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Lower rate-pressure product during submaximal walking: a link to fatigue improvement following a physical activity intervention among breast cancer survivors

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Abstract

PURPOSE—Research showing a link between exercise-induced changes in aerobic fitness and reduced fatigue after a cancer diagnosis has been inconsistent. We evaluated associations of fatigue and rate-pressure product (RPP), a reliable index of myocardial oxygen demand, at rest and during submaximal walking following a physical activity intervention among post-primary treatment breast cancer survivors (BCS).

METHODS—Secondary analyses of 152 BCS in a randomized controlled trial testing a physical activity intervention (INT) versus usual care (UC) were performed. The INT group completed counseling/group discussions along with supervised exercise sessions tapered to unsupervised exercise. Evaluations were made at baseline and immediately post-intervention (M3) on measures of physical activity (accelerometry), graded-walk test, and average fatigue over the previous 7 days. RPP was calculated by dividing the product of heart rate and systolic blood pressure by 100.

RESULTS—Resting and submaximal RPPs were significantly improved in both groups at M3, however, the magnitude of change () was greater in the INT group from stage 1 (RPP1; INT -13 ± 17 vs. UC -7 ± 18 ; $p=0.03$) through stage 4 (RPP4; INT -21 ± 26 vs. UC -9 ± 24 ; $p<0.01$) of

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Compliance with Ethical Standards

Statement of Human Rights: All procedures performed involving human participants were in accordance with the ethical standards of the University of Alabama at Birmingham and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the present study.

the walk test. The INT group reported significantly reduced fatigue (INT -0.7 ± 2.0 vs. UC $+0.1 \pm 2.0$; $p=0.02$) which was positively associated with RPP during stages 2–4 of the walk test but not aerobic fitness.

CONCLUSIONS—Lower RPP during submaximal walking was significantly associated with reduced fatigue in BCS.

IMPLICATIONS FOR CANCER SURVIVORS—Exercise/physical activity training programs that lower the physiological strain during submaximal walking may produce the largest improvements in reported fatigue.

Keywords

cardiovascular; exercise; heart rate; systolic blood pressure

Introduction

Advances in breast cancer treatment have decreased mortality such that in the United States long-term survival often exceeds 90% [1]. Regrettably, among these women, cardiovascular disease-related mortality is now more common than breast cancer-related death [2]. Harmful systemic effects arising from cancer treatment-induced toxicity can contribute to acute and chronic myocardial pathologies [3], both of which severely compromise aerobic fitness [4]. When coupled with fatigue and possible weight gain after treatment [5], participation in free-living physical activities can be especially difficult for breast cancer survivors (BCS). Multifactorial in its etiology, fatigue often varies with regard to its clinical expression and in some cases is unremitted for many years [6]. Further evidence suggests more than half of all BCS report persistent fatigue after treatment [7]. As the projected number of BCS continues to grow [8], additional research is needed to evaluate the possible physiological underpinnings of fatigue, as well as effective strategies to enhance functional capacity.

Within the setting of breast cancer survivorship, fatigue may be perpetuated by disruption of the autonomic nervous system [9,10]. Generally classified as two divergent branches, the sympathetic and parasympathetic systems are key regulators of energy mobilization and restorative function, respectively. Thayer and Lane [11] have posited that a combination of sympathetic overactivity and parasympathetic underactivity may be linked to adverse health outcomes and fatigue in non-cancer populations [12]. Since heightened sympathetic activity increases unnecessary energy demand [13], it is possible that fatigue may be associated with a relative autonomic imbalance. Recently, Jones and colleagues [14] found resting heart rates were on average $7\text{--}16 \text{ beats} \cdot \text{min}^{-1}$ higher in early-stage breast cancer patients following treatment compared to age-matched controls. Given that heart rate is largely under parasympathetic influence at rest, values outside the normative range may in part suggest an autonomic imbalance [11]. Therefore, it is possible that the utility of increased physical activity and exercise training to improve fatigue in BCS [15] may involve the restoration of autonomic equilibrium [16].

