Contemporary Clinical Trials Communications 8 (2017) 213–217

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

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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ARTICLE INFO

Keywords:
Carcinoma
Sport therapy
Rehabilitation
Aerobic exercise
FiO_2
Exercise medicine
HIIT

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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http://dx.doi.org/10.1016/j.conctc.2017.11.002
Received 11 July 2017; Received in revised form 31 October 2017; Accepted 1 November 2017
Available online 06 November 2017

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.

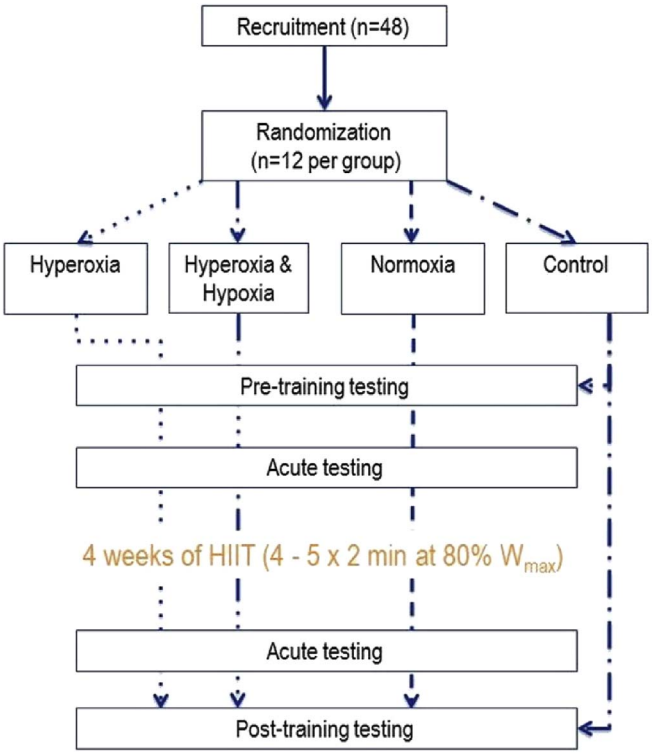

Fig. 1. Overall study design.

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

Table 1
In- and exclusion criteria.

Inclusion criteria	Exclusion criteria
●Men and women with carcinoma undergoing the first cycle of chemotherapy ● Patients treated with conventional chemotherapy: – Alkylating agents – Antimetabolites – Anthracyclines – Taxanes – Vincaalcaloides AND/OR Patients treated with antibody therapy ● ECOG performance status 0-1	● Patients with lung and bronchial carcinomas ● Recent serious cardiovascular events (including but not limited to poorly controlled hypertension and congestive heart failure) ● Medical conditions such as uncontrolled infection or cardiac disease that would make this protocol unreasonably hazardous for the patient ● Psychiatric illness, preventing the patient from giving informed consent or adhering to the study protocol ● Known spinal cord compromise or instrumentation due to metastatic disease. ● Peripheral neuropathy ≥ grade 3 ● Patients participating in vigorous aerobic exercise for more than 60 min per week or resistance exercise two or more days per week ● Shortness of breath, chest discomfort, or palpitations when performing activities of daily living ● Ongoing restriction of physical activity with physician documentation

recovery at 40% of W_{max}. Training will be synchronized with the individual drug administration and scheduled medical appointments of the patients. In order to allow for sufficient recovery, two subsequent training sessions will be separated by at least 48 h.

Normobaric hyperoxia and hypoxia will be supplied by a HYPOXcontrol device (Medicap homecare GmbH, Ulrichstein, Germany). A gas-air mixture will be directly supplied via a flexible tube from the "device to the respiration mask, where it will be further mixed with ambient air. Subjects in the hyperoxia group will train at an increased oxygen concentration throughout all training sessions (FiO_2 0.30). Subjects in the intermittent hyperoxia and hypoxia group will receive additional oxygen supply during each high-intensity bout (FiO_2 0.30), while the inspired concentration of oxygen will be reduced during the rest periods (FiO_2 0.15). The FiO_2 will be blinded to the subjects, while patients in the normoxia group will perform the training without a mask.

2.6. Measurement time points

All study outcomes will be assessed both before and after 4 weeks of training. In order to determine the acute responses of a single training session, selected measurements will also be performed before and after the first (week 1) and last training session (week 4).

2.7. Endpoints and measurements

2.7.1. Primary endpoint

The primary outcome of this study is to investigate the feasibility and compliance, tolerance and safety of the prescribed training.

