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Feasibility of high-intensity interval training with hyperoxia vs. intermittent hyperoxia and hypoxia in cancer patients undergoing chemotherapy – Study protocol of a randomized controlled trial

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ABSTRACT

Exercise has been well demonstrated to potentially reduce chemotherapy-induced side effects and possibly aid slowing down tumor growth in cancer patients but exercise training adherence is typically low. Thus, training regimens which are perceived less strenuous but do not compromise the training-induced beneficial adaptations will help to increase adherence to exercise and reduce attrition.

This 4-armed study aims to investigate the effects of high intensity interval training (HIIT) in hyperoxia versus intermittent hyperoxia and hypoxia in cancer patients undergoing chemotherapy. Forty-eight cancer patients will be randomized into either of three intervention groups or a no-training control group. Patients in the intervention groups will perform twice weekly HIIT on a cycle ergometer in hyperoxia, intermittent hyperoxia and hypoxia or normoxia. Study outcomes will be assessed before and after 4 weeks of training, while selected measures will also be performed pre- and post the first and last training session. The primary aim of this study is to investigate the feasibility, compliance, tolerance and safety of the training. Secondary endpoints will include measures of quality of life, aerobic capacity, transcutaneous oxygen saturation, red blood cell deformability, as well as the assessment of anabolic and catabolic hormone concentrations, reactive oxygen species, cytokine profiles and NK-cell cytotoxicity.

To the best of our knowledge, this is the first study investigating the combined effects of exercise with modified fraction of inspired O_2 in cancer patients. As such, we provide a novel approach for exercise as an adjuvant therapy in cancer patients undergoing chemotherapy.

1. Introduction

Despite advances in medical therapies, cancer is still ranked among the most common causes of death worldwide. While the treatment options are manifold, neoadjuvant and/or perioperative chemotherapy are considered essentially important for the progression-free and overall survival of cancer patients [6]. However, it is well known that the high toxicity of chemotherapy leads to a number of tremendous short- and long-term adverse effects (i.e. chemo toxicity), presenting a dramatic impact on the quality of life of these patients. Most common short-term side effects include nausea, emesis and cancer-related fatigue, while long-term effects are characterized by declines in physical performance and decreased quality of life, accompanied by neutropenia-induced declines in immune function [7,18,27,30].

Physical exercise is known for its potential to reduce chemo toxicity throughout a wide range of cancer entities [14,24,26,29,31,32]. However, the observed absolute effects of exercise are often only moderate [8,31]. This outcome may be especially related to a poor training adherence, which is typically reported in these patients [13]. Moreover, most of the available studies have utilized low to moderate exercise intensities in training regimes, while studies specifically investigating high-intensity interval training for the adjuvant treatment of cancer are rare.

Previous studies have indicated that increasing (i.e. hyperoxia) or decreasing (i.e. hypoxia) the fraction of inspired oxygen (FiO_2) during exercise training may induce substantial physiological alterations both in diseased [4,16] and healthy populations [34,35], and may, thus, also enhance the effects of exercise as an adjuvant therapy for cancer

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patients. For example, Moore and colleagues [16] showed in patients with chronic heart failure that exercise in hyperoxia led to increased arterial oxygen saturation, while concomitantly reducing minute ventilation, cardiac output and subjective scores for fatigue. Similar findings were also observed in a previous pilot study in diabetic patients during sub-maximal aerobic cycling exercise [4]. Both moderate and high-intensity exercise in mild hypoxia, on the other hand, have previously been shown to mobilize NK-cells and improve NK-cell cytotoxicity [34,35] in healthy subjects, which would possibly aid slowing down tumor growth in cancer patients. The effects of strenuous exercise in hyperoxia on immune function have yet to be investigated.

According to Craike and colleagues [5], exercise regimes which are perceived less strenuous but do not compromise or even optimize the training-induced physiological and patient-related outcomes will help to increase adherence to exercise and reduce attrition. The aim of this 4-armed study is, thus, to investigate the feasibility of a high-intensity interval training (HIIT) performed with increased FiO_2 as compared to the same training performed in normoxia. As patients undergoing chemotherapy may not be able to perform strenuous exercise training in hypoxic conditions, a third group will be included into this study performing all high-intensity interval bouts with an increased FiO_2, while during the rest periods FiO_2 will be reduced (i.e. hypoxia). In other words, we are aiming to assess whether the physiological and patient-reported outcomes can be improved, while the perceived effort is reduced when FiO_2 during strenuous exercise as well as the rest periods are modified.