During exercise, sympathetic activity rises in accord with inputs from higher brain function and contracting skeletal muscles to produce an intensity-dependent increase in heart rate and

blood pressure [17]. Regular exercise stimulates key cardiovascular adaptations that attenuate the increase in physiological strain for a given workload. While lowered resting heart rate and blood pressure are known phenotypic responses to aerobic exercise training, less is known about how such changes may influence fatigue in BCS. Moreover, the product of heart rate and systolic blood pressure, termed rate-pressure product (RPP), provides an index of myocardial oxygen demand [18] and thus offers an integrative perspective concerning autonomic function, cardiovascular health and hemodynamic responses to exercise. Due to the increased risk of occult cardiovascular disease and cardiomyopathies in BCS, it is of clinical interest to evaluate RPP in this population. Additionally, given the inconsistent link between aerobic fitness and fatigue in cancer survivors [19–22], research exploring the association between other cardiovascular fitness indicators and fatigue is needed.

Previously, our group has demonstrated the efficacy of the BEAT Cancer (Better Exercise Adherence after Treatment for Cancer) intervention to significantly improve physical activity, aerobic fitness, and quality of life in BCS [23]. Given improvements in aerobic fitness, secondary analyses were performed to explore the usefulness of RPP in BCS and to generate future hypotheses related to the possible link to fatigue in preparation for multivariate analyses of mediators regarding fatigue response. Therefore, the purpose of this study was to examine the relationship of fatigue and RPP at rest and during submaximal walking following the BEAT Cancer intervention. Furthermore, we were interested in investigating the relationship between measures of RPP and predicted peak oxygen uptake (predicted $\text{VO}_{2\text{peak}}$), along with weekly minutes of moderate-to-vigorous physical activity (MVPA). Our hypotheses were as follows: 1) After the intervention, resting and submaximal RPPs would be reduced and these changes would be positively associated with changes in fatigue; and 2) Reduced resting and submaximal RPP would be negatively associated with both predicted $\text{VO}_{2\text{peak}}$ and total weekly minutes of MVPA.

Methods

Participants and Design

The study design and procedures have been described at-length in previous publications [23,24]. Briefly, a two-armed randomized controlled trial enrolled BCS from physician referral, newspaper advertisement, media releases, and local cancer support groups. Participants were ambulatory and not anticipated to undergo elective surgery during the intervention period. In addition, all participants had physician medical clearance and were required to be English-speaking females between 18–70 years of age with a history of ductal carcinoma in situ or Stage I-III breast cancer not receiving or planning to receive chemo-/ radiation therapy. In the previous 6 months, participants on average engaged in less than 30 minutes of vigorous- or 60 minutes of self-reported moderate-intensity physical activity per week. Participants with dementia or other cognitive disorders that could interfere with full participation in the study were excluded. Further exclusion criteria were as follows: 1) metastatic or recurrent breast cancer; 2) participating in another exercise study; and/or 3) contraindication to participate in regular physical activity. Recruitment took place from January 2010 to September 2013. All study procedures were approved by the local

institutional review board (IRB) and conformed to the guidelines set forth by the Declaration of Helsinki. Potential participants were contacted by research staff and screened using an IRB approved telephone script. Eligible individuals were then scheduled for an orientation visit to cover all study protocols and expectations. Interested individuals then provided written informed consent and were scheduled for baseline assessment. Randomization occurred in blocks of 4 using computer-generated numbers to determine intervention. Group placement was kept in sealed envelopes and opened by the study coordinator in the order in which participants completed baseline measures.

Physical Activity Behavior Change Intervention (INT)

The 3-month BEAT Cancer intervention has previously been described [23,24]. In short, participants completed 12 supervised exercise sessions during the initial 6 weeks with a certified (or certification eligible) exercise specialist that tapered to entirely home-based workouts during the final 6 weeks. The prescribed exercise training was gradually advanced from baseline fitness with the goal of meeting 150 minutes of moderate-intensity exercise corresponding to $\approx 40\text{--}59\%$ of heart rate reserve [25] in the concluding 4 weeks of the intervention. Updates to the exercise prescription were performed by the exercise specialist as needed. Treadmill walking was the required mode of exercise during the supervised sessions, however, after the 6th week participants were free to engage in other forms of physical activity provided they adhered to intensity and duration targets. Heart rate monitors (Polar Electro, Kempele, Finland) were provided to appropriately evaluate heart rate during supervised and unsupervised workouts. At the conclusion of each supervised exercise sessions, participants completed a total-body stretching routine. During the concluding 6 weeks, participants attended face-to-face counseling sessions with the exercise specialist at 2 week intervals (i.e., 3 total). Attendance at 6 group discussions were also required to address issues related to self-efficacy, exercise barriers, time/stress management, safety, and goal setting (see reference for complete details) [23]. Education notebooks with supplemental materials concerning exercise-specific information, exercise safety, healthy nutrition, and exercise log sheets were provided to each participant to complement group sessions.