2.7.2. Secondary endpoints

The following secondary endpoints will be assessed:

- Questionnaire-assessed patient-related outcomes such as quality of life, fatigue and cognitive function
- Chronic changes in aerobic capacity
- Chronic changes in body composition
- Acute and chronic changes in deep tissue and transcutaneous oxygen saturation
- Chronic changes in arterial stiffness
- Acute and chronic changes in red blood cell deformability
- Acute and chronic changes in anabolic and catabolic hormone concentrations, reactive oxygen species (ROS), cytokine profiles and NK-cell toxicity

2.7.3. Measurements

All assessments will be performed prior to the start of the training (baseline) as well as after 4 weeks. Selected measurements will also be performed both before and after a single training session in week 1 and 4 (i.e. session 2 and 8), respectively (immune status, red blood cell deformability, heart rate variability and transcutaneous oxygen saturation).

The following measurements will be performed:

2.7.4. Feasibility and compliance

In this study, feasibility will be assessed by trial completion, training adherence and compliance, program tolerance and patient safety. Program adherence and compliance will be assessed using exercise diaries indicating the number of training sessions performed and the total duration spent at high- and low training intensities. Program tolerance will be assessed by means of visual analogue scales (VAS, 0–10) and recordings of perceived exertion (Borg Scale, 0–10) during each training session. Furthermore, autonomous nervous function will be assessed non-invasively by heart rate variability (Firstbeat Technologies, Jvsäkylä, Finland) before, during and after the training intervention. Safety will be determined by the number of reported adverse events.

2.7.5. Questionnaire-assessed patient-related outcomes

Perceived fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F]), the quality of the treatment (Functional Assessment of Chronic Illness Therapy – Treatment rating [FACIT-TS-G]), cognitive function (Functional Assessment of Cancer Therapy – Cognitive Function [FACT-Cog]), sleep quality (Pittsburgh Sleep Quality Index [PSQI]), pain (Brief-Pain Inventory - Short Form [BPI-SF]) and quality of life (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30) will be assessed by questionnaires before and after the study.

2.7.6. Aerobic capacity

An incremental test on a cycle ergometer will be performed in order to assess the maximal aerobic capacity of the subjects. In agreement with the guidelines provided by the WHO, the test will commence at 25 Watts, while the load will be increased by 25 Watts every 2 min until voluntary exhaustion. Patients are requested to maintain a pedalling frequency of 60 rpm. Throughout the test, ECG will be recorded and followed-up by a cardiologist. Furthermore, capillary blood samples will be collected from the earlobe at the end of each stage for the determination of blood lactate concentrations. Additionally, breathing gases and heart rate will be monitored throughout the test.

2.7.7. Deep tissue and transcutaneous oxygen saturation

Deep tissue oxygenation will be assessed by near-infrared spectroscopy (moorVMS-NIRS, Moor Instruments, Devon, UK) and transcutaneous oxygen concentrations will be assessed subcutaneously by an optical $tcpO_2$ probe (HYPOXcontrol, Medicap homecare GmbH, Ulrichstein, Germany). Oxygen saturation will be assessed from the M. Rectus Femoris as well as M. Bizeps Brachii both, throughout the first

and last training sessions.

2.7.8. Arterial stiffness

Arterial stiffness will be assessed by a pulse wave analysis (Mobil-O-Graph, IEM, Stolberg, Germany) through oscillometry, both before and after the 4 weeks of training.

2.7.9. Red blood cell deformability

Capillary blood samples will be drawn from the earlobe (20 µl) and mixed with an isotonic viscous polyvinylpyrrolidone (PVP) solution to assess red blood cell (RBC) deformability both before and after the 4 weeks of training as well as both before and after the second and last training session, respectively. The deformability will be measured by a laser-assisted optical rotational cell analyzer (LORCA; RR Mechatronics, Hoorn, the Netherlands), as has been described previously [11].

2.7.10. Venous blood sampling

In this study, venous blood samples will be collected at 6 time points (prior to and after the intervention, as well as prior to and after the second and last training session, respectively). Collected serum will be used to determine anabolic and catabolic hormone concentrations (Testosterone, Cortisol, Catecholamines) as well as ROS. Collected EDTA blood will be analyzed for cytokine profiles as well as NK-cell cytotoxicity.

