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LETTER TO THE EDITOR

Interindividual changes in peak oxygen consumption in patients with colorectal cancer following endurance training: a secondary analysis of the I-WALK-CRC study

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Introduction

Surgical resection with adjuvant chemotherapy according to stage and risk profile is the main treatment option for non-metastatic colorectal cancer (CRC). However, pervasive side effects, including reductions in peak oxygen uptake ($\dot{V}O_{2peak}$) have been documented [1]. Evidence suggests that $\dot{V}O_{2peak}$ is an independent predictor of cancer-specific mortality [2,3], thus counteracting strategies are warranted.

Physical exercise has been widely applied with the purpose of ameliorating cancer treatment-induced cardiovascular impairments [4]. However, previous work examining the effect of endurance training on $\dot{V}O_{2peak}$ in post-treatment CRC patients is equivocal, with studies documenting no effect [5] and others showing improvement [6]. Our group recently presented the findings of the Interval Walking in Colorectal Cancer (I-WALK-CRC) study, a randomized controlled trial examining the effect of interval walking on cardiometabolic profile in post-treatment CRC patients [7]. While interval walking improved glycemic control and counteracted fat gains, we found no change in $\dot{V}O_{peak}$, the primary outcome of the trial.

It has long been recognized that cardiovascular adaptations to exercise vary substantiable between sedentary subjects [8–10], and recent studies in cancer patients report considerable interindividual heterogeneity in change in $\dot{V}O_{2peak}$ ($\Delta\dot{V}O_{2peak}$) following endurance training [11,12]. The identification of interindividual variability in $\Delta\dot{V}O_{2peak}$ as well as possible predictors may be adopted to develop patient-tailored exercise prescriptions. Therefore, we performed an explorative, secondary analysis of the I-WALK-CRC trial to examine interindividual variability in $\Delta\dot{V}O_{2peak}$ and to identify possible predictors of $\Delta\dot{V}O_{2peak}$.

Material and methods

This study is a secondary analysis of the I-WALK-CRC study, which has been described in detail previously [7,13]. I-WALK-CRC was conducted at Centre for Physical Activity Research, Righospitalet, Copenhagen, Denmark, and has been approved by the Committees of Biomedical Research Ethics, Capital Region of Denmark.

Participants

Patients who had completed surgery for Union for International Cancer Control (UICC) stage I or IIa CRC or surgery with adjuvant chemotherapy for UICC stage IIb or III CRC were eligible for inclusion. Exclusion criteria were <18 years of age, major surgery scheduled within 24 weeks, pregnancy, other current malignancy, performance status >1, >150 min/week self-reported moderate intensity physical activity, and inability to read and understand Danish.

Study assessments

The participants were tested in the laboratory on three study visits; at baseline and after 12 and 24 weeks. Study assessments included DXA-assessed body composition, blood samples, glycemic control by oral glucose tolerance test, and $\dot{V}O_{2peak}$. For assessment of $\dot{V}O_{peak}$, the participants performed 3 min warm-up at 70 watts on an ergometer bicycle (E839, Monark Exercise AB, Vansbro, Sweden), followed by 20 watts/min increases until voluntary exhaustion. Gas exchange (Quark CPET, COSMED, Rome, Italy) was measured continuously, and $\dot{V}O_{peak}$ was defined at the highest 20-seconds $\dot{V}O_2$ average. Besides voluntary exhaustion, attainment of at least two of the following criteria was used to verify $\dot{V}O_{peak}$; a plateau in $\dot{V}O_2$, a respiratory exchange (RER) ratio ≥1.10, and a rating of perceived exertion ≥17 (Borg 6–20 scale). A $\dot{V}O_2$ plateau was defined as follows: Linear regression was used to model the $\dot{V}O_2$ slope (L/min) of the submaximal part of the test, i.e. excluding the warm-up (to account for the $\dot{V}O_2$ slow component) and the last two stages (to account for a

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possible plateau). The linear model was then extrapolated to the end of the test. A plateau was considered evident if the mean difference between the modeled $\dot{V}O_2$ and the actual $\dot{V}O_2$ (i.e. the residuals) of the last minute of the test was greater than half of the modeled $\dot{V}O_2$ slope [14].