Usual Care (UC)

Participants randomized to the usual care group received materials from the American Cancer Society describing current physical activity guidelines. Further exercise-related instruction and/or separate recommendations concerning physical activity were not provided.

Instrumentation and Measurements

Assessments for this report were made at baseline and after month 3 (i.e., M3; immediately post-intervention). Self-reported information regarding the following were obtained by questionnaires: age, ethnicity, race, cancer stage, months since diagnosis, history of chemotherapy, history of radiation, current hormonal therapy, menopausal status, smoking status, and alcohol use. Standing height and body weight were measured in duplicate and averaged for analysis. Body mass index (BMI) was used to estimate body composition from the following equation: $[\text{body weight (kg)} / \text{standing height (m}^2\text{)}]$. Predicted $\text{VO}_{2\text{peak}}$ was evaluated by treadmill using a modified Naughton protocol due to the possibility of balance

difficulties in this population. Workload was increased by adjusting treadmill speed and grade at 2 minute intervals until participants reached 85% of age-predicted maximum heart rate. Peak VO_2 was estimated from published regression equations and expressed in mL/kg/min [25]. Since stage 4 of the protocol predicts a $\text{VO}_{2\text{peak}}$ of 15.6 mL/kg/min , closely matching the minimum aerobic capacity needed for functional independence [26], stages 1–4 were of interest and included for analyses. Resting heart rate (by heart rate monitor) and blood pressure were measured by research staff after a 5-minute period of quietly sitting and also during the final minute of each stage. Blood pressure from the brachial artery was recorded as the first and fifth Korotkoff sounds using auscultation methods [27]. Rate-pressure product was calculated by dividing the product of heart rate and systolic blood pressure by 100 [18]. Physical activity was objectively measured by accelerometry (GT3X, Actigraph, Pensacola, FL) worn at the hip over 7 consecutive days. Each accelerometer was numbered such that participants used the same device during each assessment period (i.e., baseline and M3). Data were reduced and analyzed according to previously published guidelines [28]. Similar to a previous report [23], cut-points were used to examine the time spent (minutes/day) at specific intensities: [moderate (1952–5724 counts/minute), and vigorous (5725 counts/minute)] [29]. In accordance with suggestions made in physical activity guidelines [30], vigorous-intensity minutes were multiplied by 2 then added to moderate-intensity minutes. Participants rated their average level of fatigue over the preceding 7 days using a Likert-scale format anchored by the following: 1) “not at all fatigued” through 10) “as fatigued as I could be” (i.e., higher score indicates more severe fatigue) [31].

Statistical Analyses

Independent t-tests were used to compare differences between groups where appropriate. Two (time) by two (group) analysis of variance with repeated measures for time were used to compare differences in variables of interest at baseline and M3. In instances where the assumption of sphericity was violated, subsequent degrees of freedom (df values) for within-subject effects were adjusted using the Greenhouse-Geisser correction. Changes (deltas; Δ) in variables were made by determining the differences between M3 and baseline. Bivariate correlation analyses among all participants were used to evaluate the relationships of fatigue, predicted $\text{VO}_{2\text{peak}}$, MVPA, and RPP (rest-stage 4) at M3 and deltas from baseline. Based on the results of bivariate correlations, multiple linear regressions were used to examine the independent effects of BMI, predicted $\text{VO}_{2\text{peak}}$, and MVPA at M3 on RPP (rest-stage 4). Collinearity of diagnostics for all variables were within acceptable limits and variable inflation factors for all models were less than 1.12. Additionally, the direct and indirect effects of group randomization on fatigue through RPP2-4 and predicted $\text{VO}_{2\text{peak}}$ were assessed using a path-analytic approach. The PROCESS macro for SPSS described by Hayes [32] was selected as it utilizes a bootstrapping approach to overcome the limitations of the Sobel test [33] and is less influenced by sample size. Briefly, the bootstrapping procedure is accomplished by taking a large number of samples from the original dataset via random sampling with replacement. The result is an empirically derived sampling distribution of the indirect effect in which the upper and lower bounds of the 95% confidence interval (CI) match the 2.5% and 97.5% points of the sampling distribution. When the CIs do not contain zero, mediation is indicated. All data were analyzed with SPSS

(version 22; IBM Corporation, NY). Statistical significance was assumed if p -values were 0.05.

