positive effects of strength training in cancer survivors (Santos et al., 2017; Hanson et al., 2016), the management of RI between sets remains imprecise. A systematic review on exercise training applied to cancer survivors (Battaglini et al., 2014) showed that only one study had reported the specific RI applied between sets during a ST program. Despite the relevance of managing RI to achieve physical gains, the initial study that evaluated the effect of RI in oncological patients focused on breast cancer survivors and was published in 2015 by Vieira et al. Nevertheless, it is important to know that HLS are typically younger than breast cancer survivors and often experience more severe side effects such as poor level energy due to aggressive treatment protocols (Fiuza-Luces et al., 2017; Malysse et al., 2021).

Bottaro et al., (2010) suggested that individuals with lower force production and work capacity require less RI. In addition, several studies have shown a positive relationship between force production capacity and fatigue during strength training (Pincivero & Campy 2004; Stossel et al., 2020). This is because stronger individuals experience higher intramuscular pressures (Pincivero & Campy 2004), blood flow occlusion, metabolites accumulation, and impairment of oxygen delivery to the muscles (Pincivero & Campy 2004; Stossel et al., 2020; Pincivero, Lephart & Karunakara, 1997). Therefore, the similar force production capacity between HLS and CNT observed in this study contributes to equivalent responses in resistance exercise.

Although several studies have proposed that cancer survivors experience a consistent decline of skeletal muscle tissue and strength (Yildiz Kabak et al., 2019; Wurz et al., 2021), a study proposed that hematological cancer survivors who engage in regular physical activity can preserve their physical characteristics and muscle function at levels similar to those healthy subjects (de Lima et al., 2018). In the context of this study, HLS assessed reported a moderate level of physical activity.

This finding could potentially account for the absence of differences in PT and TW between the group and the comparison group. Otherwise, Hodgkin's lymphoma survivors have a higher level of fatigue than the general population (Loge, Abrahamsen, Ekeberg & Kaasa, 1999), even years after treatment (Rüffer et al., 2003). Unfortunately, cancer related fatigue was not assessed in this study, however, this may be the reason why the group of Hodgkin lymphoma survivors evaluated in this study showed a significant reduction in PT between all 1 and 2-minute RI sets.

Furthermore, Vieira et al., (2015) compared the acute effects of 1 and 2 minutes of RI and concluded that even with a 2-minute RI, muscle performance could not be preserved during a resistance exercise session in breast cancer survivors. However, the researchers showed that breast cancer survivors had lower strength and work capacity compared to control healthy subjects who were matched by age and sex. Such differences may justify the dissociated responses in terms of PT and TW between groups. Nonetheless, it is important to notice that both breast cancer survivors and healthy subjects studied by Vieira et al., (2015) were physically-inactive postmenopausal women, aged between 44 to 65 years. These inherent characteristics alone could explain the different responses observed between breast cancer and Hodgkin's lymphoma survivors. Age, sex and level of physical activity are known factors that influence RI between sets of resistance exercises (Bottaro et al., 2010; Morales et al., 2021).

Recovery between sets during a resistance exercise session should promote muscle and metabolic recovery, attenuate fatigue, and preserve work capacity (Morales et al., 2021). Therefore, an adequate RI between sets allows an increase in training volume and induces greater physical adaptations (Bottaro et al., 2010). These physical adaptations are related to mechanical stress induced by ST with suitable RI (Schoenfeld, 2013). Considering that cancer survivors often experience fatigue and muscle tissue loss (Wurz et al., 2021), clinicians and exercise specialists should recommend intervention that minimizes metabolic stress while promoting as much muscle gain as possible.

Therefore, this study proposes that HLS aiming for maximal training volume during a resistance exercise session may benefit from employing rest intervals of at least 2 to 3 minutes between sets, according to the observation of performances in both intervals and their result, which is categorized as a long rest interval, based on the existing literature (Schoenfeld, 2010). Importantly, these findings hold significance in guiding the selection of optimal rest intervals for isokinetic testing.

This study does have certain limitations that hinder the generalizability of the results. The sample size is attributed to the relatively low prevalence of Hodgkin's lymphoma in comparison to other types of cancer. Additionally, the assessment was limited to lower body strength. However, this study should be seen as a hypothesis-generating study, providing initial information about the management of acute training variables during a resistance exercise session in Hodgkin's lymphoma disease. For future research, it's recommended that other cancer types, other fatigue assessments, other muscle groups, and a larger sample size should be considered.

Conclusions

The results of this study indicate that Hodgkin's lymphoma survivors benefit from utilizing at least 2-minutes of RI to preserve muscle performance during a ST session. As a result, exercise professionals can apply extended rest intervals (longer than 120 seconds) to ensure proper recovery between sets and maximize ST goals in this population. Considering that Hodgkin's lymphoma survivors might experience fatigue and declines in physical function, emphasizing strength training gains becomes essential in order to mitigate potential long term side effects of the treatments. Further investigations are paramount in order to discover if new strategies, such as exercise, can become more specific in alleviating or even reversing this debilitating side effect that significantly affect the quality of life of cancer patients.

Conflict of Interest Statement

There are no conflicts of interest to disclose.

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