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UNIVERSIDAD CATÓLICA DE MURCIA

ESCUELA INTERNACIONAL DE DOCTORADO

Programa de Doctorado Ciencias de la Salud

Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss

Autor:

Domingo Jesús Ramos Campo

Director:

Dr. D. Jacobo Ángel Rubio Arias

Murcia, 15 de mayo de 2019

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AUTORIZACIÓN DE LO/S DIRECTOR/ES DE LA TESIS
PARA SU PRESENTACIÓN

El Dr. D. Jacobo Ángel Rubio Arias como Director de la Tesis Doctoral titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss" realizada por D. Domingo Jesús Ramos Campo en el Doctorado de Ciencias de la Salud, **autoriza su presentación a trámite** dado que reúne las condiciones necesarias para su defensa.

Lo que firmo, para dar cumplimiento al Real Decreto 99/2011, 1393/2007, 56/2005 Y 778/98, en Murcia a 15 de Mayo de 2019

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PUBLICACIONES

La presente tesis titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss" se defiende en formato compendio de trabajos. Los artículos que comprenden esta tesis doctoral son:

1.- Ramos-Campo DJ, Girard O, Pérez A, Rubio-Arias JA Additive stress of normobaric hypoxic conditioning to improve body mass loss and cardiometabolic markers in individuals with overweight or obesity: A systematic review and meta-analysis. *Physiol Behav*. 2019; 207:28-40.

2.- Ramos-Campo DJ, Scott BR, Alcaraz PE, Rubio-Arias JA. The efficacy of resistance training in hypoxia to enhance strength and muscle growth: a systematic review and meta-analysis. *Eur J Sport Sci.* 2018; 18(1): 92-103.

3.- Ramos-Campo DJ, Rubio-Arias JÁ, Freitas TT, Camacho A, Jiménez-Diaz JF, Alcaraz PE. Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions. *J Strength Cond Res.* 2017; 31(4): 1040-1047.

4.- Ramos-Campo DJ, Rubio-Arias JA, Dufour S, Chung L, Ávila-Gandía V, Alcaraz PE. Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia. *Eur J Appl Physiol.* 2017; *117*(4): 809-818.

5.- Ramos-Campo DJ, Martínez-Guardado I, Olcina G, Marín-Pagán C, Martínez-Noguera FJ, Carlos-Vivas J, Alcaraz PE, Rubio JÁ. Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability. *Scand J Med Sci Sports*. 2018; 28(10): 2135-2143.

6.- Ramos-Campo DJ, Martínez-Guardado I, Rubio JA, Freitas T, Andreu L, Othalawa S, Timón R, Alcaraz PE, Rubio JÁ. Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia. *J Strength Cond Res*. 2019.

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ÍNDICE GENERAL

RESUMEN Y ABSTRACT

Resumen

La investigación previa en el uso del entrenamiento en hipoxia se ha centrado en las adaptaciones y respuestas fisiológicas derivadas de estos programas en deportes de resistencia y deportes colectivos. Además, en los últimos años ha surgido una aplicación terapéutica del uso de la hipoxia como tratamiento coadyuvante en patologías como la obesidad, la diabetes o la enfermedad pulmonar obstructiva crónica. A pesar de estos estudios, el análisis de la efectividad de estos tratamientos sobre el aumento de la masa muscular y el descenso de la masa grasa, así como de la mejora de diferentes capacidades y componentes del fitness cardiorrespiratorio y otras adaptaciones neuromusculares no ha sido estudiada previamente a pesar de su vital importancia para una correcta aplicación y dosificación de esta estrategia terapéutica. Por ello, se planteó la presente tesis doctoral, cuyo objetivo fue analizar la eficacia del condicionamiento hipóxico como herramienta para la mejora fisiológica, neuromuscular y de la composición corporal. Para ello, en primer lugar, se analizó a través de dos meta-análisis la respuesta del condicionamiento hipóxico sobre el aumento de la masa muscular y sobre el descenso de la masa grasa, peso y otros marcadores cardiometabólicos. Por otro lado, se analizó la respuesta fisiológica y el rendimiento ante una sesión de entrenamiento en circuito en condiciones de hipoxia moderada y alta y, por último, se analizó el efecto de un programa de 8 semanas de duración de este tipo de entrenamiento sobre la composición corporal, variables neuromusculares y cardiorrespiratorias en sujetos activos entrenados en fuerza. Los resultados mostraron que desde el punto de vista meta-analítico, el condicionamiento hipóxico reduce el peso corporal, la masa grasa, el ratio cintura-cadera, la circunferencia de la cintura y muestra una tendencia a una mayor ganancia de masa muscular, área de sección transversal del músculo y un aumento de la fuerza. Además, el entrenamiento o exposición a hipoxia desciende los triglicéridos con una tendencia a tener un efecto adicional sobre el mismo programa en normoxia. También, el condicionamiento hipóxico desciende el LDL

y la presión arterial sistólica y diastólica. Por otro lado, una sesión de entrenamiento en circuito en hipoxia desciende la potencia y la fuerza desarrollada, aumenta la percepción de esfuerzo y produce un mayor estrés sobre el sistema nervioso autónomo, un mayor desequilibrio ácido-base, una mayor contribución del metabolismo anaeróbico y un mayor gasto calórico posterior al ejercicio. Además, 8 semanas de entrenamiento en circuito bajo hipoxia incrementa la hipertrofia del músculo, aumentan la fuerza y cambian la arquitectura muscular. También, este tipo de programa mejora el índice de fatiga de un test sprints repetidos e incrementa la capacidad cardiorrespiratoria de los participantes. Estos resultados, nos permiten tener un mejor conocimiento de la efectividad de estos programas para optimizar la composición corporal y mejorar el estado de forma física y la capacidad cardiorrespiratoria y parámetros cardiometabólicos que podrán ser utilizados para mejorar los tratamientos y entrenamientos tanto en pacientes como en deportistas.

Abstract

Previous research in hypoxia training has been focused on the effect of this type of training on physiological responses and adaptations in endurance and team sports. Recently, a therapeutic application of the use of hypoxia has emerged as a coadjutant treatment in pathologies such as obesity, diabetes or chronic obstructive pulmonary disease. Despite these studies, the analysis of the effectiveness of these treatments on muscle growth and the decrease in fat mass, as well as the improvement of different capacities and components of cardiorespiratory fitness and other neuromuscular adaptations has not been previously studied. However, these factors are very interesting to develop a correct application and dosage of this therapeutic strategy. For this reason, the present doctoral thesis was proposed. The aim of the present thesis was to analyze the efficacy of hypoxic conditioning to improve physiological, neuromuscular and body composition variable. To reach this objective, firstly, the response of hypoxic conditioning on the increase of muscle mass and on the decrease of fat mass, weight and other cardiometabolic markers was analyzed through two meta-analysis. On the other hand, the physiological response and performance were analyzed in a circuit training session under moderate and high hypoxia. Finally, the effect of an 8-week program of this type of training on the body composition, neuromuscular and cardiorespiratory variables in active subjects trained in strength was analyzed. Meta-analysis showed that hypoxic conditioning reduces body weight, fat mass, waist-hip ratio, waist circumference. A tend a greater gain of muscle mass, cross sectional area of the muscle and an increase in strength were observed. In addition, training or exposure to hypoxia reduced triglycerides with a tendency to have an additional effect on the same program in normoxia. Also, hypoxic conditioning decreases LDL and systolic and diastolic blood pressure. On the other hand, a circuit training

session in hypoxia decreased the power and force performed and increased the rate of perceive exertion and produced greater stress on the autonomic nervous system, a greater acid-base imbalance, a greater contribution of anaerobic metabolism and a greater caloric expenditure after the exercise. In addition, 8 weeks of circuit training under hypoxia increased muscle hypertrophy, improved strength performance and changed the muscle architecture. Also, this type of program improved the fatigue index of a repeated sprint test and increased the cardiorespiratory capacity of the participants. These results allow us to have a better knowledge of the effectiveness of these programs to optimize body composition and improve cardiorespiratory fitness and cardiometabolic parameters that can be used to optimize the treatments and training for both patients and athletes.

I INTRODUCCIÓN

I - Introducción

Desde la antigüedad, algunos seres humanos habitan en zonas geográficas situadas en grandes altitudes. Sin saberlo, durante cientos de años, los organismos de los nativos de esta superficie terrestre han ido adaptándose fisiológicamente en un instinto de supervivencia, a los ambientes extremos donde vivían. Esta exposición a altitudes elevadas sobre el nivel del mar lleva consigo una disminución de la presión parcial de oxígeno en el estado gaseoso definida como hipoxia(1). En normoxia hay una relación equilibrada entre la aportación de oxígeno y la demanda de éste. En condiciones de hipoxia se altera este ratio, existiendo una menor disponibilidad de O_2(1).

El interés científico y deportivo sobre las respuestas y adaptaciones que produce la hipoxia sobre el deportista tiene como punto de partida los Juegos Olímpicos celebrados en Ciudad de México en 1968 (2250 m sobre el nivel del mar) por los resultados deportivos tan dispares que se obtuvieron en pruebas más vinculadas a la resistencia aeróbica y en pruebas de una menor duración (velocidad, saltos…). Desde este punto de partida han surgido diferentes estrategias de entrenamiento en altitud.

A raíz de este evento han surgido numerosas estrategias para analizar y aprovechar las posibilidades que ofrece el entrenamiento en altitud. Así, en la actualidad, los deportistas de alto nivel incorporan a su entrenamiento los siguientes programas y métodos de entrenamiento en condiciones de altura o hipóxicas: i) *Live high-train high* (LHTH) o altitud natural; ii) *Live high-train low* (LHTL) (2–4) que consiste en vivir y realizar los entrenamientos de baja intensidad a una altitud moderada y los entrenamientos de alta intensidad a nivel del mar o baja altitud (<1300 m)(5); iii) *Live low-train high* (LLTH) o vivir en un ambiente normobárico y normoxico y exponer al deportista a intervalos relativamente cortos (5-180 min) de hipoxia simulada que puede ser pasiva (exposición a hipoxia intermitente, IHE) o activa (entrenamiento en hipoxia intermitente (IHT) (4).

A pesar de las diferencias sustanciales entre los diferentes métodos de hipoxia, todos tienen el mismo objetivo, inducir adaptaciones en el organismo del deportista que incrementen su rendimiento físico a nivel del mar. Estas adaptaciones se relacionan, entre otras, con la estimulación e incremento de la eritropoyetina (EPO) y del volumen de glóbulos rojos (6), además de incrementar la densidad mitocondrial en el músculo, la capilarización de la fibra y el área de sección transversal de la misma (7).

Centrándonos en el IHT, que es el método a analizar en esta tesis doctoral, el estrés al que se somete al organismo con un programa de entrenamiento, junto con el estímulo hipóxico, producen adaptaciones que aumentan el rendimiento del deportista. Esta mejora se debe a diferentes cambios bioquímicos y estructurales del sistema músculo-esquelético que mejoran el proceso oxidativo (8,9). La teoría más común sobre el mecanismo para incrementar el rendimiento a consecuencia de un programa de hipoxia, se relaciona con el aumento de la capacidad de transportar oxígeno en sangre. Esto se produce por un cambio en los parámetros hematológicos, fundamentalmente por el incremento de la secreción de la hormona eritropoyetina (EPO), la hemoglobina (Hb) y los eritrocitos(5,10). Además, algunos estudios han observado una mejora del rendimiento anaeróbico (11,12), justificada por un incremento de la capacidad tampón del músculo y un aumento de la actividad enzimática (13). En este sentido, los programas de IHT muestran ser un método eficaz para incrementar el rendimiento aeróbico a nivel del mar (8,11,14), si bien otros estudios tan solo muestran un mantenimiento del rendimiento de los deportistas sometidos a estudio (15–17).

Progresivamente, la utilización del entrenamiento en hipoxia se ha ido expandiendo a otros campos de estudio durante las últimas décadas. Así, esta herramienta ha demostrado tener un efecto beneficioso adicional para deportistas de deportes colectivos que el entrenamiento de sprint repetido en normoxia al mejorar la habilidad para repetir sprints (18) . De este modo, el entrenamiento de sprint repetido en hipoxia es más eficiente para mejorar significativamente el rendimiento de sprint repetido promedio y puede producir un efecto positivo adicional en el sprint y el VO_2 max(18).

Además, recientemente, algunos estudios (19–21) han examinado la utilidad del entrenamiento de fuerza (RT) en hipoxia (RTH) para mejorar el rendimiento muscular. Por ejemplo, los ejercicios de fuerza realizados en condiciones hipóxicas han demostrado aumentar el estrés metabólico intramuscular (FiO_2= 13%) (19), mejorar la señal hipertrófica y la hipertrofia muscular (FiO_2 14.4%) (22), así como aumentar la concentración de hormonas anabólicas (19). Además, otros estudios han observado que con carga moderada (3 series de 10 repeticiones al 60% de 1RM), en hipoxia (FiO_2 = 16%) se consigue aumentar la activación muscular (23) sin afectar a la potencia (24). En este sentido, recientes estudios han demostrado que la aplicación de RTH mejora la fuerza muscular (↑ 15% de la contracción voluntaria máxima), tamaño muscular (↑ 6% la sección transversal del músculo) y resistencia muscular (↑ 23% el número de repeticiones a 20% 1RM) en atletas de netball después de 5 semanas de entrenamiento a 20% 1RM y 80% SaO_2 (25).

Estos efectos beneficiosos que se logran sobre el organismo con el uso del IHT han hecho que recientemente se empiece a analizar el potencial terapéutico de esta herramienta en diferentes problemas de salud como la sarcopenia o sobre la obesidad. Específicamente, la capacidad de generar fuerza es un parámetro asociado al riesgo cardiometabólico y que ha sido asociado con la morbilidad en poblaciones adultas y de avanzada edad (26) así como se relaciona directamente con la probabilidad de padecer síndrome metabólico a largo plazo (27). Del mismo modo, numerosos estudios han mostrado que una menor producción de fuerza manual se asocia con patologías como la sarcopenia (28), limitaciones funcionales y discapacidades(29). Numerosos estudios también sugieren que la masa muscular es un factor determinante para el rendimiento físico en personas ancianas (30,31). Por lo tanto, la fuerza muscular y el mantenimiento de la masa muscular es un factor potencial para predecir la morbilidad y mortalidad en la población adulta y de edad avanzada (32,33). Así pues, el aumento o mantenimiento de los valores de fuerza y masa muscular parecen ser un factor clave para diferentes poblaciones con patologías, así como en personas sanas como medida preventiva.

Para ello, es necesario precisar un entrenamiento de fuerza que optimice estos valores. Tal como comentábamos anteriormente, en los últimos años, la alteración del ambiente intramuscular a través de la hipoxia ha recibido interés de

investigación como otro método para mejorar la respuesta fisiológica del entrenamiento de fuerza (34). Las ya citadas respuestas del ejercicio de fuerza en hipoxia, con una mayor dependencia del metabolismo anaeróbico y un mayor estrés metabólico (35), así como un mayor reclutamiento de unidades motoras (23), y respuestas endocrinas después de RTH (19,36,37) , hacen que se deba analizar el poder coadyuvante de este tratamiento en patologías que necesiten un aumento de masa muscular.

Por otro lado, las estrategias de entrenamiento hipóxico como RTH también pueden tener beneficios terapéuticos para las poblaciones clínicas que no pueden tolerar el ejercicio vigoroso, como los que sufren alteraciones musculoesqueléticas(38). Además, varios estudios recientes han usado la exposición hipóxica como una nueva estrategia terapéutica para mejorar los síntomas de una variedad de enfermedades cardiovasculares, metabólicas y pulmonares, incluida la obesidad (39–41).

La obesidad es la pandemia del siglo XXI y se caracteriza por la acumulación excesiva de masa grasa y una inflamación sistémica crónica, que probablemente predispone a sufrir en los individuos con obesidad otras enfermedades metabólicas(42). En 2014, más de 1.900 millones de adultos tenían sobrepeso y, de ellos, más de 600 millones tenían obesidad(43). Aunque surge de una etiología multifactorial (genética, estilo de vida, estado socioeconómico,…) (42), la obesidad o el sobrepeso generalmente se debe a un balance energético positivo, que resulta de un aumento en la ingesta de alimentos, una disminución del gasto energético, o ambos (41). La obesidad está asociada con un mayor riesgo de mortalidad prematura y otras comorbilidades como dislipidemia, diabetes mellitus tipo 2, hipertensión, cáncer, accidente cerebrovascular y enfermedades coronarias del corazón (44,45). Llevar peso adicional también produce cargas articulares excesivas, lo que eventualmente lleva al desarrollo de patologías musculoesqueléticas (ej: osteoartritis) que a su vez producen capacidades funcionales(46).

Por otro lado, el entrenamiento o exposición a hipoxia activa el factor inducible por hipoxia (HIF), el cual desempeña un papel esencial en la regulación efectiva del metabolismo (en relación al mantenimiento del peso corporal, la homeostasis de la glucosa y el metabolismo del hígado) y, por lo tanto, en la prevención de la obesidad(42). Según se informa, la hipoxia pasiva y activa

estimula la producción de HIF-1 (7), mejorando la utilización y el transporte de glucosa, la glucólisis, la producción de lactato para proporcionar ATP (8) y el transporte de oxígeno y la sensación de saciedad (47) entre otros. Además, el metabolismo de los lípidos puede mejorarse aún más cuando el entrenamiento con ejercicios se realiza en entornos con privación de O_2 (48). Sin embargo, otros estudios con hipoxia no demostraron resultados positivos similares en el metabolismo de los lípidos (49) y sobre el manejo de la pérdida de peso (49,50). Por lo tanto, existe evidencia contradictoria en relación con la efectividad del entrenamiento en hipoxia como herramienta para mejorar la pérdida de peso y la oxidación de los lípidos en personas con sobrepeso u obesidad.

Hasta la fecha, varios estudios han analizado el efecto del entrenamiento de baja intensidad (55-65% del consumo máximo de oxígeno (VO_2max))(48,50–53) en hipoxia sobre la pérdida de peso y los marcadores cardiometabólicos en individuos con sobrepeso u obesidad. En comparación con el entrenamiento en normoxia, el entrenamiento hipóxico a baja intensidad en pacientes con obesidad puede inducir aumentos superiores en los niveles de noradrenalina, vasodilatación periférica, número de mitocondrias, actividad de las enzimas glucolíticas, la sensibilidad a la insulina y sobre la reducción de los niveles de leptina(40). Otros efectos positivos del entrenamiento o exposición a hipoxia han sido observados sobre la presión arterial (54) y marcadores metabólicos como los triglicéridos (55,56) o el colesterol (56), que no se encontraron (o en menor medida) con un entrenamiento normóxico equivalente. Sin embargo, otros estudios no encontraron ningún efecto adicional del trabajo en hipoxia sobre la presión arterial (48,57), los trigliceridos(49,53) o la glucosa sanguínea (56,58). Hasta la fecha, existen hallazgos contradictorios en la literatura sobre el efecto adicional del entrenamiento de baja intensidad en hipoxia en la mejora de los marcadores cardiometabólicos.

Por lo tanto, parece que el entrenamiento o la exposición a hipoxia puede tener un efecto beneficioso adicional sobre la pérdida de peso, el aumento de la masa magra y diferentes parámetros cardiorrespiratorios y de fitness que han de ser estudiados. Por todo ello, se plantea los siguientes objetivos de la presente tesis doctoral.

II – OBJETIVOS E HIPÓTESIS

II - OBJETIVOS

Objetivos:

Objetivo general:

Analizar la eficacia condicionamiento hipóxico como herramienta para la mejora fisiológica, neuromuscular y de la composición corporal.

Objetivos Específicos:

1. Realizar una revisión sistemática con meta-análisis de los estudios que han investigado el efecto adicional del entrenamiento de fuerza en hipoxia respecto al entrenamiento de normoxia, sobre el área de sección transversal o la masa libre de grasa, así como sobre la fuerza muscular en sujetos físicamente activos.
2. Realizar una revisión sistemática y un meta-análisis para investigar el uso del HC pasivo y activo para maximizar la pérdida de peso y mejorar los marcadores cardiometabólicos en individuos con sobrepeso u obesidad.
3. Examinar si esta estrategia terapéutica es más efectiva en individuos con sobrepeso en comparación con individuos con obesidad.
4. Determinar si una sesión de entrenamiento de fuerza en circuito de alta intensidad con hipoxia produce mayores efectos agudos en el rendimiento físico, gases sanguíneos, metabolitos y electrolitos sanguíneos que la misma sesión en normoxia.
5. Analizar los efectos agudos que provoca el entrenamiento en circuito de alta intensidad bajo dos niveles (moderado y alto) de hipoxia sistémica sobre el rendimiento físico y las variables fisiológicas y metabólicas.

6. Analizar el efecto de 8 semanas de entrenamiento en circuito de alta intensidad en hipoxia y normoxia sobre el rendimiento aeróbico, el gasto de energía en reposo, la capacidad de repetir sprines y sobre variables hematológicas.
7. Analizar el efecto de 8 semanas de entrenamiento en circuito de alta intensidad en hipoxia sobre la arquitectura muscular y variables neuromusculares en hombres físicamente activos.

Hipótesis:

Las hipótesis de estudio son:

-El condicionamiento hipóxico es una herramienta válida para combatir el exceso de peso y controlar los factores cardio-metabólicos en individuos con sobrepeso u obesidad.
-El entrenamiento mediante circuito de alta intensidad en hipoxia producirá un mayor estrés metabólico, una mayor demanda fisiológica y bioquímica y una mayor percepción de esfuerzo.
-El entrenamiento mediante circuito de alta intensidad en hipoxia producirá un descenso del rendimiento de fuerza y potencia durante la sesión de entrenamiento.
--El entrenamiento mediante circuito de alta intensidad en hipoxia generará unas mayores adaptaciones cardiorespiratorias, de rendimiento aeróbico y anaeróbico, la fuerza, e incrementará el grosor del músculo sin producir cambios a nivel hematológico.

III – ESTUDIO I: "Additive stress of normobaric hypoxic conditioning to improve body mass loss and cardiometabolic markers in individuals with overweight or obesity: A systematic review and meta-analysis"

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Review

Additive stress of normobaric hypoxic conditioning to improve body mass loss and cardiometabolic markers in individuals with overweight or obesity: A systematic review and meta-analysis

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ABSTRACT

We performed a systematic review and meta-analysis to determine if hypoxic conditioning, compared to similar training near sea level, maximizes body mass loss and further improves cardiometabolic markers in overweight and obese individuals. A systematic search of PubMed, Web of Science and the Cochrane Library databases (up to January 2019) was performed. This analysis included randomized controlled trials with humans with overweight or obesity assessing the effects of HC on body mass loss or cardiometabolic markers. A subgroup analysis was performed to examine if HC effects differed between individuals with overweight or obesity. 13 articles (336 participants) qualified for inclusion. HC significantly decreased body mass (p = .01), fat mass (p = .04), waist/hip ratio (p < .001), waist (p < .001), LDL (p = .01), diastolic (p < .01) and systolic blood pressure (p < .01) with these effects not being larger than equivalent normoxic interventions. There were trends towards higher triglycerides decrement (p = .06) and higher muscle mass gain in hypoxic (p = .08) compared with normoxic condition. Also, the two BMI categories displayed no difference in the magnitude of the responses. Compared to normoxic equivalent, HC provides greater reductions in triglycerides and greater muscle growth, while body mass changes are similar. In addition, HC responses were essentially similar between individuals with overweight or obesity.

1. Introduction

Obesity is the pandemic of the 21st century. It is characterized by excessive fat mass accumulation and chronic systemic inflammation, which likely predisposing individuals with obesity to metabolic diseases [1]. Obesity is generally defined as a body mass index (BMI) of 30 kg/m^2 and above, while overweight is defined as a BMI between 25 and 30 kg/m^2 [2]. Although it arises from a multifactorial etiology (e.g., genetics, lifestyle, socioeconomic status) [1] being obesity or overweight typically is caused by a positive energy balance, which results from an increased food intake, a decreased energy expenditure, or both [3]. Obesity is associated with increased risk of premature mortality and other comorbidities such as dyslipidemia, type 2 diabetes mellitus, hypertension, cancer, stroke and coronary heart diseases [4,5]. Carrying additional weight also produces excessive joint loads, eventually leading to the development of musculoskeletal pathologies (i.e osteoarthritis) that in turn limit functional capabilities [6].

There is an urgent need for effective interventions to treat obesity. During the last decades, caloric restriction and exercise interventions have been primarily implemented as treatment for obesity [7]. Current exercise recommendations suggest that individuals with obesity should undertake 30–60 min of moderate-intensity physical activity on most, if not all, days of the week [8]. However, adherence to exercise often declines over time, and perhaps even more so in diseased populations [9]. This may lead to a plateau of body mass loss with a partial or total recovery of lost body mass only 6 months after the start of the nutrition and/or exercise interventions [9]. Today, it is imperative that innovative, non-pharmacological approaches are developed for individuals with overweight or obesity to match current exercise recommendations [5].

Several recent studies have used hypoxic exposure as a new therapeutic strategy to improve the symptoms of a range of cardiovascular, metabolic and pulmonary diseases including obesity [3,9,10]. Hypoxia is defined as a reduced O_2 supply to tissues caused by decreases in O_2

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saturation of arterial blood [11]. Hypoxic conditioning (HC) relates to passive (i.e., during rest) or active (i.e., during exercise) recurrent exposure to systemic (whole body) and/or local (tissue) hypoxia. By decreasing arterial O_2 availability, HC has the potential to further improve cardio-metabolic health, functional performance and well-being of individuals with chronic diseases and/or sustaining acute musculo-skeletal injuries [12]. HC that activates the hypoxia-inducible factor (HIF) may play an essential role in effective metabolism regulation (i.e. body mass maintenance, glucose homeostasis and liver metabolism) and thereby in the prevention of obesity [1]. Reportedly, passive and active hypoxia stimulate HIF-1 production [13], improving glucose intake and transport, glycolysis, lactate production to provide ATP [14] and oxygen transport and satiety [15] among others. Also, lipid metabolism can be further enhanced when exercise training is conducted in O_2-deprived environments [16]. However, other HC studies failed to demonstrate similar positive results on lipid metabolism [17] and body mass loss management [17,18]. Thus, there is conflicting evidence in relation to the effectiveness of HC as a tool to improve body mass loss and lipid oxidation in individuals with overweight or obesity.

To date, several studies have analyzed the effect of low intensity training (55–65% of maximum oxygen uptake (VO_2max)) [16,18–21] in hypoxia on body mass loss and cardiometabolic markers in individuals with overweight or obesity. Compared to normoxia, hypoxic training at low intensity in patients with obesity can induce higher increases in noradrenaline levels, peripheral vasodilatation, number of mitochondria, glycolytic enzyme activity, insulin sensitivity and/or reduction of leptin levels [9]. Other positive effects of HC have been observed on blood pressure [21] and metabolic markers such as triglycerides [22,23] or cholesterol [23], which were not found (or to a lower extent) with equivalent normoxic training. However, other studies did not found any additional effect of HC on blood pressure [16,24], tryglicerides [17,20] or blood glucose [23,25]. To date, contradictory findings exist in the literature about the additional effect of low-intensity training HC on improvement of cardiometabolic markers.

During the past few years, new training paradigms under hypoxic conditions have been introduced. It is well established that high intensity training (HIT) in hypoxia can improve cardiorespiratory function (i.e VO_2max) and performance (i.e best and mean sprint during an repeat sprint ability test) [26] in athletic populations, while the usefulness of this training modality in patients as a tool to improve body mass loss and cardiometabolic markers is more recent [10,27]. Recent evidence suggests that HIT in hypoxia is more effective at increasing lean mass than normoxic exercise in women with overweight and obesity [28]. For instance, additional body mass loss and body fat reduction with also a concomitant increase in muscle mass have been reported after 12 weeks of HIT in hypoxia [10]. However, another HIT study [29] failed to report a positive change in body composition after a 5-wk training period. Contradictory findings exist regarding whether or not HC facilitates body mass loss compared to equivalent normoxic training.

Previous literature reviews (mainly narrative in nature) have critically discussed the potential of passive and active HC as a therapeutic intervention to loose body mass and improve health-related markers [3,5,9,30–32] in individuals with obesity. Limitations of this previous work include the analysis of the effect of HC on some other diseases (i.e pulmonary and cardiovascular), inclusion of non-randomized controlled trials and an analysis period up to until 2017. Only in 2018, six additional randomized controlled trials [10,17,22,23,25,28] have been published that represent half of the total number of studies that were available until then. Remarkably, only one of these reviews is a systematic review [5], while it included both animals and humans (6 randomized controlled trials (RCT)) research. This 2017 systematic review that featured inconsistent findings for triglycerides and cholesterol markers. A potential limitation of a systematic review is that it does not include a data synthesis and statistical analysis to determine summary effect of the intervention on the outcomes measures. This implies that the results obtained in the literature review by Hobbins et al [5] could be oversized without a specific statistical analysis that offers a more accurate and general picture of the HC effects on body composition and health markers. Taken as a whole, this clearly demonstrates the growing interest around HC potential and the need to conduct new analysis.

Previous studies found that body composition and physiological adaptations to training may differ between individuals with normoweight, with overweight or with obesity [33]. For instance, a recently study [23] has shown a positive effect of low intensity training in hypoxia in overweight, but not normoweight, individuals on cardiometabolic markers such as triglycerides or high-density lipoprotein (HDL). To our knowledge, no meta-analysis study exists that specifically analyzed the influence of participant background on the magnitude of body mass loss and cardiometabolic health responses.

Therefore, our aim was to perform a systematic review and meta-analysis to determine if hypoxic conditioning, compared to similar training near sea level, maximizes body mass loss and further improves cardiometabolic markers in overweight and obese individuals.

2. Methods

2.1. Study design

The review was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42018117868). The methodological process was based on the recommendations formulated in the PRISMA declaration [34]. For the meta-analysis, only randomized controlled trials investigating the effects of normobaric HC on body mass loss and/or cardiometabolic markers were considered.

2.2. Data sources and search profile

A comprehensive literature search was performed using PubMed-Medline, Web of Science and the Cochrane Library from database inception up to January 2019. The database searches were performed independently by two authors (AP and DJRC) and the results obtained were the same. The flow diagram of the search process is shown in Fig. 1. The following combination of terms was used: “hypoxia” or “intermittent hypoxia” or “hypoxic training” or altitude training” or “passive hypoxic exposure”. The Boolean operator “AND” was used to combine these descriptors with: “obesity” or “overweight” or “weight loss”.

2.3. Selection criteria

The specific inclusion criteria were: [1] original studies with a randomized controlled design; [2] human experimentation; [3] participants with overweight (BMI > 25 kg/m^2) or/and obesity (all obesity categories; BMI > 30 kg/m^2); [4] studies examining the effect of passive or active normobaric HC intervention; [5] studies assessing at least body mass of tested participants; [6] studies published in English; and [7] chronic interventions with a minimal duration of two weeks. Research studies were excluded if they: [1] only focussed on sport performance outcomes; [2] included physically active participants who performed moderate-intensity aerobic physical activity for a minimum of 30 min/d on 5 d/week or vigorous-intensity aerobic activity for a minimum of 20 min/d on 3 d/wk.; [3] were clinical studies; [4] examined the effect of hypobaric hypoxia (terrestrial altitude and hypobaric hypoxia in a climatic chamber) or used other devices that do not reduce the FiO_2 (i.e altitude training mask); [5] were reviews or assessed the effects of an acute intervention; and [6] were not an original investigation published in full.

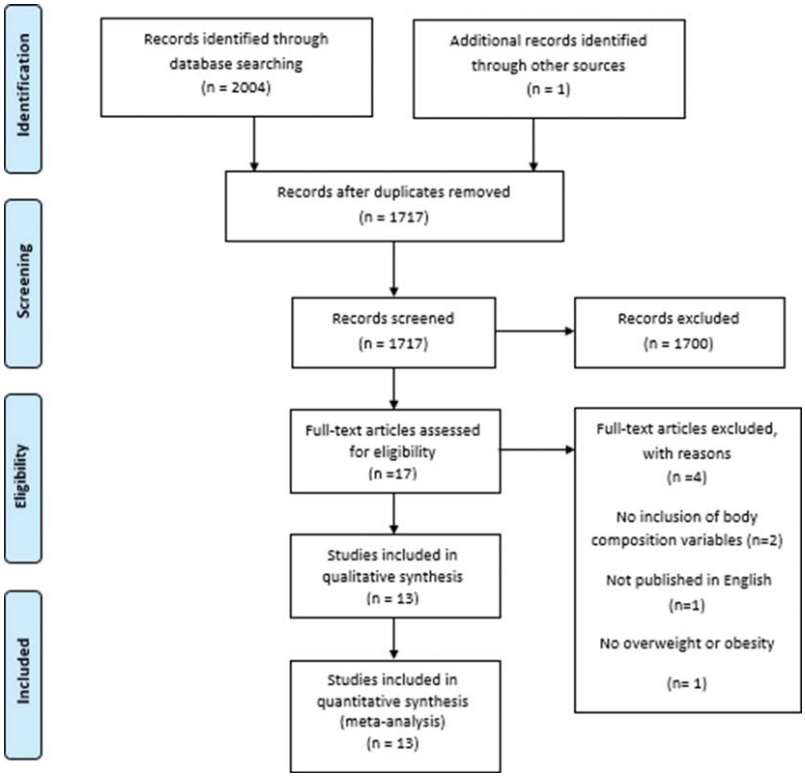

Fig. 1. Search process flow diagram.

2.4. Study selection and data extraction

Retrieved articles were reviewed independently by two authors (AP and DJRC) in order to select relevant articles. In addition to the literature search, references were scanned for further relevant articles and were included in our analysis if they met the inclusion criteria. Also, authors of selected studies were contacted for non-reported information. Two authors (AP and DJRC) independently extracted data from the included studies. The following information was extracted: authors of the paper, study design, number of participants included in each group, age, gender and BMI. Regarding the characteristics of the hypoxic intervention, the information extracted included: type of hypoxic exposure (passive, active or combination of both), protocol and training characteristics (volume, intensity, frequency, rest…), duration (number of weeks) and level of hypoxia.

2.5. Outcomes

The primary outcome was body mass loss. The secondary outcomes were: i) BMI; ii) waist circumference; iii) waist/hip (W/H) ratio; iv) muscle mass; v) fat mass; vi) Low-density lipoprotein (LDL); vii) HDL; viii) triglycerides; ix) blood glucose; x) systolic blood pressure (SBP); and xi) diastolic blood pressure (DBP).