Results

Overview

As described previously [24], 453 women met preliminary inclusion criteria for age and history of breast cancer diagnosis. Based on further screening, 222 BCS were enrolled and randomized to the investigation. However, for this secondary analysis, only participants with complete datasets for each variable of interest were included for calculation and further analyses ($n = 152$; 76 INT and 76 UC). Both study groups were balanced with no between-group differences emerging among descriptive characteristics at baseline. Mean data for all participants were as follows: age, 55 ± 8 years; height, 163.5 ± 6.2 cm; weight, 79.5 ± 17.1 kg; BMI, 29.8 ± 6.2 kg/m²; predicted VO_{2peak}, 21.8 ± 5.0 mL/kg/min; weekly MVPA, 167 ± 85 ; fatigue, 4.6 ± 2.0 ; resting heart rate (HR_{rest}), 88 ± 14 bpm; resting systolic blood pressure (SBP_{rest}), 122 ± 12 mm Hg; resting RPP (RPP_{rest}), 107 ± 21 ; and months since diagnosis, 54.2 ± 54.6 .

Month 3 (M3) Follow-Up

There was a significant time by group interaction favoring the BEAT Cancer intervention compared to usual care for fatigue (INT -0.7 ± 2.0 vs. UC $+0.1 \pm 2.0$; $p = 0.02$). Predicted VO_{2peak} ($+1.9 \pm 4.2$ mL/kg/min) increased whereas HR_{rest} (-3 ± 12 bpm), SBP_{rest} (-3 ± 11 mm Hg), and RPP_{rest} (-6 ± 19) decreased (time effect; $p < 0.05$) among all participants. However, as shown in Figure 1, between-group differences concerning the changes (i.e., deltas from baseline to M3) in submaximal RPPs emerged at stage 1 and continued through stage 4 of the modified Naughton protocol. A significant linear time by group interaction ($p = 0.03$) was observed, indicating the magnitudes of change (from baseline) for stages 1–4 were greater in the INT group.

To examine the hypothesized relationships, cross-sectional correlation analyses at M3 revealed multiple significant positive associations between fatigue and RPP_{rest} through stage 4 (RPP4) of the modified Naughton protocol (Table 1). Predicted VO_{2peak} and MVPA were also positively related ($r = 0.197$; $p < 0.05$). Significant negative associations were found between predicted VO_{2peak} and RPP_{rest} through RPP4. Likewise, MVPA was negatively associated with RPP1 through RPP4. Shown in Table 2, additional analyses revealed a positive association among deltas (from baseline to M3) between fatigue and RPP from stages 2–4. Delta predicted VO_{2peak} and MVPA were positively related ($r = 0.252$; $p < 0.01$). Significant negative associations were found between predicted VO_{2peak} and RPP_{rest} through RPP4. Multiple linear regressions were used to test the independent effects of BMI, predicted VO_{2peak}, and MVPA at M3 on RPP1 through RPP4 (Table 3). Body mass index and predicted VO_{2peak} were independently related to RPP1 through RPP4 such that positive and negative associations were found for BMI and predicted VO_{2peak}, respectively.

Using the PROCESS macro for SPSS [32], the effect of group randomization on fatigue was assessed directly and indirectly through RPP4 as no significant mediation effects were found for RPP2, RPP3 or predicted $\text{VO}_{2\text{peak}}$. A significant effect of group randomization on RPP4 was found, $\beta = -11.9$, 95% CI $[-20.0, -3.9]$. Delta RPP4 was positively associated with fatigue, $\beta = 0.014$, 95% CI $[0.0012, 0.027]$ such that lower RPP during stage 4 was associated with lower reported fatigue, independent of group randomization. Finally, a significant indirect effect of group randomization on fatigue through RPP4 was observed, $\beta = -0.167$, 95% CI $[-0.46, -0.06]$ indicating that decreased physiological strain during submaximal walking contributed to an improved fatigue response. Since the CI did not include zero, a significant ($p < 0.05$) mediation effect was confirmed.