2.8. Data analysis

Within- and between-group analyses will be performed in order to investigate 1) basal adaptations induced by 4 weeks of training, 2) acute loading responses and recovery before the training intervention, 3) acute loading responses and recovery after 4 weeks of training and 4) training- or exercise-induced changes in acute loading responses and recovery. Data will be checked for normality and log transformed prior to applying parametric statistics. Group × time interactions for basal measures and acute exercise responses will be analyzed by a mixed ANOVA of co-variance, by taking into account the initial individual values at baseline (for comparisons of basal values) or the pre-loading values (acute for comparisons of acute exercise responses). Changes in the acute exercise responses induced by the training will then be assessed by a paired *t*-test using the relative changes of each training session (from pre-exercise to post-exercise), respectively. All results will be analyzed by the intention-to-treat approach to provide unbiased comparisons among the treatment groups. The statistical significance for all tests will be set at 0.05. In order to determine clinical significance of the findings, effect sizes for both within and between-group comparisons will be reported as Cohen's d. Statistical analysis will be performed by IBM SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

3. Discussion

This study provides an innovative approach for exercise with modified FiO_2 as an adjuvant therapy in cancer patients undergoing chemotherapy. While it has been well documented that physical exercise may aid in reducing chemotherapy-induced side effects in various types of cancer [1,2,14,24,26,29,31,32], little is known on the effects of exercise with modified systemic oxygen concentrations on cancer-specific outcomes and this knowledge stems from studies in healthy subjects [34,35].

The primary outcome of this study is to investigate the feasibility and compliance of HIIT with increased FiO_2 as well as both increased FiO_2 during exercise bouts and reduced FiO2 during rest intervals in cancer patients treated with chemotherapy. Based on previous studies in patients with diabetes [4] and chronic heart failure [16], we hypothesize that such training will significantly reduce the perceived effort and, thus, the physical strain of strenuous exercise. This will be assessed by patient-related outcomes, such as fatigue and pain scales, as well as RPE-scores. As a novel tool in this population, we will also implement the assessment of autonomous nervous function by means of heart rate variability, throughout the exercise protocol as well as the consecutive nights. Furthermore, measures of hormone concentrations will provide an objective measure to determine the anabolic or catabolic state, acutely induced by a single exercise session and chronically after 4 weeks of training [36].

Despite the investigation of feasibility and compliance, we are also aiming to gain initial insights into the physiological adaptations of such training regimen in cancer patients. In a previous review in healthy individuals, it was shown that exercise in hyperoxic conditions may acutely enhance endurance and sprint interval performance by accelerating recovery processes. Furthermore, studies clearly indicate that an increased FiO_2 leads to an enhanced cellular diffusion of oxygen [15,23], but significantly less is known about physiological adaptations to prolonged training [28]. Thus, in the present study oxygen delivery capacities will be assessed by means of oxygen consumption during an incremental bike ergometer test, pulse wave analysis, near-infrared spectroscopy and red blood cell deformability.

Both moderate and intensive exercise in hypoxia have previously been associated with increased NK-cell mobilization and cytotoxicity in healthy individuals [34,35]. It is likely that these effects were in part triggered by an increased secretion of stress hormones (e.g. catecholamines) due to an increased selective detachment of NK-cells from endothelial cells as shown both in animal [19] and human studies [3]. Even though in the present study hypoxic air will only be administered during rest periods in between bouts of HIIT, changes in catecholamines will also be assessed and possible associations with potentially improved NK-cell mobility will be determined.

Much of the beneficial effects of aerobic exercise in both healthy subjects and patients are thought to be brought about by oxidative stress [12]. Initially the production of reactive oxygen species (ROS) induced by exhaustive exercise may induce tissue damage [21] and, thus, blunt muscle contractions [22]. In fact, it has also been shown that increased ROS potentially contribute to the progression of cancer [10]. However, this transient increase in ROS is typically accompanied by an adaptive up-regulation of antioxidant genes, improving immune function [9] and stimulating adaptive systemic responses [17]. Because it is reasonable to assume that modified FiO_2 during exercise will impact on the oxidative stress response, this will be assessed in the present study.

To the best of our knowledge, to date no studies have investigated the combined effects of exercise and hyperoxic and/or hypoxic conditions in cancer patients. Based on findings of previous studies in both diseased and healthy populations, it is reasonable to assume that such method may substantially increase the adherence to regular exercise in these patients, while it may at the same time provide a larger window for beneficial physiological adaptations.

References

[1] L. Adamsen, M. Quist, C. Andersen, et al., Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial, BMJ Clin. Res. Ed. 339 (2009) b3410, http://dx.doi.org/10.1136/bmj.b3410 eng.

[2] F.T. Baumann, L. Kraut, K. Schule, W. Bloch, A.A. Fauser, A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation, Bone Marrow Transplant. 45 (2) (2010) 355–362, http://dx.doi.org/10.1038/bmt.2009.163 eng.