2.6. Evaluation of the methodology of the studies selected

The methodological quality of the selected studies was assessed with the Cochrane risk-of-bias tool [35] that includes the following parameters: [1] random sequence generation (selection bias); [2] allocation concealment (selection bias); [3] blinding of participants and personnel (performance bias); [4] blinding of outcome assessment (detection bias); [5] incomplete outcome data (attrition bias); [6] selective reporting (reporting bias) and [7] other bias. For each study, each item was described as having either a low risk of bias, an unclear risk of bias or a high risk of bias. Risk of bias was assessed independently by two authors (JARA and DJRC) using the Cochrane risk-of-bias tool [35].

2.7. Data synthesis and statistical analysis

The meta-analysis and the statistical analysis were conducted using the Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK). A random effects meta-analysis was conducted to determine the effect of HC on body composition (BMI, waist, W/H ratio, muscle mass, fat mass, and body mass) and cardiometabolic markers (LDL, HDL, triglycerides, blood glucose, SBP and DBP. The effects sizes of outcomes between hypoxic and normoxic conditioning as well as the differences between before and after training intervention were expressed as standard mean differences (SMD) and their 95% confidence intervals (CI). The threshold values for SMD were > 0.2 (small), > 0.6 (moderate), > 1.2 (large), and > 2.0 (very large). Also, the mean

Table 1
Main characteristics of included studies in the meta-analysis.

Study	Participants characteristics				Intervention				
	Participants	Age	Weight	BMI	Exposure type	Type of training	Protocol	Duration	FiO_2
Fernández-Menéndez et al. [17]	12 (F), 2 (M)	34.8 (4.7)	96.8 (9.5)	34.1 (2.6)	Active	Aerobic	Walking 60 min	3 wk. 3 d/wk.	14.5
	11 (F), 2 (M)	32.2 (8.4)	96.6 (9.6)	32.9 (2.7)	–			60 min/s	20.9
Kong et al. [21]	5(M), 5(F)	19.8 (2.2)	99 (19.5)	34.7 (5.3)	Active	Aerobic + strength	Aerobic: Running, Cycling. Stepping (60–70% of HRmax) Strength: Strength training at 40–50% 1R, 4–6 training motions,	4 wk.; 8 s of N (16 h) and 3 s of H (6 h) per wk	16.4/ 14.5
	5(M), 3(F)	22.3 (1.7)	103.4 (24.7)	33.8 (5.6)	–		3 × 15–20 reps Dumble: 4–6 motions,3 × 10–15 reps with light weight exercise (< 5 lb)	11 s of N (22*h*)	21
Shin et al. [23]	8(M)	45.6 (20.9)	78.3 (8.4)	26.8 (2.3)	Active	Aerobic	Running in treadmill at 60% of the maximum HR 50′ (Included 5′ warm-up; 40′ main set and 5′ cold down)	4 wk. 3 d/wk	14.5
	9 (M)	46.0 (20.5)	79.8 (11.0)	27.0 (3.0)	–				20.9
Netzer al. [20]	2 (M),8 (F)	50.1	89.8 (7.4)	33.4 (3.3)	Active	Aerobic	90 min at 60% of the maximum HR stepper, treadmill, bicycle ergometer	8 wk. 3 d/wk	15
	2 (M), 8 (F)	45.5	91.5 (10.7)	32.8 (7.1)	–				20.1
Yang et al. [38]	8 (M), 8 (F)	14.3 (1.4)	93.0 (15.1)	32.9 (3.5)	Passive	Aerobic	Training low: Swimming and basketball (6 MET) aerobic exercise (7.5 MET)	4 wk. 6 d/wk.	14.7
	11 (M), 8 (F)	13.9 (0.9)	86.9 (12.8)	31.5	–		Living High: Sleeping during 10 h	2 S/d	21
Wiesner et al. [16]	10 (M), 14 (F)	42.2 (0.2)	93.4 (2.6)	33.1 (0.3)	Active	Aerobic	60 min in a treadmill at HR of 65% of maximum oxygen consumption	4 wk. 3 d/wk	15
	8 (M), 13 (F)	42.1 (1.7)	87.5 (3.6)	32.5 (0.8)	–				21
Camacho-Cardenosa et al. [10,28]	13 (F)	44.4 (7.2)	80.1 (18.9)	30.0 (6.4)	Active	Aerobic	X intervals: 3 min at 90% Wmax followed by 3 min of active recovery (55–65%Wmax)	12 wk. 3d/wk.	17.2
	13 (F)	43.1 (7.7)	80.4 (16.3)	29.6 (5.2)	–			N° Intervals: wk. 1–2: 3 wk. 3–5: 4	20.9
	18 (F)	37.4 (10.2)	73.7 (11.1)	27.7 (4.5)	Active	HIIT	X intervals: 30 s of all-out (130%Wmax) followed by 3 min of active recovery at 55–65% Wmax	wk. 6–8: 5 wk. 9–12: 6	17.2
	15 (F)	40 0.0 (8.7)	77.9 (11.3)	28.7 (4.8)	–				20.9
Kong et al. [29]	14 (F)	–	69.5 (5.8)	26.0 (2.4)	Active	HIIT	60 × 8 s all out in a bike ergometer with 12-s of recovery	5 wk. 4 d/wk	15
	15 (F)	–	68.2 (8.1)	25.7 (2.2)	–				21
Gatterer et al. [19]	12 (F), 4 (M)	50.3 (10.3)	105.5 (20.0)	37.9 (8.1)	Active + Passive	Aerobic	90 min at 65–70% of maximum HR (cycle ergometer, treadmill or cross trainer) and rested for additional 90 min in normobaric hypoxic chambers*	8 months 2 d/wk	14
	10 (F), 6 (M)	52.4 (7.9)	103.2 (15.1)	36.3 (4.0)	–		When treadmill or cross trainer was used, the target HR was increased by 10 beats/min		21
De Groote et al. [22]	3 (M), 4 (F)	14.3 (1.1)	104.6 (13.6)	37.9 (8.1)	Active	Aerobic + Strength	Aerobic: 12 min on a cycloergometer: S1: 2 min at 50%MAP and 10 min at 70%MAP.	6 wk. 3 d/wk.	15
	3 (M), 4 (F)	13.7 (1.39	97.5 (25.9)	36.3 (4.0)	–		S2: 2 min at 50% MAP and 5 × 1 min 80%–1 min 50% MAP S3: incremental training started at 40% MAP with an increase of 10% MAP each 2 min. Strength: abdominal. Quadriceps. and biceps muscles (15 repetitions at 50% 1RM + 4 × 6 repetitions at 70% 1RM; resting time: 2 min)	50–60 min per S	21

(*continued on next page*)

Table 1 (*continued*)

Study	Participants characteristics				Intervention				
	Participants	Age	Weight	BMI	Exposure type	Type of training	Protocol	Duration	FiO_2
Morishima et al. [18]	9 (M)	30.0 (2.0)	74.4 (4.2)	25.6 (1.2)	Active	Aerobic	60 min cycling at 55% of the maximal oxygen uptake	4 wk. 3 d/wk.	15
	11 (M)	32.0 (3.0)	73.8 (4.0)	25.4 (0.9)	–			60 min per S	21
Klug et al. [25]	12 (M)	55.0 (2.1)	109.1 (5.2)	35.5 (1.4)	Active	Aerobic	60 min with 3 × 15 min of walking on a treadmill with 5 min of rest	6 wk. 3 d/wk.	15
	11 (M)	57.6 (2.2)	108.5 (3.0)	34.1 (0.9)				60 min per S	21

M: male; F: female; wk.: weeks; S: sessions; d: days; H: Hypoxia; N: Normoxia; FiO_2: inspired fraction of oxygen; kg: kilogram; HR: Hear rate; 1RM: one-repetition maximum; *: Only for hypoxic group; HIIT: High intensity interval training; MAP: maximal aerobic power; Wmax: maximal power achieved during the last 3 min step complete during the incremental test; Mean (standard deviation).

difference (MD) was used when all the studies assessed the same outcome and measured it in the same way. Each difference of the means was weighed according to the inverse variance method [36].

The heterogeneity between the studies was evaluated through the I^2 statistic, and between-study variance using the tau-square (Tau^2) [37]. I^2 values of 30–60% represented a moderate level of heterogeneity. A $p < .1$ value suggests the presence of substantial statistical heterogeneity. The publication bias was evaluated through an asymmetry test as estimated from a funnel plot. In addition, the Egger's test was used to assess publication bias. A $p < .05$ value was considered to be statistically significant. Finally, subgroup analyses were used to find the effects of the initial BMI (individuals with overweight versus individuals with obesity) of the individuals on the effectiveness of the HC. The cut-off value of the BMI variable was: individuals with overweight (25 kg/m^2 < BMI < 30 kg/m^2) and individuals with obesity (BMI > 30 kg/m^2). The effects were expressed as SMD and MD and their 95% of confidence intervals.

3. Results

3.1. General characteristics of studies

The initial search identified 2004 articles from databases and 1 article from other sources. After excluding duplicate articles, 1717 article abstracts were screened. Thereafter, 1700 articles were excluded and 17 were screened as full-texts. Finally, 13 articles [10,16–23,25,28,29,38] that met the inclusion criteria were left, and these were selected for the meta-analysis (Fig. 1). The effects of HC (passive and active) on body mass loss were analyzed in 13 articles and 336 participants. The analysis of secondary outcomes is based on the following number of studies: BMI = 10; waist = 7; W/H = 5; muscle mass = 10; fat mass = 11; LDL = 8; HDL = 8; triglycerides = 11; blood glucose = 8; DBP = 7; SBP = 7. The number of participants analyzed in these secondary outcomes ranged between 66 and 166 participants. All selected studies were published between 2009 and 2018.

Table 1 provides an overview of the intervention and participants characteristics of the studies included in the quantitative analysis (meta-analysis). The age and BMI ranged from 13.7 to 52.4 years and 25.7 to 38.6 kg/m^2, respectively. The exercise program duration ranged from 3 to 34 weeks and from 2 to 12 sessions per week. Also, the FiO_2 applied in normoxic and hypoxic groups ranged from 20.0 to 20.9% and from 12.2 to 17.2%, respectively.

3.2. Risk-of-bias assessment

Risk-of-bias assessment is shown in Fig. 2. Overall, the risk of bias was 'high' in all studies due to lack of random sequence of participants, the allocation concealment and the blinding of participants and researchers to assigned training conditions. The regression test funnel plot asymmetry showed no significant heterogeneity for the following body composition outcomes: BMI (Z = 0.600, $p = .549$), muscle mass (Z = 0.169, $p = .866$), fat mass (Z = 0.416, $p = .677$) and body mass (Z = 0.502, $p = .615$). However, significant heterogeneity was observed in the following cardiometabolic outcomes: triglycerides (Z = 4.504, $p \leq .001$), LDL (Z = 3.626, $p \leq .001$) and HDL (Z = 2.522, $p = .012$) and blood glucose (Z = 4.148, $p < .001$).

3.3. Meta-analysis

3.3.1. Effects on body composition

Regarding body composition variables, a significant body mass loss was found in participants who trained under normoxic (MD = −1.61, 95% CI = −2.90, −0.33, p = .01; $I^2 = 0\%$, $p = .99$) and hypoxic (MD = −1.42, 95% CI = −2.76, −0.09, $p = .04$; $I^2 = 0\%$, $p = .98$) conditions. In addition, significant decreases in fat mass were found in participants who trained under hypoxia (SMD = −0.26, 95%

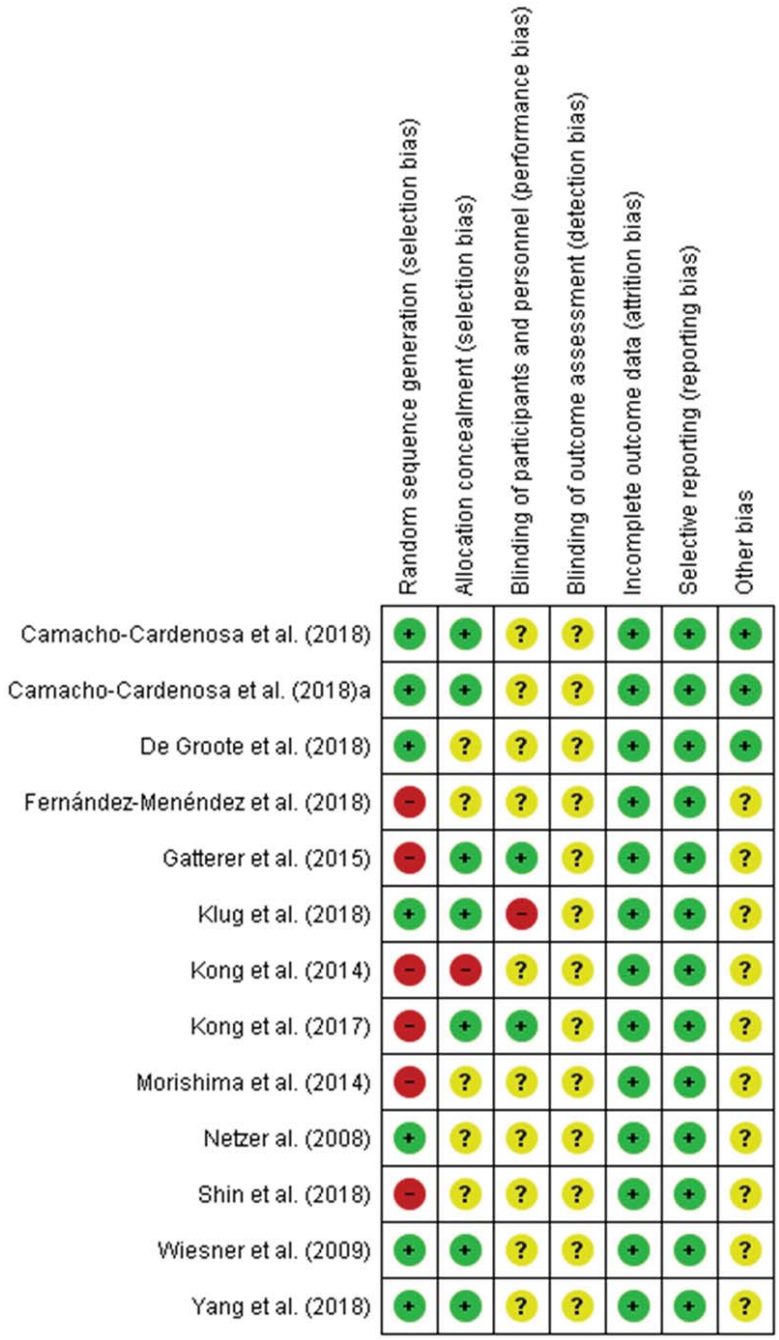

Fig. 2. Assessment of risk of bias in included randomized controlled trials.

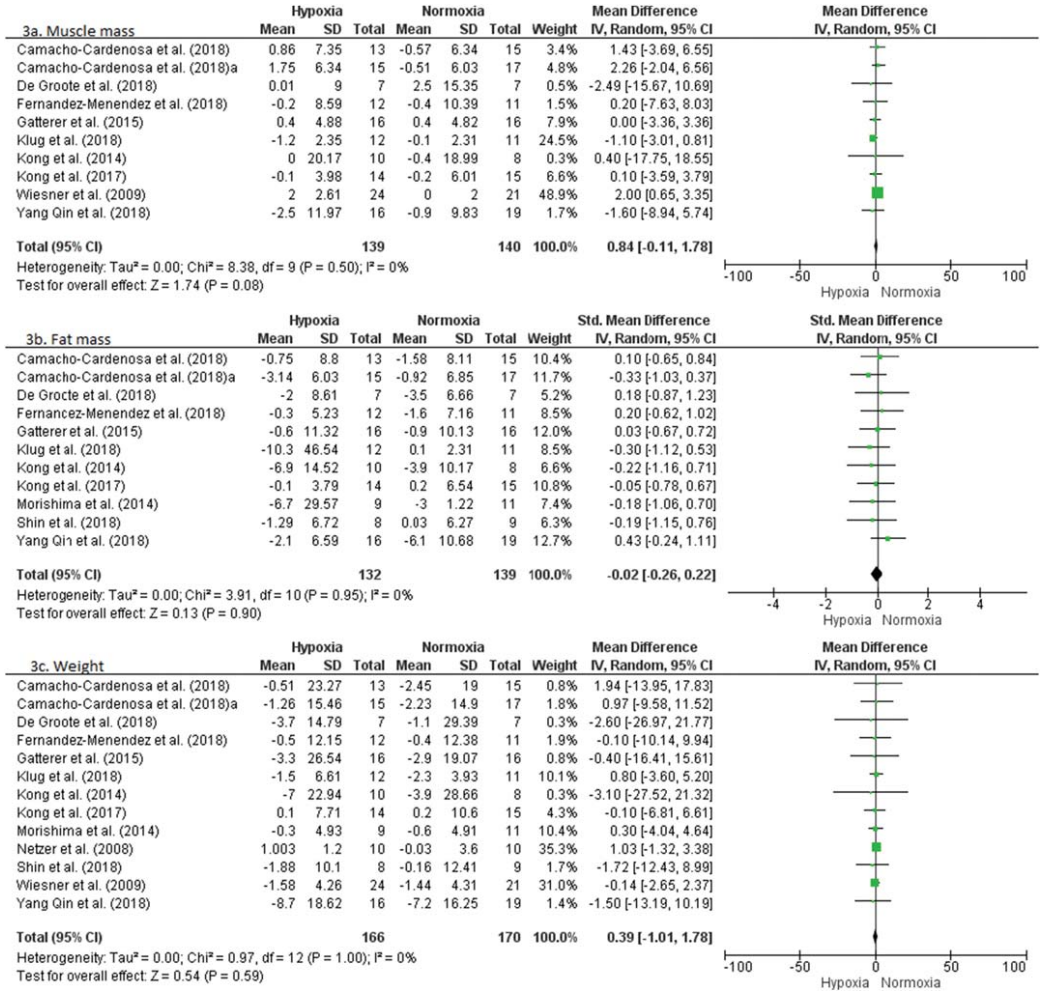

Fig. 3. Total effects of treatment on muscle mass (a), fat mass (b) and weight (c) hypoxic group vs. normoxic group.

CI = −0.50, −0.01, p = .04; I^2 = 0%, p = .99) but not in normoxia. Also, BMI (MD = −0.54, 95% CI = −1.01, −0.07, p = .03; I^2 = 0%, p = .75) decreased significantly in normoxic but not in hypoxic condition. Moreover, no significant post-training changes were observed on muscle mass in normoxic (p = .86) and hypoxic (p = .47) conditions. However, a trend towards higher muscle mass gain in hypoxic than in normoxic condition (p = .08) was observed. Furthermore, no significant differences between conditions were observed for fat mass (p = .90) and body mass changes (p = .59) (Fig. 3).

The W/H ratio decreased after both normoxic (MD = −0.02, 95% CI = −0.03, −0.01, p = .003; I^2 = 0%, p = .86) and hypoxic (MD = −0.02, 95% CI = −0.04, −0.01, p < .001; I^2 = 0%, p = .76) conditioning, yet with no statistical significant differences between conditions (Fig. 4a). Likewise, waist circumference decreased to the same extent in hypoxic (MD = −3.52, 95% CI = −4.75, −2.30, p < .001; I^2 = 0%, p = .86) and normoxic (MD = −2.09, 95% CI = −3.37, −0.81, p = .001; I^2 = 0%, p = .99) conditions (Fig. 4b). BMI decreased significantly after training under normoxic (MD = −0.50, 95% CI = −0.98, −0.03, p = .04; I^2 = 0%, p = .73) but not hypoxic condition (Fig. 4c).

3.3.2. *Effect on cardiometabolic markers*

A significant decrease in triglycerides was observed after training under hypoxic (SMD = −0.67, 95% CI = −1.02, −0.32, p < .001; I^2 = 41%, p = .09) and normoxic (SMD = −0.57, 95% CI = −0.98, −0.15, p = .008; I^2 = 61%, p = .006) conditions (Fig. 5a), also with a more favourable effect (p = .06; Chi^2 = 8.20, p = .61) due to hypoxia.

LDL decreased in normoxia (SMD = −0.46, 95% CI = −0.75, 0.17, p = .002; I^2 = 0%, p = .60) and hypoxia (SMD = −0.51, 95% CI = −0.9, −0.12, p = .01; I^2 = 41%, p = .12), with no difference between conditions (Fig. 5b). Compared to before, no significant HDL level differences occurred after training in either normoxic

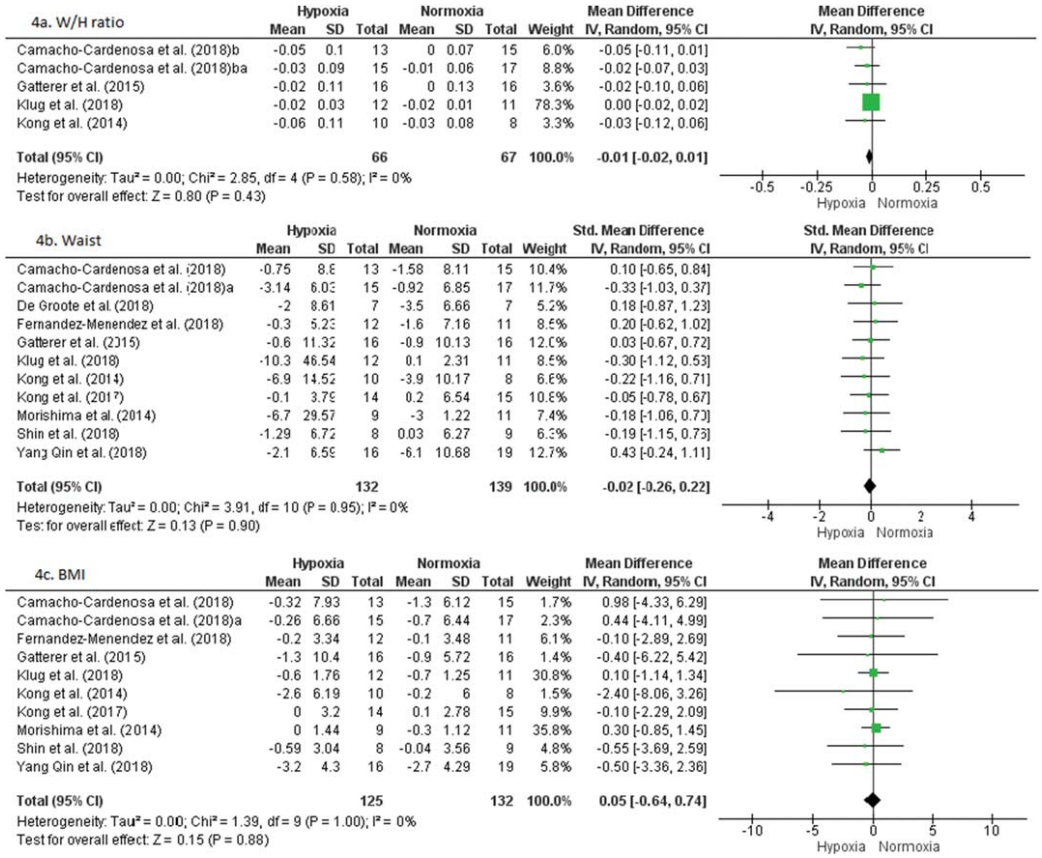

Fig. 4. Total effects of treatment on W/H ratio (a), waist (b) and BMI (c) hypoxic group vs. normoxic group.

(SMD = −0.14, 95% CI = −0.49, 0.21, p = .42; I^2 = 28%, p = .22) or hypoxic (SMD = −0.20, 95% CI = −0.66, 0.26, p = .40; I^2 = 55%, p = .04) conditions (Fig. 5c).

After training under hypoxic conditions, there was a trend towards lower blood glucose levels (SMD = −0.39, 95% CI = −0.79, 0.02, p = .06; I^2 = 48%, p = .06), while no change were observed in normoxia (SMD = −0.38, 95% CI = −0.97, 0.21, p = .21; I^2 = 77%, p < .001) (Fig. 5d).

DBP was lowered after training in normoxia (MD = −2.99, 95% CI = −5.52, −0.47, p = .02; I^2 = 58%, p = .03) and hypoxia (MD = −2.67, 95% CI = −3.59, −1.76, p < .01; I^2 = 0%, p = .61), yet with no significant differences between conditions (Fig. 6a). Similarly, SBP was similarly decreased after training in normoxia (MD = −6.08, 95% CI = −11.19, −0.97, p = .02; I^2 = 76%, p < .001) and hypoxia (MD = −4.96, 95% CI = −7.90, −2.02, p < .01; I^2 = 49%, p = .07) (Fig. 6b).

3.4. Sub-analysis

When a statistical comparison between individuals with overweight and obesity was performed, no significant differences were observed between conditions on fat mass (SMD = −0.01, 95% CI = −0.25, 0.23, p = .29; I^2 = 0%, p = .96), body mass (MD = 0.01, 95% CI = −0.20, 0.23, p = .86; I^2 = 0%, p = 1.0) and muscle mass (MD = 0.83, 95% CI = −0.1, 1.77, p = .86; I^2 = 0%, p = .49).

4. Discussion

This systematic review with meta-analysis aimed to analyse the effect of HC as a means of further reducing body mass and improving cardiometabolic markers compared to similar training near sea-level. A secondary objective was also to examine if this intervention is more effective in overweight versus obese individuals. The major findings indicate that HC significantly reduces body mass, fat mass, W/H ratio, waist circumference and improve several cardiometabolic markers (triglycerides, LDL, HDL, SBP and DBP). However, only the magnitude of triglycerides decrease and muscle mass growth were greater in hypoxic than in normoxic condition. Moreover, the sub-analysis found no significant interaction for initial BMI level indicating that HC effects were similar in overweight and obese individuals.

4.1. Effect of HC on body composition

We observed a significant positive effect on body mass loss for both

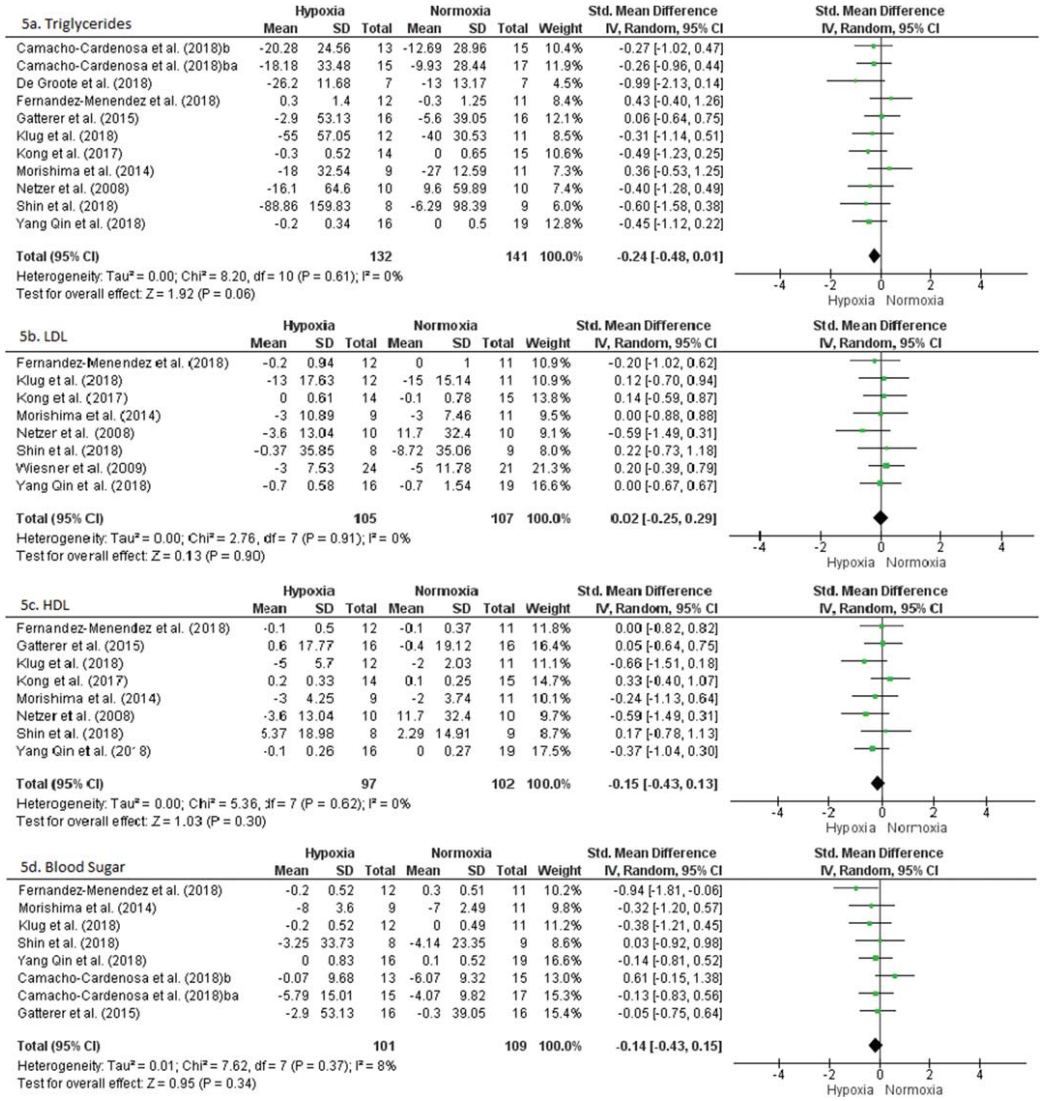

Fig. 5. Total effects of treatment on triglycerides (a), LDL (b), HDL (c) and blood glucose (d) hypoxic group vs. normoxic group.

hypoxic and normoxic conditioning, with also no significant differences between conditions (MD = 0.39, 95% CI −1.01, 1.78). A close inspection of the literature highlights four separate studies (3 with active and 1 with passive HC) reporting significantly larger body mass loss in hypoxia versus normoxia [20,21,23,38], while three other studies using active HC displayed similar body mass losses in the two conditions [19,22,25]. One possible explanation for these discrepant findings may relate to the hypoxic dose during the session and the entire HC program. In general, studies reporting no body mass loss had HC session with shorter duration [28,29] (i.e less than one hour) and/or had a lower total number of hours of hypoxic exposure during the program (i.e 9 [17] to 12 h [18]). Also, HC protocols that increase basal metabolic rate and energy expenditure likely benefit body mass loss in individuals with overweight and obesity [3]. Pending confirmatory research, this metabolic rate increment could result from an optimization of substrate utilization and mitochondrial oxidative capacity via signalling pathways that stimulate GLUT-4 transport [39]. This supports a view that prescribing HC with an appropriate dose may be relevant in individuals with overweight and obesity to lose more body mass.

Our meta-analysis showed a trend towards higher muscle mass gain in hypoxia versus normoxia (Z = 1.74; p = .08). Increased muscle growth is a positive adaptation in individuals with obesity who are

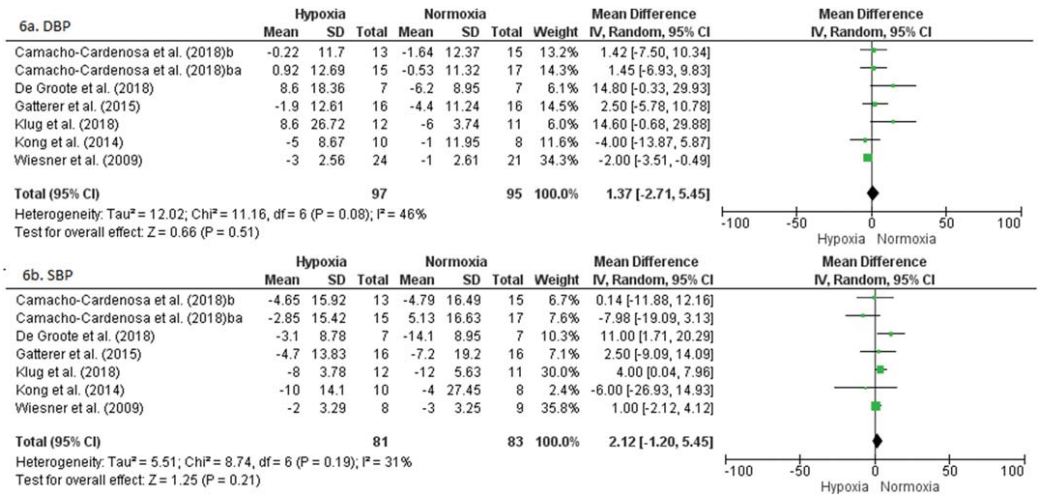

Fig. 6. Total effects of treatment on DBP (a) and SBP (b) hypoxic group vs. normoxic group.

commonly suffering from sarcopenia [40]. Regarding muscle mass, we report three separate studies displaying significant increases (2–4%) following active HC [10,16,28] or decreases (−1.5%) following passive [38] HC, while no changes occurred in normoxic condition. Another study also showed significant improvements in both normoxic and hypoxic conditions [22]. Disparate findings between studies could be due to alterations in the structure of the HC program (e.g., active or passive, intensity, FiO_2) performed. Specifically, passive HC seems to reduce muscle mass in the same terms as normoxia, while active HC would produce greater increases of muscle mass. Regarding active HC, only one study reported that four weeks of low intensity HC (65% of VO_2max) can improve fat-free mass (+2%) in hypoxia without changes in normoxic condition [16]. The most common type of exercise performed to increase muscle mass is resistance training. Reportedly, resistance training under hypoxia may lead to larger muscle gains than the same training in normoxia [41], primarily due to increases in metabolic stress and anaerobic glycolysis [41–43]. Other proposed mechanism involved in muscle growth are cellular swelling from metabolite accumulation in the cells and hypoxia-mediated increases in motor unit recruitment [41–44]. It is therefore possible that HIT may produce larger structural muscle adaptations by stimulating glucose-dependent metabolic pathways and consequently an acidic environment [45]. In fact, two of the studies with improved muscle mass [10,28] applied a HIT training of 12 weeks of duration at 17.2% FiO_2 increasing muscle mass by 2–4%. Taken as a whole, active HC at high-intensity may provide a small added benefit for muscular development over the same training performed in normoxia. An advantage of HC programs over normoxic training in patients who suffer from orthopaedic limitations is that this treatment may participate to reduce the risk of orthopaedic injury while also enhancing metabolic efficiency [28].