Discussion

Despite the prevalence and clinical significance of fatigue among BCS, the underlying mechanisms remain insufficiently understood. Here, we report significant positive associations between fatigue and RPP at rest and through stage 4 of the modified Naughton protocol after the BEAT Cancer intervention. Though both study groups showed improvement in RPP at M3, the magnitude of these changes was superior in participants randomized to the intervention. In addition, only the intervention group showed a decrease in average fatigue during the previous 7 days whereas no changes were seen in the usual care group. Importantly, among all participants, we found that changes in fatigue (i.e., from baseline to M3) were positively associated with changes in RPP at submaximal walking intensities (e.g., Stages 2–4). Simply put, participants with lower submaximal RPPs also reported lower levels of fatigue over the past week. Path analyses revealed a significant indirect effect of group randomization on fatigue through RPP4 which was not seen for predicted $\text{VO}_{2\text{peak}}$. These results suggest that further research concerning autonomic function and role of the cardiovascular system is needed to understand how increased physical activity/exercise training can mediate fatigue improvement in BCS.

While increased aerobic fitness has long been recognized as a factor associated with reduced all-cause mortality [34], our current data suggests that even relatively modest gains ($+1.0 \text{ mL/kg/min}$) [24] in aerobic fitness (i.e., predicted $\text{VO}_{2\text{peak}}$) can be of clinical value to BCS. In the traditional sense, the BEAT Cancer intervention was a behavior change study rather than an exercise training study [35]. The intervention group performed just 12 supervised exercise sessions, after which a transition was made to unsupervised exercise with the goal of meeting 150 weekly minutes of moderate-intensity exercise. Among all participants, we observed a significant association between predicted $\text{VO}_{2\text{peak}}$ and MVPA, though not surprising, as this has been well-documented in non-cancer populations [36]. However, participants randomized to the intervention reported a significant decrease in fatigue compared to the usual care group, which is in agreement with a recent systematic review supporting the role of supervised aerobic exercise training to reduce fatigue in BCS [37].

At the onset of exercise, the extent to which heart rate increases is dependent on the metabolic demands of the activity and on existing aerobic fitness. As anticipated, the intervention group exhibited greater improvement in submaximal RPPs, and as such, were

under less physiological strain at each workload compared to the usual care group. Though speculative, these results may have important implications as previous research has shown that ease of walking (i.e., lowered heart rate) is significantly associated with non-exercise activity thermogenesis (NEAT) [38]. Given that NEAT makes up a considerable portion of total energy expenditure in sedentary individuals [39], increased NEAT may be critical to weight control during/after cancer treatment. It seems reasonable that an individual may be more inclined to ambulate and engage in other forms of free-living physical activity if the tasks were less physiologically difficult. Consistent with this premise, we found significant associations at M3 between MVPA and submaximal RPPs (e.g., Stages 1–4). It should be noted that our findings also suggest that predicted $\text{VO}_{2\text{peak}}$ and BMI both independently predict submaximal RPPs. This implies that aerobic fitness and body composition independently influence myocardial oxygen demand during physical activity. Therefore, efforts should be made to concurrently increase $\text{VO}_{2\text{peak}}$ and decrease body fat in BCS in order to reduce myocardial strain and the likelihood of an acute cardiac event, while ultimately supporting greater participation in free-living physical activity.

As of late, the autonomic nervous system has received attention with regard to the etiology of fatigue in breast cancer. Studies using spectral analysis to explore the patterns of cardiac autonomic modulation have found evidence for autonomic dysregulation at rest in BCS [9,40]. Since a delicate balance exists between sympathetic and parasympathetic activity to govern heart rate and blood pressure responses, reduced R-to-R variance and baroreflex gain may indicate impaired vagal performance among BCS [9]. Though spectral analysis was not performed in the present study, average baseline resting heart rate was $88 \text{ beats}\cdot\text{min}^{-1}$ or $8\text{--}9 \text{ beats}\cdot\text{min}^{-1}$ higher than normative values in adult women [41], in part suggesting reduced parasympathetic activity. At M3, HRrest and SBPrest decreased significantly in both groups to a similar extent. While RPPrest was significantly associated with fatigue at M3, we did not observe a relationship between RPPrest and fatigue. From a clinical perspective, females (aged 50–64 yrs.) with a resting heart rate $>76 \text{ beats}\cdot\text{min}^{-1}$ are 47% more likely to have a coronary event compared to women with a resting heart rate $\leq 62 \text{ beats}\cdot\text{min}^{-1}$ [42]. Indeed, the utility of aerobic exercise to elicit systemic cardiovascular adaptations including reduced HRrest has important health applications. Because regular physical activity and exercise training are known to lower heart rate at rest and during submaximal intensities, future work should determine if autonomic dysfunction is present in BCS independent of aerobic fitness and body composition.