Group allocation

Following baseline assessment, the participants were randomized 1:1 to an interval walking intervention group (IWALK) or a waiting-list control group (CON).

Interval walking group

IWALK performed 24 weeks 150 min/week interval walking by use of the InterWalk application [15]. The InterWalk application consists of a test function and a training function. The test function is audio guided and comprises four consecutive walking stages: 2 min slow walking, 2 min intermediate walking, 2 min fast walking, and 1 min very fast walking. The walking speed of each stage is self-selected. The training function comprises an audio guided walking program, consisting of repeating cycles of 3 min slow walking and 3 min fast walking. The speed of the 'fast walking' corresponds to the average of the walking speed during last 30 s of the intermediate stage and the fast stage of the test. The speed of the 'slow walking' interval corresponds to the average of the walking speed during last 30 s of the slow stage and the intermediate stage of the test. Participants were introduced to the InterWalk application during the baseline visit and were instructed to perform an individual test every third week. It was optional how the 150 min of interval walking was distributed across a given week. The participants were instructed to register the weekly duration of interval walking in exercise logs.

Waiting-list control group

The CON group was instructed to maintain their level of physical activity. After the 12-week follow-up visit, the CON group performed 12 weeks 150 min/week interval walking.

Statistical analyses

Data obtained in IWALK (week 1–12) and data obtained in CON (week 13–24) were pooled for analyses. We determined individual $\dot{V}O_{2peak}$ levels in absolute (L/min) and body-mass adjusted values (mL/kg/min), and furthermore as $\dot{V}O_{peak}$ relative (in percentage) to age- and sex-specific reference values [16]. A change in $\dot{V}O_{2peak}$ was defined as an increase or a decrease of more than 5%. This is the technical error (measurement error plus day-to-day variation) of assessments of $\dot{V}O_{2peak}$ previously reported in untrained individuals [17,18]. Pearson's bivariate correlation was used to examine the relationship between $\Delta\dot{V}O_{2peak}$ and continuous variables (baseline $\dot{V}O_{2peak}$, baseline and Δbody weight, baseline and Δtotal fat mass, baseline and Δlean mass, and time since completion of treatment). Variables significantly associated with $\Delta\dot{V}O_{2peak}$ were subsequently entered as independent variables into multiple linear regression models to assess the effect of adding additional variables separately. Two-sample t-tests were used to compare participants with and without exercise logs and participants that achieved and did not achieve a $\dot{V}O_2$ plateau. Continuous data are presented as mean ± SD and categorical variables and proportions are presented as *n* (%), unless otherwise stated. The level of significance was 0.05

Results

Thirty-one participants completed a 12-week interval walking period with successful pre- and post-assessments of $\dot{V}O_{2peak}$ (Figure 1(A), Table 1). Exercise logs were available from 17 participants, reporting 144 ± 42 min interval walking per week. There was no difference between participants with and without exercise logs in absolute (−0.01 ± 0.15 and −0.01 ± 0.14 L/min, respectively; $p = .902$) or body-adjusted $\Delta\dot{V}O_{2peak}$ (−0.3 ± 1.7 and −0.2 ± 1.6 mL/kg/min, respectively; $p = .881$).

Individual baseline $\dot{V}O_{2peak}$ values were compared to normative reference [16]. Male participants had a baseline $\dot{V}O_{2peak}$ of 29.5 ± 6.0 mL/kg/min (101.7 ± 17.2% of age-expected; Figure 1(B)), and female participants had a baseline $\dot{V}O_{2peak}$ of 22.7 ± 4.7 mL/kg/min (92.7 ± 17.1% of age-expected; Figure 1(C)). Twenty-one participants (68%) achieved a plateau in the baseline test, and 19 participants (61%) achieved a plateau in the follow-up test. In plateau non-achievers, the mean RER was 1.18 ± 0.08 at baseline and 1.19 ± 0.08 at follow-up. There was no difference between plateau achievers and non-achievers in absolute $\dot{V}O_{2peak}$ (2.15 ± 0.61 and 2.15 ± 0.60 L/min, respectively; $p = .998$), body-adjusted $\dot{V}O_{2peak}$ (26.6 ± 5.9 and 24.4 ± 6.6 mL/kg/min, respectively; $p = .379$), absolute $\Delta\dot{V}O_{2peak}$ (−0.02 ± 0.15 and 0.01 ± 0.15 L/min, respectively; $p = .585$), or body-adjusted $\Delta\dot{V}O_{2peak}$ (−0.5 ± 1.7 and 0.3 ± 1.5 mL/kg/min, respectively; $p = .244$).