[3] R.J. Benschop, F.G. Oostveen, C.J. Heijnen, R.E. Ballieux, Beta 2-adrenergic stimulation causes detachment of natural killer cells from cultured endothelium, Eur. J. Immunol. 23 (12) (1993) 3242–3247, http://dx.doi.org/10.1002/eji.1830231230 eng.

[4] C. Brinkmann, A. Metten, P. Scriba, et al., Hypoxia and hyperoxia affect serum angiogenic regulators in T2DM men during cycling, Int. J. Sports Med. 38 (2) (2017) 92–98 eng.

[5] M. Craike, C.J. Gaskin, K.S. Courneya, et al., Predictors of adherence to a 12-week exercise program among men treated for prostate cancer: ENGAGE study, Cancer Med. 5 (5) (2016) 787–794, http://dx.doi.org/10.1002/cam4.639 eng.

[6] D. Cunningham, W.H. Allum, S.P. Stenning, et al., Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, N. Engl. J. Med. 355

(1) (2006) 11–20, http://dx.doi.org/10.1056/NEJMoa055531 eng.
[7] F. Dimeo, S. Fetscher, W. Lange, R. Mertelsmann, J. Keul, Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy, Blood 90 (9) (1997) 3390–3394 eng.
[8] A.C. Furmaniak, M. Menig, M.H. Markes, Exercise for women receiving adjuvant therapy for breast cancer, Cochrane Database Syst. Rev. 9 (2016) CD005001, http://dx.doi.org/10.1002/14651858.CD005001.pub3 eng.
[9] M.-C. Gomez-Cabrera, E. Domenech, J. Vina, Moderate exercise is an antioxidant: upregulation of antioxidant genes by training, Free Radic. Biol. Med. 44 (2) (2008) 126–131, http://dx.doi.org/10.1016/j.freeradbiomed.2007.02.001 eng.
[10] G. Gupta-Elera, A.R. Garrett, R.A. Robison, K.L. O'Neill, The role of oxidative stress in prostate cancer. European journal of cancer prevention, Off. J. Eur. Cancer Prev. Organ. (ECP) 21 (2) (2012) 155–162, http://dx.doi.org/10.1097/CEJ.0b013e32834a8002 eng.
[11] M.R. Hardeman, J.G. Dobbe, C. Ince, The laser-assisted optical rotational cell analyzer (LORCA) as red blood cell aggregometer, Clin. Hemorheol. Microcirc. 25 (1) (2001) 1–11 eng.
[12] F. He, J. Li, Z. Liu, C.-C. Chuang, W. Yang, L. Zuo, Redox mechanism of reactive oxygen species in exercise, Front. Physiol. 7 (2016) 486, http://dx.doi.org/10.3389/fphys.2016.00486 eng.
[13] A.M.L. Husebo, S.M. Dyrstad, J.A. Soreide, E. Bru, Predicting exercise adherence in cancer patients and survivors: a systematic review and meta-analysis of motivational and behavioural factors, J. Clin. Nurs. 22 (1–2) (2013) 4–21, http://dx.doi.org/10.1111/j.1365-2702.2012.04322.x eng.
[14] W. Jensen, F.T. Baumann, A. Stein, et al., Exercise training in patients with advanced gastrointestinal cancer undergoing palliative chemotherapy: a pilot study, Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer 22 (7) (2014) 1797–1806, http://dx.doi.org/10.1007/s00520-014-2139-x eng.
[15] D.R. Knight, W. Schaffartzik, D.C. Poole, M.C. Hogan, D.E. Bebout, P.D. Wagner, Effects of hyperoxia on maximal leg O2 supply and utilization in men, J. Appl. Physiol. (Bethesda, Md.: 1985) 75 (6) (1993) 2586–2594 eng.
[16] D.P. Moore, A.R. Weston, J.M. Hughes, C.M. Oakley, J.G. Cleland, Effects of increased inspired oxygen concentrations on exercise performance in chronic heart failure, Lancet (London, England) 339 (8797) (1992) 850–853 eng.
[17] L. Parker, T.A. McGuckin, A.S. Leicht, Influence of exercise intensity on systemic oxidative stress and antioxidant capacity, Clin. Physiol. Funct. Imaging 34 (5) (2014) 377–383, http://dx.doi.org/10.1111/cpf.12108 eng.
[18] A.H. Partridge, H.J. Burstein, E.P. Winer, Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer, J. Natl. Cancer Inst. Monogr. 30 (2001) 135–142 eng.
[19] L. Pedersen, M. Idorn, G.H. Olofsson, et al., Voluntary running suppresses tumor growth through Epinephrine- and IL-6-dependent NK cell mobilization and redistribution, Cell Metab. 23 (3) (2016) 554–562, http://dx.doi.org/10.1016/j.cmet.2016.01.011 eng.