Previous studies reported that passive [38] or active [10,21,23,28] HC could significantly decrease fat mass. Using a meta-analytical analysis, our results showed a significant fat mass decrease in participants who trained under hypoxia but not in normoxia. This suggests a positive effect of active HC with a reduction of fat mass, which could possibly be attributed to higher post-exercise lipid oxidation [28]. In addition, a recent study [28] has shown an increase in fat oxidation at rest after 12 weeks of HIT in hypoxia, whereas an opposite trend was reported after the same training in normoxia. Thus, HIT in hypoxia likely increases lipids metabolism at rest. In addition, BMI has been significantly reduced after passive [38] or active [10,21] HC programs. However, our results indicate that training with oxygen deprivation was not more effective than in normoxia to reduce fat mass or BMI. While BMI is frequently used to estimate the prevalence of obesity [46] it does not account for variation in body fat distribution and abdominal fat mass [47]. Arguably, measurements of waist circumference and W/H ratio would be more appropriate measures of both intra-abdominal fat mass and total fat [48].

We report the original observation that waist circumference and W/H ratio decreased significantly after HC and normoxia. Interestingly, two separate studies [16,23] with decreases in waist circumference in hypoxia but not in normoxic condition, implemented a low intensity aerobic training (60 min on a treadmill at 65% of VO_2max at 14.5–15% of FiO_2). Another study [10] also demonstrated a significant decrease in waist circumference after training for 12 weeks using 30 s "all out" efforts performed at FiO_2 = 17.2%. These findings, suggest a positive effect of combined hypoxia with HIT for reducing abdominal fat, which could be attributed to higher post-exercise lipid oxidation [28]. However, a rapid plateau in the aforementioned body composition adaptations can occur if the program fails to apply an unaltered stimulus (i.e., hypoxic level, exercise intensity/duration) [19]. Such scenario has previously been reported by both Camacho-Cardeñosa et al. [10] and Gatterer et al. [19] who found similar improvements in body composition after completing either half (6 weeks and 3 months, respectively) or the entire (12 weeks and 8 months, respectively) conditioning program. Therefore, as for athletes, effective management of an HC program undoubtedly requires periodization strategies and readjusting regularly the training stimulus during the intervention.

In relation to the principle of initial value, a previous study [49] reported that the magnitude of body mass loss could largely be due to initial body composition. In support, those individuals with greater initial body fat and BMI values also were those who lost more body mass and fat after a combined exercise/diet intervention compared with those with a lower BMI [49]. In our review, overweight participants on average lost less body mass than individuals with obesity (−0.8 and −3.2 kg respectively) after HC. Similar results were obtained after low intensity HC comparing overweight vs normo-weight individuals [23]. However, the differences across the two BMI groups (individuals with obesity vs with overweight) observed in the present

review were small (no statistical differences). These results are in accordance with a previous review showing that initial BMI was not related to body mass loss during an intervention [50]. In this way, HC appears equally effective to body mass loss for individuals with overweight and obesity.

4.2. Effect of HC on cardiometabolic markers

Our study showed a higher no significant decrease of triglycerides after training under hypoxic than normoxic condition (p = .06). Three studies [10,23,38] found a larger decrease in this variable after HC than in normoxia. Interesting, the higher decrease was observed in Camacho-Cardeñosa's study [10]: i) -24.5% after 12 weeks of HIT in hypoxia using either 30-s "all out" efforts with 3 min of active recovery and ii) -27.5% after 12 weeks of training using 3 min at 90% of peak power with 3 min of active recovery both at 17.2% of FiO_2. The interplay of mechanisms of HC which may improve some cardiometabolic markers such as triglycerides and cholesterol levels are still being elucidated. However, exercise protocols increasing post-exercise lipid oxidation also seem to decrease triglyceride levels [51]. Similarly, the mechanism by which HC reduces triglycerides levels likely include increased lipid oxidation through the transcription coactivator PGC1α [14], which plays a key role in the regulation of muscle fatty acid oxidation [52]. Therefore, the use of high-intensity HC represents an effective method to increase post-exercise lipid oxidation and to reduce triglycerides values. In order to obtain a positive HC-related effects on lipid-related metabolic markers, interventions lasting at least 4 weeks would be required [5]. Our novel findings support this suggestion since the previous studies which demonstrated a significant improvement in triglycerides ranged between 4 [23,38] and 12 weeks [10,28] in duration.

Regarding cholesterol variables, our analysis showed significant decrease in LDL values after hypoxia and normoxia with no difference between conditions. In addition, our meta-analysis showed no significant increases in HDL after training in either normoxic or hypoxic conditions. Previous studies confirm that the increases in energy expenditure associated with aerobic intensity have been shown to positively influence in LDL and HDL [53]. In fact, only one low intensity HC study [25] reported a decrease in LDL, but similar changes were also observed after normoxic conditions. In addition, it has been reported that intense exercise is required to elicit reductions in LDL [54]. However, none of the HC studies using a high-intensity training program led to an improvement in HDL and LDL. Therefore, we conclude that active and passive HC may not promote any additional effect than the same normoxic program on both HDL and LDL levels.

Morishima et al. [18] found a significant decrease in glucose concentration after hypoxic (−8%) and normoxic (−7%) active training (60 min cycling at 55% of the maximal oxygen uptake at 15% of FiO_2). Although, no other study found a significant decrease in blood glucose after HC, our meta-analysis reports a trend towards lower glucose concentrations under hypoxic (p = .06) but not normoxic environments. These findings are in accordance with previous studies that reported a reduction of blood glucose [55] after passive or active HC in rats, suggesting that insulin signalling and glucose may have been upregulated following HC [9]. Thus, comparted to normoxia, HC may improve glycaemic control in individuals with overweight and obesity [9].

Regarding blood pressure, we report similar decreases in both SBP and DBP for hypoxic and normoxic conditioning. Previous studies applying active HC have shown significant improvements in SBP compared with active normoxic condition [21]. Kong et al. [21] found a significant decrease in SBP (7.6%) after 4 weeks of aerobic and strength training in hypoxia (14.5–16.4% of FiO_2) but no difference in the normoxic condition. These findings suggest that normoxic and HC have similar effectiveness to reduce blood pressure in individuals with obesity.

We found no differences in cardiometabolic markers after HC according to the baseline BMI category when expressed as a percentage from baseline. Both, individuals with overweight and with obesity demonstrated similar magnitude of improvement in tryglycerides, blood pressure, LDL, HDL and blood glucose after HC and normoxic condition. These findings are previously reported by some studies [56] which found that BMI category does not alter the benefit of body mass loss intervention on cardiometabolic markers if the results are expressed proportionally to the baseline.

4.3. Limitations, future research and practical applications

We acknowledge several limitations of this meta-analysis, which are related in part to the available RCTs and the divergent methodologies employed, including (i) the small number of studies; (ii) the number of studies using passive HC (n = 1); (iii) the different intensities, volume and training characteristics procedures applied in active HC studies; (iv) the lack of systematic information about the obesity related symptoms separating individuals with overweight and obesity; (v) the small number of studies using high-intensity training to obtain a more specific picture about the effect of this type of training in hypoxia on body composition and cardiometabolic markers; and (vi) the lack of longer studies to analyse the chronic effect of HC (only two studies had a program duration of > 8 weeks). In addition, we found that the available evidence has high risk of bias primarily due to low quality of available RCTs. Therefore, before a more comprehensive picture is depicted, further studies with a better quality design, analysing the effect of intervention of longer duration (< 8 weeks) and applying high-intensity HC programs are needed.

Previous studies [5] recommend the use of low intensity active HC at the commencement of the training program. During the first step of the treatment, according to the individual's characteristics, it is recommended that the HC program characteristics should include the following features: 4–6 weeks of 2–3 sessions of 60–90 min at 55–65% of VO_2max/60–70% of maximum heart rate at 13–14% of FiO_2. To avoid a body mass loss plateau it is also necessary to implement a new training stimulus by using other types of training with increased exercise intensity. Specifically, HC should be designed to elicit higher post-exercise lipid oxidation to reduce fat mass and body mass and to increase metabolic stress under hypoxia to maximize muscle growth. Considering the findings from studies [10,28,29] which have demonstrated benefits for HC, high intensity training may produce these two responses. In doing so, HIT sessions should include a duration of 30–60 min per session, using intervals of 8–30 s all-out followed by 3 min of active recovery at 55–65% of peak power performed 3–4 times per week. HIT should be undertaken in moderate level hypoxia (FiO_2 = 14–17.2%) though it is not known whether a dose–response relationship exists for the level of hypoxia on body mass loss. Finally, HIT sessions in hypoxia should be included progressively as a second step in the training program and always in combination with other sessions of aerobic training.

5. Conclusion

We conclude using a systematic review with meta-analysis that HC does result in significant reductions in body mass, fat mass, W/H ratio, waist circumference and in several cardiometabolic markers (triglycerides, LDL, HDL, SBP and DBP). However, only the magnitude of reductions in triglycerides and greater muscle growth was greater in hypoxic than in normoxic condition. In addition, the usefulness of HC was similar in individuals with overweight and obesity.

Potential conflicts of interest

None declared.

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IV – ESTUDIO II: "The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis"

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REVIEW ARTICLE

The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

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Abstract
Recent studies have reported that resistance training in hypoxia (RTH) may augment muscle size and strength development. However, consensus on the effects of RTH via systematic review and meta-analysis is not yet available. This work aimed to systematically review studies which have investigated using RTH versus normoxic resistance training (NRT) to improve muscular size and strength, and to perform a meta-analysis to determine the effect of RTH on these adaptive parameters. Searches were conducted in PubMed, Web of Science and the Cochrane Library from database inception until 17 June 2017 for original articles assessing the effects of RTH on muscle size and strength versus NRT. The effects on outcomes were expressed as standardized mean differences (SMD). Nine studies (158 participants) reported on the effects of RTH versus NRT for muscle cross-sectional area (CSA) ($n = 4$) or strength ($n = 6$). RTH significantly increased CSA (SMD = 0.70, 95% confidence intervals (CI) 0.05, 1.35; $p = .04$) and strength (SMD = 1.88; 95% CI = 1.20, 2.56; $p < .00001$). However, RTH did not produce significant change in CSA (SMD = 0.24, 95% CI −0.19, 0.68, $p = .27$) or strength (SMD = 0.20; 95% CI = −0.27, 0.78; $p = .23$) when compared to NRT. Although RTH improved muscle size and strength, this protocol did not provide significant benefit over resistance training in normoxia. Nevertheless, this paper identified marked differences in methodologies for implementing RTH, and future research using standardized protocols is therefore warranted.

Keywords: *Environmental physiology, musculoskeletal, performance, strength, training*

Highlights
- Intermittent hypoxic resistance training (IHRT) is a novel training method that is proposed to improve muscular development and strength gains.
- This systematic review with meta-analysis reports that while IHRT is effective for increasing muscle size and strength, these improvements are not consistently shown to be greater than resistance training in normoxia.
- Available studies into IHRT have applied vastly different training programs, levels of hypoxia, and types of participants; these divergent methodologies have likely impacted on the results of studies in this area.
- Additional studies could include trained athletes, and investigate the efficacy of high-load circuit-based training in order to increase metabolic stress during IHRT.

Introduction

Skeletal muscle is an adaptable tissue that can be altered in responses to a given stimulus. Most notably, resistance training has a potent effect on the size and strength of muscle (Kraemer, Fleck, & Evans, 1996). Traditionally, acute resistance exercise variables have been manipulated to provide a desired training stimulus, including the muscle action, loading and volume, exercise selection and performance order, inter-set rest periods, repetition velocity and training frequency (Bird, Tarpenning, & Marino, 2005). Although certain controversy exists,

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resistance exercises protocols than maximize muscle fibre recruitment, time-under-tension and metabolic stress appear to contribute to intramuscular anabolic signalling (Gonzalez, Hoffman, Stout, Fukuda, & Willoughby, 2016). In recent years, altering the intramuscular environment via hypoxia has received research interest as another method to enhance the physiological experience of resistance training (Scott, Slattery, Sculley, & Dascombe, 2014). This was originally investigated by restricting blood flow to the exercising muscles to elicit localised hypoxia, which has been repeatedly shown to increase muscle size and strength even when lifting very light loads (Scott, Loenneke, Slattery, & Dascombe, 2015a). However, considering that this strategy can only be applied to limb muscles, researchers have also begun to examine whether performing resistance exercise in systemic hypoxia (via breathing hypoxic air) can provide similar benefits for whole-body training sessions (Ho, Kuo, Liu, Dong, & Tung, 2014; Manimmanakorn, Hamlin, Ross, Taylor, & Manimmanakorn, 2013; Nishimura et al., 2010).

Considering that one of the fundamental responses to exercise in hypoxia is an increased reliance on anaerobic metabolism, the benefits of resistance training in hypoxia (RTH) are thought to be mediated largely by increases in metabolic stress (Scott, Goods, & Slattery, 2016). Increased metabolic stress has been reported in several RTH investigations (Kon et al., 2010; Kon, Ikeda, Homma, & Suzuki, 2012; Ramos-Campo et al., 2017a, 2017b; Scott, Slattery, Sculley, Lockhart, & Dascombe, 2017), and is likely related to increased motor unit recruitment (Scott et al., 2017), which indicates that a larger portion of the muscle is stimulated to adapt during exercise. In addition, large endocrine responses have been observed following RTH (Kon et al., 2010, 2012; Yan, Lai, Yi, Wang, & Hu, 2016), although the importance of systemic increases in hormone concentrations for muscle hypertrophy has been questioned (Schoenfeld, 2013a; West, Burd, Staples, & Phillips, 2010).

Considering that athletes in most sports undertake resistance training to enhance physical performance and/or attenuate injury risk while competing, there has been growing interest in RTH from sporting organisations in recent years (Inness et al., 2016). Hypoxic training strategies such as RTH may also have therapeutic benefits for clinical populations who cannot tolerate vigorous exercise, such as those suffering from musculoskeletal impairments (Millet, Debevec, Brocherie, Malatesta, & Girard, 2016). However, despite these potential benefits for RTH, there is conjecture regarding whether RTH can actually facilitate greater muscle size and strength than the equivalent normoxic resistance training (NRT) (Ho et al., 2014). Therefore, the aim of this work was to systematically review the studies which have investigated using RTH to improve muscular size and strength, and to perform a meta-analysis to determine the effect of RTH on these adaptive parameters.

Methods

Study design

The methodological process was based on the recommendations indicated by the PRISMA declaration (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). The eligibility criteria were established by the authors. For the meta-analysis, only experimental/quasi-experimental research that studied resistance training under a simulated hypoxic environment was considered. The study was approved by the University's Institutional Science Ethics Committee

Data sources and search profile

A comprehensive literature search was performed using PubMed-Medline, Web of Science and the Cochrane Library from database inception through 17 June 2017. The database searches were performed independently by two authors (JARA and DJRC) and the results obtained were the same. The following combination terms was used: "strength training" or "resistance training" or "weight training". The Boolean operator "AND" was used to combine these descriptors with: "hypoxia" or "altitude" or "hypoxic training". The flow diagram of the search process is shown in Figure 1.

Selection criteria

The specific inclusion criteria were: (1) studies examining the effect of resistance training under hypoxia for at least 4 weeks on strength performance (via repetition maximum tests) and/or cross-sectional area (CSA) and/or and lean mass; (2) the presence of a control group (NRT); (3) studies published in English and (4) studies provide information of outcomes both at baseline and follow-up. Research studies were excluded if they: (1) used a sample population with pathologies or not between 18 and 65 years of age; (2) were not an original investigation published in full; (3) did not specify the tests to be evaluated; (4) applied hypoxia via natural altitude training camps (i.e. not during resistance training alone) or other local hypoxia techniques such as blood flow restriction (5) did not provide or specify

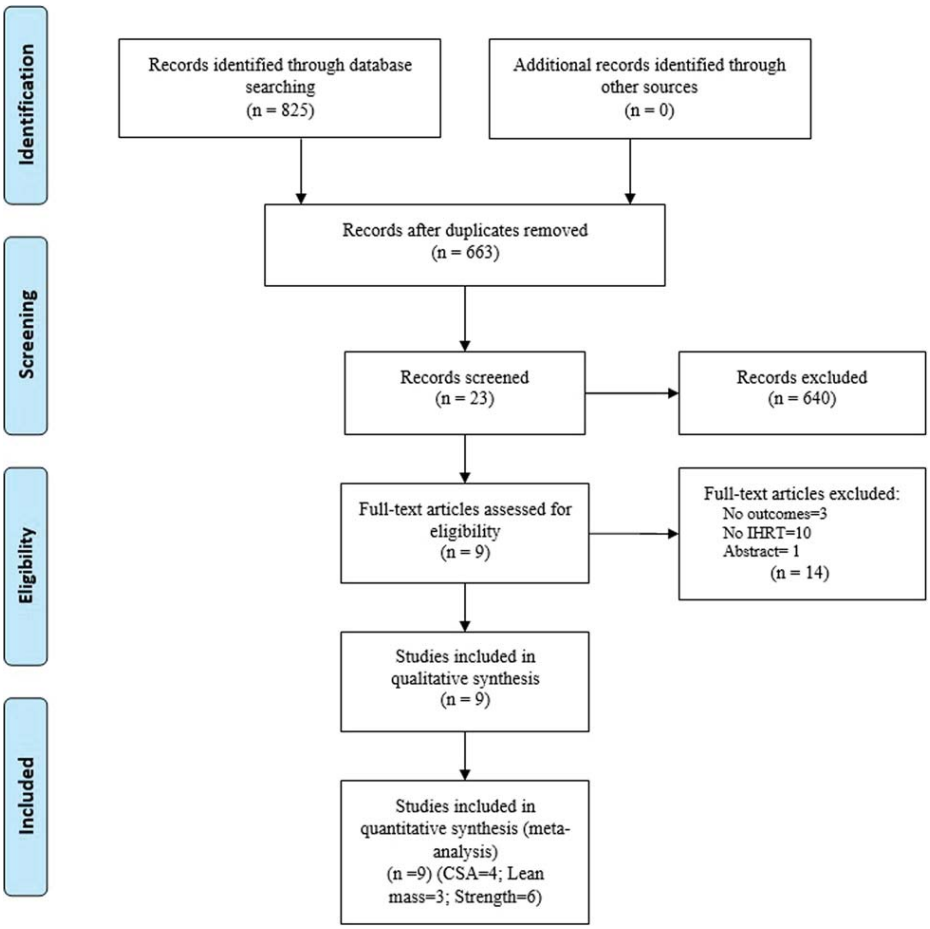

Figure 1. Search process flow diagram.

numerical data and (6) examined acute effects of interventions.

Study selection and data extraction

Retrieved articles were reviewed independently by two authors (JARA and DJRC) to choose potentially relevant articles; all disagreements on inclusion/exclusion were discussed and resolved by consensus. References of potentially relevant articles were also searched to find additional studies, and authors of selected studies were contacted for non-reported information. Two authors (JARA and DJRC) independently extracted data from the included studies. The following information was extracted: authors of the paper, number of participants included in each group, inspired fraction of oxygen (FiO_2), and the training status (untrained: subjects was not involved in regular resistance training program for at least 6 months before the study) (Ho et al., 2014); trained: participants achieved at least 12 months continuous resistance training history immediately prior to the study (Inness et al., 2016), age, weight and relative fat mass of participants. Regarding the characteristics of the resistance training programs, the information extracted included: the type of exercise, relative load lifted, training frequency (sessions/week), sets and

repetitions performed, duration of training (weeks), total number of sessions, and the outcomes measured (e.g. strength performance, CSA and/or lean mass). When the article presented the results by figures, two authors (JARA and DJRC) determined the values of the outcome using a digitizer software. When there was a greater disagreement of 3%, a third experienced investigator (PEA) also digitized the data, and the mean of the two closest assessments was used for further analysis.

Evaluation of the methodology of the studies selected

The methodological quality of the selected studies was assessed with the Cochrane risk-of-bias tool (Higgins et al., 2011) that is comprised of the following parameters: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias) and (7) other bias. For each study, each item was described as having either a low risk of bias, an unclear risk of bias or a high risk of bias. Risk of bias was assessed independently by two authors (JARA and DJRC) using the Cochrane risk-of-bias tool (Higgins et al., 2011).

Data synthesis and statistical analysis

The meta-analysis and the statistical analysis were conducted using the Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK). A random effects meta-analysis was conducted to determine summary effect of resistance training under hypoxia on strength performance, CSA and total lean mass. The effects of training on these outcomes between hypoxic and control groups were expressed as standard mean differences (SMD) and their 95% confidence intervals (CI). Differences within groups were calculated as SMD between the follow-up and baseline times, and threshold values for SMD were >0.2 (small), >0.6 (moderate), >1.2 (large) and >2.0 (very large) (Hopkins, Marshall, Batterham, & Hanin, 2009). The heterogeneity between the studies was evaluated through the I^2 statistic, and between-study variance using the tau-square (Tau^2) (Higgins, Thompson, Deeks, & Altman, 2003). The I^2 values of 30–60% represented a moderate level of heterogeneity. A p value < .1 suggests the presence of substantial statistical heterogeneity. The publication bias was evaluated through an asymmetry test as estimated from a funnel plot. A p value of less than 0.05 was considered to be statistically significant.

Results

Study selection

After the evaluation of 663 abstracts from primary sources, 640 were excluded; 23 were assessed as full texts. From these, 14 studies were excluded (Figure 1). Thus, nine studies ($n = 83$ for CSA;$n = 60$ for lean mass and $n = 143$ for strength performance) were included (Chycki et al., 2016; Friedmann et al., 2003; Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Kurobe et al., 2015; Manimmanakorn et al., 2013; Nishimura et al., 2010; Yan et al., 2016). One study (Yan et al., 2016) reported two different levels of hypoxia compared to the same control group in normoxia. All studies were published between 2003 and 2016 and had sample sizes in the range of 12–20 participants. Four analysed the effects of RTH on CSA (Friedmann et al., 2003; Kon et al., 2014; Manimmanakorn et al., 2013; Nishimura et al., 2010), three investigated the effects on lean mass (Chycki et al., 2016; Kon et al., 2014; Yan et al., 2016) and six studies analysed the effects of RTH on strength performance (Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010; Yan et al., 2016).

Participants were mostly trained subjects with mean age (SD) ranging from 21.2 (1.9) to 28.4 (1.6) (Table I). Fat mass ranged from 11.1 (6.5)% (Ho et al., 2014) to 17.3 (1.8)% (Kon et al., 2014), although some studies did not report fat mass (Table I). Exercise program duration ranged from 4 to 8 weeks with a frequency of 2–3 sessions per week. Two studies used low-load RTH and NYH (6 sets of more than 25 repetitions at 20–30% of 1-RM) (Friedmann et al., 2003; Manimmanakorn et al., 2013), and one study implemented high-load resistance training (two to four sets of three to six repetitions with ≥75% of 1-RM) (Inness et al., 2016). The remainder of the studies investigated moderate-load resistance training, similar to that typically prescribed to facilitate muscle hypertrophy (3–5 sets of 10 repetitions at 70% of 1-RM) (Chycki et al., 2016; Ho et al., 2014; Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010; Yan et al., 2016). Seven studies used lower limb exercise (Chycki et al., 2016; Friedmann et al., 2003; Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Manimmanakorn et al., 2013; Yan et al., 2016), while others used multi-joint upper body exercises such as bench press (Chycki et al., 2016; Kon et al., 2014), or single-joint arm flexion and extension exercise (Kurobe et al., 2015; Nishimura et al., 2010) (Table I).

Table I. Main characteristics of included studies in the meta-analysis.

Study	FiO_2	Participants	Training status	Age (years)	Weight (kg)	Fat mass (%)	Exercise	Weeks	Sessions	Session/ week	Repetitions	Sets	Intensity (% 1-RM)
Chycki et al. (2016)	12,9	6 (M)	Rec. resistance trained	21,0 (2,4)	80,6 (12,3)	23,3 (4,6)	Bench press + squat	6	12	2	10	3	70
	21	6 (M)		23,3 (4,6)	81,1 (7,5)	18,3 (3,0)							
Friedmann et al. (2003)	12	10 (M)	Untrained	25,1 (2,9)	77,0 (9,0)		Knee ext	4	12	3	25	6	30
	21	9 (M)		24,3 (2,5)	72,9 (9,0)								
Ho et al. (2014)	15	9 (M)	Rec.trained	21,4 (2,2)	66,5 (8,2)	11,1 (6,5)	Squat	6	18	3	10	3	70
	20	9 (M)		21,2 (1,9)	67,9 (9,5)	11,5 (4,9)							
Inness et al. (2016)	14,3	10 (M)	Strength trained		83,1 (7,5)		Squat + deadlift + lunge	7	21	3	2–4	2–4	75
	20	10 (M)			80,2 (12,0)								
Kon et al. (2014)	14,4	9 (M)	Rec. resistance trained	28,4 (1,6)	68,2 (2,2)	16,1 (1,3)	Bench press + leg press	8	16	2	10	5	70
	21	7 (M)		28,2 (1,4)	65,8 (3,7)	17,3 (1,8)							
Kurobe et al. (2015)	12,7	6 (M)	Untrained	23,0 (1,0)	60,2 (1,6)		Elbow ext	8	24	3	10	3	70
	21	7 (M)											
Manimmanakorn et al. (2013)	80% SpO_2	10 (F)	Well-trained netball players				Knee fl and ext	5	15	3	ext (each set): 28/ 24/22±2 fl:36/31/26±3	6 (3 ext + 3 fl)	20
	21	10 (F)											
Nishimura et al. (2010)	16	7 (M)	Untrained	22,7 (2,7)	66,8 (6,0)	12,3 (3,0)	Elbow fl and ext	6	12	2	10	4	70
	21	7 (M)		21,6 (1,6)	65,0 (8,1)	12,8 (4,5)							
Yan et al. (2016)	12,6	8 (M)	Rec. trained	22,2 (2,6)	70,5 (10,0)	12,0 (3,4)	Barbell back squat	5	10	2	10	5	70
	16	9 (M)				10,1 (3,1)							
	21	8 (M)				12,7 (5,6)							

Note: M: male; F: female; fl: flexion; ext: extension; FiO_2: inspired fraction of oxygen; Rec: recreationally; kg: kilogram; 1-RM: one-repetition maximum; mean (standard deviation).

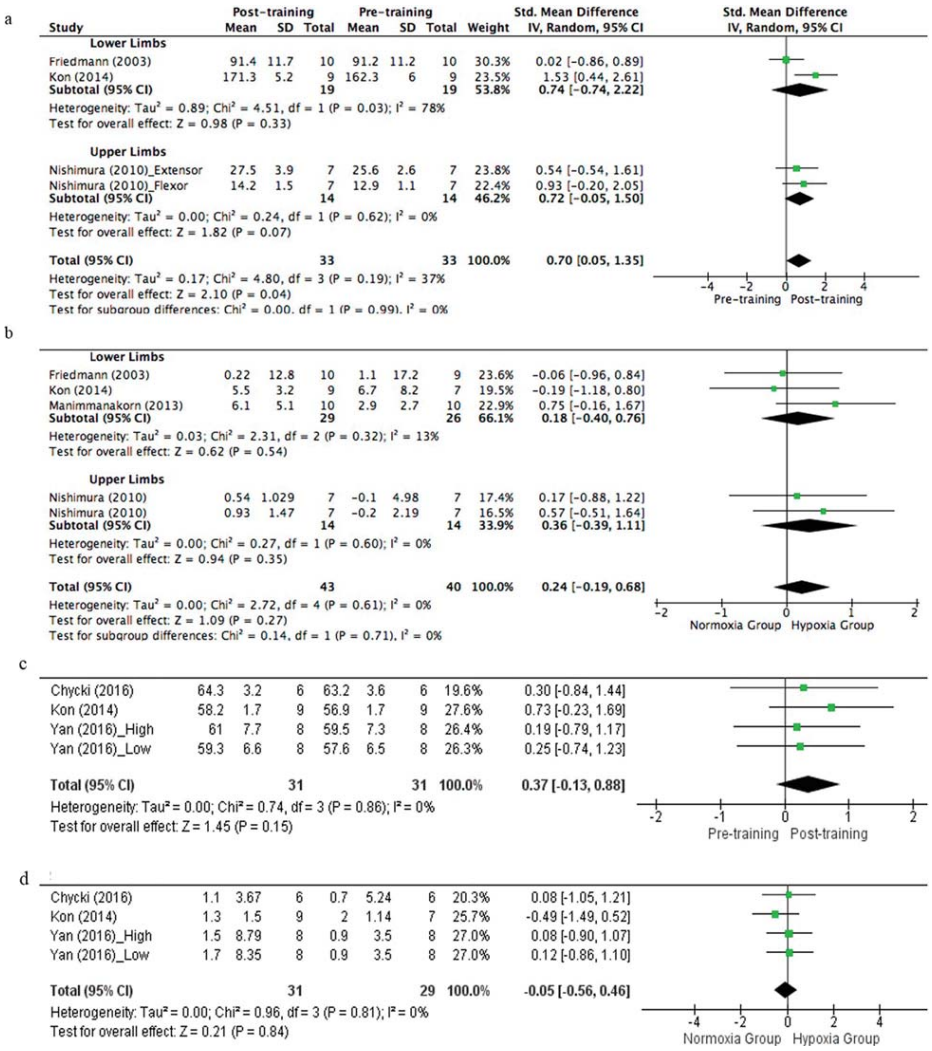

Figure 2. (a) Total effects of resistance training program on CSA pre-training vs. post-training; (b) total effects of resistance training program on CSA control group vs. hypoxic group; (c) total effects of resistance training program on Lean Mass (Dual-energy X-ray Absorptiometry) pre-training vs. post-training; and (d) total effects of resistance training program on Lean Mass control group vs. hypoxic group.

Meta-analyses

Changes in muscle size. In four groups from three studies which analysed the effects of resistance training under hypoxia on CSA (Friedmann et al., 2003; Kon et al., 2014; Manimmanakorn et al., 2013; Nishimura et al., 2010), significant increases were observed after the training programme (Figure 2 (a)) (SMD = 0.70, 95% CI 0.05, 1.35; $p = .04$). However, no significant differences were found between RTH and NRT programmes (Figure 2 (b)) (SMD = 0.24, 95% CI −0.19, 0.68, $p = .27$). The three studies (Chycki et al., 2016; Kon et al., 2014; Yan et al., 2016) (including four groups)

which investigated the effects of RTH on total lean mass did not observe significant improvement (SMD = 0.37, 95% CI −0.13, 0.88; $p = 0.15$) after the training (Figure 2(c)), or differences when compared with a NRT control group (SMD = −0.05, 95% CI −0.56, 0.46, $p = .84$) (Figure 2(d)). Heterogeneity of effects was low among studies for CSA, and lean mass ($I^2 = 0\%$).

Changes in muscle strength. In the five groups included from four studies which implemented RTH for the lower limbs (Ho et al., 2014; Inness et al., 2016; Kon et al., 2014; Yan et al., 2016), favourable effects were observed on strength performance after resistance training under hypoxia (SMD = 1.66; 95% CI = 0.81, 2.50; $p = .0001$) (Figure 3(a)). Similarly, in four groups from three studies which implemented RTH for the upper limbs (Kon et al., 2014; Kurobe et al., 2015; Nishimura et al., 2010), a significant improvement was also observed after the training programme (SMD = 2.32; 95% CI = 1.03, 3.61; $p = .0004$) (Figure 3(a)). Regarding the effects on both upper and lower limbs, a significant effect on strength performance was observed after the training (SMD = 1.88; 95% CI = 1.20, 2.56; $p < .00001$). However, resistance training under hypoxia ($n = 74$) did not produce significant change in strength performance value (SMD = 0.20; 95% CI = −0.27, 0.78; $p = .23$) when compared to NRT ($n = 69$) (Figure 3(b)). Heterogeneity of effects was low among studies for strength performance ($I^2 = 0\%$).

Risk-of-bias assessment

Risk-of-bias assessment is shown in supplemental file. Overall, the risk of bias was high in all studies due to lack of random sequence of participants, the allocation concealment and the blinding of participants and researchers to assigned training conditions.

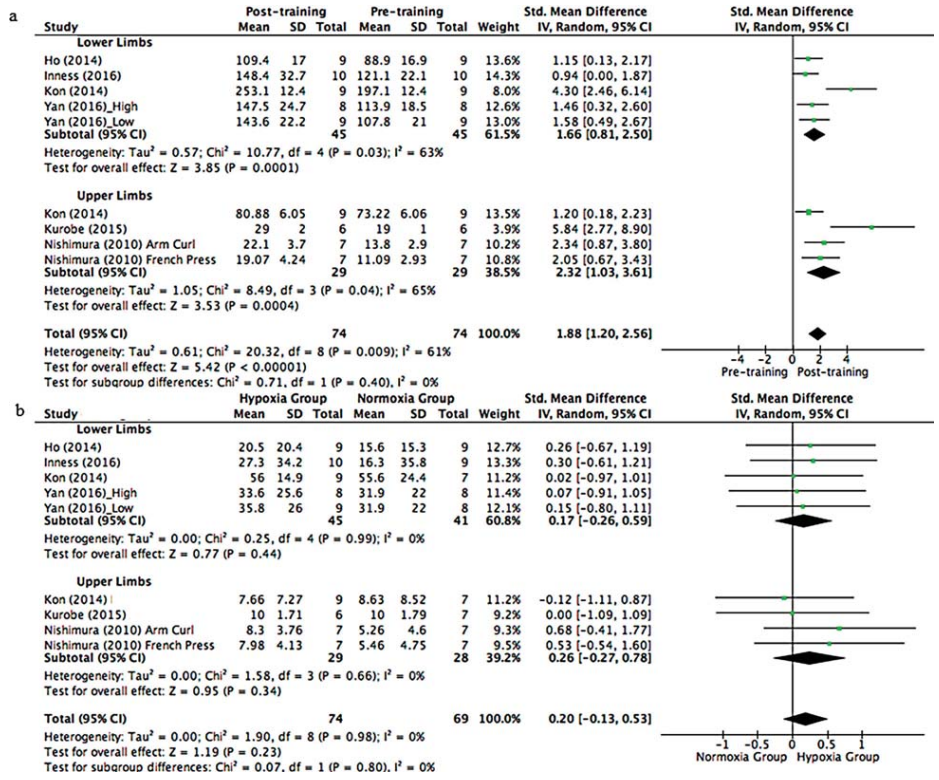

Figure 3. Total effects of resistance training program on 1-RM of upper and lower limb: (a) pre-training vs. post-training and (b) control group vs. hypoxic group.