In response to interval walking, 6 (19%) participants demonstrated a >5% increase in $\dot{V}O_{2peak}$ (mL/kg/min), whereas 7 (23%) participants demonstrated a >5% decrease in $\dot{V}O_{2peak}$ (mL/kg/min; Figure 1(D)). Baseline absolute $\dot{V}O_{2peak}$ was associated with absolute $\Delta\dot{V}O_{2peak}$ ($r = -0.416$; $p = .020$), baseline body-mass adjusted $\dot{V}O_{2peak}$ was associated with body-mass adjusted $\Delta\dot{V}O_{2peak}$ ($r = -0.525$, $p = .002$), and individual percentage of baseline age-expected $\dot{V}O_{2peak}$ was associated with percentage $\Delta\dot{V}O_{2peak}$ ($r = -0.581$; $p = .0006$; Figure 1(E)). No correlations were apparent between body-mass adjusted $\Delta\dot{V}O_{2peak}$ and age ($r = -0.09$; $p = .644$), baseline ($r = 0.16$; $p = .387$) or Δbody weight ($r = -0.06$; $p = .746$), baseline ($r = 0.314$; $p = .090$) or Δtotal fat mass ($r = -0.097$; $p = .602$), baseline ($r = -0.165$; $p = .376$) or Δtotal lean mass ($r = -0.138$; $p = .459$), baseline ($r = -0.279$; $p = .129$) or Δleg lean mass ($r = -0.167$; $p = .368$), weekly amount of interval walking ($r = -0.362$; $p = .153$), time since completion of chemotherapy ($r = -0.313$; $p = .238$), or time since surgery ($r = -0.065$; $p = .729$) (data not shown). In CON, no correlations were apparent between baseline $\dot{V}O_{2peak}$ and $\Delta\dot{V}O_{2peak}$ (absolute:

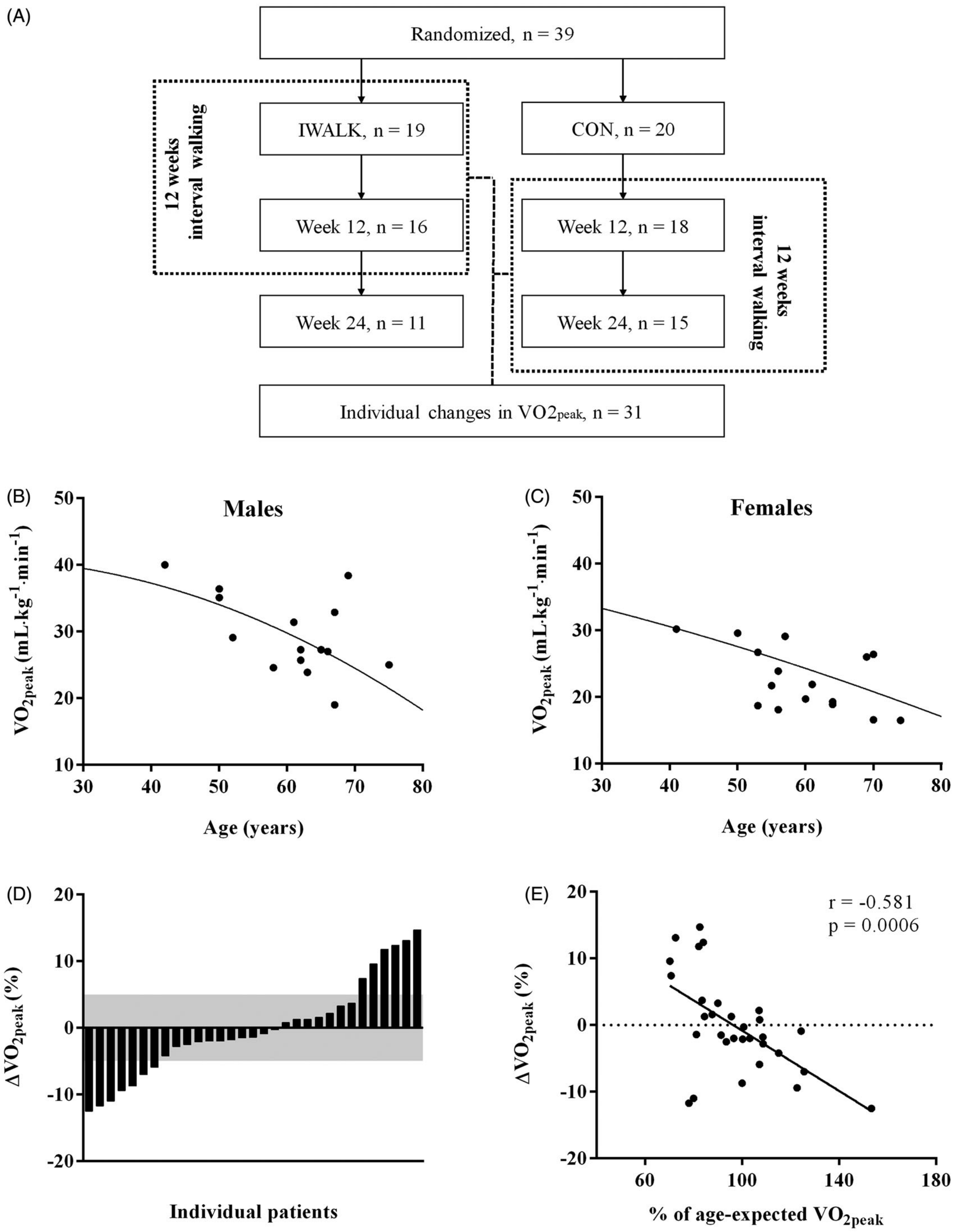

Figure 1. (A) Patient flow. (B and C) Baseline $\dot{V}O_{2peak}$ in male and female participants. The lines represent age- and sex-specific normative values [16]. (D) Individual pre- to post-test percentage changes in $\dot{V}O_{2peak}$ (mL/kg/min). The shaded area represents the typical error of measurement of ± 5%. (E) Linear correlation between pre- to post-test percentage changes in $\dot{V}O_{2peak}$ (mL/kg/min) and $\dot{V}O_{2peak}$ expressed relative to (%) age- and sex-specific normative reference values (mL/kg/min; [16]).

$r = -0.065$; $p = .824$; body mass adjusted: $r = 0.007$; $p = .981$) in the control period (week 1–12) (data not shown).

Baseline $\dot{V}O_{2peak}$ was entered into a linear regression model, and the effect of separately adding age, sex, smoking status, baseline and Δbody weight, baseline and Δtotal fat and lean mass, time since completion of chemotherapy, and employment status was examined. None of these variables affected the model significantly (data not shown).

Discussion

The main finding of this secondary analysis was that $\Delta\dot{V}O_{2peak}$ following endurance training in post-treatment CRC patients was independently associated with the initial $\dot{V}O_{2peak}$ level. This finding is in accordance with prior reports in healthy [8–10,19], diseased [20], and athletic populations [21]. Thus, it can be expected that individuals with the

Table 1. Patients baseline characteristics.

Sex	
Female	16 (52)
Male	15 (48)
Age (years)	60 (9)
Body weight (kg)	82.8 (11.6)
Body composition	
BMI (kg/m^2)	28.4 (4.0)
Total lean mass (kg)	49.0 (9.8)
Leg lean mass (kg)	15.5 (3.6)
Total fat mass (kg)	29.4 (9.4)
Cancer type	
Colon cancer	26 (84)
Rectal cancer	5 (16)
Tumor stage	
1	8 (26)
2	10 (32)
3	13 (42)
Adjuvant chemotherapy	
Yes	16 (52)
No	15 (48)
Time since treatment completion (days)	
Surgery	230 (155; 370)
Chemotherapy	48 (29; 72)
$\dot{V}O_{2peak}$	
L/min	2.12 (0.60)
mL/kg/min	26.0 (6.3)
% of age-expected	97 (19)
Employment	
Working	21 (68)
Not working	10 (32)
Smoking	
Former	15 (48)
Never	13 (42)
Current	3 (10)