Several limitations are present in this study. Aerobic fitness was estimated by performance on the modified Naughton protocol with the test concluding once participants reached 85% of their age-predicted maximum heart rate. Despite being an accepted measure when underlying fatigue and/or balance difficulties may be present, future work should include standard protocols using indirect spirometry. After week 6, participants randomized to the intervention were free to engage in other forms of exercise according to preference. It is possible that variation in exercise training (e.g., duration and frequency) may have occurred, thereby influencing the extent of physiologic adaptations among participants. Nevertheless, several aspects of the study add strength to our findings including a large study sample and randomized controlled trial design. To our knowledge, this is the first investigation to report a relationship between fatigue and RPP in BCS. Interestingly, submaximal RPPs (e.g.,

Stages 2–4) were associated with fatigue whereas predicted $\text{VO}_{2\text{peak}}$ was not. This was unexpected as we have shown that predicted $\text{VO}_{2\text{peak}}$ and submaximal RPPs are inversely related. However, since much of the day is spent at either sedentary or light-intensities, it is possible that fatigue in BCS may be more acutely sensitive to exercise-induced improvements in submaximal RPPs compared to $\text{VO}_{2\text{peak}}$. Indeed, RPP provides information concerning the status of the autonomic system and aerobic fitness concurrently. Hence, efforts should be made to increase $\text{VO}_{2\text{peak}}$ and decrease body fat both of which positively influence resting and submaximal RPP. Of note, a recent randomized controlled trial has shown that resistance training improves fatigue among BCS [43]. Given that increased strength supports ease of walking (as evidenced by lower heart rates) [38] and confers important physiological benefits not possible by endurance exercise alone, further research regarding the differential effects of exercise type is needed.

Conclusions

As hypothesized, reduced resting and submaximal RPPs were positively associated with lower fatigue following the intervention. Delta fatigue was positively associated with submaximal RPP during stages 2–4 of the modified Naughton protocol, suggesting that improved physiologic function (i.e., less myocardial strain) favorably influences reported fatigue. Additionally, a path analysis revealed a significant indirect effect of group randomization on fatigue through RPP4 but not predicted $\text{VO}_{2\text{peak}}$. Importantly, the intervention group exhibited superior exercise-induced adaptations, as evidenced by lower submaximal RPPs, which were related to improved fatigue. Future work is needed to evaluate the relationship between fatigue and additional cardiovascular parameters linked to RPP including arterial compliance/elasticity and submaximal oxygen uptake in BCS.

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Figure 1.

Data expressed as means $\pm$ s.e.m. Changes () in rate-pressure product among intervention and usual care groups from baseline to month 3 (M3) follow-up. **Significantly lower ($p < 0.05$) rate-pressure product in intervention group emerging at Stage 1 through Stage 4 of the modified Naughton protocol. P -value indicates a significant linear time by group interaction.

Table 1

Correlation matrix among variables at month 3 (M3) follow-up after physical activity intervention ($n = 152$).

Variables	Fatigue	Pred VO2	MVPA	RPPrest	RPP1	RPP2	RPP3	RPP4
<u>Fatigue</u>	--	--	--	--	--	--	--	--
<u>Pred VO2</u>	-0.113	--	--	--	--	--	--	--
<u>MVPA</u>	-0.097	0.197 [*]	--	--	--	--	--	--
<u>RPPrest</u>	0.260 [†]	-0.392 [†]	-0.090	--	--	--	--	--
<u>RPP1</u>	0.209 [†]	-0.496 [†]	-0.184 [*]	0.839 [†]	--	--	--	--
<u>RPP2</u>	0.196 [*]	-0.570 [†]	-0.235 [†]	0.769 [†]	0.918 [†]	--	--	--
<u>RPP3</u>	0.173 [*]	-0.639 [†]	-0.228 [†]	0.698 [†]	0.879 [†]	0.930 [†]	--	--
<u>RPP4</u>	0.209 [†]	-0.677 [†]	-0.221 [†]	0.628 [†]	0.794 [†]	0.856 [†]	0.919 [†]	--