Discussion

This paper aimed to systematically review studies which have examined RTH as a means of enhancing muscular hypertrophy and strength responses. The major findings indicate for the first time via meta-analysis that RTH does significantly improve muscular size and strength performance; however, these adaptations are not significantly greater than those observed after the same training in normoxia. Although these findings do not appear to support the use of RTH over NRT, this paper also highlights notable differences in the methodologies used between studies which may impact on the potential efficacy of RTH, and have led to inconsistent results between investigations.

Changes in muscle size

Although the interplay of mechanisms which facilitate muscular development are still being elucidated, resistance exercises protocols which maximize muscle fibre recruitment, time-under-tension and metabolic stress appear to benefit intramuscular anabolic signalling (Gonzalez et al., 2016), and therefore, muscle growth. Similarly, the mechanisms by which RTH may improve strength performance and increase muscular size likely include increased metabolic stress (Feriche, García-Ramos, Morales-Artacho, & Padial, 2017; Scott et al., 2016), and a resultant hypoxia-mediated increases in motor unit recruitment (Scott et al., 2017). Cellular swelling, resulting from metabolite accumulation in the cells, may also increase protein synthesis and decrease protein degradation, which would result in net protein accretion and muscle hypertrophy (Loenneke, Wilson, & Wilson, 2010). Nevertheless, despite these potential hypoxia-related mechanisms, our meta-analysis showed no statistically significant differences in hypertrophy adaptations following RTH versus NRT.

In the current study, a significant and large effect was observed for increases in muscle CSA after periods of RTH. However, when comparing muscular development between RTH and the equivalent NRT, there was a small and nonsignificant effect (SMD = 0.24, 95% CI −0.19, 0.68). In addition, there was no significant effect for changes in lean body mass between pre- and post-training time points for RTH, and no difference in lean body mass between hypoxic and normoxic training were found (SMD = −0.05, 95% CI –0.56, 0.46). Nevertheless, two separate studies have reported significantly larger increases in CSA following RTH when compared to the NRT group (Manimmanakorn et al., 2013; Nishimura et al., 2010), while another study observed significantly increased lean mass due to RTH when compared to NRT (Chycki et al., 2016). In addition, Kurobe et al. (2015) reported that increases in muscle thickness of the elbow extensors were significantly larger following RTH compared with NRT (note: this paper was excluded from our muscle size analyses as hypertrophy was not measured via CSA or lean mass). Considering these findings, it appears that RTH may provide a small added benefit for muscular development over the same training performed in normoxia (as evidenced by a small SMD in favour of RTH for CSA); however, the collective findings from this meta-analysis did not observe this effect to be significant. It is important to recognize that the disparate findings between studies published in this area are very likely due to alterations in the structure of the exercise performed and how manipulating the training structure may be affected by hypoxia.

To illustrate, research into RTH has employed varying inter-set rest intervals which range from 30 (Manimmanakorn et al., 2013) to 180 seconds (Inness et al., 2016). Although hypoxia increases reliance on anaerobic metabolism during resistance exercise and can therefore increase markers of metabolic stress (Kon et al., 2010, 2012; Ramos-Campo et al., 2017a, 2017b), longer inter-set recovery periods may increase the clearance of metabolic products from the muscles prior to the next set (Scott, Slattery, & Dascombe, 2015b). In addition, hypoxia has been demonstrated to slow, but not stop, phosphocreatine resynthesis rates following muscular contractions (Haseler, Hogan, & Richardson, 1999). It therefore stands to reason that if exercise is structured with longer than necessary inter-set recovery periods, the degree of metabolic stress in the muscles will not accumulate as it would if shorter rest periods are used, because more time is available for removal of metabolic by products and for resynthesis of phosphocreatine stores. Considering these factors along with the importance of metabolic stress for muscle hypertrophy (Gonzalez et al., 2016), it is likely that for RTH to have benefits for hypertrophy over NRT, relatively brief inter-set rest periods are necessary to take advantage of the hypoxic stimulus (Scott et al., 2015b).

It is clear that RTH place more reliance on anaerobic energy production, via an increment of blood lactate, alterations in acid–base balance (Ramos-Campo et al., 2017a), and excess post-exercise oxygen consumption (Ramos-Campo et al., 2017b). Ramos-Campo et al. (2017a) observed significant increases in blood lactate and decreases in pH during RTH under high levels of hypoxia (13% FiO_2) versus the same protocol under normoxia. However, similar to the research from Kon et al.

(2010), Ramos-Campo et al. (2017a) did not find significant differences in blood lactate or pH values between NRT and the RTH protocol performed in moderate hypoxia (16% FiO_2). These results indicate that the level of hypoxia may impact on metabolic stress via a dose–response relationship that has not yet been established for RTH. Interestingly, a recent review from Gonzalez et al. (2016) suggested that exercise-induced metabolic stress may also play a role in acute activation of mTORC1 signalling. As mentioned before, metabolic stress results from exercise that primarily relies on anaerobic glycolysis as its major energy provider. Lactate directly affects muscle cells in vitro by increasing satellite cell activity as well as mTOR and p70S6k phosphorylation (Oishi et al., 2015), and these biochemical signalling responses are therefore likely to be primary mediators if any benefits are to be gained from RTH.

Changes in muscle strength

Considering alterations in muscle strength, a large effect was observed for improved RM test performance between pre- and post-training values after RTH. However, our results indicate that hypoxic training was not significantly more effective than the same training under normoxia, and only a small effect was observed between RTH compared with NRT for muscle strength (SMD = 0.20; 95% CI = −0.27, 0.78). As previously discussed, these findings may be related to inconsistencies in the exercise structure used between studies. This is because the potential for improved strength following RTH is thought to be largely mediated through hypertrophic adaptations (Scott et al., 2014), and to our knowledge, hypoxia-mediated neural adaptations have not yet been discovered. Interestingly though, one study has employed high-load training with long inter-set rest periods (180 seconds) for strength-trained subjects, and observed significantly enhanced strength the RTH group despite no significant changes in lean mass (Inness et al., 2016). However, the authors stated that the mechanisms underpinning improved strength, but not hypertrophy, in their study are difficult to reconcile as it is not known how hypoxia could augment neural adaptations to resistance training.

As it cannot be justified solely from the findings of Inness et al. (2016) that RTH produces greater neural adaptations than NRT, these adaptations to RTH may be approached from another perspective. For instance, the Inness et al. (2016) study is the only one carried out with highly resistance-trained men. It is known that training status can affect adaptations to power training in high-level athletes, possibly due to a plateau in strength and different neuromuscular strategies being employed (Baker, 2001) Therefore, based on the findings from Inness et al. (2016), it is possible that RTH may provide benefit for enhancing strength in already resistance-trained participants when a plateau in strength is reached. Nevertheless, the exact mechanisms by which this could occur have not been elucidated, and further evidence to this point is needed.

As highlighted previously, a potential limitation of this meta-analysis is the different training programs applied in the included studies. Although the heterogeneity of the outcomes studied was low, these varying approaches to RTH may have modified the muscular development and strength adaptations observed. To illustrate, the duration of RTH programs ranged between 4 and 8 weeks, and included training frequencies of two to three sessions per week (total sessions = 10–24). Furthermore, the training sessions differed in the manipulation of acute exercise variables; these included exercise protocols comprised of between 2 and 6 sets of 3–36 repetitions at 20->75% of 1-RM, and using different types of exercise (i.e. lower limb versus upper limb, multi-joint versus single-joint). In addition, the inter-set rest periods used ranged from 30 to 180 seconds, which would likely alter the metabolic stress and potential adaptive responses associated with RTH, as discussed previously (Scott et al., 2015b).

In addition, factors aside from acute exercise variables differed considerably between the studies included in this paper. The actual FiO_2 implemented in hypoxic conditions ranged from 13% to 16%, and it is possible that the level of hypoxia may impact on the magnitude of adaptations to RTH following a dose–response relationship (though this is yet to be investigated). In addition, the training status of participants used in these studies included untrained, recreationally trained and well-trained individuals. With increased metabolic stress being a likely driver for hypoxia-related hypertrophy, it is possible that well-trained individuals and athletes with already enhanced abilities to complete anaerobic exercise (e.g. improved buffering capacity) may not receive an equivalent physiological stimulus during RTH compared to an untrained individual. Finally, apart from the study by Manimmanakorn et al. (2013), a paucity of research has investigated the effects of RTH on women. Previous research using blood flow restriction to facilitate increased metabolite accumulation during knee extension exercise has shown that females have a greater muscular endurance capacity compared with males, possibly due to differences in muscle fibre type composition, glycogen usage or adenosine triphosphate breakdown (Labarbera, Murphy, Laroche, & Cook, 2013). It is

therefore possible that adaptations to RTH may be different between males and females.

Although divergent methodologies have been employed and disparate findings published between the investigations included in this paper, some clear trends have emerged. Importantly, RTH was found to cause significant increases in muscle CSA and strength. While the results from this meta-analysis suggest that RTH does not augment these responses over those observed following NRT, the addition of hypoxia may still have additional benefits. For example, Kon et al. (2014) reported that plasma vascular endothelial growth factor and capillary-to-fiber ratio were significantly higher following 8 weeks of RTH compared with NRT, and these responses were accompanied by an increase in muscular endurance. These results follow the data obtained by Vogt et al. (2001) showing that high intensity training under hypoxia increases vascular endothelial growth factor and evokes an adaptation in HIF-1 pathway. Therefore, exercise in hypoxia appears to result in a large range of functional adaptations in skeletal muscle (Lundby, Calbet, & Robach, 2009).

It is important for those seeking to implement RTH that they also consider the impacts of hypoxia on exercise performance. Data indicate that breathing hypoxic air during traditionally structured high-load resistance exercise (5 × 5 repetitions with 80% 1-RM and 180 seconds inter-set rest) does not cause declines in performance during training (Scott, Slattery, Sculley, Hodson, & Dascombe, 2015c), while performing high-load RTH using a circuit-based format (3 × 3 exercises at 6-RM with 35 seconds rest between exercises and 180 seconds rest between circuits) does result in decreased bench press (Ramos-Campo et al., 2017a) and half-squat (Ramos-Campo et al., 2017b) performance. These divergent findings are likely related to the structure of exercise and resultant metabolic stress, as Scott et al. (2015c) did not observe hypoxia to augment blood pH or lactate values, while Ramos-Campo et al. (2017a, 2017b) observed hypoxia to augment blood markers of metabolic stress (pH and lactate), and heightened post-exercise energy cost and oxygen consumption.

Practical implications

Although research investigating RTH is in its infancy, this study has provided an opportunity to make recommendations for both practitioners and researchers in this field. While no significant benefits were observed for RTH compared with NRT, small effects were evident in favour of larger increases in muscle CSA and strength following RTN. This suggests that some individuals may benefit more from RTH compared with normoxia, which would be important in well-trained athletic cohorts where small changes in physical attributes are difficult to achieve, and may therefore be meaningful (Inness et al., 2016). Further research is required to investigate these responses in more detail, but it appears that the efficacy of RTH strategies have been impacted by large variations in the structure of exercise performed and the level of hypoxia implemented. Exercise should be designed to elicit increases in metabolic stress under hypoxia, which may be achieved by using relatively brief inter-set rest periods and sufficient repetition volume (Scott et al., 2015b). Considering the findings from studies which have demonstrated benefits for RTH, inter-set rest periods should be very brief for low-load exercise (~30% 1-RM; ~30 seconds) and brief for moderate-load exercise (~70% 1-RM; ~60 seconds). RTH should be undertaken in moderate-level hypoxia (FiO_2 = 13–16%), though it is not known whether a dose–response relationship exists for the level of hypoxia on muscular development. Finally, it is possible that RTH may impair performance during training (Ramos-Campo et al., 2017a, 2017b), though this has not been consistently demonstrated (Scott et al., 2015c). Taken together, these preliminary findings indicate that RTH may be more suitable for individuals who are training for muscular hypertrophy, whereby the aim is to elicit a substantial metabolic stimulus, rather than those seeking to optimize maximal strength and power, where an emphasis is placed on complete recovery between sets and concentric performance during repetitions.

Conclusions

The current meta-analysis concludes that while RTH does result in significant increases in muscular size and strength, these responses may not be larger than NRT. Nevertheless, the findings from this meta-analysis are likely impacted by the divergent methodologies employed in RTH studies, particularly around the structure of exercise, level of hypoxia used and the types of participants recruited. The findings of this meta-analysis indicate the importance of additional detailed studies to analyse the effects of this novel training stimulus on muscular size and strength performance.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data

Supplemental data for this article can be accessed http://dx.doi.org/10.1080/17461391.2017.1388850.

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V - ESTUDIO III: Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions

Acute Physiological and Performance Responses to High-Intensity Resistance Circuit Training in Hypoxic and Normoxic Conditions

Domingo J. Ramos-Campo,[1,2] Jacobo Á. Rubio-Arias,[1,2] Tomás T. Freitas,[2] Arturo Camacho,[1,2] José F. Jiménez-Diaz,[3] and Pedro E. Alcaraz[1,2]

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Abstract

Ramos-Campo, DJ, Rubio-Arias, JÁ, Freitas, TT, Camacho, A, Jiménez-Diaz, JF, and Alcaraz, PE. Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions. *J Strength Cond Res* 31(4): 1040–1047, 2017–The aim of this study was to analyze physical performance and physiological variables during high-intensity resistance circuit training (HRC) with the addition of 2 levels (moderate and high) of systemic hypoxia. Twelve resistance-trained young male subjects participated in the study. After a 6 repetition maximum testing session, participants performed 3 randomized trials of HRC: normoxia (NORM: fraction of inspired oxygen [FiO_2] = 0.21; ~0 m altitude), moderate hypoxia (MH: FiO_2 = 0.16; ~2.100 m altitude), or high hypoxia (HH: FiO_2 = 0.13; ~3.800 m altitude), as controlled by a hypoxic generator. Bench press force, heart rate and heart rate variability, rating of perceived exertion, resting metabolic rate, energy cost, and countermovement jump were assessed in each session. Heart rate variability in HH was significantly lower (standard deviation of all normal NN intervals [intervals between two "normal" beats] = 111.9 vs. 86.7 milliseconds; standard deviation of the difference between consecutive NN intervals = 19.5 vs. 17.0 milliseconds; $p \leq 0.05$) in comparison with NORM. There were significant differences in rating of perceived exertion between NORM and HH (11.6 vs. 13.8 points). Peak and mean force on the bench press were significantly lower ($p \leq 0.05$) in HH when compared with MH (peak: 725 vs. 488 N; mean: 574 vs. 373 N). Energy cost was significantly higher ($p \leq 0.01$) in both hypoxic conditions compared with NORM (NORM: 10.4; MH: 11.7; HH: 13.3 $kJ \cdot min^{-1}$). There were no differences between conditions in heart rate and countermovement jump variables. These results indicate that hypoxic stimuli during HRC exercise alter physical performance and physiological variables and affect how strenuous the exercise is perceived to be. High-intensity resistance circuit training in hypoxia increases the stress on the performance and physiological responses, and these differences must be taken into account to avoid an excessive overload.

Key Words force, countermovement jump, HRC, resistance training, heart rate variability

Introduction

Developing the most effective and efficient method to maximize strength has been the focus of scientists and coaches for a long time. In recent years, endurance and team sports coaches have paid special attention to strength training because it leads to adaptations related to superior aerobic performance, such as increments in maximal strength, mechanical power, muscle hypertrophy, and rate of force development (RFD) (19,21).

In this sense, one of the most specific strength training protocols for this kind of sports is the high-intensity resistance circuit training (HRC). This type of resistance training has a beneficial impact on the cardiorespiratory and neuromuscular systems and also on body composition (1,2). In fact, HRC has been shown to increase muscle hypertrophy, strength, and power output and to decrease fat mass because of a higher metabolic impact and cardiovascular response (1,2). High-intensity resistance circuit training has positive effects on physical performance similar to those of a concurrent strength and endurance training method, but with shorter session durations (~30–40 minutes) (2). Moreover, it involves both the aerobic and anaerobic metabolisms and improves the resting metabolic rate (RMR) and energy cost (EC) after training more than a traditional strength training session (18).

Another typical strategy used to improve athletic performance in both endurance and team sports is altitude or hypoxic training. These types of training methods produce

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structural and functional adaptations of the skeletal muscle (15). Most recently, different studies (3,13,27) have applied strength training in hypoxic environments to enhance muscular performance. Resistance training in hypoxia produces beneficial changes in the musculoskeletal system and increases strength and muscular endurance (26). Research has also shown that hypoxic environments improve intramuscular metabolic stress (28), increasing hypertrophic signaling, muscular hypertrophy (31), and hormonal concentrations (29). In addition, low-intensity resistance hypoxic training results in an increase of motor unit recruitment (29) and muscular endurance (14,17) and maintains maximal anaerobic power capacity measured with a countermovement jump (4). Reeves et al. (24) demonstrated that exercise under hypoxia conditions causes an increase in respiratory and cardiovascular mechanisms and induces a sympathetic activation that can be noninvasively evaluated by studying heart rate variability (HRV) (22). Based on current evidences, performing HRC training with different levels of hypoxia can be a good method to improve athletic performance with shorter volume and duration of the session.

Although the physiological responses that are produced by the effects of hypoxia on strength training adaptations are known, the acute effects of this stressful resistance training in trained athletes on physiological and performance responses are unclear. To our knowledge, no research has investigated the effects of adding systemic hypoxia to HRC. Therefore, the aim of this study was to analyze physical performance and physiological and metabolic variables during HRC training with the addition of 2 levels (moderate and high) of systemic hypoxia.

Methods

Experimental Approach to the Problem

A comparative, double-blind (no participant or supervisor know the normoxic or hypoxic situation), randomized crossover design was applied to examine whether different levels of hypoxia affect HRC training performance. The subjects completed a HRC protocol randomized under 3 conditions: (a) normoxia (NORM; fraction of inspired oxygen [FiO_2] = 0.21; ~0 m altitude); (b) moderate hypoxia (MH; FiO_2 = 0.16; ~2.100 m altitude); and (c) high hypoxia (MH; FiO_2 = 0.13; ~3.800 m altitude). During each session, subjects breathed through a mask connected to a hypoxic generator (GO2 Altitude hypoxicator; Biomedtech, Moorabbin, Australia).

Subjects

Twelve healthy, nonsmoking, male subjects (age: 25.1 ± 4.8 years; age range: 20–29 years; height: 174.6 ± 5.3 cm; weight: 70.3 ± 6.8 kg; fat mass: 12.1 ± 1.8%; bench press 6 repetition maximum [6RM]: 57.1 ± 12.8 kg; half-squat 6RM: 95.9 ± 21.6 kg) participated in this study. Participants had at least 4 years of resistance training experience and exercised 3 times per week. None of the subjects had any musculoskeletal disorder or reported exposure to altitude 3 months before the study. All experimental procedures were explained to the participants, and a written consent was obtained from each subject. The present research was approved by the Institutional Science Ethic Committee.

Procedures

All testing sessions took place in the laboratory during a 3-week period and were carried out at the same time of day. In total, subjects had to report to the laboratory 4 times. During the first visit, body composition was assessed with a segmental multifrequency bioimpedance analyzer (Tanita BC-601; Tanita Corp., Tokyo, Japan) with measurements obtained as described by the manufacturer. Moreover, the 6RM loads were determined for the 6 exercises of the HRC protocol. After 3 days of rest, subjects performed the first training session (second visit) in 1 of the 3 training conditions. Then, after at least 72 hours of rest, the second training session (third visit) was conducted. Finally, again after at least 72 hours of rest, the last training session (fourth visit) was carried out. The 3 HRC training sessions were performed in randomized order (Figure 1). The participants were instructed to maintain their regular dietary consumption during the study and to avoid ingesting caffeine or alcohol at least 24 hours before each visit. The participants agreed not to take ergogenic aids, supplements, or medications that might influence performance.

Six-Repetition Maximum Determination. Before testing, a warm-up consisting of 5 minutes of cycling at 75 W

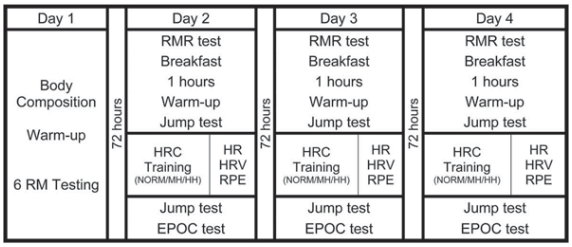

Figure 1. Research design. RM = repetition maximum; RMR = resting metabolic rate; HRC = high-intensity resistance circuit training; NORM = normoxia; MH = moderate hypoxia; HH = high hypoxia; HR = heart rate; HRV = heart rate variability; RPE = rating of perceived exertion; EPOC = excess postexercise oxygen consumption.

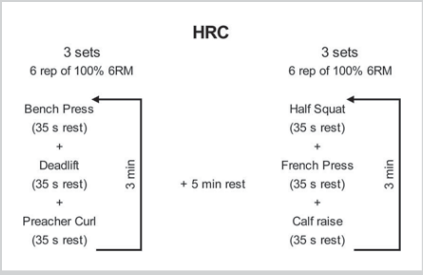

Figure 2. High-intensity resistance circuit training (HRC) protocol.

followed by active stretching was carried out. To calculate the 6RM loads, participants performed 3 sets of each exercise using the following sequence: 10 repetitions at 50% of estimated 6RM, 1-minute rest, 8 repetitions at 75% of estimated 6RM, 2-minute rest, and 1 set of the exercises to volitional fatigue at 100% of estimated 6RM (2). If a participant performed ±1 repetition, the training load was adjusted by approximately ±2.5 and if a subject completed ±2 repetitions, the training load was adjusted by ±5% (5). The participants were allowed to do 5 attempts as maximum with 5-minute rest between each attempt. Bench press, deadlift, elbow flexion (preacher curl), half-squat, elbow extension (french press), and ankle extension (calf raise) 6RM loads were assessed.

Training Protocol. A general warm-up that involved 5 minutes of submaximal cycling at 75 W and 75–100 rpm followed by 5 minutes of active stretching of all major muscle groups was performed before the workout. Also, a specific warm-up consisting of 3 sets of the exercises of the first block was completed using the following sequence: 10 repetitions at 50% of 6RM for each exercise, 1-minute rest, 8 repetitions at 75% of 6RM, 2-minute rest, and repetitions to failure with the 6RM load. The training load ensures that subjects lifted loads that allowed only 6 repetitions (~85–90% of 1 repetition maximum [1RM]). If participants performed ±1 or ±2 repetitions, the training load was adjusted as described above. To standardize the dynamics of the exercises, the eccentric phase of each exercise was performed in 3 seconds (controlled by a digital metronome), whereas the concentric phase was performed at maximum velocity. The exercises were chosen to emphasize both major and minor muscle groups using single- and multijoint exercises, based on recommendations of the American College of Sports Medicine (ACSM) (10). Subjects were supervised by an experienced lifter to ensure that volitional fatigue was achieved safely and rest periods were strictly controlled.

The HRC protocol was based on the one proposed by Alcaraz et al. (2), and it consisted of 2 short circuits (blocks) completed with a 35-second rest between exercises (which allowed enough time to move safely from one exercise to the next), a 3-minute rest between each series of 3 exercises within a block, and a 5-minute rest between blocks. The protocol was completed with 6 repetitions at 100% of 6RM in each exercise. Each series was performed 3 times. The first block consisted of bench press, deadlift, and elbow flexion (preacher curl) exercises, and the second block consisted of half-squat, elbow extension (french press), and ankle extension (calf raise) (Figure 2).

Testing Procedures. ***Heart Rate and Heart Rate Variability.*** Heart rate (HR) and HRV were recorded during the entire session. Heart rate data were recorded by a Polar RS800 (Polar, Polar Electro OY, Kempele, Finland) HR monitor. Heart rate variability was examined with the software Kubios HRV (University of Kuopio, Kuopio, Finland). The following parameters of time-domain were analyzed: (a) average of NN intervals (in milliseconds) (variation in the time interval between normal heart beats);

Table 1. Heart rate and RPE values of high-intensity resistance circuit training in the 3 environment conditions.*†

	Heart rate ($b \cdot min^{-1}$)			RPE		
	NORM	MH	HH	NORM	MH	HH
Basal	66.7 ± 8.2	66.9 ± 10.3	64.4 ± 8.6	6.0 ± 0.0	6.0 ± 0.0	6.0 ± 0.0
Block 1	150.9 ± 15.4	151.7 ± 11.4	153.0 ± 24.0	12.1 ± 1.8	12.6 ± 2.0	14.2 ± 3.1
Block 2	146.3 ± 15.4	149.3 ± 14.7	149.7 ± 17.3	11.6 ± 1.2‡	11.9 ± 1.9	13.82 ± 2.5§

*NORM = normoxia; MH = moderate hypoxia (0.16% fraction of inspired oxygen); HH = high hypoxia (0.13% fraction of inspired oxygen).
†Data are presented as mean ± *SD*.
‡Significant differences between NORM and HH.
§Significant differences between MH and HH ($p \leq 0.05$).

Table 2. Heart rate variability of high-intensity resistance circuit training in the 3 environment conditions.*†

	Heart rate variability		
Variable	NORM	MH	HH
Average NN (ms)	529.9 ± 98.7	537.2 ± 83.0	553.2 ± 93.4
SDNN (ms)	111.9 ± 43.4	101.4 ± 48.1	86.7 ± 37.3‡
SDSD (ms)	19.5 ± 4.5	17.6 ± 3.5	16.9 ± 4.0‡
PNN50 (%)	1.1 ± 1.1	0.7 ± 0.6	2.4 ± 2.3
RMSSD (ms)	12.8 ± 4.7	12.5 ± 4.9	12.2 ± 4.5

*NORM = normoxia; MH = moderate hypoxia (0.16% fraction of inspired oxygen); HH = high hypoxia (0.13% fraction of inspired oxygen); SDNN = standard deviation of all normal NN intervals; SDSD = standard deviation of the difference between consecutive NN intervals; PNN50 = percentage of the number of differences between adjacent normal NN intervals higher than 50 milliseconds; RMSSD = square root of the mean of the sum of the squared differences between adjacent normal NN intervals.
†Data are presented as mean ± *SD*.
‡Significant differences between NORM and HH ($p \leq 0.05$).

(b) standard deviation of all normal NN intervals (in milliseconds); (c) standard deviation of the difference between consecutive NN intervals (in milliseconds); (d) percentage of the number of differences between adjacent normal NN intervals higher than 50 milliseconds (in percentage); and (e) square root of the mean of the sum of the squared differences between adjacent normal NN intervals (in milliseconds).

Resting Metabolic Rate and Excess Postexercise Oxygen Consumption. Before (RMR) and after (excess postexercise oxygen consumption [EPOC]) each training session, RMR and EPOC tests were carried out during 10 minutes (RMR) and 20 minutes (EPOC) respectively, using a breath-by-breath gas analyzer (Metalyzer 3B; Cortex-Medical, Leipzig, Germany). The gas analyzer system was calibrated before each test using the manufacturer's recommendations. Subjects reported to the laboratory fasted and were resting supine during both tests. After the RMR test, participants had a breakfast consisting of a sandwich and a glass of juice. One hour later, they started the training session. Values of $\dot{V}O_2$, RER, and EC were continuously recorded and averaged every minute. Later, averaged values of $\dot{V}O_2$ and EC during the 10 minutes (RMR) or 20 minutes (EPOC), respectively, were used.

Bench Press Force. Force values (in Newton) obtained when performing the bench press exercise were monitored during each set with a linear position transducer (Chronojump, Barcelona, Spain) that was attached to the bar. Later, force values of each block of 6 repetitions were averaged to determine the mean force of each block of 6RM. Moreover, the peak force (in Newton) of each block was analyzed.

Countermovement Jump. Countermovement jump was assessed 1 hour after the RMR and after each training session and immediately before the EPOC test (we assume that this exercise can disturb the EPOC analysis; however, we did the jump in all the situations, so all the conditions were stable). The jump was performed on a Kistler 9286BA portable force platform with a sampling rate of 1,000 Hz (Kistler Group, Winterthur, Switzerland). Subjects were instructed to perform the eccentric phase of the movement as fast as possible and to keep the hands on the hips throughout the execution to minimize any contribution of the upper body to jump impulse. All participants had experience in these types of actions. Three attempts were carried out, and the best result was considered. A 2-minute rest was allowed between jumps to diminish the effects of

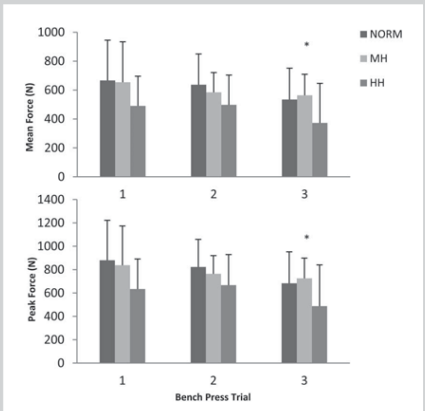

Figure 3. Peak and mean force during bench press (mean ± *SD*). NORM = normoxia; MH = moderate hypoxia; HH = high hypoxia. *Significant differences between MH and HH ($p \leq 0.05$).

Table 3. Mean and peak force during each set of bench press of high-intensity resistance circuit training in the 3 environment conditions.*†

	Mean force (N)			Peak force (N)		
	NORM	MH	HH	NORM	MH	HH
Set 1	666.9 ± 278.2	654.5 ± 205.5	490.5 ± 205.5	879.9 ± 342.0	837.7 ± 335.9	633.9 ± 256.9
Set 2	636.7 ± 213.2	584.7 ± 136.6	497.7 ± 206.3	822.7 ± 236.0	763.5 ± 156.3	666.7 ± 262.2
Set 3	534.7 ± 216.6	563.5 ± 146.0	372.5 ± 274.2‡	682.6 ± 269.7	724.9 ± 173.9	487.5 ± 352.8‡

*NORM = normoxia; MH = moderate hypoxia (0.16% fraction of inspired oxygen); HH = high hypoxia (0.13% fraction of inspired oxygen).
†Data are presented as mean ± *SD*.
‡Significant differences between moderate and high hypoxia ($p \leq 0.05$).

fatigue. Jump height (in centimeters), maximal power output (in Watts per kilogram), and RFD (in Newton per second) were determined. Jump height (h) was calculated from the take-off vertical velocity (vi) using the following equation: $h = vi^2 \cdot 2\ g^{-1}$. Power was calculated from the data extracted from the force platform as the product of vertical force by instantaneous vertical velocity of the system's center of mass. Rate of force development was determined as the rate of rise on vertical force. In addition, the change between basal values and after-training values of jump variables was analyzed.

Rating of Perceived Exertion. Rating of perceived exertion (RPE) was assessed immediately after each block using a 6–20 RPE scale to determine the stress of HRC training. Participants had previous experience in the use of this scale.

Statistical Analyses

Data collection, treatment, and analysis were performed using the SPSS for Windows statistical package (version 20.0; SPSS, Inc., Chicago, IL, USA). Descriptive statistics (mean and *SD*) were calculated. Before using parametric tests, the assumption of normality and homoscedasticity were verified using the Shapiro-Wilks W-test. A 2-way analysis of variance test with repeated measures and Bonferroni post hoc test were used to investigate differences in variables. For all procedures, a level of $p \leq 0.05$ was set to indicate statistical significance.

Results

The results presented in Table 1 showed no significant differences in HR values among the 3 conditions. There were no significant differences between the pretest values for all variables analyzed. Regarding RPE, significant differences ($p \leq 0.05$) were observed between NORM and high hypoxia (HH) and between MH and HH in the last block. No significant differences were observed in other parameters. Furthermore, significant differences ($p \leq 0.05$) between NORM and HH session in standard deviation of all normal NN intervals and standard deviation of the difference between consecutive NN intervals (in milliseconds) variables were found (Table 2).

Figure 3 and Table 3 showed significant differences ($p \leq 0.05$) in mean and peak force between MH and HH in the third set of bench press.

Table 4. Values of energy cost and $\dot{V}O_2$ after each session of high-intensity resistance circuit training.*†

	Energy cost ($kJ \cdot min^{-1}$)			$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)		
	NORM	MH	HH	NORM	MH	HH
Basal	8.2 ± 1.7	8.2 ± 1.4	8.4 ± 1.1	5.6 ± 1.1	5.6 ± 0.8	5.7 ± 0.7
After training	10.4 ± 1.8	11.7 ± 2.2‡	13.3 ± 2.8§	7.1 ± 0.9	7.9 ± 1.2‡	9.1 ± 2.1§

*NORM = normoxia; MH = moderate hypoxia (0.16% fraction of inspired oxygen); HH = high hypoxia (0.13% fraction of inspired oxygen).
†Data are presented as mean ± *SD*.
‡Significant differences between NORM and MH ($p \leq 0.01$).
§Significant differences between NORM and HH.

Table 5. Change in height jump, relative and absolute power, and rate of force development (%) between before and after the session.*†

	Jump performance		
Variable	NORM	MH	HH
Height jump (%)	−5.7 ± 6.2	−0.4 ± 5.3	−3.3 ± 5.8
Relative power (%)	−3.2 ± 4.2	−2.9 ± 5.7	−2.3 ± 5.1
Absolute power (%)	−3.7 ± 3.9	−3.3 ± 5.5	−1.8 ± 3.8
Rate of force development (%)	8.3 ± 3.3	4.5 ± 3.0	−1.3 ± 6.4

*NORM = normoxia; MH = moderate hypoxia; HH = high hypoxia.
†Data are presented as mean ± *SD*.

Significant differences in $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$) and the energy consumption ($kJ \cdot min^{-1}$) during the 20 minutes after the session between NORM and MH ($p < 0.01$) and between NORM and HH ($p < 0.01$) were found (Table 4). No significant differences were observed between MH and HH.

On the other hand, no significant before-after session differences were observed in decrement of absolute and relative power output, RFD, and jump height (%) among conditions (Table 5).