[20] S. Persoon, M.J.M. ChinAPaw, L.M. Buffart, et al., Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: results from the EXIST study, PLoS One 12 (7) (2017) e0181313, http://dx.doi.org/10.1371/journal.pone.0181313 eng.
[21] S.K. Powers, M.J. Jackson, Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production, Physiol. Rev. 88 (4) (2008) 1243–1276, http://dx.doi.org/10.1152/physrev.00031.2007 eng.
[22] S.K. Powers, W.B. Nelson, M.B. Hudson, Exercise-induced oxidative stress in humans: cause and consequences, Free Radic. Biol. Med. 51 (5) (2011) 942–950, http://dx.doi.org/10.1016/j.freeradbiomed.2010.12.009 eng.
[23] F. Prieur, H. Benoit, T. Busso, J. Castells, A. Geyssant, C. Denis, Effects of moderate hyperoxia on oxygen consumption during submaximal and maximal exercise, Eur. J. Appl. Physiol. 88 (3) (2002) 235–242, http://dx.doi.org/10.1007/s00421-002-0707-0 eng.
[24] M.E. Schmidt, J. Wiskemann, P. Armbrust, A. Schneeweiss, C.M. Ulrich, K. Steindorf, Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial, Int. J. Cancer 137 (2) (2015) 471–480, http://dx.doi.org/10.1002/ijc.29383 eng.
[25] S.V.W. Schulz, R. Laszlo, S. Otto, et al., Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study, Disabil. Rehabil. (2017) 1–8 eng.
[26] R.J. Segal, R.D. Reid, K.S. Courneya, et al., Resistance exercise in men receiving androgen deprivation therapy for prostate cancer, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 21 (9) (2003) 1653–1659, http://dx.doi.org/10.1200/JCO.2003.09.534 eng.
[27] R. Sinclair, M. Navidi, S.M. Griffin, K. Sumpter, The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma, Ann. R. Coll. Surg. Engl. 98 (6) (2016) 396–400, http://dx.doi.org/10.1308/rcsann.2016.0135 eng.
[28] B. Sperlich, C. Zinner, A. Hauser, H.-C. Holmberg, J. Wegrzyk, The impact of hyperoxia on human performance and recovery, Sports Med. (Auckland, N.Z.) 47 (3) (2017) 429–438, http://dx.doi.org/10.1007/s40279-016-0590-1 eng.
[29] F. Streckmann, S. Kneis, J.A. Leifert, et al., Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 25 (2) (2014) 493–499, http://dx.doi.org/10.1093/annonc/mdt568 eng.
[30] K. Strojnik, K. Mahkovic-Hergouth, B.J. Novakovic, B. Seruga, Outcome of severe infections in afebrile neutropenic cancer patients, Radiol. Oncol. 50 (4) (2016) 442–448, http://dx.doi.org/10.1515/raon-2016-0011 eng.
[31] D.R. Taaffe, R.U. Newton, N. Spry, et al., Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: a Year-long randomised controlled trial, Eur. Urol. (2017) eng.
[32] R.J. Thomas, S.A. Kenfield, A. Jimenez, Exercise-induced biochemical changes and their potential influence on cancer: a scientific review, Br. J. Sports Med. (2016) eng.
[33] K. Toohey, K.L. Pumpa, L. Arnolda, et al., A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors, Peer J. 4 (2016) e2613, http://dx.doi.org/10.7717/peerj.2613 eng.
[34] J.-S. Wang, T.-P. Weng, Hypoxic exercise training promotes antitumour cytotoxicity of natural killer cells in young men, Clin. Sci. (London, England: 1979) 121 (8) (2011) 343–353, http://dx.doi.org/10.1042/CS20110032 eng.
[35] J.-S. Wang, C.-K. Wu, Systemic hypoxia affects exercise-mediated antitumor cytotoxicity of natural killer cells, J. Appl. Physiol. (Bethesda, Md.: 1985) 107 (6) (2009) 1817–1824, http://dx.doi.org/10.1152/japplphysiol.00687.2009 eng.
[36] S.J. Winters, Male Hypogonadism: Basic, Clinical and Therapeutic Principles, Springer International Publishing, Cham, 2017, p. 1452 (Contemporary Endocrinology). ISBN: 9783319532967. Available from: http://ebookcentral.proquest.com/lib/gbv/detail.action?docID=4848059 eng.