2. Materials and methods

The current study will be carried out in accordance with the declaration of Helsinki and received ethical approval by the Ethics Committee of the German Sport University, Cologne. All participants are requested to provide written informed consent prior to participation. The study is registered both at the German and the WHO trial registers (DRKS00011689) and is accredited by the German Cancer Society (ST-U051).

2.1. Study design

This study will be performed as a randomized controlled trial (RCT) consisting of 4 arms (Fig. 1). Following recruitment and pre-screening, subjects will be randomized into one of the following four groups:

Normoxia:	High-intensity interval training in normoxia (FiO_2 0.21).
Hyperoxia:	High-intensity interval training with both exercise and rest-periods performed in hyperoxia (FiO_2 0.3).
Hyperoxia/ Hypoxia:	High-intensity interval training with exercise performed in hyperoxia (FiO_2 0.3) and rest-periods performed in hypoxia (FiO_2 0.15).
Control:	"Usual care", i.e. no prescribed Training and no modifications in inspired oxygen concentrations.

2.2. Sample size calculation

A priori calculation was performed in order to assess the sample size needed to detect both statistically and clinically significant findings. Due to the novelty of the present study, the sample size calculation was based on previous studies investigating intense physical exercise during cancer treatment [1,20,25,31,33] and was performed by G*power (version 3.1.9.2, Heinrich Heine University, Dusseldorf, Germany). The calculation was based on group × time interaction effects with a 4 × 2 mixed analysis of variance (mixed ANOVA) for the primary endpoint (adherence). In order to achieve an effect size of 0.7 with a power (1-ß) of 0.95, for most of the questionnaire-assessed patient related outcomes as well as changes in aerobic performance (i.e. secondary endpoint) at least a total of 40 subjects (n = 10 per group) are required. Based on our previous experience and the relatively short duration of the study, we are expecting the overall drop-out rate to be approximately 10%. Thus, 12 subjects per group will be recruited, leading to a total of 48 subjects.

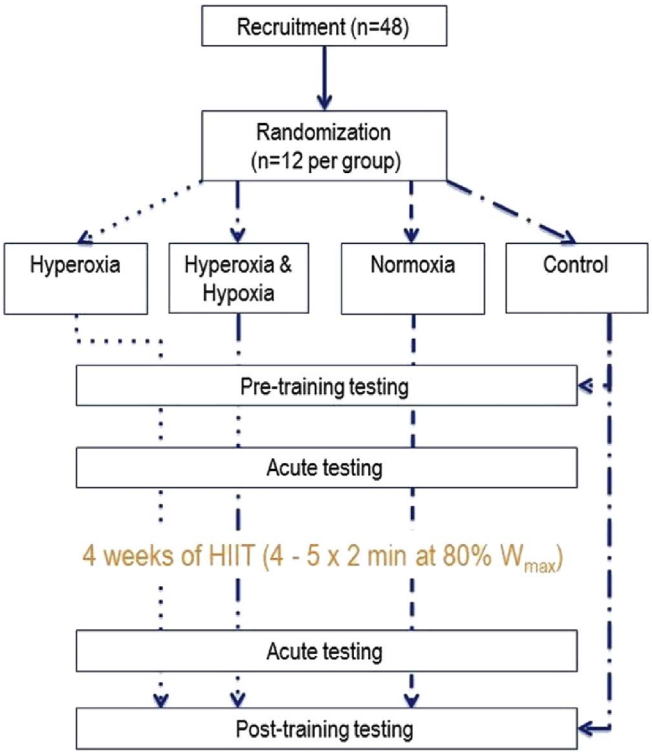

Fig. 1. Overall study design.

2.3. Inclusion and exclusion criteria

This study will be conducted with cancer patients, currently undergoing chemotherapy. The in- and exclusion criteria are presented in Table 1. Due to the pilot character of this study and the feasibility as a primary outcome, the study is not restricted to any type of cancer with the exception of lung- and/or bronchial carcinoma.

2.4. Screening and randomization

Patients will be screened by an oncologist prior to being included into the present study. Subjects will the undergo an additional medical check through a cardiologist in order to assess that intensive aerobic training can be performed without any concerns. After the medical screening and baseline testing, the stratified randomization using a minimization approach will be carried out by using RITA software (Randomization In Treatment Arms, Evident, Germany). The stratification factors will include 1) patients age and 2) gender.

2.5. Training intervention

The prescribed exercise training will consist of high-intensity interval (HIIT) training on a bike ergometer for 4 weeks. The training intensities will be determined by percentage of the maximal Wattage (W_{max}) obtained during an initial performance test at baseline. Training will be performed twice per week and will consist of 4–5 × 2 min high-intensity training bouts at 80% of the W_{max}, separated by 3 min of