Discussion

To our knowledge, this is the first study that examined physical performance and cardiovascular, perceptual, and metabolic responses during HRC under normoxia and 2 levels of hypoxia conditions in resistance-trained athletes. The main findings of this investigation demonstrated that HRC in HH affected autonomic modulation of the participants during exercise and, in the first 20 minutes after the session, higher energy consumption was needed. High-intensity resistance circuit training in HH produced a significantly higher decrease in mean and maximum forces in bench press when compared with NORM or MH. However, jump performance and HR remain unchanged. Finally, HH significantly increased the RPE of the exercise when compared with NORM and MH.

The influence of resistance training on HRV under acute hypoxia has not been described. The results of this study showed that HRC under HH causes an additional decrease in HRV compared with exercising in MH or NORM. The decrement in HRV can be explained by an increased sympathetic activity during hyperventilation (22), suggesting a reduced vagal control of the heart (8). An increase in sympathetic and a decrease in parasympathetic activity in submaximal exercise at high altitude have been reported in some studies (8,22). In this regard, changes in HRV could be an indicator of an imbalance related to resistance training and environment-induced stress (8). Furthermore, HRC in hypoxia represents 2 types of stress that cause modifications in the sympatho-vagal balance. Thus, HRV may be used as a tool to monitor the stress caused on the athlete's body and can be applied to determine the acclimatization effect of a hypoxia program.

On the other hand, there are no significant differences in HR values. However, it is observed an increase tending to significance in HR with the hypoxic situations. Similar results were obtained by Scott et al. (27). These findings likely show an increment in cardiac output because of hypoxia in response to muscular oxygen deprivation (12). This fact can improve the aerobic resynthesis of phosphocreatine (11), which is crucial for performance during subsequent bouts (20). In this regard, HR is not sensitive enough to detect changes after hypoxic conditions. Therefore, in future studies, researchers should use other intensity variables more related to strength training protocols, i.e., lactate. According to our results, RPE seems to be a better indicator for controlling the load training.

Another notable finding in this study was that the environment where the training session was performed affects energy consumption during the next 20 minutes after training. Hence, hypoxia increases the EC and the $\dot{V}O_2$. The rapid component of EPOC after training is thought to reflect the oxygen cost of phosphocreatine resynthesis (30); therefore, the increased EPOC after hypoxic HRC training may indicate increased phosphocreatine turnover during the sets. Furthermore, $\dot{V}O_2$ can be attributed to replacement of O_2 in circulation and in muscle, elevated ventilatory rate, elevated heart activity, oxidation of lactate, glycogen resynthesis, and sodium-potassium pump activity (9). These results were similar those reported by Marín-Pagán et al. (18) for EC in a study applying HRC compared with traditional circuit weight training. These authors showed that EC and $\dot{V}O_2$ values were greater when the intensity of the circuit was increased. This fact may decrease the athlete's mass and optimize body composition after a hypoxia training program (23). In fact, there are some studies using HRC protocols with both trained participants (2) and older adults (25) that produced significant decrements in fat mass (absolute and

relative values). Thus, HRC in hypoxia conditions may be an effective method to increase the EC after the session and decrease body fat mass.

Exercise under acute systemic hypoxia influences muscular performance (peak and mean force during bench press). Previous studies have shown that acute exercise performed in hypoxia reduces anaerobic performance (6,7). However, other studies have demonstrated no change (15,27). In this study, significant differences were observed in peak and mean force in the last trial of bench press between HH and MD. Thus, exercise with HH condition might produce more fatigue because of the changes in autonomic modulation and in metabolic stress than produces resistance exercise in NORM or MH environment. This fact may be explained by an accumulation of neuromuscular and metabolic fatigue and a decrease in HRV. From a performance point of view, coaches should carefully manipulate the magnitude of the load imposed by HRC protocol under HH, because this kind of effort is more stressful than MH or NORM and can affect the training stimuli or physical target to achieve during the session.

As expected, at the end of the HH training session, RPE values were significantly greater than during the MH and NORM conditions. In this sense, HH was perceived as more difficult than MH and NORM, with the last set of the session considered the heaviest. These results are in accordance with the study by Alvarez-Herms et al. (4), who obtained significant differences in RPE scores between HH ($FiO_2 = 13.5\%$) and NORM environments during a series of 6 consecutive jumps, lasting for 15 seconds with an intervening rest period of 3 minutes. However, Scott et al. (27) showed no significant differences in RPE values during a high-intensity resistance training session (5×5 repetitions at 80% 1RM, with 3 minutes rest between sets) at the same hypoxic levels as in our study (MH = 16% FiO_2 and HH = 13% FiO_2). These discrepancies may be because of the type of training protocol (traditional vs. circuit training; at an intensity of 80 vs. 85% 1RM, respectively). Furthermore, a relationship between volume and intensity of a training session and RPE values exists, correlated with physiological variables, intensity parameters, muscle activation, and metabolic stress markers (16).

Practical Applications

The results of this study indicate that coupling systemic hypoxia with HRC exercise significantly affects physical performance. Furthermore, hypoxic conditions modify physiological variables and alter the perception of this type of strenuous exercise. High-intensity resistance circuit training exercise with systemic hypoxia may be useful for resistance-trained athletes, as it produces added stress on the physiological responses and on performance. Coaches may find this type of specific training useful to increase endurance and strength adaptations while reducing the time devoted to resistance training. However, using HRC on HH environment can adversely affect the imposed physical training dosage, which should be adjusted appropriately to optimize performance. Performance and body composition may also improve in endurance athletes or team sports players using shorter session duration. Coaches should bear in mind that it is possible to produce the same performance outcomes at the sea level by using a simulated hypoxic environment with 0.16% of FiO_2 (~2.100 m altitude) in combination with HRC. Our findings show that exercise intensity can be monitored with RPE, which is extremely useful in the field or in artificial rooms to control the load in HRC session under hypoxic conditions.

This research opens a new perspective in the optimization of future resistance training protocols with hypoxic conditions, in an effort to develop the most effective and efficient method to maximize strength performance, metabolic adaptations, body composition, and time spent on resistance training. More research is needed to elucidate the chronic morphological, metabolic, and strength adaptations and the neural and endocrine responses to HRC under hypoxic conditions.

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VI - ESTUDIO IV: Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia.

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ORIGINAL ARTICLE

Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia

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Abstract
Purpose The aim of this study was to analyze the effect of hypoxia on metabolic and acid–base balance, blood oxygenation, electrolyte, and half-squat performance variables during high-resistance circuit (HRC) training.
Methods Twelve resistance-trained subjects participated in this study. After a 6RM testing session, participants performed three randomized trials of HRC: normoxia (NORM: $FiO_2 = 0.21$), moderate hypoxia (MH: $FiO_2 = 0.16$), or high hypoxia (HH: $FiO_2 = 0.13$), separated by 72 h of recovery in normoxic conditions. HRC consisted of two blocks of three exercises (Block 1: bench press, deadlift and elbow flexion; Block 2: half-squat, triceps extension, and ankle extension). Each exercise was performed at 6RM. Rest periods lasted for 35 s between exercises, 3 min between sets, and 5 min between blocks. Peak and mean force and power were determined during half-squat. Metabolic, acid–base balance, blood oxygenation and electrolyte variables, arterial oxygen saturation (SaO_2), and rating of perceived exertion (RPE) were measured following each block.
Results During the first set, peak force and power were significantly lower in HH than MH and NORM; whereas in the second set, mean and peak force and power were significantly lower in HH than NORM. At the end of the HRC training session, blood lactate and RPE in HH were significantly higher than in MH and NORM. SaO_2, pH, HCO_3^-, and pO_2 values were significantly lower in all hypoxic conditions than in NORM.
Conclusion These results indicate that simulated hypoxia during HRC exercise reduce blood oxygenation, pH, and HCO_3^-, and increased blood lactate ultimately decreasing muscular performance.

Keywords Hypoxic · HRC · Lactate · Power · Resistance training

Abbreviations

ACSM	American college of sports medicine
ATP	Adenosine triphosphate
Ca^{2+}	Calcium
Cl^-	Chloride
cm	Centimeter
FiO_2	Fraction of inspired oxygen
Glu	Glucose
H^+	Hydrogen
HCO_3	Bicarbonate
HH	High hypoxia
HRC	High-resistance circuit
K^+	Potassium
l	Litre
m	Meter
MH	Moderate hypoxia
min	Minute
kg	Kilogram
Na^+	Sodium

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NORM	Normoxia
pCO_2	Carbon dioxide partial pressure
PCr	Phosphocreatine
pO_2	Oxygen partial pressure
RM	Maximum repetition
RPE	Rating of perceived exertion
RT	Resistance training
RTH	Resistance training under hypoxia
s	Second
SaO_2	Arterial oxygen saturation
SPSS	Statistical package for the social sciences
W	Watt

Introduction

Resistance training (RT) is an effective method to modify muscle morphology (i.e., increasing muscle mass) and to stimulate neuromuscular adaptations to increase strength, power, and local muscular endurance, ultimately leading to enhanced athletic performance (Garber et al. 2011; Scott et al. 2015a). Structural and functional adaptations of skeletal muscle can be finely tuned by modifying the exercise stimuli, such as training volume, training intensity, and/or environmental condition (Kon et al. 2014). Recently, some studies (Scott et al. 2015a; Kon et al. 2012; Alvarez-Herms et al. 2015b) have examined the utility of RT under hypoxia (RTH) to enhance muscular performance. For instance, strength exercises performed in hypoxic conditions have shown to increase intramuscular metabolic stress ($FiO_2 = 13\%$) (Kon et al. 2012), enhance hypertrophic signaling and muscle hypertrophy (FiO_2 14.4%) (Kon et al. 2014), as well as increase the concentration of anabolic hormones (Kon et al. 2012). Furthermore, studies have observed that one moderate-load resistance (i.e., 3 sets of 10 repetitions at 60% of 1RM) and hypoxic training session ($FiO_2 = 16\%$) can increase muscle activation (Scott et al. 2016) but does not affect maximal anaerobic power capacity (Alvarez-Herms et al. 2015a). In addition, exercising in hypoxia is known to induce greater respiratory and cardiovascular responses and increases sympathetic activation (Reeves et al. 1992).

The application of RTH in sports has been shown to improve muscle strength (↑ 15% of 3-s maximal voluntary contraction; ↑ 18% the area under 30-s force curve), muscle size (↑ 6% cross-sectional-area) and muscle endurance (↑ 23% the number of repetitions at 20% 1RM) in netball athletes after 5 weeks of training at 20% 1RM and at 80% SaO_2 (Manimmanakorn et al. 2013). Nonetheless, there are several disadvantages with RT (and consequently with RTH) that include: (a) the lengthy time required to complete a training session that consists of many exercise sets with reasonable inter-set rest durations, (b) moderate cardiovascular benefits when compared to other forms of training (e.g., aerobic training), and (c) minimal loss of body fat after a period of training (Alcaraz et al. 2011).

To address the excess time devoted to RT, a "novel" high-intensity resistance circuit training (HRC) was presented and showed positive effects on muscular hypertrophy, strength, and power performance while decreasing fat mass, due to the higher total metabolic and cardiovascular demand incurred either during the training session or during the post-training recovery phase (Alcaraz et al. 2008, 2011; Romero-Arenas et al. 2013). Thus, HRC training produces similar positive effects on physical performance and body composition as RT methods but with the advantage of a much shorter training session (~30–40 min) (Alcaraz et al. 2011). Therefore, the addition of systemic hypoxia to HRC is as an interesting strategy to improve athletic performance and further metabolic adaptations using a lower exercise volume and shorter session duration when compared to RTH. However, it is still unclear how the level of hypoxia can impact one's ability to perform an HRC training session. Therefore, in the perspective to develop future HRC training programs in hypoxia, the aim of this study was to determine if an HRC training session under hypoxia produces greater acute effects on physical performance than on blood gases, blood metabolites, and blood electrolyte responses. Our hypothesis was that an HRC training session under high and moderate hypoxic conditions produces negative acute effects on strength and power, with greater blood lactate concentration, and blood electrolytes changes compared to normoxia.

Methods

Design

This study used a comparative, double-blind, randomized crossover design to test the effect of high and moderate hypoxia on metabolic and acid–base balance, blood oxygenation, electrolyte, and half-squat performance acute responses to a HRC training session. Subjects performed a HRC protocol under three conditions of O_2 availability, each on separate occasions in a random order: (1) normoxia (NORM; fraction of inspired oxygen (FiO_2) = 0.21; ~0 m altitude); (2) moderate hypoxia (MH; $FiO_2 = 0.16$; ~2.100 m altitude); and (3) high hypoxia (HH; $FiO_2 = 0.13$; ~3.800 m altitude). During each session (exercise and recovery), subjects wore a mask that was connected to a hypoxic generator (GO2 Altitude hypoxicator, Biomedtech, Australia), which controlled the availability of oxygen. All subjects were blinded to the level of FiO_2 for each trial. No specific familiarization trials were conducted as all participants had the previous experience with HRC training. All

HRC sessions were well tolerated by the subjects, and no one reported any side effects.

Subjects

Twelve healthy, nonsmoking, male subjects (age: 25.1 ± 4.8 years; height: 174.6 ± 5.3 cm; weight: 70.3 ± 6.8 kg; fat mass: 12.1 ± 1.8%; bench press 6RM: 57.1 ± 12.8 kg; half-squat 6RM: 95.9 ± 21.6 kg) participated in this study. The subjects were physically active and experienced with resistance training as they performed resistance exercise on average three times per week in the 4 years prior to the study. Subjects did not have any musculoskeletal disorder and reported not having been exposed to moderate or high altitude in the 3 months prior to the study. All subjects gave signed, informed consent and the study was approved by the University's Institutional Science Ethics Committee.

Procedures

Subjects came to the laboratory a total of four times during a 3-week period, each visit was separated by at least 72 h of recovery under natural conditions (normoxia). In the first visit, body composition was assessed using a segmental multifrequency bioimpedance analyzer (Tanita BC-601, Tanita Corp., Tokyo, Japan) and the load for each subject's 6 repetition maximum (6-RM) for each of the six exercises of the HRC protocol was determined. Three days later, subjects performed the HRC protocol under one of the environmental conditions. The third and fourth training sessions consisted of the same HRC protocol but under the remaining experimental conditions. The order of the conditions for each HRC training session was randomized, and each subject performed the protocol at the same time of day for each visit. In addition, subjects were asked to maintain their habitual diet and hydration status and not to ingest caffeine or alcohol at least 24 h before each testing session nor to perform an exhaustive training bout in the 48 h preceding each visit.

6RM testing

The 6-RM was used to measure muscle strength in each of the following six exercises: bench press, deadlift, biceps flexion (preacher curl), half-squat, triceps extension, and ankle extension (calf raise). Prior to testing, subjects warmed-up on a stationary bicycle for 5 min at 75 W. Afterwards, subjects performed ten repetitions at 50% of the perceived 1-RM, followed by active stretching. Next, standard procedures were used to determine each subject's 6-RM loads for each of the exercises (ACSM 2009; Alcaraz et al. 2008).

Experimental trials of high-resistance circuit sessions (HRC)

Subjects started with a general warm-up, which involved sub-maximal cycling on a stationary bike for 5 min at 75 W while maintaining 75–100 rpm. This was followed by 5 min of active stretching of all major muscle groups. Subjects then performed a specific warm-up, which consisted of three sets of three exercises (bench press, deadlift, and elbow flexion), using the following sequence: ten repetitions at 50% of 6-RM, 1-min rest, eight repetitions at 75% of 6-RM, 2-min rest, and repetitions to failure with a 6-RM load. The 6-RM load was adjusted by ±2.5% if a subject performed ±1 repetitions or by ±5% if a subject performed ±2 repetitions (ACSM 2009). Afterwards, subjects rested for 3-min prior to starting the HRC session. During the last minute of the resting period, subjects were asked to put on the mask and start breathing in the hypoxic air.

In each HRC training session, there were two short circuits (blocks) of three sets, with three different exercises in each set. Resting periods were passive and lasted for 35 s between exercises (which was sufficient time to move safely from one exercise to the next), 3-min between sets within a block, and 5-min between blocks. Subjects lifted loads where only 6 repetitions could be performed (6-RM, ~85–90% of 1-RM). Block 1 was composed of three sets of bench press, deadlift and elbow flexion (preacher curl). Block 2 was comprised three sets of half-squat, triceps extension (French press), and ankle extension (calf raise). Block 1 always proceeded before Block 2 in each HRC training session (Fig. 1). To standardize the protocol, the eccentric phase of each exercise was performed over 3 s (controlled by digital metronome), whereas the concentric phase was performed at maximum velocity (Alcaraz et al. 2008, 2011). These single- and multi-joint exercises were chosen to work both major and minor muscle groups, which were based on ACSM (2009) recommendations. All sessions were supervised by an experienced lifter to ensure

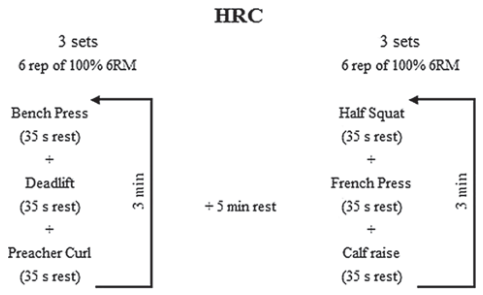

Fig. 1 High-resistance circuit training (HRC) protocol

that volitional fatigue was achieved safely and rest periods were strictly controlled. A linear position transducer (Chronojump, Barcelona, Spain) was attached to the bar and used to measure force and power during each set of the half-squat exercise. The half-squat exercise was chosen only to measure peak force and power, as it activates higher muscle mass than the other exercises and also provides the appropriate conditions to position the encoder for accurate measurement. The rating of perceived exertion (RPE; 6–20 scale) was also obtained immediately following each set.

Finally, finger prick blood extractions at rest and at the end of each block were performed on the right hand, while the subjects stood with their arms flexed. A capillary tube of 65 µl was used to collect the blood sample. The following parameters were analyzed to quantify blood gases, metabolites, electrolytes, and acid–base status (ABL 90 Flex, Radiometer, Westlake, USA.): pH, CO_2 partial pressure (pCO_2; mmHg), O_2 partial pressure (pO_2; mmHg), arterial oxygen saturation (SaO_2), bicarbonate (HCO_3; mmol/l), sodium (Na^+; mmol/l), potassium (K^+; mmol/l), calcium (Ca^{2+}; mg/dl), chloride (Cl; mmol/l), lactate (mmol/l), and glucose (Glu; mg/dl) concentrations.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS for Windows; v.20.0) was used for all statistical analyses. Descriptive statistics (mean ± standard deviation) were calculated. The assumption of normality and homoscedasticity was verified using the Shapiro–Wilks W-test prior to using the parametric tests. A two-way, repeated-measures analysis of variance (group x time) with Bonferroni post hoc analysis was used to investigate differences in variables. Statistical significance was set at $p \leq 0.05$.

Results

Figure 2 and Table 1 show that peak power in the first set of half-squat was lower in HH compared to NORM (−23%) and MH (−20%). Similarly, peak force was also reduced in HH compared to NORM and MH (both −20%). Moreover, lower mean force (−13%) and power (−5%) were observed in HH compared to NORM. In the second set of half-squat, peak power and peak force were also lower in HH compared to NORM (−23 and −20% respectively). No differences were observed between NORM and MH in the first two sets of half-squat, and no significant differences in peak force and power during the final set among the different conditions were observed (Fig. 2). No differences in mean force and power during the first and the final sets were observed among the different conditions. Regarding the subject´s perceived exertion, higher RPE values were observed in HH (Basal: 6.0 ± 0.0; end of block 1: 14.2 ± 3.1; end of block 2: 13.82 ± 2.5) compared to both NORM (Basal: 6.0 ± 0.0; end of block 1: 12.1 ± 1.8; end of block 2: 11.6 ± 1.2) and MH (Basal: 6.0 ± 0.0; end of block 1: 12.6 ± 2.0; end of block 2: 11.9 ± 1.9) in the last block ($p \leq 0.05$). No significant differences among the different conditions were observed in RPE at the end of the first block.

Table 2 shows the results of blood gases at the end of each block of HRC training in the three environmental conditions. There were no significant differences in basal values of pO_2 or in SaO_2. However, at the end of the first block, lower pO_2 and SaO_2 were observed in MH (pO_2: −9%; SaO_2: −4%) and HH (pO_2: −11%; SaO_2: −11%) compared to NORM. Similar statistical trends were also observed in the second block, with pO_2 and SaO_2 tending to be lower in HH compared to NORM ($p = 0.057$ and $p = 0.064$, respectively). Furthermore, reduced pCO_2 was shown in HH compared to NORM in the first (−8%) but not in the second block.

No differences in acid–base parameters were observed in basal conditions (Table 3). At the end of the first block, pH was similar among the different conditions, but higher blood lactate and reduced blood HCO_3^- were observed in HH compared to NORM (+37 and −15%, respectively) and MH (+32 and −14%, respectively). At the end of the second block, blood pH and HCO_3^- were lower in HH compared to NORM (−1 and 18%, respectively) and MH (−1 and −16%, respectively), whereas blood lactate was higher compared to NORM (+44%) and MH (+41%).

No differences in blood electrolytes and glucose concentration were shown under basal conditions. However, Na^+ concentration was higher in HH compared to NORM in the first (+1%) and second (+2%) blocks. Furthermore, Cl^- concentration was greater in HH and MH compared to NORM in the last block (+2 and +1%, respectively) (Table 4). No significant differences in Ca^{2+}, $K^{+,}$ and glucose concentrations were observed among the different conditions at the end of the first and second blocks (Table 4).

Discussion

To our knowledge, this is the first study that investigated the effects of moderate and high systemic hypoxia on physical performance, blood gases, acid–base balance, and blood electrolytes during a HRC training session. The main findings show that: (i) high ($FiO_2 = 0.13$) but not moderate ($FiO_2 = 0.16$) hypoxia decreased muscular performance in the early sets of a HRC training session; (ii) high hypoxia significantly reduced blood oxygenation in the first but not the second block of the HRC training session; (iii) high but

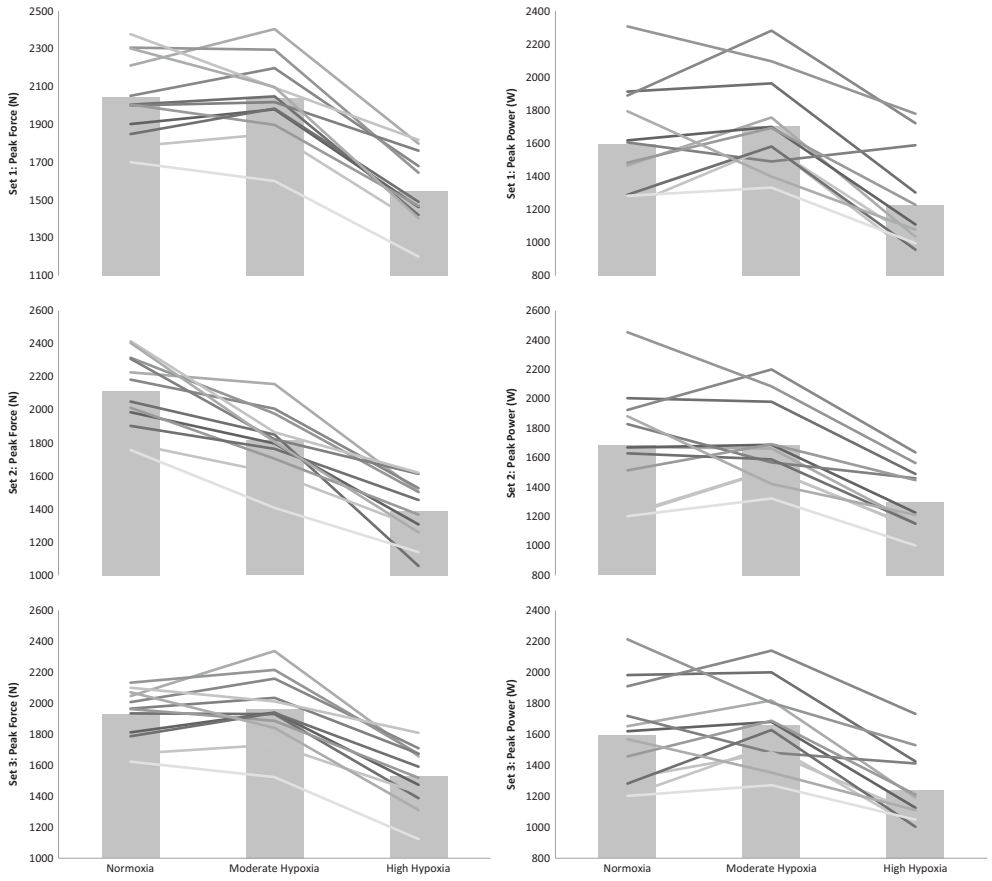

Fig. 2 Individual and mean of peak force and power during each set of half-squat

not moderate hypoxia markedly increased blood lactate and reduced blood HCO_3^- leading to reduced blood pH at the end of the HRC training session; and (iv) high hypoxia induced minor changes to blood electrolytes and blood glucose responses during a HRC training session.

Effect of hypoxia on the performance of a HRC training session

The previous studies have shown that acute exercise performed in hypoxia reduces anaerobic performance (Brosnan et al. 2000; Bowtell et al. 2014). However, other studies have reported no change in peak and mean power between varying conditions of oxygen availability in 5×5 repetitions at 80% 1RM, with 3 min of squat and deadlift (Scott et al. 2015a) and 5×14 repetitions at 50% 1RM with 1 min of rest in bench press and leg press (Kon et al. 2012). We observed a significant decrease in peak force and peak power during the first two sets of the half-squat sequence between HH and NORM conditions and a significant decrease in mean force and power during the second set between HH and NORM. This response is associated to exacerbated perturbations of cellular homeostasis in active muscles. Higher blood lactate concentrations, lower blood pH, and decreased oxygen availability (under HH) suggest increased reliance on glycolysis to maintain ATP supply, indicating a greater anaerobic energy release with acute hypoxia (Scott et al. 2015b). Therefore, when aerobic

Table 1 Mean and peak force and power during each set of half-squat of HRC training under three different conditions

	Peak force (N)			Peak power (w)		
	NORM	MH	HH	NORM	MH	HH
Set 1	2050.3 ± 396.4*	2040.2 ± 316.3$^{\$}$	1705.7 ± 669.8	1597.0 ± 561.2*	1544.7 ± 461.1$^{\$}$	1228.4 ± 603.6
Set 2	2114.0 ± 438.6*	1815.4 ± 682.8	1687.8 ± 845.3	1684.1 ± 561.5*	1387.1 ± 655.9	1298.4 ± 711.6
Set 3	1926.0 ± 713.2	1962.2 ± 717.3	1656.3 ± 882.4	1593.4 ± 680.6	1529.0 ± 629.4	1240.3 ± 726.5
	Mean force (N)			Mean power (w)		
	NORM	MH	HH	NORM	MH	HH
Set 1	1617.9 ± 338.2	1645.43 ± 347.6	1515.3 ± 561.5	751.5 ± 211.9	737.0 ± 220.3	728.0 ± 300.6
Set 2	1625.1 ± 272.0*	1537.4 ± 573.9	1425.6 ± 547.9	625.7 ± 325.2*	599.9 ± 266.6	596.1 ± 328.3
Set 3	1363.6 ± 554.7	1311.7 ± 667.4	1301.9 ± 700.6	721.3 ± 157.0	702.7 ± 266.5	642.1 ± 262.5

Mean ± Standard deviation; NORM = normoxia; MH = 0.16% FiO_2; HH = 0.13% FiO_2

*Significant differences between normoxia and high hypoxia, $^{\$}$Significant differences between moderate and high hypoxia, *$p < 0.05$

Table 2 Blood gases and arterial oxygen saturation (SaO_2) values of HRC training under three different conditions

	pCO_2 (mmHg)			pO_2 (mmHg)			SaO_2 (%)		
	NORM	MH	HH	NORM	MH	HH	NORM	MH	HH
Basal	39.6 ± 2.5	39.6 ± 2.4	39.1 ± 2.8	78.5 ± 7.9	76.6 ± 11.6	77.5 ± 10.4	98.1 ± 0.2	98.1 ± 0.3	98.2 ± 0.4
Block 1	40.5 ± 3.2**	39.6 ± 3.1	37.4 ± 2.7	75.5 ± 13.3**	68.4 ± 4.7††	67.0 ± 12.4	94.4 ± 2.9*	91.0 ± 2.4†††	84.1 ± 5.6$^{\$\$}$
Block 2	35.3 ± 2.8	34.5 ± 2.8	33.8 ± 4.2	74.2 ± 15.0	70.8 ± 18.7	69.8 ± 11.5	93.8 ± 3.3	92.7 ± 6.0	89.9 ± 6.5

Mean ± Standard deviation; NORM = normoxia; MH = 0.16% FiO_2; HH = 0.13% FiO_2; pCO_2 = carbon dioxide pressure; pO_2 = oxygen pressure

*Differences between normoxia and high hypoxia, †Differences between normoxia and moderate hypoxia, $^{\$}$Differences between moderate and high hypoxia, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; $^{\dagger\dagger}p < 0.01$; $^{\dagger\dagger\dagger}p < 0.001$; $^{\$\$}p < 0.01$

Table 3 Acid–base values of HRC training under three different conditions

	HCO_3 (mmol/l)			La (mmol/l)			pH		
	NORM	MH	HH	NORM	MH	HH	NORM	MH	HH
Basal	25.9 ± 1.2	26.0 ± 1.1	26.1 ± 1.3	2.3 ± 0.8	2.0 ± 0.7	2.3 ± 0.9	7.42 ± 0.01	7.41 ± 0.06	7.42 ± 0.02
Block 1	19.0 ± 2.9*	18.9 ± 2.2	16.2 ± 2.6$^{\$}$	8.7 ± 2.9*	9.0 ± 3.6	11.9 ± 2.1$^{\$}$	7.33 ± 0.05	7.33 ± 0.04	7.27 ± 0.05
Block 2	19.5 ± 3.5*	19.1 ± 2.7	16.0 ± 2.9$^{\$}$	8.6 ± 3.5*	8.8 ± 3.3	12.4 ± 2.6$^{\$}$	7.35 ± 0.06*	7.35 ± 0.05	7.28 ± 0.07$^{\$}$

Mean (standard deviation); NORM = normoxia; MH = 0.16% FiO_2; HH = 0.13% FiO_2; *La* lactate

*Differences between normoxia and high hypoxia, $^{\$}$Differences between moderate and high hypoxia, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

metabolism is not capable of meeting ATP demand, the breakdown of phosphocreatine and activation of anaerobic glycolysis can be further elevated to meet the short-term requirements for ATP (Calbet et al. 2003).

Furthermore, an increase in the rate of PCr hydrolysis rate can also occur during hypoxic conditions, resulting in an increase in Pi. Moreover, an increase in intracellular acidosis due to glycolytic pyruvate production results in elevated lactate, which, in turn, can contribute to muscular fatigue (Bowtell et al. 2014). Thus, during hypoxia, there is increased reliance on non-aerobic metabolism to compensate for the limitation in aerobic ATP production (Calbet et al. 2003). In addition, limited oxygen availability and brief rest intervals affect the muscle's ability to maintain the balance between ATP breakdown and ATP production, thereby limiting PCr recovery as well as cellular recovery after each exercise bout (Hogan et al. 1999). Furthermore, increased activities of cellular processes, such as ion pumps, try to achieve homeostasis during rest intervals require ATP, much of which is derived from aerobic glycolysis (Colliander et al. 1988). Thus, lower muscular performance during HH in the first two sets of half-squat exercises is likely due to an inadequate supply of ATP from aerobic and non-aerobic metabolism to meet the demand, as a consequence of limited O_2 availability, with ensuing accumulation of

Table 4 Electrolytes and glucose values of HRC training under three different conditions

	Ca^{2+} (mg/dl)			Na^{+} (mmol/l)		
	NORM	MH	HH	NORM	MH	HH
Basal	5.0 ± 0.2	5.1 ± 0.4	5.2 ± 0.4	142.3 ± 2.4	143.8 ± 2.8	144.0 ± 2.0
Block 1	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	145.5 ± 2.0**	146.5 ± 1.4	147.5 ± 1.4
Block 2	5.1 ± 0.2	5.1 ± 0.3	5.1 ± 0.3	144.5 ± 2.3*	146.2 ± 2.3	147.1 ± 1.5
	K^{+} (mmol/l)			Cl^{-} (mmol/l)		
	NORM	MH	HH	NORM	MH	HH
Basal	5.2 ± 0.8	4.9 ± 0.6	5.0 ± 0.9	108.6 ± 3.1	107.6 ± 2.3	108.1 ± 1.4
Block 1	5.3 ± 0.8	4.8 ± 0.7	4.9 ± 0.6	108.2 ± 2.2	109.9 ± 1.1	109.9 ± 2.7
Block 2	5.1 ± 0.6	5.2 ± 0.6	4.9 ± 0.4	107.7 ± 1.8*	109.3 ± 1.0†	109.6 ± 2.4

Glucose (mg/dl)

	NORM	MH	HH
Basal	106.6 ± 22.4	106.0 ± 14.1	103.4 ± 6.3
Block 1	99.7 ± 6.0	98.2 ± 7.1	100.1 ± 13.6
Block 2	102.2 ± 6.5	99.1 ± 6.3	107.4 ± 9.2

Mean ± Standard Deviation; NORM = normoxia; MH = 0.16% FiO_2; HH = 0.13% FiO_2

*Differences between normoxia and high hypoxia, †Differences between normoxia and moderate hypoxia, $*p < 0.05$

metabolic products and ionic imbalances that together impair muscle function.

For the third set, peak and mean power and force were not different among the different conditions, suggesting that during the last set, half-squat performance was not only dependent on O_2 availability but more affected by the accumulation of cellular metabolites (i.e. Pi or H^+). The imbalance in cellular electrolytes also limits performance under hypoxic conditions compared to normoxia. These results are in accordance with those obtained recently by Scott et al. (2016). They showed an increase in the concentration of metabolic products that promote higher levels of muscular fatigue, which induces the activation of additional motor units and leads to higher muscle activation during hypoxic resistance exercise. Thus, given that metabolic acidosis inhibits muscle contractility and subsequently promotes the recruitment of additional high-threshold motor units, these results suggest the presence of higher levels of lactate under hypoxic conditions of the current study.