[†] Significance at $p < 0.01$;

^{*} Significance at $p < 0.05$;

Fatigue, average over 7 day period; Pred VO2, predicted peak oxygen uptake (mL/kg/min); MVPA, weekly minutes of moderate-to-vigorous physical activity as indexed by accelerometry; RPPrest, resting rate-pressure product [(HRrest x SBPrest)/100]; RPP1-4, rate-pressure product at Stage 1 through Stage 4 of the modified Naughton protocol.

Table 2

Correlation matrix among variables on changes () from baseline to month 3 (M3) follow-up after physical activity intervention ($n = 152$).

Variables	Fatigue	Pred VO2	MVPA	RPPrest	RPP1	RPP2	RPP3	RPP4
<u>Fatigue</u>	--	--	--	--	--	--	--	--
<u>Pred VO2</u>	-0.050	--	--	--	--	--	--	--
<u>MVPA</u>	-0.100	0.252 [†]	--	--	--	--	--	--
<u>RPPrest</u>	0.091	-0.341 [†]	-0.071	--	--	--	--	--
<u>RPP1</u>	0.091	-0.398 [†]	-0.142	0.750 [†]	--	--	--	--
<u>RPP2</u>	0.170 [*]	-0.449 [†]	-0.128	0.668 [†]	0.835 [†]	--	--	--
<u>RPP3</u>	0.178 [*]	-0.459 [†]	-0.161	0.586 [†]	0.771 [†]	0.869 [†]	--	--
<u>RPP4</u>	0.211 [*]	-0.482 [†]	-0.108	0.510 [†]	0.627 [†]	-0.759 [†]	0.815 [†]	--

[†] Significance at $p < 0.01$;

^{*} Significance at $p < 0.05$;

Fatigue, average over 7 day period; Pred VO2, predicted peak oxygen uptake (mL/kg/min); MVPA, weekly minutes of moderate-to-vigorous physical activity as indexed by accelerometry; RPPrest, resting rate-pressure product [(HRrest x SBPrest)/100]; RPP1-4, rate-pressure product at Stage 1 through Stage 4 of the modified Naughton protocol.

Table 3

Multiple regression models of rate-pressure product among all participants at month 3 (M3) follow-up ($n = 152$).

	Model R	R ²	Slope	Standardized β	Partial r	p-value
Model 1: <i>RPP1</i>	0.578	0.33	124.669			
BMI			0.867	0.291	0.323 [‡]	< 0.001
Pred VO2			-1.528	-0.407	-0.427 [‡]	< 0.001
MVPA			-0.009	-0.065	-0.078	0.357
Model 2: <i>RPP2</i>	0.651	0.42	139.259			
BMI			0.996	0.302	0.356 [‡]	< 0.001
Pred VO2			-1.942	-0.468	-0.505 [‡]	< 0.001
MVPA			-0.016	-0.102	-0.130	0.122
Model 3: <i>RPP3</i>	0.713	0.51	163.217			
BMI			1.170	0.314	0.394 [‡]	< 0.001
Pred VO2			-2.526	-0.537	-0.588 [‡]	< 0.001
MVPA			-0.014	-0.080	-0.110	0.189
Model 4: <i>RPP4</i>	0.748	0.56	187.856			
BMI			1.328	0.321	0.421 [‡]	< 0.001
Pred VO2			-2.993	-0.575	-0.635 [‡]	< 0.001
MVPA			-0.013	-0.066	-0.097	0.248

[‡] Significance at $p < 0.001$.

BMI, body mass index (kg/m^2); Pred VO2, predicted maximal oxygen uptake (mL/kg/min); MVPA, weekly minutes of moderate-to-vigorous physical activity as indexed by accelerometry; RPP1-4, rate-pressure product [(heart rate $\times$ systolic blood pressure)/100] at Stage 1 through Stage 4 of the modified Naughton protocol.