Categorical variables are presented as *n* (%) and continuous variables are presented as mean (SD), except from time since treatment completion, which is presented as median (IQR). BMI: Body mass index. Age-expected $\dot{V}O_{2peak}$ is calculated as measured $\dot{V}O_{2peak}$ (mL/kg/min) relative to age- and sex-specific normative reference values [16].

lowest level of aerobic capacity have the greatest potential for improvement. It was nonetheless surprising to observe 23% of the participants with a > 5% decline in $\dot{V}O_{2peak}$ following the walking intervention. This suggests that 'high-fitness' individuals require considerable training stimuli just to maintain $\dot{V}O_{2peak}$, which walking training, even at alternating high and low paces, was not sufficient to induce. Conversely, it was an important observation that all participants with >5% increases in $\dot{V}O_{2peak}$ presented with approximately 80% of age-expected value. This indicates that interval walking can be an effective cardiovascular training modality in 'low-fitness' individuals, but more research is needed to determine potential modality-specific cutoff levels. Collectively, our findings strongly suggest that maximal exercise testing should be used to develop patient-tailored endurance training interventions in the oncology setting, where exercise commonly is prescribed without adjusting exercise training principles to the individual patients [22,23]. While maximal exercise testing is considered safe and feasible in post-treatment CRC patients [6,24], it is important to consider, that submaximal tests can yield satisfactory estimates of $\dot{V}O_{2peak}$ [25] and may be used where personnel and/or required instrumentation are unavailable. The present intervention did not follow the principle of individualization, as it was designed as a pragmatic, home-based program for patients to perform without supervision as a possible alternative to specialized, hospital-based programs. Importantly, we did find this was an effective strategy to improve glycemic control and counteract unfavorable changes in body composition, as previously reported [7].

Notably, the mean $\dot{V}O_{peak}$ of the included CRC patients was comparable (97 ± 19% of age-expected) to reference values [16]. This finding was unexpected considering that treated CRC patients previously have been reported to display reduced values [1] and since inactivity was an inclusion criteria in this study. Of importance, we used German normative reference values for $\dot{V}O_{peak}$ [16], which may not be representative for the Danish population given possible differences in exercise training habits, and our findings should be interpreted with caution. Nonetheless, our finding emphasizes the need to measure $\dot{V}O_{peak}$ to individualize exercise prescription in clinical practice, even in a seemingly homogeneous group of inactive CRC post-treatment patients.

This explorative analysis has limitations, the most important being the low number of included patients. Further, the I-WALK-CRC trial was not designed to identify predictors of $\Delta\dot{V}O_{peak}$ and this secondary analysis should be considered explorative. Lastly, the inverse association between baseline level and $\Delta\dot{V}O_{2peak}$ could be a result of 'regression to the mean'. However, $\dot{V}O_{2peak}$ was assessed using objective methods and strict verification criteria, and no correlation was found between baseline $\dot{V}O_{2peak}$ and $\Delta\dot{V}O_{2peak}$ in CON following the control period. This suggests that the association apparent following the training period was underpinned by physiological factors rather than being an artefactual consequence of extreme values regressing toward the mean as measurements of $\dot{V}O_{2peak}$ were repeated.

In conclusion, short-term interval walking may be insufficient to improve $\dot{V}O_{2peak}$ in post-treatment CRC patients with moderate to high baseline levels relative to age-specific normative values. Conversely, among patients exhibiting low levels of initial $\dot{V}O_{2peak}$ relative to age-specific normative values, interval walking seems to be adequate to induce improvements. This suggests that assessment of baseline $\dot{V}O_{2peak}$ may be applied to adopt individualized exercise prescriptions, potentially enhancing the efficacy of endurance training in post-treatment CRC patients.

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Clinical trial information

www.clinicaltrials.gov no. NCT02403024 registered March 31st 2015.

Disclosure statement

The authors declare no conflicts of interest.

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