As expected, RPE values were significantly higher at the end of the HH training session than in MH and NORM conditions, suggesting that the HH session was perceived as more difficult than MH and NORM. These results are in accordance with Alvarez-Herms et al. (2015b), who have shown significant differences in RPE score between high hypoxia ($FiO_2 = 13.5\%$) and normoxia during a series of six consecutive jumps (lasting 15 s with rest periods of 3 min). In contrast, Scott et al. (2015a) showed no significant differences in RPE scores during a high-intensity resistance training session (5 set of 5 repetitions at 80% of 1RM with 3-min rest between sets) using the same hypoxic levels as our study. These conflicting results can be explained by the different types of training (traditional vs. high circuit training) and the slight differences in intensity level (80 vs. 85% 1RM). Nevertheless, perceived exertion is a useful variable to confirm the intensity level of the training protocol, as demonstrated by this study.

Effect of hypoxia on blood oxygenation during an HRC training session

Oxygenation levels (pO_2) was higher in NORM compared to MH and HH at the end of the first block. The previous studies are in accordance with our findings showing increased muscle deoxygenation in hypoxic conditions during maximal contractions (Richardson et al. 2006). This observation is in line with the known effect of hypoxia on the acute ventilatory, cardiac, and vascular responses to exercise, all of which contribute to maintain adequate O_2 supply to tissues despite progressive pO_2 reduction (Cerretelli and Samaja 2003). Nevertheless, the lower pO_2 observed in the exercising muscle cells in hypoxia likely acts as a potent signal to trigger specific muscle responses to training (Bowtell et al. 2014). Interestingly, a significant decline in SaO_2 values was observed, which was related to the increased hypoxia level at the end of the first block. Larger decreases in SaO_2 during hypoxia are associated with greater anaerobic energy production (Alvarez-Herms et al. 2015b; Calbet et al. 2003). The previous studies have showed similar findings after anaerobic exercise under hypoxia (Scott et al. 2015a; Alvarez-Herms et al. 2015b). However, in our study, no significant differences in pO_2, pCO_2, and SaO_2 were observed in the second block. This is in agreement with a recent study by Scott et al., (2016), who obtained lower levels of SaO_2 in hypoxia than in normoxia but no difference in muscle oxygenation status between conditions during moderate-load resistance training (3 sets of 10 repetitions at 60% of 1RM; $FiO_2 = 16\%$). According to these authors, these findings can be explained by the type of resistance exercise applied during the training session and the level of hypoxia employed (Scott et al. 2016). Further research to elucidate this point is needed.

Effect of hypoxia on blood acid–base balance during a HRC training session

The previous studies showed no significant differences in lactate values during an explosive strength session (Alvarez-Herms et al. 2015b) under normoxia or hypoxia or after 30–40 s of supramaximal exercise (McLellan et al. 1990). In contrast, our study showed significantly higher blood lactate concentrations at the end of the two blocks with HH compared to MH and NORM. Our results agree with those shown by Calbet et al. (2003) in cyclists using an anaerobic test. A reduction in oxygen availability can explain the higher lactate levels observed during intense exercise and reflect a greater contribution of anaerobic glycolysis to supply ATP (Calbet et al. 2003).

In addition, acid–base balance is an important limiting factor in physical exercise because of its mechanistic role in regulating energy metabolism and ion homeostasis (Juel 2008). During intense muscle activity, an increase in cellular production of lactate and H^+ greatly contributes to acidosis (Juel 2008). The removal of $H^+$and lactate via monocarboxylate cotransporters (Juel 1998), as well as the presence of carbonic anhydrase which affects the rate of H^+ and HCO_3^- transport (Zoll et al. 2006), works together to help regulate pH in the muscle. Previously, Buchheit et al. (2012) indicated that acute high-intensity interval training under hypoxia (2400 m of simulated altitude) modifies skeletal muscle acid–base balance response via increases in H^+ fluxes from the muscle to the blood, resulting in a decrease in blood pH and HCO_3^-. Similarly, we found that blood pH was lower in HH compared to NORM and MH (−1% in both cases) at the end of the second block. Moreover, blood HCO_3^- was reduced in HH compared to

NORM and MH at the end of the first and second blocks (−14 to −18%), indicating that an HRC training session under hypoxic conditions produces a higher muscle buffering response to reduce the pH fluctuations and to maintain blood pH near the physiological level (Juel 2008).

Effect of hypoxia on the blood electrolytes response to an HRC training session

Intense exercise increases lactic acid and H^+ concentrations and induces pronounced perturbations in Na^+, K^+, and Cl^- (Sejersted and Sjogaard 2000). These electrolyte changes are linked with fatigue and contribute to the decrease in muscle force and performance (McKenna et al. 2008). Similarly, intense fatiguing contractions have been shown to induce cellular K^+ efflux and Na^+ and Cl^- influx, causing pronounced perturbations in interstitial K^+ and Na^+ concentrations (McKenna et al. 2008). Furthermore, Na^+ and Cl^- ions can affect muscle function and fatigue and can also modulate muscle H^+ via the strong differences in plasma ion (Cairns et al. 2004). In addition, it has been reported that a net Cl influx (from plasma to muscle) occurs during intense large muscle mass exercise, indicating that Cl^- ions are taken up by the muscle (Mckenna et al. 1997). In addition, HCO^-/Cl^- exchange across the erythrocyte (RBC) membrane (chloride shift) transport plays a key role in maintaining electrical balance across the red cell membrane and producing a buffering response of RBC to maintain the pH near the physiological level (Böning et al. 2007). These chloride responses could explain the significantly higher blood Cl^- concentration observed in this study in HH and MH compared to NORM in the last block. Therefore, our results show that Cl^- ions were altered with acute strength training under hypoxia.

Moreover, we observed that blood Na^+ concentration significantly increased in HH compared to NORM at the end of each block. This small elevation in plasma Na^+ has been observed with exercise (Street et al. 2005), which suggests a higher Na^+ release by the contracting muscle causing an increase in plasma Na^+ concentration (Sostaric et al. 2006) under high hypoxic conditions. Thus, higher blood electrolyte concentrations (Cl^- in HH and MH vs. NORM and Na^+ in HH vs. NORM) likely contribute to higher fatigue under hypoxic environment. Although the development of severe fatigue is multifactorial, ionic interactions appear to play an important role in the physiological and performance responses to intense exercise (e.g., HRC training session) (Cairns et al. 2004).

Practical application

This research contributes to the understanding of the acute physiological response of HRC training session under different levels of hypoxia. It provides evidence for its potential applicability to sports that use resistance strength training in their training programs. HRC training sessions performed in hypoxia do not produce the similar acute responses as the same training session performed under normoxic conditions.

These differences must be taken into account when designing and optimizing the training load for short-term adaptations. Therefore, coaches must be careful when designing resistance training sessions under high hypoxic conditions, as it is more stressful than moderate hypoxia or normoxia and can affect the training stimuli or the goal of the training session. The subjects of this study were well-trained athletes, experienced in resistance training. Thus, the findings of this study are more applicable to resistance-trained athletes who aim to enhance strength performance than to other populations who remained to be tested. Nevertheless, due to the high response of glycolysis to HH training, the results of this study apply to other athletes such as team sports players, sprinters, or endurance athletes who may want to optimize their strength training sessions using shorter duration.

Conclusions

The results of this study showed that HRC performed in high, but not moderate hypoxia decreased muscular performance and increased the rating of perceived exertion. HRC under high hypoxic conditions also reduced blood oxygenation, increased blood lactate, and reduced blood HCO_3^- and pH. In addition, high hypoxia induced minor changes to blood electrolyte and blood glucose responses to an HRC training session. Further research is needed to examine neural and endocrine responses, as well as the morphological and strength adaptations to HRC under hypoxic conditions. In addition, more work is needed to clarify if this training method can promote hypertrophic, metabolic, and strength gains.

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VII – ESTUDIO V: Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability.

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ORIGINAL ARTICLE

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Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability

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Abstract

Recent acute studies have shown that high-intensity resistance circuit-based (HRC) training in hypoxia increases metabolic stress. However, no intervention studies have yet proven their effectiveness. This study aimed to analyze the effect of 8 weeks of HRC in hypoxia on aerobic performance, resting energy expenditure (REE), repeat sprint ability (RSA) and hematological variables. Twenty-eight subjects were assigned to hypoxia (FiO_2 = 15%; HRC_{hyp}: n = 15; age: 24.6 ± 6.8 years; height: 177.4 ± 5.9 cm; weight: 74.9 ± 11.5 kg) and normoxia (FiO_2 = 20.9%; HRC_{norm}: n = 13; age: 23.2 ± 5.2 years; height: 173.4 ± 6.2 cm; weight: 69.4 ± 7.4 kg) groups. Each training session consisted of two blocks of three exercises (Block 1: bench press, leg extension, front pull down; 2: deadlift, elbow flexion, ankle extension). Each exercise was performed at 6 repetitions maximum. Participants exercised twice weekly for 8 weeks and before and after the training program blood test, REE, RSA and treadmill running test were performed. Fatigue index in the RSA test was significantly decreased in the HRC_{hyp} (−0.9%; $P < .01$; ES = 2.75) but not in the HRC_{norm}. No changes were observed in REE and hematological variables. Absolute (4.5%; $P = .014$; ES = 0.42) and relative (5.2%; $P = .008$; ES = 0.43) maximal oxygen uptake (VO_2max), speed at VO_2max (4%; $P = .010$; ES = 0.25) and time to exhaustion (4.1%; $P = .012$; ES = 0.26) were significantly increased in HRC_{hyp} but not in the HRC_{norm}. No significant differences between groups were found. Compared with normoxic conditions, 8 weeks of HRC training under hypoxic conditions efficiently improves aerobic performance and RSA without changes in REE and red blood O_2-carrying capacity.

KEYWORDS
hypoxic training, resistance training, VO_2max

1 | INTRODUCTION

Sport performance is determined by the proper development of aerobic/anaerobic metabolism,[1,2] strength,[3,4] power,[5,6] speed and agility.[7,8] Failure or success is largely associated with an optimal training plan applied to optimize these abilities, which are often trained simultaneously (ie concurrent training). The most traditional concurrent training method is resistance circuit-based training (RCT) which comprises single or several sets of different exercises completed in succession, performed at low (40%-60% 1-RM) or high loads (>60% 1-RM) and with a high (12-15) or lower (<12) number of repetitions and with little rest between exercise. Thus, a recent meta-analysis has shown that RCT is an effective

training method for the concurrent development of maximum oxygen consumption (VO_2max) and strength performance in healthy adults.[9]

On the other hand, traditional aerobic training in hypoxia has garnered much attention. This method has shown improvements in oxygen transport capacity by enhancing erythropoietin secretion and haemoglobin mass and enhancing VO_2max,[10] anaerobic threshold[11,12] and exercise performance.[10] Recently, there is growing interests in performing RCT in hypoxia as another method that could improve aerobic performance with shorter volume and duration of the session, in addition to the associated gains in strength, power, and muscle mass.[9] Previous acute studies applying circuit-based training in hypoxia have reported beneficial responses in anaerobic metabolism and metabolic stress[13,14] and an increase in anaerobic performance.[15] However, to the best of our knowledge, there are no studies which analyze the effect of this type of training on aerobic performance.

Another benefit associated with exercise in hypoxia is improvement in the repeated-sprint performance. For instance, repeated-sprint training in hypoxia is more efficient than repeated-sprint training in normoxia to significantly improve mean repeated-sprint performance and may produce an additional positive effect on repeated sprint and VO_2max.[16] Despite the fact that resistance training[17] enhances RSA performance, no studies have analyzed the effect of concurrent training in hypoxia on RSA performance.

Moreover, resting energy expenditure increases after resistance[18] and high-intensity resistance circuit-based (HRC) training programs.[19] Also, HRC in hypoxia increases energy consumption after a training session.[14] This fact can be attributed to higher phosphocreatine turnover, replacement of O_2 in circulation and in the muscle, elevated ventilatory rate, elevated cardiac activity, oxidation of lactate, glycogen resynthesis, and sodium-potassium pump activity.[20] However, resting energy expenditure findings after hypoxic treatments are conflicting. While some studies indicate that hypoxia decreases resting energy expenditure,[21] others show an increment[22] or no change in this parameter[23] after chronic exposure to simulated hypoxia. However, the effect of a short-term resistance training program in hypoxia on resting energy expenditure has remained unexamined.

Therefore, the aim of this work was to analyze the effect of 8 weeks of HRC training in hypoxia and normoxia on aerobic performance, resting energy expenditure, repeat sprint ability and hematological variables. Our hypothesis was that HRC training in hypoxia would exacerbate increases in aerobic performance through VO_2max enhancement. We additionally hypothesized that the addition of hypoxia to the training program would increase resting energy expenditure and repeat sprint ability but red blood O_2-carrying capacity would remain unchanged.

2 | METHODS

2.1 | Design

To test the effects of 8 weeks of an HRC training in normoxia and hypoxia on aerobic performance, resting energy expenditure, repeat sprint ability and hematological variables, a single-blinded randomized controlled trial with pre- and post-test was developed. Participants were allocated in randomized order to two experimental groups: a) performing 8 weeks of HRC in normobaric hypoxia (HRC_{hyp}; $FiO_2 = 15\%$), and b) performing the same training in normoxic condition (HRC_{norm}; $FiO_2 = 20.9\%$). The sessions of the hypoxic group were performed in a normobaric chamber (CAT 430, Colorado Altitude training, USA) using a generator (CAT-12, Colorado Altitude Training, USA).

2.2 | Participants

Twenty-eight healthy, non-smoking, male subjects participated in this study. Participants had at least 4 years of resistance training experience and exercised three times per week. None of the subjects had any musculoskeletal disorder or reported exposure to altitude for 3 months prior to the study. Also, all participants were living at sea-level during the study. Before the testing sessions, participants were randomized into HRC_{hyp} ($n = 15$; age: 24.6 ± 6.8 years; height: 177.4 ± 5.9 cm; weight: 74.9 ± 11.5 kg) or HRC_{norm} ($n = 13$; age: 23.2 ± 5.2 years; height: 173.4 ± 6.2 cm; weight: 69.4 ± 7.4 kg). In the first visit to the lab, all experimental procedures were explained to the participants and written informed consent was obtained from each subject. The present research was approved by the Institutional Science Ethics Committee. Figure S1 shows the flow diagram of the research according to CONSORT guidelines.

2.3 | Testing protocol

The testing protocol was divided into three visits to the laboratory. During the first visit, all participants visited the laboratory to familiarize themselves with testing and training procedures the week prior to starting the training sessions. Three days later, participants performed the first testing session, which included the following tests in order: resting energy expenditure, blood test and RSA.

The following day, after 24 hours of rest, during the second visit, the aerobic test was performed. The same testing procedure was applied during the week after the training program was completed. Figure 1 shows the testing procedure and study design.

2.3.1 | Resting energy expenditure (REE)

During the first visit, participants came to the laboratory in a fasted state to start the testing protocol. REE was measured with indirect calorimetry (Metalyzer 3B; Cortex-medical, Leipzig, Germany) using the same procedures as in a previous study.[24] The test was performed between 8 AM and 10 AM. The room was dimly lit and quiet, and the ambient temperature was at approximately 22°C. The participants laid in a supine position wearing light clothing for 15 minutes. Data were then collected for 30 minutes, and only the last 20 minutes were used to calculate substrate-based utilization of energy (carbohydrates and lipids). The system was calibrated before each measurement using calibration syringes and precision oxygen and carbon dioxide gas mixtures. Subjects were requested to abstain from caffeine or alcohol consumption for 24 hours prior to the measurement.

2.3.2 | Blood test

Before the REE test, blood extraction was performed while the subject was seated. A portion of each blood sample (3 mL) was introduced into a tube with EDTA to determine haemoglobin concentration and hematocrit and erythrocytes counts using a hematology analyzer (Sysmex XS-1000i, Kobe, Kansai, Japan).

2.3.3 | Repeat sprint ability test (RSA)

Two hours after participants had a standardized breakfast, the RSA test was performed. The RSA test consisted of 10 × 30 m sprints with a 180º turn at the 15 m mark separated by 30 seconds of passive recovery.[25] The athlete started 0.5 m behind the start line, which was marked by a photocell (Witty, Microgate, Italy). Before starting, the athletes were instructed to run as fast as possible to the end of the 30 m course. Before testing, a warm-up consisting of 5 minutes of running at 10 km/h followed by active stretching and three submaximal sprints was performed. Following each sprint, athletes decelerated and walked to the starting line ready for the subsequent sprint. The best and mean sprint time were recorded as the performance indices. The fatigue index was calculated according to the following equation proposed by Spencer et al[26] where RSA_{total} is the total time of the 10 sprints and RSA_{best} is the best sprint time.

$$\text{Fatigue Index} = \left(\left(\frac{RSA_{total}}{RSA_{best} \times 10}\right) \times 100\right) - 100$$

Capillary blood samples (5 μL) for blood lactate concentration ([La-]) analysis were collected from a finger prick 5 minutes after the end of the RSA test and analyzed using a Lactate Pro analyzer (Lactate Pro, Arkay, Inc, Kyoto, Japan).

2.3.4 | Treadmill running test

Finally, during the last testing visit to the lab, participants completed an incremental test to exhaustion on a treadmill (Run Med Technogym, Cessena, Italy) in standard environmental conditions, with the grade set at 1%. The tests were performed between 10 AM and 12 PM in the laboratory with room temperature kept between 20 and 22°C. The subjects were instructed not to ingest caffeine for four hours before the test, to ingest a light meal two hours before and to avoid intense physical efforts the day before. Participants started running at 8 km/h for 5 minutes. Subsequently, the work rate was increased by 1 km/h every minute in a progressive manner until exhaustion to obtain the value of maximum oxygen consumption (VO_2 max). The corresponding heart rate was also determined by a Polar RS800CX heart rate monitor (Polar Electro, Kempele, Finland). Verbal encouragement was given to ensure maximum physical effort. The test was concluded according to traditional physiological criteria[27]: (i) occurrence of a plateau despite an increase in speed; (ii) elevated blood lactate concentration (≥8 mmol/L); (iii) elevated respiratory exchange ratio ($r \geq 1.0$); (iv) elevated heart rate (≥90% of [220-age]); and (v) maximal perceived

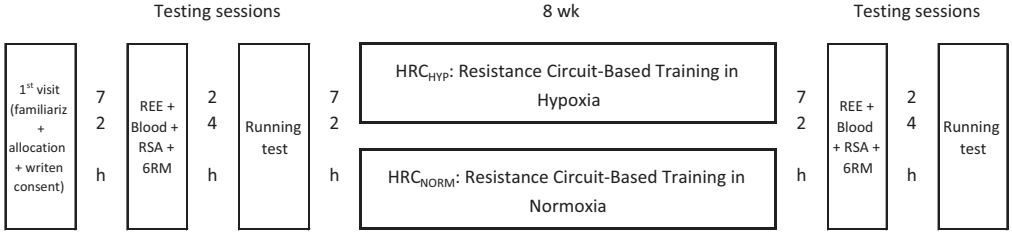

FIGURE 1 Research design. Familiariz, familiarization session; REE, resting energy expenditure; RSA, repeat sprint ability; HRC_{hyp}, hypoxic group; HRC_{norm}, normoxia group

exertion. Inflection points over time were used to determine thresholds of the ventilatory equivalent (VE) of carbon dioxide (VE/VCO_2), the ventilatory equivalent of oxygen (VE/VO_2), and the VE. The second increase in VE with a concomitant rapid increase in VE/VO_2 and VE/VCO_2 was defined as VT2.[28]

2.4 | Training program procedure

The training session protocol was based on a HRC training[13,14] and it consisted of two short circuits (blocks) completed with 35 seconds of rest between exercises (which allowed enough time to move safely from one exercise to the next), 3 minutes rest between each series of 3 exercises within a block, and 5 minutes rest between blocks. Each set was performed 3 times. The first block consisted of bench press, leg extension, and front pull down exercises whilst the second block consisted of deadlift, elbow flexion (preacher curl), and ankle extension (calf raise). A general warm-up in normoxia that involved 5 minutes of sub-maximal running at 8.5 km/h was followed by 5 minutes of active stretching of all major muscle groups before the workout. Also, a specific warm-up consisting of 3 sets of the exercises of the first block was completed using the following sequence: 10 repetitions at 50% of 6 repetitions maximum (6RM) for each exercise, 1 minute rest, 8 repetitions at 75% of 6RM, 2 minutes rest, and repetitions to failure with the 6RM load. In this way, it was possible to ensure that subjects lifted loads that allowed only 6 repetitions (~85%-90% of 1RM) to be performed and, if necessary, the training load was adjusted by approximately ±2.5% if a subject performed ±1 repetitions and by approximately ±5% if a subject completed ±2 repetitions. Specific warm-up and the main part of the training session were performed in hypoxia or in normoxia. Subjects were supervised by an experienced lifter to ensure that volitional fatigue was achieved safely and rest periods were strictly controlled. Table 1 shows the training program performed over the course of 8 weeks. Two training sessions per week were performed for each participant. There were more than 48 hours between each training session. The session duration lasted for 60 minutes, and the participants were exposed to hypoxia for a total time of approximately 16 hours during the entire training program.

Previously, during the first testing session and two hours after the RSA test, the 6RM loads were determined according to standard procedures[14] for all the exercises included in the training program because the training protocol would be performed with such loads. Before testing, a warm-up consisting of 5 minutes of cycling at 75 w followed by active stretching and 10 repetitions at 50% of the perceived 1RM for each exercise was performed. Bench press, leg extension, front pull down, deadlift, elbow flexion (preacher curl), and ankle extension (calf raise) 6RM loads were assessed.

2.5 | Statistical analysis

Data collection, treatment and analysis were performed using SPSS for Windows statistical package (v.20.0). Descriptive statistics (mean and standard deviation) were calculated. Before using parametric tests, the assumption of normality and homoscedasticity was verified using the Shapiro-Wilks W-Test. A two-way analysis of variance with repeated measures and Bonferroni post hoc was used to investigate differences in variables. The effect size (ES) of the intervention was calculated using Cohen's guidelines. Threshold values for ES were >0.2 (small), >0.6 (moderate),>1.2 (large) and >2.0 (very large).[29] For all procedures, a level of $P \leq .05$ was selected to indicate statistical significance.

3 | RESULTS

Table 2 shows the RSA test before and at the end of the training program in both groups. There were no significant differences in HRC_{norm} between pre- and post-training values. Also, no significant differences were observed between groups before and after the training program. However, after training, a lower fatigue index was observed in HRC_{hyp} (−0.9%; $F = 8.3$; $P < .01$; ES = 2.75) compared to pre-training values but no changes were shown in blood lactate or in any other RSA variables measured.

The results of the effects on hematological variables (Table 3) before and after hypoxia resistance training showed no significant differences in any variable or between groups. Also, Table 4 shows no significant changes in REE between groups or before and after the training program.

For the running aerobic test (Table 5), there were significant improvements in HRC_{hyp} before training in absolute (4.5%; $F = 7.2$; $P = .014$; ES = 0.42) and relative (5.2%; $F = 8.6$; $P = .008$; ES = 0.43) VO_2max, in the speed of VO_2max (4%; F = 8.0; $P = .010$; ES = 0.25) and in the time to exhaustion (4.1%; $F = 7.6$; $P = .012$; ES = 0.26). No changes were observed in HRC_{norm} for any variable. Moreover, there were no significant differences between groups after or before the training program.

4 | DISCUSSION

To our knowledge, this is the first study that investigated the effects of 8 weeks of HRC training in hypoxia (15% FiO_2) and normoxia on aerobic performance, REE, RSA, and hematological variables. The main findings show that: (i) hypoxia but not normoxia HRC training improved fatigue index in RSA test; (ii) HRC_{hyp} training increased aerobic performance and maximum oxygen uptake; (iii) No changes in REE and blood O_2-carrying capacity were observed after

TABLE 1 Training program performed during the study

Week	1	2	3	4	5	6	7	8
Set	2	3	3	2	3	3	4	2
Repetitions	6	6	6	6	6	6	6	6
% 6RM	90	95	100	100	100	100	100	100

RM, repetition-maximum.

hypoxia and normoxia HRC training. Therefore, these results demonstrate that HRC under systemic hypoxia promotes adaptations that are more commonly associated with endurance exercise training in skeletal muscle in recreationally endurance and strength-trained participants.

4.1 | Effect of HRC training in hypoxia on RSA

Previous studies showed that strength training can improve fatigue index (21%-23%) in RSA.[30,31] This affirmation is in accordance with the results obtained in our study and this improvement is likely to be accounted for, at least in part, by strength gains,[16] although this study did not measure strength variables and more research is warranted to check this hypothesis. However, other factors may also be involved because previous resistance training that includes a high metabolic stress may best improve RSA performance, possibly via greater improvements in H^+ regulation.[30] In this way, HRC training in hypoxia induces higher metabolic stress than normoxia training[13,14] and this response can justify the improvement in fatigue index after the training program performed in this study. Also, other factors can affect RSA performance and specifically recover between sprints including the increase in aerobic fitness (VO_2max) which is directly related to the rate of phosphocreatine resynthesis.[16] Our results showed an improvement in VO_2max in the hypoxia group, therefore, it is possible that this increase in aerobic fitness can be related to the improvement in fatigue index by a greater rate of PC resynthesis during recovery intervals. Thus, according to our results, the training program proposed in the present study seems to be an effective method to decrease fatigue index and it can be used in team sports and other exercises where RSA is a key factor in sport performance.

4.2 | Effect of HRC training in hypoxia on REE

No differences in REE were observed after the HRC training in hypoxia and normoxia, which is in line with previous reports showing unaltered REE after hypoxic exposures.[23] However, this fact contrasted with our hypothesis and previous studies[22,32] showing increased REE after hypoxia exposures due to hypoxia inducing beta-sympathetic activation.[33] Also, another study demonstrated decreased REE[21] after hypobaric hypoxia exposures. On the other hand, resting energy expenditure increased after resistance[18] and high intensity circuit training programs[19,34] due to the increase in the β-adrenergic system and changes in hormonal variations.[35] Our data are not in accordance with these previous studies and these discrepancies can be related to different experimental settings, environmental factors, and different intensities in the training program.[23] Therefore, HRC training in hypoxia does not provoke a beneficial effect on REE.

TABLE 2 Repeat sprint ability results before and after training in both training groups

	Pre-training		Post-training				95% confidence interval for difference		
	Mean	SD	Mean	SD	ES	*P*	Mean difference	Lower bound	Upper bound
Hypoxia group									
Mean sprint (s)	6.5	0.5	6.4	0.4	0.12	.233	−0.1	−0.2	0
Best sprint (s)	6.2	0.4	6.2	0.4	0.07	.573	0	0.1	−0.1
Fatigue index	4.7	0.5	3.2	0.3	2.75	.008**	−1.4	−2.4	0.4
Lactate (mMol/L)	15.1	3.3	13.6	2.6	0.45	.211	−1.6	−4	0.9
Normoxia group									
Mean sprint (s)	6.4	0.5	6.3	0.4	0.16	.136	−0.1	−0.2	0
Best sprint (s)	6.1	0.4	6.1	0.4	0.04	.744	0	−0.1	0.1
Fatigue index	4.3	0.5	3.4	0.3	1.74	.08	−0.9	−1.9	0.1
Lactate (mMol/L)	14.9	5.4	14.1	3.9	0.14	.504	−0.8	−3.3	1.7

Mean ± (SD).
ES, Effect size.
**Significant difference from pre- to post-training ($P < .01$).

TABLE 3 Resting energy expenditure results before and after training in both training groups

	Pre-training		Post-training				95% confidence interval for difference		
	Mean	SD	Mean	SD	ES	*P*	Mean difference	Lower bound	Upper bound
Hypoxia group									
Kcal/min	1.5	0.2	1.5	0.3	0.18	.605	0	−0.2	0.1
Carbohydrate (%)	54.0	21.4	60.3	13.4	0.27	.237	6.3	−16.9	4.4
Fat (%)	46.0	21.4	39.7	13.4	0.27	.237	−6.3	−4.4	16.9
Normoxia group									
Kcal/min	1.5	0.3	1.4	0.16	0.17	.478	−0.1	−0.2	0.1
Carbohydrate (%)	64.9	19.4	64.3	18.6	0.03	.902	−0.6	−10.8	9.6
Fat (%)	35.1	19.4	35.7	18.4	0.03	.902	0.6	−9.6	10.8

Mean ± (SD).
ES, effect size.

4.3 | Effect of HRC training in hypoxia on hematological variables

The results of hematological parameters obtained in this study are in accordance with Kon et al[36] after 8 weeks of resistance training under hypoxia. In both cases, erythropoietic variables remained unchanged. The main reason for these results is related to a quite low hypoxic dose performed in the study (~2 hours per week for 8 weeks), which did not stimulate the erythropoietic pathway enough.[37] Thus, the efficacy of this program may rely on specific skeletal muscle tissue adaptations mediated by an oxygen-sensing pathway.[16]

4.4 | Effect of HRC training in hypoxia on aerobic performance

To our knowledge, this is the first study that has demonstrated a significant HRC training-induced increase in VO_2max in the hypoxia group. Improvements in VO_2max are influenced by increases in maximal stroke volume and maximal cardiac output and other peripheral factors like increases in capillarization, activities of metabolic enzymes and improvement in muscle buffering.[38] Similarly, Haennel et al[39] concluded that the main responses of the cardiovascular system to resistance circuit training included a significant increase in VO_2max, together with a maximal stroke volume and maximal cardiac output. Recently, a meta-analysis showed that RCT improves relative VO_2max (~9%); however, our results showed VO_2max values in normoxia group remained unchanged. Thus, the improvements in VO_2max in the hypoxia group may not be due to circuit training but to hypoxia exposure adaptations. Thus, strength training under systemic hypoxia induces greater increase in plasma vascular endothelial growth factor (VEGF) concentration and capillary-to-fibre ratio, showing an increase in skeletal muscle angiogenesis and in muscular endurance after 8 weeks of resistance training in hypoxia ($FiO_2 = 14.4\%$).[36] Moreover, the same conclusions

TABLE 4 Hematological results before and after training in both training groups

	Pre-training		Post-training				95% confidence interval for difference		
	Mean	SD	Mean	SD	ES	*P*	Mean difference	Lower bound	Upper bound
Hypoxia group									
Hematocrit (%)	43.1	2.5	43.5	2.0	0.14	.490	0.4	1.4	−0.5
Hemoglobin (g/dL)	14.9	0.7	14.9	0.7	0.04	.878	0	−0.4	0.4
Red cells ($x10^6$/mmc)	5.0	0.3	5.1	0.3	0.14	.479	0.1	−0.1	0.2
Normoxia group									
Hematocrit (%)	43.9	2.6	44.3	2.7	0.13	.527	0.4	1.46	−0.5
Hemoglobin (g/dL)	15.3	0.8	15.3	0.9	0.10	.661	0	−0.3	0.5
Red cells ($x10^6$/mmc)	5.1	0.3	5.1	0.3	0.19	.442	0	−0.1	0.2

Mean ± (SD).
ES, effect size.

TABLE 5 Running test results before and after training in both training groups

	Pre-training		Post-training				95% confidence interval for difference		
	Mean	SD	Mean	SD	ES	*P*	Mean difference	Lower bound	Upper bound
Hypoxia group									
HRVT2 (bpm)	176.8	3.9	177.7	2.6	0.22	.737	0.9	−4.7	6.5
vVT2 (km/h)	13.4	2.5	13.3	2.6	0.05	.681	−0.1	−0.9	0.6
VO_2 at VT2 (L/min)	3.3	0.6	3.5	0.5	0.22	.055	0.2	0	0.3
VO_2 at VT2 (mL/kg/min)	45.5	8.2	47.6	6.3	0.24	.058	2.1	−0.1	4.3
% VO_2max at VT2	87.1	11.3	88.6	6.5	0.13	.419	1.5	−2.4	5.5
HRVO_2max (bpm)	188.8	7.4	189.3	6.0	0.07	.726	0.5	−2.8	4.0
vVO_2max (km/h)	15.6	2.4	16.2	1.9	0.25	.010**	0.6	−0.2	−1.1
VO_2max (L/min)	3.7	0.4	3.9	0.4	0.42	.014*	0.2	0	−0.3
VO_2max (mL/kg/min)	50.9	5.9	53.6	5.6	0.43	.008**	2.7	−0.8	−4.6
Time to exhaustion (s)	942.0	143.2	980.7	116.7	0.26	.012*	38.7	−9.6	−67.5
Normoxia group									
HRVT2 (bpm)	183.1	3.9	185.4	2.6	0.55	.404	2.3	−7.8	3.3
vVT2 (km/h)	13.9	1.9	14.0	1.6	0.04	.817	0.1	−0.7	0.8
VO_2 at VT2 (L/min)	3.4	0.3	3.5	0.2	0.23	.219	0.1	−0.1	0.2
VO_2 at VT2 (mL/kg/min)	49.3	4.7	50.2	4.0	0.18	.392	0.9	−1.3	3.1
% VO_2max at VT2	89.3	5.5	91.0	3.7	0.30	.367	1.7	−2.2	5.6
HRVO_2max (bpm)	197.8	8.7	197.3	7.4	0.06	.754	−0.5	−4.1	3.0
vVO_2max (km/h)	16.9	1.2	16.7	1.3	0.14	.441	−0.2	−0.7	0.3
VO_2max (L/min)	3.8	0.3	3.9	0.3	0.09	.589	0.1	−0.1	0.2
VO_2max (mL/kg/min)	55.7	5.0	56.3	4.9	0.10	.571	0.7	−1.4	2.5
Time to exhaustion (s)	1008.0	56.4	1005.3	77.4	0.05	.854	−2.7	−33.1	27.7

Mean ± (SD).

ES, effect size; RE, running economy; VT2, second ventilatory threshold; VO_2max, maximum oxygen consumption; VO_2, oxygen consumption; HR, heart rate; v, speed.

*Significant difference from pre- to post-training ($P < .05$).

**$P < .01$.

have been obtained in endurance training under hypoxia programs.[40] Moreover, exercising in hypoxia may increase the relative contribution of peripheral factors (ie, muscle perfusion, peripheral diffusion, and mitochondrial capacity) to O_2 delivery and utilization.[12] Conversely, as we reported above, blood O_2-carrying capacity was similar in both groups, before vs after training. These results suggest that O_2 delivery capacity may represent a cause of the VO_2 max improvement in the HRC_{hyp} after training. Therefore, it is possible that the increase in VO_2max following HRC training in hypoxia was influenced by changes in capillarization; however, VEGF and capillary variables were not measured in our study. These variables should be analyzed in future studies. Thus, novel training methods could be a good training for coaches in order to improve aerobic performance.

A major finding of the present study is that time to exhaustion is specifically improved after hypoxic training (+4.1%) but unchanged after normoxic training. Also, another important result of this study is the running speed improvements at VO_2max in the HRC_{hyp}. Moreover, VO_2max and vVO_2max improved concomitantly with time to exhaustion in the HRC_{hyp}, in accordance with previous studies.[12] These findings suggest that a hypoxic training effect was present in the HRC_{hyp} over the 8-week period, through an additional effect of hypoxic vs normoxic training on aerobic power. Our results are in agreement with previous observations that used endurance training under hypoxia[12] showing a significant increase in these variables. One possible reason to explain our results are that changes in O_2 fluxes (ie, VO_2max) and/or running velocities (ie, vVO_2max) can be related to time to exhaustion improvement that we found and as previously reported by Dufour et al.[12]

The results of this study contribute to the understanding of the effects of HRC training in hypoxia on aerobic performance and RSA. It provides evidence for its potential applicability to sports that use resistance strength training in their training programs in order to improve aerobic performance and in sports that need a good RSA such as

sports teams. RCT in hypoxia produces different adaptations when compared to a similar training program in normoxia. Therefore, this novel training method can be used by athletes of different sports considering hypoxia produces added stress on physiological responses and performance. These differences must be taken into account in order to optimize performance. Furthermore, these findings could be used by coaches to develop specific training programs to reduce the time devoted to resistance training, and increase endurance and RSA adaptations. The participants in this study had considerable previous experience in resistance training and, so, the findings of this study may only be applicable to resistance-trained athletes. Nevertheless, due to the improvements in aerobic performance and RSA, the results of this study can apply to other athletes such as team sports players or endurance athletes who may want to optimize their strength training sessions using shorter duration. However, it is necessary to conduct more research with endurance athletes to obtain more information about aerobic improvements after HRC in hypoxia in people with high VO_2max values. This research opens a new line to optimize future resistance training protocols under hypoxic conditions in an effort to develop the most effective and efficient method to maximize sports performance by reducing the time for resistance training. More research is needed to elucidate the morphological, biochemical, and molecular adaptations to HRC training under hypoxic conditions in order to clarify whether this training method can promote additional fitness benefits.

5 | CONCLUSION

Compared with normoxic conditions, 8 weeks of RCT under hypoxic conditions efficiently improves aerobic performance and RSA without changes in REE and blood O_2-carrying capacity.

6 | PERSPECTIVE

Compared to previous resistance training research using hypoxia, this is the first study that investigated the effects of HRC training in hypoxia on aerobic performance, REE, RSA, and hematological variables. This study examined the effect of this type of concurrent training on aerobic capacity and specifically investigates the effect of hypoxia in the HRC_{hyp} group. We found that HRC under systemic hypoxia may not only stimulate classical resistance training adaptations but also promotes adaptations more commonly associated with endurance exercise training in skeletal muscle in recreationally endurance and strength trained participants. We acknowledge some study limitations which should be considered for data interpretation, and furthermore practical recommendations should be restricted to recreationally endurance and strength trained participants. Nevertheless, due to the improvements in aerobic performance and RSA, it can be reasonably suggested from our data that the findings of this study can apply to other athletes such as team sports players or endurance athletes who may want to optimize their strength training sessions using shorter duration. However, it is necessary to conduct more research with endurance athletes to obtain more information about aerobic improvements after HRC in hypoxia in people with high VO_2max values.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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VIII ESTUDIO VI: Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia.

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Muscle Architecture and Neuromuscular Changes After High-Resistance Circuit Training in Hypoxia

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Abstract

Ramos-Campo, DJ, Martínez-Guardado, I, Rubio-Arias, JA, Freitas, TT, Othalawa, S, Andreu, L, Timón, R, and Alcaraz, PE. Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia. *J Strength Cond Res* XX(X): 000–000, 2019—This study aimed to analyze the effect of 8 weeks of high-resistance circuit (HRC) training in hypoxia on muscle architecture, strength, and neuromuscular variables. Twenty-eight resistance-trained participants were assigned to a hypoxia (FiO_2 = 15%; HG: n = 15; age: 24.6 ± 6.8 years; height: 177.4 ± 5.9 cm; and weight: 74.9 ± 11.5 kg) or normoxia group (FiO_2 = 20.9%; NG: n = 13; age: 23.2 ± 5.2 years; height: 173.4 ± 6.2 cm; and weight: 69.4 ± 7.4 kg). Each training session consisted of 2 blocks of 3 exercises (block 1: bench press, leg extension, and front lat pulldown; block 2: deadlift, elbow flexion, and ankle extension). Each exercise was performed with a 6 repetition maximum load. Participants exercised twice weekly and, before and after the training program, vastus lateralis muscle thickness and pennation angle, knee extensors electromyographic activity, maximum voluntary contraction (MVC), and rate of force development (RFD) and H-Reflex (Hmax), M-wave of the soleus muscle were assessed. Both training groups showed similar improvements in muscle thickness (effect size [ES] = HG: 0.23; NG: 0.41), pennation angle (ES = HG: 0.86; NG: 0.15), MVC (ES HG: 0.63; NG: 0.61), Hmax (ES = HG: 0.96; NG: 0.40), RFD at 200 milliseconds (ES = HG: 0.31; NG: 0.61) and peak RFD (ES = HG: 0.21; NG: 0.66). No significant between-group differences were found. In conclusion, similar morphological and neuromuscular adaptations can be achieved after 8 weeks of HRC training under hypoxic or normoxic conditions.

Key Words: altitude, hypoxic training, hypertrophy, maximum voluntary contraction, resistance training

Introduction

Strength training under hypoxic conditions is a novel method currently being used by coaches and athletes in an attempt to further increase strength levels and to obtain additional muscle mass gains (24), when compared with programs performed in normoxic conditions. The main benefits of resistance training in hypoxia are largely associated with a higher metabolic stress (23) under such conditions, as it has been reported in several investigations (11,18,20), mainly because of a greater reliance on the anaerobic metabolism via an increment on blood lactate concentration and alterations in acid-base balance (23). In fact, metabolic acidosis has been linked to some potential mediators for muscle hypertrophy such as higher motor unit recruitment, and cellular swelling as well as increased growth hormone concentrations (23). As a consequence, potentially higher hypertrophic and muscle structural adaptations can be expected after hypoxic training.

Of note, previous interventions (15,17) that altered the intramuscular environment using systemic hypoxia reported potentially greater positive adaptations in strength and muscle hypertrophy that seemingly support the previous hypothesis. However, a recent meta-analysis (21) found that, although hypoxic resistance training is effective for increasing muscle size and strength, the improvements reported in hypoxia have not been consistently shown to be greater than the ones obtained with resistance training in normoxia. This fact may be explained by the different training programs, levels of hypoxia, and participant characteristics in the studies that have applied intermittent hypoxic resistance training (IHRT) (19).

Interestingly, IHRT has been shown to lead to an increment in maximal contractile muscle force (17), not only by an increased muscle cross-sectional area or volume, but also by neural adaptations that contribute to a greater muscle force generation (2). In fact, increased motor unit recruitment (25) has been reported during acute resistance exercise in hypoxia, which can be related to a higher metabolic stress. Yet, although the effect of IHRT on muscle morphology has been more extensively examined, little is known about the specific neural mechanism responsible for the improvements in muscle strength. In this context, a previous study (10) found a significant improvement in strength, without muscle growth, after an IHRT focused on possible neural adaptations (3–6 repetitions at 80–110% 1RM). Nevertheless, there are no studies analyzing the adaptive change in neural function.

Research has also shown that IHRT increases anabolic hormone concentrations (i.e., growth hormone, testosterone, etc.), which may be related to muscle mass gains (11,12,28). In addition, IHRT has been found to induce greater increments in plasma vascular endothelial growth factor concentration and capillary-to-fiber ratio, reflecting an increase in skeletal muscle angiogenesis that can improve muscular endurance (13). Previous studies from our research group applying high-resistance circuit (HRC) training in hypoxia have reported greater responses from the

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anaerobic metabolism, higher metabolic stress (18,20), and an increase in aerobic and anaerobic performance (19). However, to our knowledge, no study has analyzed the neuromuscular adaptations to this type of training program.

Understanding such effects can open a new perspective into the optimization of future resistance training protocols under hypoxic conditions. It is of great interest to develop the most effective and efficient method to maximize neuromuscular adaptations, sports performance, and to optimize time spent on resistance training. Therefore, the aim of this pilot study was to analyze the effect of 8 weeks of HRC in hypoxia on muscle architecture and neuromuscular variables in resistance-trained men. We hypothesized that HRC in hypoxia would result in greater muscle growth, neural adaptations, and muscle strength when compared with a normoxic condition.

Methods

Experimental Approach to the Problem

To test the effects of 8 weeks of HRC training in normoxia and hypoxia on muscle architecture and neuromuscular variables, a single-blinded randomized controlled trial with pre and posttests was conducted. Participants were randomly allocated to 2 experimental groups: (a) Hypoxia group (HG; FiO_2 = 15%), performing 8 weeks of HRC training in normobaric hypoxia and (b) Normoxia group (NG; FiO_2 = 20.9%), performing the same training in normoxic conditions. The sessions of the HG were performed in a normobaric chamber (CAT 430, Colorado Altitude training, USA) using 2 generators (CAT-12, Colorado Altitude Training, USA), whereas the normoxic group performed their training sessions outside the hypoxic chamber. Researchers responsible for each measurement did not know whether a subject was allocated to NG or HG.

Subjects

Twenty-eight healthy nonsmoking male volunteers participated in this study. Participants had at least 4 years of resistance training experience and exercised 3 times per week. None of the subjects had any musculoskeletal disorder or reported exposure to altitude in the 3 months before the study. Participants were asked to refrain from their regular training program during the study intervention period and the consumption of supplements to aid muscular growth was not allowed. Before the testing sessions, participants were divided, in randomized order, into the HG (n = 15; age: 24.6 ± 6.8 years; height: 177.4 ± 5.9 cm; weight: 74.9 ± 11.5 kg) or NG (n = 15). Two of the participants in NG did not complete all the training sessions and, as a consequence, they were excluded from the analysis. Therefore, only 13 participants were analyzed in the NG (n = 13; age: 23.2 ± 5.2 years; height: 173.4 ± 6.2 cm; weight: 69.4 ± 7.4 kg). All experimental procedures were explained to the participants and a written consent was obtained from each volunteer in accordance with the Declaration of Helsinki. The study was approved by the Catholic University of Murcia Ethics Committee (Ref. 6511).

Testing Protocol. Testing procedures were carried out on 2 separate days, 1 week apart, and at the same time of the day in both evaluations. On the first day, all participants visited the laboratory to familiarize themselves with the testing and training protocols, the week before starting the training sessions. Pre and posttests were carried out 72 hours after the last intense workout to allow complete recovery from the training. The testing session included muscle architecture and neuromuscular performance assessment (maximum voluntary contraction [MVC], motor response [M-wave] and Hoffman reflex [H-reflex]), and the strength training load determination. The week after the training program was completed, the same testing procedures were applied. Figure 1 depicts all procedures and study design. [F1]

Muscle Architecture Data Collection. A real-time B-mode computerized ultrasound system (Edan dus 60, Shangai International Holding Corp. Hamburg, Germany) with a linear array probe of 7.5–12 MHz wave frequency was used to record longitudinal ultrasonic images of the vastus lateralis (VL) of the right leg. To obtain the sonographs, subjects laid supine with a 45° knee flexion, legs supported, and muscles relaxed. To aid acoustic contact and remove the need to directly touch the skin, eliminating the deformation of the muscle, a water gel was applied to the probe, positioned parallel to the muscle fascicles and perpendicular to the skin. The assessment was performed by the same examiner in both pre and posttests. The examiner had more than 10 years of experience in muscle ultrasound. Frames were obtained at proximal and distal sites on VL following previous recommendations (5). Pennation angle and muscle thickness were analyzed in 1 frame of each part of the muscle, as performed in a previous study (5).

Neuromuscular Testing: Maximum Voluntary Contraction Test, H-Reflex, and M-Wave. The M-wave and H-reflex of the right leg soleus muscle were measured, at rest, 2 hours after participants had a standardized breakfast. Volunteers sat comfortably on a Biodex System 3 chair (Biodex Medical Systems, Shirley, NY, USA) with their right foot on a 30° of plantar flexion position (6). Two electromyography (EMG) electrodes and an EMG mobile receiving sensor (Noraxon Inc., Scottsdale, AZ, USA) were placed 20 mm apart, on the 1/3 distal part of the length between the malleolus medialis and the epicondyle medialis of the tibia, following the SENIAM recommendations (7). To determine the M-wave and H-reflex recruitment curves, the posterior tibial nerve was stimulated using an electrical constant-current stimulator (Digitimer model DS7A; Garden City, United Kingdom). A motor point pen electrode (cathode) was positioned in the popliteal fossa, whereas the anode was placed over the patella. The M-wave recruitment curve was obtained by gradually increasing current intensity (1 mA steps) until a plateau in the response was reached. The H-reflex recruitment curve was determined by performing a ramp measurement with small increases in intensity (0.5 mA, every 2–5 seconds), until the maximum response was identified. The highest peak-to-peak amplitude for the M-wave (Mmax) and H-reflex (Hmax) were obtained from the unrectified EMG signals. Hmax was normalized to Mmax (Hmax/Mmax ratio).

After the Mmax and Hmax measurements and after completing a warm-up consisting of 10 minutes of cycling at 75 W, participants' knee extensors MVC was assessed. While sitting on the Biodex System 3 chair with legs flexed at 90°, volunteers were fully strapped to the chair and had their right ankle tied (above the 2 malleoli) directly to a load cell (SML500; Interface, Scottsdale, AZ, USA). Before data collection, they performed a specific warm-up consisting of 2 submaximal isometric knee extensions for 5 seconds, with their arms crossed on the chest. Then, 2 maximal trials separated by 3 minutes of rest were performed. If the difference on force production in the 2 MVCs was higher than 10%, a third trial was completed. The highest MVC was used for

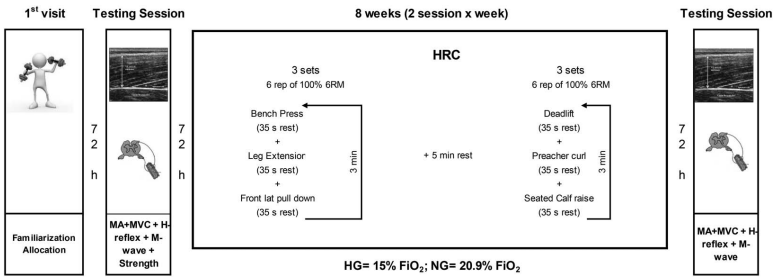

Figure 1. Research design.

analysis. During the test, participants had 2 EMG electrodes and an EMG mobile-receiving sensor (Noraxon INC, Scottsdale, AZ, USA) placed on the VL, 20 mm apart on the 1/3 distal part of the line between the anterior-superior iliac spine and the lateral part of the patella bone, according to SENIAM guidelines (7). The MR 3.4 Noraxon software was used for all neuromuscular testing (Noraxon Inc, Scottsdale, AZ, USA). Before EMG electrode placement, the skin area was trimmed with an electric razor and cleaned with alcohol swabs. Rate of force development (RFD) was assessed during the isometric contractions of the knee extensors, following the recommendations by Maffiuletti et al. (14). Participants were instructed to apply "as much force as possible, as fast as possible" and were verbally encouraged to ensure a maximal explosive effort. Previous literature on the methodological considerations for the assessment of RFD stated that trials used to measure MVC force should be separated from those used to measure RFD (14). In this regard, even though RFD was assessed in the same contractions used to measure MVC, the RFD data used for analysis consisted on the average of the highest value obtained in each trial performed (i.e., even in the trials that did not coincide with the contraction in which the greater MVC value was obtained). The onset of contraction of each repetition was identified manually from the data extracted from the MR 3.4 Noraxon software, using a customized spreadsheet. To maximize reliability of manual onset detection, a systematic approach that identified and considered "the last trough before force deflects above the range of the baseline noise" was used (14).

Six-Repetition Maximum Determination. After the neuromuscular assessment, the 6RM loads of all exercises included in the training program were determined, following standard procedures (19), to evaluate muscular strength, but also because the training protocol would be performed with such loads. The order of the exercises was the same used in the training protocol: bench press, leg extension, front lat pulldown, deadlift, elbow flexion (preacher curl), and ankle extension. To calculate the 6RM loads, participants performed 3 sets of each exercise using the following sequence: 10 repetitions at 50% of the perceived 6RM, 1 minute of rest, 8 repetitions at 75% of estimated 6RM, 2 minutes of rest, and 1 set of the exercises to volitional fatigue at 100% of estimated 6RM. If a participant performed ±1 repetition, the training load was adjusted by approximately ±2.5 and if a subject completed ±2 repetitions, the training load was adjusted by ±5% (5). The participants were allowed to do 5 attempts as maximum with 5 minutes of rest between each attempt. The rest period between exercise was 5 minutes.

Training Program. The training protocol is shown in Table 1. It consisted of 2 blocks (interspersed by 5 minutes of rest), and 3 sets of 3 exercises (3 minutes of rest between sets and 35 seconds between consecutive exercises) at an intensity inducing volitional fatigue after 6RM. The first block consisted of bench press, leg extension, and front lat pulldown, whereas the second block consisted of deadlift, elbow flexion (preacher curl), and ankle extension (seated calf raise). A general warm-up in normoxia that involved 5 minutes of submaximal running at 8.5 $km \cdot h^{-1}$ followed by 5 minutes of active stretching of all major muscle groups was performed before the workout. Also, a specific warm-up consisting of 3 sets of the exercises of the first block was completed, using the following sequence: 10 repetitions at 50% of 6RM for each exercise, 1 minute of rest, 8 repetitions at 75% of 6RM, 2 minutes of rest, and repetitions to failure with the 6RM load. This procedure ensured that subjects lifted loads that allowed only 6 repetitions (~85–90% of 1RM) to be performed and, if necessary, the training load was adjusted every session following previous recommendations (19). The specific warm-up and the main part of the training session were performed in HG or in NG. Subjects were supervised by an experienced lifter to ensure that volitional fatigue was achieved safely and rest periods were strictly controlled. In addition, after the end of the warm-up, the SaO_2 levels were measured using a pulse oximeter (Onyx; Nonin, USA). The mean SaO_2 values displayed were: HG = 93.1 ± 2.3%; NG = 98.1 ± 0.8%. Participants performed 2 training session per week, separated by more than 48 hours.

Statistical Analyses

Data treatment and analysis were performed using the SPSS for Windows statistical package (v.24.0). Descriptive statistics (mean and *SD*) were calculated. Before using parametric tests, the assumption of normality and homoscedasticity were verified with the Shapiro-Wilk's W-Test. A 2-way analysis of variance with repeated measures and Bonferroni post-hoc were used to

Table 1
Training program performed during the study.*

Week	1	2	3	4	5	6	7	8
Set	2	3	3	2	3	3	4	2
Repetitions	6	6	6	6	6	6	6	6
% 6RM	90	95	100	100	100	100	100	100

*RM = repetition-maximum.

Table 2

Neuromuscular and architecture results before and after training in both training groups.*

	Time × group					Time effect					Pre-training			Post-training			95% confidence interval		
	F	df	*p*	Power	ES η_p^2	*F*	df	*p*	Power	ES η_p^2	Group	Mean	*SD*	Mean	*SD*	ES	Mean difference	Lower bound	Upper bound
RFD_{50} ($N \cdot s^{-1}$)	3.309	1	0.082	0.414	0.126	0.054	1	0.818	0.056	0.002	HG	86.5	30.0	71.0	28.8	0.37	−15.5	−11.1	42.0
											NG	85.6	29.3	97.5	30.2	0.36	11.9	−8.2	32.1
RFD_{100} ($N \cdot s^{-1}$)	2.716	1	0.118	0.352	0.106	0.365	1	0.552	0.089	0.016	HG	188.6	46.4	181.2	39.0	0.31	−7.4	−7.8	22.6
											NG	198.4	57.0	214.4	51.4	0.37	16.0	−10.2	42.2
RFD_{200} ($N \cdot s^{-1}$)	1.882	1	0.183	0.26	0.076	5.57	1	**0.027**	0.618	0.195	HG	358.7	76.9	369.1	67.8	0.31	10.4	−11.9	32.7
											NG	381.2	100.0	420.6	100.2	0.61	39.4	0.2	78.4
RFDpeak ($N \cdot s^{-1}$)	0.687	1	0.416	0.125	0.029	5.546	1	**0.028**	0.608	0.191	HG	1,812.7	606.1	1,860.0	608.7	0.21	47.3	−222.5	317.2
											NG	1,791.3	561.8	1,952.1	553.4	0.66	160.8	14.0	307.6
MVC (N)	0.000	1	0.986	0.050	0.000	7.247	1	**0.013**	0.733	0.232	HG	646.5	133.2	690.7	119.2	0.63	44.3	11.5	100.1
											NG	684.5	174.5	729.4	186.4	0.61	44.9	−3.5	93.2
Mmax (mV)	0.287	1	0.597	0.081	0.012	5.494	1	**0.028**	0.612	0.193	HG	8.2	3.7	10.5	2.7	0.56	2.3	0.2	4.9
											NG	8.4	2.5	9.9	2.7	0.38	1.5	−0.9	4.0
Hmax (mV)	1.117	1	0.303	0.172	0.053	6.605	1	**0.018**	0.686	0.248	HG	1.9	0.9	3.8	3.9	0.96	1.9	0.2	4.0
											NG	3.7	2.4	4.4	2.5	0.4	0.7	−0.4	2.1
Hmax/Mmax	0.067	1	0.798	0.057	0.004	2.122	1	0.162	0.283	0.100	HG	0.3	0.2	0.4	0.2	0.18	0.1	−0.3	0.2
											NG	0.4	0.2	0.5	0.3	0.41	0.1	−0.1	0.2
EMG peak (mV)	2.126	1	0.165	0.277	0.124	1.146	1	0.301	0.171	0.071	HG	381.2	122.4	428.4	177.5	0.24	47.2	−93.9	188.2
											NG	400.5	163.1	450.9	187.5	0.42	50.4	−39.2	141.1
EMG mean (mV)	0.372	1	0.551	0.088	0.024	0.708	1	0.413	0.124	0.045	HG	248.9	76.5	258.1	107.2	0.09	9.2	−65.9	84.3
											NG	226.6	100.7	262.0	95.8	0.52	35.4	−13.5	84.4
VLP α (°)	2.457	1	0.133	0.320	0.109	5.563	1	**0.029**	0.612	0.218	HG	14.3	2.5	16.6	2.5	0.86	2.3	0.5	4.1
											NG	17.6	2.1	18.1	1.7	0.15	0.5	−1.2	2.1
VLD α (°)	0.77	1	0.391	0.133	0.037	0.034	1	0.856	0.054	0.002	HG	19.2	2.5	19.6	1.3	0.33	0.4	−1.4	2.2
											NG	19.9	1.4	19.3	1.9	0.52	−0.6	−2.3	1.0
VLP thickness (mm)	0.179	1	0.677	0.069	0.009	4.776	1	**0.041**	0.548	0.193	HG	23.8	3.1	24.9	4.4	0.23	1.1	−0.2	2.5
											NG	23.6	4.0	24.4	3.7	0.41	0.8	−0.5	2.0
VLD thickness (mm)	1.571	1	0.225	0.223	0.073	4.631	1	**0.05**	0.442	0.154	HG	24.4	2.5	25.8	2.7	0.19	1.4	0.0	2.9
											NG	26.1	3.4	26.4	2.8	0.08	0.3	−1.0	1.6

*df = degree of freedom; EMG = electromyography; ES = effect size; Hmax = maximum H-reflex; HG = hypoxia group; MA = muscle architecture; MVC = maximum voluntary contraction; Mmax = maximum M-wave; NG = normoxia group; RFD = rate of force development; VLD = vastus lateralis distal; VLP = vastus lateralis proximal; α = pennation angle.

investigate differences in the study variables. The effect size (ES) between pre and posttests was calculated using Cohen's guidelines for each intervention, using threshold values >0.2 (small), >0.6 (moderate), >1.2 (large), and >2.0 (very large) (9). For all procedures, a level of $p \leq 0.05$ was selected to indicate statistical significance. In addition, to determine the reliability of ultrasound assessments for muscle thickness and pennation angle, the intraclass correlation coefficients (ICCs), and confidence intervals (CIs) were calculated.

Results

[T2] Table 2 shows the muscle architecture variables. No main effect of training group × time was observed in the architecture variables. There was a main effect of time on muscle thickness in the distal site ($F = 4.631$; $p = 0.05$; $\eta^2 = 0.154$) and the proximal site ($F = 4.776$; $p = 0.041$; $\eta^2 = 0.193$) of the VL. In addition, a main effect of time on pennation angle in the proximal site of VL (VLP) was found ($F = 5.563$; $p = 0.029$; $\eta^2 = 0.218$). The ES from pre to posttraining pennation angle values in VLP was moderate in HG ($d = 0.89$) and small in NG ($d = 0.15$). However, no main effect of time was observed in pennation angle in the distal site of VL. Data for the measurement of muscle architectural parameters showed high ICCs: muscle thickness = ICC: 1.00; CI = 1.00–1.00; and pennation angle: ICC = 0.99; CI = 0.96–1.00.

Concerning the neuromuscular adaptations investigated, no main effect of training × time was observed in any variable measured. In addition, no main effect of time was observed on EMG peak and EMG mean, RFD_{50}, RFD_{100}, and on Hmax/Mmax. There was a main effect of time on RFD_{200} ($F = 5.57$; $p = 0.027$; $\eta^2 = 0.195$), RFDpeak ($F = 5.546$; $p = 0.028$; $\eta^2 = 0.191$), MVC ($F = 7.247$; $p = 0.013$; $\eta^2 = 0.232$), Mmax ($F = 5.494$; $p = 0.028$; $\eta^2 = 0.193$), and Hmax ($F = 6.605$; $p = 0.018$; $\eta^2 = 0.248$). The pre-to-posttraining program ES was: RFD_{200}: small in NG ($d = 0.31$) and moderate in NG ($d = 0.61$); RFD peak: small in HG ($d = 0.21$) and moderate in NG ($d = 0.66$); MVC: moderate in both groups (0.63 in HG and 0.61 in NG); Mmax = small in both groups (0.56 in HG and 0.38 in NG); Hmax = small in NG ($d = 0.40$) and moderate in HG ($d = 0.96$).

Discussion

To our knowledge, this is the first study to investigate the effects of 8 weeks of HRC training in hypoxia (15% FiO_2) and normoxia on muscle architecture and different neuromuscular variables. The main results showed similar neuromuscular and muscle morphological responses in both training conditions. Despite no significant between-group statistical differences, some main time effects were depicted. Of note, a moderate ES in HG and small in NG were obtained for Hmax and pennation angle. Thus, HRC in hypoxia enhanced spinal excitability of α-motoneuron and transmission efficiency in Ia afferent synapses (Hmax) and improved muscle pennation angle. In addition, a moderate ES in NG and small ES in NG were observed in RFD.

Previous studies have shown that resistance training in hypoxia may enhance muscle growth (13,16,17). This improvement is likely associated, at least in part, to higher metabolic stress and anaerobic glycolysis (11), particularly when exercises are organized in circuit under hypoxia conditions (19,20). In addition, it is probable that the increased metabolic stress induced during strength training in hypoxia causes hypoxia-mediated increases in motor unit recruitment (25) and cellular swelling from metabolite accumulation inside the cells (23). Remarkably, the potential increase of metabolite accumulation may also drive skeletal muscle growth (21). However, in the present study, no differences between training conditions were observed on the muscle thickness variables, supporting the findings of a previous research (16). A possible reason that explains the small magnitude of the observed muscle thickness changes in both groups is likely related to the short number of weeks of intervention and the high-intensity and power-oriented training program applied herein (4).

On another note, our results showed a main effect of time on pennation angle in the VLP. As we previously reported, the ES from pre to posttraining pennation angle values in VLP was moderate in HG ($d = 0.89$) and small in NG ($d = 0.15$). No previous studies analyzed this parameter after normobaric hypoxic training, but similar improvements have been reported after strength training in a study by Aagaard et al. (1). The increment of the fiber angulation most probably improves force generation due to better exploitation of both the force-velocity and length-force relationship of the fiber, and to the greater quantity of contractile material that can attach to the tendon or aponeurosis (3). It is clear that having large fiber angles can be considered beneficial to high-force production and, the fact that HRC in hypoxia produced an improvement in this angulation, may explain, at least in part, the increase obtained in specific force variables (i.e., MVC). In summary, according to our results, HRC seems to provide a moderate effect to improve muscle architecture when performed under hypoxic conditions as opposed to performing the same training in normoxia, in which only a small ES was found.

Regarding neuromuscular adaptations, there was a main effect of time on MVC. Moderate pre-post ES was found in both groups (0.63 in HG and 0.61 in NG), which supports the findings obtained by Morales-Artacho et al. (16) following 8 weeks of resistance training in hypobaric hypoxia. Previous studies have shown that the increase in force-generating capacity after resistance traini ng could be partially explained by improvements in neural drive (2). Notably, the current study is the first to investigate M-wave and H-reflex responses under hypoxic conditions showing a main effect of time on Hmax. In particular, the ES was moderate after HRC in hypoxia ($d = 0.96$) and small after HRC in normoxia ($d = 0.40$). The H-reflex is an electromyographical estimate of the spinal excitability of the α-motoneuron and the transmission efficiency in Ia afferent synapses (2). Therefore, the improvement in MVC observed after HRC in hypoxia could somehow be linked to the Hmax response obtained in this condition. The fact that increases in Hmax amplitude were identified after training indicates that neural adaptations occurred at the spinal level (2), potentially contributing to an enhancement of motor unit recruitment and to an increase of motor unit discharge rate (8). However, previous data reported that H-reflex was found to remain unchanged after resistance training (2), but in contrast, to be affected after endurance training (27). Notably, the type of exercise proposed in the present study (i.e., HRC under hypoxia) has been previously reported to be an effective method to improve endurance capacity (19). Thus, the findings obtained herein regarding Hmax amplitude could be explained not by the resistance training-induced adaptations, but instead, by the potential of HRC in hypoxia to lead to adaptations similar to those found after endurance exercise and associated to changes in Hmax responses (27). Also of interest is the fact that our results showed a main effect of time on Mmax with small ES found after HRC in hypoxia ($d = 0.56$) and normoxia ($d = 0.38$). According to Rodriguez-Falces (22), the increase in Mmax can be associated to increases in muscle mass as seen in both groups. Therefore, based on the data obtained herein,

both types of training (hypoxia and normoxia) appear to lead to adaptations related to strength gains, spinal excitability of the α-motoneuron, and transmission efficiency of Ia afferent synapses.

Interestingly, the present results showed a main effect of time on RFD_{200} and RFDpeak. The ES from baseline to posttraining of these variables were moderate in NG and small in HG (RFD_{200}: NG ($d = 0.31$); NG ($d = 0.61$); RFDpeak: HG ($d = 0.21$); NG ($d = 0.66$). This seemingly controversial discovery may be because of the characteristics and fatigue elicited by the training proposed in the current study performed under hypoxia conditions (18,20). It has been proposed that, to improve RFD, the intention to apply force rapidly in every repetition is crucial (26). However, previous studies analyzing the acute effects of HRC in hypoxia (18,20) found a significant decline in power output, force, and barbell acceleration during the session. These findings may help explain the results of the present investigation, because HG probably induced higher fatigue than NG, leading to slower movement velocities (specifically in the training sessions where loads of 100% of 6RM were applied) which may negatively affect RFD adaptations in HG. Furthermore, this group increased muscle thickness and pennation angle, 2 variables known to be related to increased force production, but detrimental to higher muscle shortening velocities, hence, RFD. Thus, if the aim is to improve RFD and power output, fatigue management is crucial and hypoxic training sessions may not provide the most appropriate stimulus.

In summary, this study brings further understanding on the neuromuscular and muscle size adaptations following HRC in hypoxia and normoxia by being the first to report similar adaptations under both conditions. It provides evidence for its potential applicability to sports that use resistance training as part their program to improve muscle mass or strength. This research unveils a new line of resistance training protocols under hypoxic conditions, in an effort to develop the most effective and efficient method to maximize performance, while also reducing the time spent on each workout. The main limitation of the present study was the small sample size of each group and the high variability observed in the individual response of the participants. Concerning the methodological procedures used herein, the fact that RFD and MVC were assessed in the same trials may also be considered as a potential limitation. In this regard, practitioners are advised to take the abovementioned aspects and limitations into consideration when interpreting the data.

Practical Applications

From an applied perspective, strength and conditioning coaches and sport scientists should keep in mind that, if the aim of the training program is to increase maximal isometric force and spinal excitability, HRC training under hypoxia is a suitable method given its positive effect on muscle architecture variables (i.e., pennation angle) and Hmax amplitude. The training program should consist of 2 blocks of 3 exercises of upper and lower limbs (e.g., block 1: bench press, leg extension, and front pulldown; block 2: deadlift, elbow flexion, and ankle extension). To induce metabolic stress, each exercise should be performed with heavy loads (i.e., 6RM) and in an environment of a FiO_2 of 15%. Rest periods between consecutive exercises should last around 35 seconds, whereas 3 minutes should be allowed between sets and 5 minutes between blocks. An intervention duration of 8 weeks is recommended, based on the present results. In contrast, when prescribing HRC in normoxia, coaches should be aware that adaptations will have a greater orientation toward an enhanced RFD and power output and, to a lesser extent, toward maximal strength gains (i.e., MVC). This last aspect should be considered especially for athletes that seek an increase in muscle's explosive capability without an excessive muscle mass gain and in sports where maximum strength is not a key performance indicator.

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IX – RESUMEN GLOBAL DE LOS RESULTADOS Y DISCUSIÓN

Resumen de los resultados y discusión

Efecto del entrenamiento o la exposición a hipoxia sobre la composición corporal: Centrándonos en los resultados de la evidencia científica publicada y revisada sistemáticamente y con meta-análisis sobre la composición corporal, los resultados de la presente tesis doctoral muestra que:

El entrenamiento o exposición a hipoxia reduce el peso corporal (MD = -1.42, 95% CI = -2.76, -0.09, p = 0.04; I^2 = 0%, p = 0.98) la masa grasa (SMD = -0.26, 95% CI = -0.50, -0.01, p = 0.04; I^2 = 0%, p = 0.99), la relación cintura cadera (MD= -0.02, 95% CI = -0.04, -0.01, p < 0.001; I^2 = 0%, p = 0.76) y la circunferencia de la cintura (MD= -3.52, 95% CI = -4.75, -2.30, p < 0.001; I^2 = 0%, p = 0.86). Además, hay una tendencia hacia una mayor ganancia de masa muscular con el trabajo en hipoxia que con el mismo trabajo en normoxia (p = 0.08).

Con respecto al trabajo de fuerza en hipoxia, éste aumenta de forma significativa el área de sección transversal del músculo (SMD= 0.70, 95% CI 0.05, 1.35; p = .04). Sin embargo, no hay diferencias con respecto al mismo entrenamiento en normoxia.

Por otro lado, analizando el efecto de 8 semanas de HRC en hipoxia sobre la composición corporal y la arquitectura muscular se observa un aumento del grosor muscular en la parte distal (Δ5.7%; p=0.05; ES=0.52) y proximal (p=0.09; ES=0.41) del vasto lateral. También existe un aumento del ángulo de penneación en la zona proximal del vasto lateral (Δ16.1%; p=0.01; ES=0.86).

Efecto del entrenamiento o la exposición a hipoxia sobre factores cardiometabólicos:

El entrenamiento o exposición a hipoxia desciende los triglicéridos (SMD = -0.67, 95% CI = -1.02, -0.32, p < 0.001; I^2 = 41%, p = 0.09) con una tendencia a tener un efecto adicional sobre el mismo programa en normoxia (p=0.06; Chi^2 = 8.20, p = 0.61). También, el condicionamiento hipóxico desciende el LDL (SMD = -0.51, 95% CI = -0.9, -0.12, p = 0.01; I^2 = 41%, p = 0.12) y la presión arterial diastólica (MD = -

2.67, 95% CI = -3.59, -1.76, $p < 0.01$; $I^2 = 0\%$, $p = 0.61$) y sistólica (MD = -4.96, 95% CI = -7.90, -2.02, $p < 0.01$; $I^2 = 49\%$, $p = 0.07$).

Efecto de una sesión de entrenamiento en circuito de alta intensidad en hipoxia sobre parámetros bioquímicos, de rendimiento y fisiológicos:

Una sesión de entrenamiento de HRC en HH desciende la potencia y la fuerza pico desarrollada en press de banca y en media sentadilla en comparación con la misma sesión en normoxia o hipoxia moderada. También se desarrolla menos fuerza y potencia media si comparamos HH y NORM

Existe una percepción de esfuerzo superior desde el punto de vista estadístico si comparamos HH con NORM o MH.

Desde el punto de vista del ácido-base y de los gases, existe una menor pO_2 and SaO_2 en ambas condiciones de hipoxia que en NORM. Además, hay una mayor reducción de pCO_2 en HH en comparación con NORM. También existe una mayor concentración de lactato, y una mayor reducción del HCO_3 y del pH en HH en comparación con MH and NORM. También hay diferencia en la concentración de lactato entre MH y NORM.

El Na^+ tiene una mayor concentración en HH que en NORM y el Cl^- es superior en MH y HH que en NORM.

La frecuencia cardíaca del HRC no se modifica de forma significativa en función de la altitud simulada, pero existe una mayor variabilidad de la frecuencia cardíaca en HH que en NORM.

Por último, una sesión de HRC en hipoxia (HH o MH) tiene un mayor consumo de oxígeno y gasto calórico que el mismo trabajo en NORM.

Efecto del entrenamiento de fuerza en hipoxia sobre variables neuromusculares y de fuerza:

Desde el punto de vista de la revisión sistemática y meta-análisis realizado a lo largo de esta tesis, el entrenamiento de fuerza en hipoxia, mejora la fuerza de miembros inferiores (SMD= 1.66; 95% CI = 0.81, 2.50; p = .0001) y superiores (SMD= 2.32; 95% CI = 1.03, 3.61; p = .0004). Sin embargo, este efecto no es superior al mismo entrenamiento realizado en normoxia.

Además, ocho semanas de entrenamiento de HRC en hipoxia aumentan la MVC (Δ6.4%; p=0.05; ES=0.63) y el Hmax (Δ49.9%; p=0.001; ES=0.93). El mismo

entrenamiento en normoxia mejora la RFD a 200 ms (Δ9.4%; p=0.05; ES=0.61) y la RFD pico (Δ8.2%; p=0.03; ES=0.66).

Efecto del entrenamiento de fuerza en hipoxia sobre variables cardio-respiratorias y hematológicas:

Ocho semanas de entrenamiento de HRC en hipoxia mejoran el índice de fatiga de un test de RSA −0.9%; p < .01; ES = 2.75) pero no en normoxia. Dico programa no produce cambios sobre variables hematológicas ni sobre el consumo energético en reposo (REE). Sin embargo, 8 semanas de HRC en hipoxia mejoran el consumo de oxígeno máximo absoluto (4.5%; p = .014; ES = 0.42) y relativo (5.2%; p = .008; ES = 0.43), la velocidad a la que se alcanza dicho consumo máximo de oxígeno (4%; p = .010; ES = 0.25) y el tiempo hasta la extenuación (4.1%; p = .012; ES = 0.26).

X – CONCLUSIONES

Conclusiones

A continuación, procederemos a exponer las conclusiones de esta tesis doctoral.

En respuesta al **objetivo general**: Analizar la eficacia condicionamiento hipóxico como herramienta para la mejora fisiológica, neuromuscular y de la composición corporal.

Podemos concluir que:
El condicionamiento en hipoxia normobárica optimiza el aumento de la masa muscular, produce una adaptación neuromuscular y tiene un efecto beneficioso adicional sobre el rendimiento aeróbico y anaeróbico

En respuesta al **objetivo específico 1**: Realizar una revisión sistemática con meta-análisis de los estudios que han investigado el efecto adicional del entrenamiento de fuerza en hipoxia respecto al entrenamiento de normoxia, sobre el área de sección transversal o la masa libre de grasa, así como sobre la fuerza muscular en sujetos físicamente activos.

Podemos concluir que:
Aunque el entrenamiento de fuerza en hipoxia aumenta el volumen muscular y la fuerza, estas respuestas no son superiores al entrenamiento de fuerza en normoxia.

En respuesta al **objetivo específico 2**: Realizar una revisión sistemática y un meta-análisis para investigar el uso del HC pasivo y activo para maximizar la pérdida de peso y mejorar los marcadores cardiometabólicos en individuos con sobrepeso u obesidad.

Podemos concluir que:
Realizando una revisión sistemática con meta-análisis el condicionamiento hipóxico produce una reducción significativa del peso, la masa grasa, el índice cintura-cadera, la circunferencia de la cintura, así como varios marcadores cardiometabólicos (triglicéridos, LDL, HDL, tensión arteríal sistólica y diastólica). Sin embargo, únicamente la magnitud de la reducción en los triglicéridos y del aumento en la masa grasa son superiores en hipoxia que en normoxia.

En respuesta al **objetivo específico 3**: Examinar si esta estrategia terapéutica es más efectiva en individuos con sobrepeso en comparación con individuos con obesidad.

Podemos concluir que:
La utilidad del condicionamiento hipóxico es similar en individuos con sobrepeso y con obesidad.

En respuesta al **objetivo específico 4**: Determinar si una sesión de entrenamiento de fuerza en circuito de alta intensidad con hipoxia produce mayores efectos agudos en el rendimiento físico, gases sanguíneos, metabolitos y electrolitos sanguíneos que la misma sesión en normoxia.
Podemos concluir que:

El entrenamiento en circuito de alta intensidad en hipoxia alta, pero no moderada, desciende el rendimiento e incrementa la percepción de esfuerzo de la sesión. El entrenamiento en circuito de alta intensidad en hipoxia reduce la oxigenación de la sangre, incrementa el lactato sanguíneo y reduce el HCO_3 y el pH. Además, una sesión de entrenamiento en circuito de alta intensidad en hipoxia alta, produce cambios en los electrolitos sanguíneos y en la glucosa.

En respuesta al **objetivo específico 5**: Analizar los efectos agudos que provoca el entrenamiento en circuito de alta intensidad bajo dos niveles (moderado y alto) de hipoxia sistémica sobre el rendimiento físico y las variables fisiológicas y metabólicas.

Podemos concluir que:
El entrenamiento en circuito de alta intensidad en hipoxia disminuye de forma significativa al rendimiento durante la sesión. Además, las condiciones de hipoxia modifican la respuesta fisiológica y la percepción de esfuerzo de este tipo de entrenamiento.

En respuesta al **objetivo específico 6**: Analizar el efecto de 8 semanas de entrenamiento en circuito de alta intensidad en hipoxia y normoxia sobre el rendimiento aeróbico, el gasto de energía en reposo, la capacidad de repetir sprines y sobre variables hematológicas.
Podemos concluir que:
En comparación con normoxia, 8 semanas de entrenamiento de fuerza en circuito en condiciones de hipoxia, mejora de forma eficiente el rendimiento aeróbico y el RSA sin producir cambios en el REE ni en la capacidad de la sangre de transportar oxígeno.

En respuesta al **objetivo específico 7:** Analizar el efecto de 8 semanas de entrenamiento en circuito de alta intensidad en hipoxia sobre la arquitectura muscular y variables neuromusculares en hombres físicamente activos.
Podemos concluir que:

Ocho semanas de entrenamiento en circuito en hipoxia aumenta el grosor muscular, mejora el ángulo de penneación, la máxima contracción voluntaria y el reflejo H. Por otro lado, el mismo entrenamiento en normoxia mejora la RFD pero no variables relacionadas con la arquitectura muscular.

In the same way and taking in account that we are defending an International Thesis we also presented the conclusions in English language.

In response to **general objective:** to analyze the effectiveness of hypoxic conditioning as a tool to improve physiological and neuromuscular variables and body composition.

We conclude that:
Normobaric hypoxic conditioning optimizes muscle growth and produces neuromuscular and physiological adaptations which improve aerobic and anaerobic performance.

In response to **specific objective 1:** to systematically review the studies which have investigated using resistance training in hypoxia to improve muscular size and strength, and to perform a meta-analysis to determine the effect of resistance training in hypoxia on these adaptive parameters

We conclude that:
while resistance training in hypoxia does result in significant increases in muscular size and strength, these responses may not be larger than resistance training in normoxia.

In response to **specific objective 2:** to perform a systematic review and meta-analysis to investigate the use of passive and active HC to maximize weight loss and improve cardiometabolic markers in both individuals with overweight or obesity.

We conclude that:
We conclude using a systematic review with meta-analysis that HC does result in significant reductions in weight, fat mass, W/H, waist circumference and in several cardiometabolic markers (triglycerides, LDL, HDL, SBP and DBP). However, only the magnitude of reductions in triglycerides and greater muscle growth was greater in hypoxic than in normoxic condition.

In response to **specific objective 3:** to examine if hypoxic conditioning is more effective in individuals with overweight *versus* with obesity.

We conclude that:
The usefulness of HC was similar in individuals with overweight and obesity.

In response to **specific objective 4**: to determine if an HRC training session under hypoxia produces greater acute effects on physical performance than on blood gases, blood metabolites, and blood electrolyte responses.

We conclude that:
HRC performed in high, but not moderate hypoxia decreased muscular performance and increased the rating of perceived exertion. HRC under high hypoxic conditions also reduced blood oxygenation, increased blood lactate, and reduced blood HCO_3^- and pH. In addition, high hypoxia induced minor changes to blood electrolyte and blood glucose responses to an HRC training session.

In response to **specific objective 5:** to analyze physical performance and physiological and metabolic variables during high-resistance circuit training with the addition of 2 levels (moderate and high) of systemic hypoxia

We conclude that:
coupling systemic hypoxia with high-resistance circuit training significantly affects physical performance. Furthermore, hypoxic conditions modify physiological variables and alter the perception of this type of strenuous exercise.

In response to **specific objective 6:** to analyze the effect of 8 weeks of HRC training in hypoxia and normoxia on aerobic performance, resting energy expenditure, repeat sprint ability and hematological variables.

We conclude that:
Compared with normoxic conditions, 8 weeks of resistance circuit training under hypoxic conditions efficiently improves aerobic performance and RSA without changes in REE and blood O_2-carrying capacity.

In response to **specific objective 7:** to analyze the effect of 8 weeks of HRC in hypoxia on muscle architecture and neuromuscular variables in resistance-trained men.

We conclude that:
When performed in hypoxia, 8 weeks of HRC enhance muscle thickness, pennation angle, MVC and H-reflex amplitude. In contrast, HRC training in normoxia improves RFD but no variables related to muscle architecture.

XI – LIMITACIONES Y FUTURAS LÍNEAS DE INVESTIGACIÓN

Limitaciones

Las principales limitaciones de la presente tesis doctoral han sido en un primer lugar el número de estudios incluidos en los estudios de revisión, junto con la divergencia y heterogeneidad hace que no obtengamos una imagen clara de los hallazgos. Además, el número reducido de participantes en los estudios realizados para analizar los efectos agudos y las adaptaciones del entrenamiento.

A pesar de que siempre es un hándicap la logística, los recursos materiales, humanos y económicos que requiere la realización de un estudio de estas características, siempre el conseguir una muestra mayor es un punto a favor de los resultados estadísticos. Además, tenemos que admitir que el llevar a cabo los estudios experimentales con sujetos entrenados en fuerza, aunque no profesionales, se aleja de una población con patología y es algo que hace que tengamos que tomar los datos con cautela a la hora de extrapolarlos a otras poblaciones. Por otro lado, es otra limitación el no control de algunas hormonas y parámetros como el HIF o el VEGF para la evaluación de la angiogénesis, que se vio limitada por la limitación de recursos económicos de este trabajo de investigación. Por último, La no evaluación de la ecografía en los miembros superiores y el incluir la evaluación de la RFD y la MVC durante el mismo protocolo, así como el no incluir una evaluación de la saturación muscular a través de espectroscopia del infrarrojo cercano, evaluaciones identificadas a posteriori una vez analizados los resultados y que en futuros estudio recomendaríamos tener en cuenta.

Futuras líneas de investigación

Las principales futuras líneas de investigación derivadas de los resultados de esta tesis doctoral estarían encaminadas a evaluar la efectividad de entrenamientos con de fuerza de alta intensidad en hipoxia con pacientes con patologías como obesidad, sobrepeso, sarcopenia o poblaciones con osteopenia y osteoporosis. También es interesante como futuras líneas de investigación incluir este tipo de actividad en personas que por problemas locomotores no puedan realizar un estímulo muy intenso de ejercicio, debido al estrés extra que incluye la hipoxia. El incorporar este tipo de trabajo optimizaría el proceso de entrenamiento y abarataría costes en fármacos y demás conceptos vinculados a la salud.

Es necesario analizar también el efecto de este tipo de entrenamiento en otras poblaciones deportistas, como individuos que quieran mejorar su masa muscular o deportistas de deportes colectivos que deben desarrollar de forma simultanea varias capacidades físicas, obteniendo el mismo resultado en menos tiempo. Por último, hay que utilizar otras modalidades de ejercicio de fuerza, diferentes números de repeticiones y series, FiO_2, junto con descansos y frecuencias para poder conocer el efecto de estas características del entrenamiento y de esta forma poder ir pudiendo generar la dosis óptima de entrenamiento en hipoxia para cada individuo. También, recomendamos estudios longitudinales de mayor duración para conocer el efecto a largo plazo de este ejercicio.

XII - REFERENCIAS BIBLIOGRÁFICAS

REFERENCIAS BIBLIOGRÁFICAS

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XIII - ANEXOS

ANEXO 1: Criterios de calidad de los artículos.

ANEXO 1: Criterios de calidad de los artículos.

InCites Journal Citation Reports

Clarivate Analytics

2017 Journal Performance Data for: EUROPEAN JOURNAL OF APPLIED PHYSIOLOGY

ISSN: 1439-6319
eISSN: 1439-6327
SPRINGER
233 SPRING ST, NEW YORK, NY 10013
GERMANY (FED REP GER)

TITLES
ISO: Eur. J. Appl. Physiol.
JCR Abbrev: EUR J APPL PHYSIOL

LANGUAGES
English

CATEGORIES
PHYSIOLOGY - SCIE

SPORT SCIENCES - SCIE

PUBLICATION FREQUENCY
12 issues/year

InCites Journal Citation Reports

Clarivate Analytics

Journal Impact Factor Calculation

$$\text{2017 Journal Impact Factor} = \frac{1{,}126}{469} = 2.401$$

How is Journal Impact Factor Calculated?

$$\text{JIF} = \frac{\text{Citations in 2017 to items published in } \mathbf{2015\ (634) + 2016\ (492)}}{\text{Number of citable items in } \mathbf{2015\ (249) + 2016\ (220)}} = \frac{1{,}126}{469}$$

InCites Journal Citation Reports

Clarivate Analytics

Rank

Rank 2017

JCR Impact Factor

JCR Year	PHYSIOLOGY			SPORT SCIENCES		
	Rank	Quartile	JIF Percentile	Rank	Quartile	JIF Percentile
2017	45/83	Q3	46.386	28/81	Q2	66.049
2016	45/84	Q3	47.024	24/81	Q2	70.988
2015	38/83	Q2	54.819	18/82	Q1	78.659
2014	44/83	Q3	47.590	21/81	Q2	74.691
2013	42/81	Q3	48.765	19/81	Q1	77.160
2012	29/80	Q2	64.375	12/84	Q1	86.310
2011	37/79	Q2	53.797	18/85	Q1	79.412
2010	41/78	Q3	48.077	23/80	Q2	71.875
2009	40/75	Q3	47.333	16/73	Q1	78.767
2008	43/74	Q3	42.568	15/71	Q1	79.577
2007	44/78	Q3	44.231	14/72	Q1	81.250
2006	48/78	Q3	39.103	19/73	Q2	74.658
2005	49/75	Q3	35.333	17/70	Q1	76.429
2004	49/74	Q3	34.459	17/71	Q1	76.761
2003	42/74	Q3	43.919	10/71	Q1	86.620
2002	43/73	Q3	41.781	12/69	Q1	83.333
2001	45/74	Q3	39.865	15/68	Q1	78.676
2000	38/76	Q2	50.658	11/61	Q1	82.787

InCites Journal Citation Reports

Clarivate Analytics

2017 Journal Performance Data for: PHYSIOLOGY & BEHAVIOR

ISSN: 0031-9384
PERGAMON-ELSEVIER SCIENCE LTD
THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND
USA

TITLES
ISO: Physiol. Behav.
JCR Abbrev: PHYSIOL BEHAV

LANGUAGES
Multi-Language

CATEGORIES
BEHAVIORAL SCIENCES - SCIE

PUBLICATION FREQUENCY
12 issues/year

InCites Journal Citation Reports

Clarivate Analytics

Journal Impact Factor Calculation

$$\text{2017 Journal Impact Factor} = \frac{2{,}504}{995} = 2.517$$

How is Journal Impact Factor Calculated?

$$\text{JIF} = \frac{\text{Citations in 2017 to items published in } \textbf{2015 (1,481) + 2016 (1,023)}}{\text{Number of citable items in } \textbf{2015 (557) + 2016 (438)}} = \frac{2{,}504}{995}$$

Rank

Rank 2017

JCR Impact Factor

JCR Year	BEHAVIORAL SCIENCES		
	Rank	Quartile	JIF Percentile
2017	24/51	Q2	53.922
2016	30/51	Q3	42.157
2015	24/51	Q2	53.922
2014	19/51	Q2	63.725
2013	21/49	Q2	58.163
2012	19/49	Q2	62.245
2011	19/48	Q2	61.458
2010	18/48	Q2	63.542
2009	15/49	Q2	70.408
2008	17/47	Q2	64.894
2007	18/45	Q2	61.111
2006	19/42	Q2	55.952
2005	21/42	Q2	51.190
2004	22/41	Q3	47.561
2003	21/40	Q3	48.750
2002	25/39	Q3	37.179
2001	29/39	Q3	26.923
2000	23/39	Q3	42.308
1999	26/38	Q3	32.895
1998	26/39	Q3	34.615
1997	27/38	Q3	30.263

InCites Journal Citation Reports

Clarivate Analytics

2017 Journal Performance Data for: JOURNAL OF STRENGTH AND CONDITIONING RESEARCH

ISSN: 1064-8011
eISSN: 1533-4287
LIPPINCOTT WILLIAMS & WILKINS
TWO COMMERCE SQ, 2001 MARKET ST, PHILADELPHIA, PA 19103
USA

TITLES
ISO: J. Strength Cond. Res.
JCR Abbrev: J STRENGTH COND RES

LANGUAGES
English

CATEGORIES
SPORT SCIENCES - SCIE

PUBLICATION FREQUENCY
12 issues/year

InCites Journal Citation Reports

Clarivate Analytics

Journal Impact Factor Calculation

$$\text{2017 Journal Impact Factor} = \frac{2{,}088}{898} = 2.325$$

How is Journal Impact Factor Calculated?

$$\text{JIF} = \frac{\text{Citations in 2017 to items published in } \textbf{2015 (1,203) + 2016 (885)}}{\text{Number of citable items in } \textbf{2015 (474) + 2016 (424)}} = \frac{2{,}088}{898}$$

Rank

Rank 2017

JCR Impact Factor

JCR Year	SPORT SCIENCES		
	Rank	Quartile	JIF Percentile
2017	29/81	Q2	64.815
2016	28/81	Q2	66.049
2015	25/82	Q2	70.122
2014	23/81	Q2	72.222
2013	29/81	Q2	64.815
2012	31/84	Q2	63.690
2011	30/85	Q2	65.294
2010	33/80	Q2	59.375
2009	34/73	Q2	54.110
2008	46/71	Q3	35.915
2007	26/72	Q2	64.583
2006	28/73	Q2	62.329
2005	28/70	Q2	60.714
2004	31/71	Q2	57.042
2003	36/71	Q3	50.000
2002	36/69	Q3	48.551
2001	38/68	Q3	44.853
2000	37/61	Q3	40.164
1999	36/60	Q3	40.833
1998	38/58	Q3	35.345

InCites Journal Citation Reports

Clarivate Analytics

2017 Journal Performance Data for: SCANDINAVIAN JOURNAL OF MEDICINE & SCIENCE IN SPORTS

ISSN: 0905-7188
eISSN: 1600-0838
WILEY
111 RIVER ST, HOBOKEN 07030-5774, NJ
DENMARK

TITLES
ISO: Scand. J. Med. Sci. Sports
JCR Abbrev: SCAND J MED SCI SPOR

LANGUAGES
English

CATEGORIES
SPORT SCIENCES - SCIE

PUBLICATION FREQUENCY
6 issues/year

InCites Journal Citation Reports

Clarivate Analytics

Journal Impact Factor Calculation

$$\text{2017 Journal Impact Factor} = \frac{1{,}431}{395} = 3.623$$

How is Journal Impact Factor Calculated?

$$\text{JIF} = \frac{\text{Citations in 2017 to items published in } \mathbf{2015\ (919) + 2016\ (512)}}{\text{Number of citable items in } \mathbf{2015\ (238) + 2016\ (157)}} = \frac{1{,}431}{395}$$

InCites Journal Citation Reports

Clarivate Analytics

Rank

Rank 2017

JCR Impact Factor

JCR Year	SPORT SCIENCES		
	Rank	Quartile	JIF Percentile
2017	9/81	Q1	89.506
2016	9/81	Q1	89.506
2015	11/82	Q1	87.195
2014	11/81	Q1	87.037
2013	8/81	Q1	90.741
2012	8/84	Q1	91.071
2011	10/85	Q1	88.824
2010	8/80	Q1	90.625
2009	12/73	Q1	84.247
2008	8/71	Q1	89.437
2007	8/72	Q1	89.583
2006	9/73	Q1	88.356
2005	9/70	Q1	87.857
2004	9/71	Q1	88.028
2003	28/71	Q2	61.268
2002	21/69	Q2	70.290
2001	32/68	Q2	53.676
2000	32/61	Q3	48.361
1999	32/60	Q3	47.500
1998	15/58	Q2	75.000
1997	14/24	Q3	43.750

InCites Journal Citation Reports

Clarivate Analytics

2017 Journal Performance Data for: European Journal of Sport Science

ISSN: 1746-1391
eISSN: 1536-7290
TAYLOR & FRANCIS LTD
2-4 PARK SQUARE, MILTON PARK, ABINGDON OR14 4RN, OXON, ENGLAND
ENGLAND

TITLES
ISO: Eur. J. Sport Sci.
JCR Abbrev: EUR J SPORT SCI

LANGUAGES
English

CATEGORIES
SPORT SCIENCES - SCIE

PUBLICATION FREQUENCY
6 issues/year

InCites Journal Citation Reports

Clarivate Analytics

Journal Impact Factor Calculation

$$\text{2017 Journal Impact Factor} = \frac{631}{245} = 2.576$$

How is Journal Impact Factor Calculated?

$$\text{JIF} = \frac{\text{Citations in 2017 to items published in } \textbf{2015 (335) + 2016 (296)}}{\text{Number of citable items in } \textbf{2015 (93) + 2016 (152)}} = \frac{631}{245}$$

Rank

Rank 2017

JCR Impact Factor

JCR Year	SPORT SCIENCES		
	Rank	Quartile	JIF Percentile
2017	22/81	Q2	73.457
2016	15/81	Q1	82.099
2015	30/82	Q2	64.024
2014	41/81	Q3	50.000
2013	47/81	Q3	42.593
2012	48/84	Q3	43.452
2011	54/85	Q3	37.059
2010	50/80	Q3	38.125
2009	53/73	Q3	28.082
2008	49/71	Q3	31.690

ANEXO 2: Certificado del comité de ética.

UCAM
UNIVERSIDAD CATÓLICA SAN ANTONIO

COMITÉ DE ÉTICA DE LA UCAM

DATOS DEL PROYECTO

Título:	"Efectos agudos y adaptaciones del entrenamiento de fuerza tradicional vs. alta intensidad en circuito en hipoxia y normoxia"

Investigador Principal	**Nombre**	**Correo-e**
Dr.	Domingo Jesús Ramos Campo	djramos@ucam.edu

INFORME DEL COMITÉ

Fecha	**28/10/2016**

Tipo de Experimentación

Investigación experimental clínica con seres humanos.	X
Utilización de tejidos humanos procedentes de pacientes, tejidos embrionarios o fetales.	
Utilización de tejidos humanos, tejidos embrionarios o fetales procedentes de bancos de muestras o tejidos.	
Investigación observacional con seres humanos, psicológica o comportamental en humanos.	
Uso de datos personales, información genética, etc.	X
Experimentación animal.	
Utilización de agentes biológicos de riesgo para la salud humana, animal o las plantas.	
Uso de organismos modificados genéticamente (OMGs).	

Comentarios Respecto al tipo de Experimentación
NADA OBSTA

Comentarios Respecto a la metodología de experimentación
NADA OBSTA

ANEXO 3: Aceptación de los coautores para que el doctorando presente los mismos como parte de su tesis doctoral y renuncia de los coautores a presentarlos como parte de otra tesis doctoral.

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D.: Vicente Ávila Gandía

DNI 73569372 co-autor de la siguiente publicación: Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, 1 de Mayo de 2019

Firmado: Vicente Ávila Gandía

.

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: Ismael Martínez Guardado con DNI 76023823-Z co-autor de la siguiente publicación:

MUSCLE ARCHITECTURE AND NEUROMUSCULAR CHANGES AFTER HIGH-RESISTANCE CIRCUIT TRAINING IN HYPOXIA.

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Cáceres, a 16 de Mayo de 2019

Firmado: Ismael Martínez Guardado

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: Ismael Martínez Guardado con DNI 76023823-Z co-autor de la siguiente publicación:

EFFECT OF HIGH-INTENSITY RESISTANCE CIRCUIT-BASED TRAINING IN HYPOXIA ON AEROBIC PERFORMANCE AND REPEAT SPRINT ABILITY.

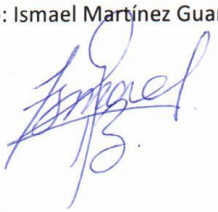
En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Cáceres, a 16 de Mayo de 2019

Firmado: Ismael Martínez Guardado



Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: ARTURO CANACHO VALERA

DNI ~~77722689-P~~ co-autor de la siguiente publicación: Acute Physiological and Performance Responses to High-Intensity Resistance Circuit Training in Hypoxic and Normoxic Conditions

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En XXX, 6 de Mayo de 2019

Firmado: _____

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: Jacobo Á. Rubio Arias

DNI 06261910E co-autor de la siguiente publicación:

· Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia

· Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions

· Additive stress of normobaric hypoxic conditioning to improve body mass loss and cardiometabolic markers in individuals with overweight or obesity: A systematic review and meta-analysis

· The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

· Biochemical responses and physical performance during high intensity resistance circuit training in hypoxia and normoxia

· Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En 06, de mayo de 2019

Firmado: _____

JACOBO Á. RUBIO - ARIAS
06261910

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

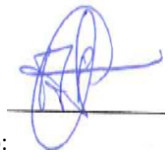
D. /Dª.: Andrés Pérez Hernández con DNI 77720294-M co-autor de la siguiente publicación: Additive stress of normobaric hypoxic conditioning to improve body mass loss andcardiometabolic markers in individuals with overweight or obesity: A systematicreview and meta-analysis

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, 1 de Mayo de 2019

Firmado: 

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Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: CRISTIAN MARÍN PAGÁN

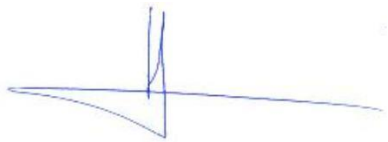
DNI 77713059-S co-autor de la siguiente publicación: *Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability*

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, 2 de mayo de 2019



Firmado: Cristian Marín Pagán

.

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: _JOSE FERNANDO JIMENEZ DIAZ con DNI 03798206D co-autor de la siguiente publicación:

Acute Physiological and Performance Responses to High-Intensity Resistance Circuit Training in Hypoxic and Normoxic Conditions

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

En Toledo 2, de Mayo de 2019

Firmado: Jose Fernando Jimenez Díaz

.

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

Dª. Linda H. Chung, con NIE Y1463302-X, es co-autora de la siguiente publicación: Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia.

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autora sean presentados como parte de otra tesis doctoral.

En Murcia, 2 de Mayo de 2019

Firmado: 

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. GUILLERMO J. OLCINA CAMACHO

DNI 44399860-Q co-autor de la siguiente publicación: "Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability".

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Cáceres, 13 de Mayo de 2019

Firmado: Guillermo J. Olcina Camacho

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Thesis by compendium of publications.
Document of agreement and resignation of co-authors.

D. /Dª.: Brendan Richard Scott, co-author of the following publication:

The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

In accordance with the **doctoral thesis rules which regulates the ordinance of doctoral studies at the Catholic University of Murcia.**

States his/her approval to the presentation of this publication as a part of the doctoral thesis written by D. /Dª. Domingo Jesús Ramos Campo, entitled "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

And expresses his/her resignation to present said publication as a part of another doctoral thesis at any other University.

In 2nd of May, 2019

Signed: _____

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

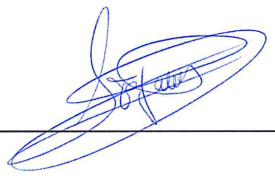
D. /Dª.: Francisco Javier Martínez Noguera con DNI 48491772-K co-autor de la siguiente publicación: Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, 06 de Mayo de 2019

Firmado: 

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

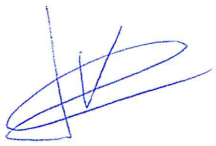
D. /Dª.: **Jorge Carlos Vivas** con DNI **76126599 A** co-autor de la siguiente publicación: *Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability.*

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, a 2 de Mayo de 2019



Firmado: Jorge Carlos Vivas

Thesis by compendium of publications.
Document of agreement and resignation of co-authors.

D. /Dª.: Stéphane DUFOUR

DNI o Passport: 090367802653 co-author of the following publication:

Biochemical responses and physical performance during high-intensity resistance circuit training in hypoxia and normoxia

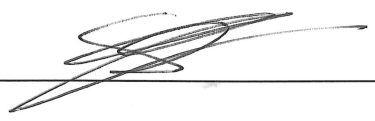
Eur J Appl Physiol, 2017 ; 117(4):809-818

In accordance with the **doctoral thesis rules which regulates the ordinance of doctoral studies at the Catholic University of Murcia.**

States his/her approval to the presentation of this publication as a part of the doctoral thesis written by D. /Dª. Domingo Jesús Ramos Campo, entitled "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

And expresses his/her resignation to present said publication as a part of another doctoral thesis at any other University.

In Strasbourg, France, 2nd of May, 2019

Signed: 

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D. /Dª.: __Pedro Emilio Alcaraz Ramón _____

DNI ___23014777-B_____ co-autor de las siguientes publicaciones:

· Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia

· Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions

· The efficacy of resistance training in hypoxia to enhance strength and muscle growth: A systematic review and meta-analysis

· Biochemical responses and physical performance during high intensity resistance circuit training in hypoxia and normoxia

· Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability

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En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, a 21 ____ de Mayo de 2019

Firmado: _____ PEDRO E. ALCARAZ

Tesis por compendio de publicaciones
Documento de aceptación y renuncia de los co-autores

D./Dª._____Tomás T. Freitas_____
DNI _____Y3994629A_____ co-autor de las siguientes publicaciones:

- Muscle architecture and neuromuscular changes after high-resistance circuit training in hypoxia.

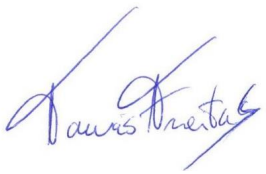
- Acute physiological and performance responses to high-intensity resistance circuit training in hypoxic and normoxic conditions

En acuerdo con la **normativa reguladora de los estudios de doctorado que rige en la Universidad Católica de Murcia (UCAM).**

-Acepto por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de la tesis doctoral de Domingo Jesús Ramos Campo titulada "Hypoxia and exercise: novel treatment strategy for muscle growth and weight loss".

-Renuncio por escrito que los siguientes artículos de los que soy co-autor sean presentados como parte de otra tesis doctoral.

En Murcia, 17 de Mayo de 2019



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