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ORIGINAL ARTICLE

Neuromuscular evaluation of arm-cycling repeated sprints under hypoxia and/or blood flow restriction

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Abstract

Purpose This study aimed to determine the effects of hypoxia and/or blood flow restriction (BFR) on an arm-cycling repeated sprint ability test (aRSA) and its impact on elbow flexor neuromuscular function.

Methods Fourteen volunteers performed an aRSA (10 s sprint/20 s recovery) to exhaustion in four randomized conditions: normoxia (NOR), normoxia plus BFR (N_{BFR}), hypoxia ($FiO_2 = 0.13$, HYP) and hypoxia plus BFR (H_{BFR}). Maximal voluntary contraction (MVC), resting twitch force (Db10), and electromyographic responses from the elbow flexors [biceps brachii (BB)] to electrical and transcranial magnetic stimulation were obtained to assess neuromuscular function. Main effects of hypoxia, BFR, and interaction were analyzed on delta values from pre- to post-exercise.

Results BFR and hypoxia decreased the number of sprints during aRSA with no significant cumulative effect (NOR 16 ± 8; N_{BFR} 12 ± 4; HYP 10 ± 3 and H_{BFR} 8 ± 3; $P < 0.01$). MVC decrease from pre- to post-exercise was comparable whatever the condition. *M*-wave amplitude ($-9.4 \pm 1.9\%$ vs. $+0.8 \pm 2.0\%$, $P < 0.01$) and Db10 force ($-41.8 \pm 4.7\%$ vs. $-27.9 \pm 4.5\%$, $P < 0.01$) were more altered after aRSA with BFR compared to without BFR. The exercise-induced increase in corticospinal excitability was significantly lower in hypoxic vs. normoxic conditions (e.g., BB motor evoked potential at 75% of MVC: $-2.4 \pm 4.2\%$ vs. $+16.0 \pm 5.9\%$, respectively, $P = 0.03$).

Conclusion BFR and hypoxia led to comparable aRSA performance impairments but with distinct fatigue etiology. BFR impaired the muscle excitation–contraction coupling whereas hypoxia predominantly affected corticospinal excitability indicating incapacity of the corticospinal pathway to adapt to fatigue as in normoxia.

Keywords Corticospinal excitability · Transcranial magnetic stimulation · Occlusion · Neuromuscular fatigue · BFR

Abbreviations

1RM	One-repetition maximum
AMT	Active motor threshold
ANOVA	Analysis of variance
aRSA	Repeated arm-cycling sprint ability test
BB	Biceps brachii
BFR	Blood flow restriction
CMEP	Cervicomedullary motor evoked potential
CSP	Cortical silent period
EMG	Electromyography
EMS	Electrical muscle stimulation
ENS	Electrical nerve stimulation
ERT	Estimated resting twitch
ESM	Electronic supplementary material
FiO_2	Fraction of inspired oxygen
GABA	Gamma-aminobutyric acid
H_{BFR}	Hypoxia with BFR
HYP	Hypoxia
MEP	Motor evoked potential
M_{max}	Amplitude of the muscle compound action potential
mRNA	Messenger ribonucleic acid

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M_{SUP}	Amplitude of the muscle compound action potential during maximal voluntary contraction
MVC	Maximal voluntary contraction
M-wave	Muscle compound action potential
N_{BFR}	Normoxia with blood flow restriction
NIRS	Near-infra-red spectroscopy
NME	Neuromuscular function evaluation
NOR	Normoxia
PFC	Pre-frontal cortex
Pmax	Maximal power
POST	After repeated arm-cycling sprint ability test
PRE	Before repeated arm-cycling sprint ability test
RMS	Root mean square
RSA	Repeated sprint ability
SD	Standard deviation
SICI	Short-interval intracortical inhibition
SIT	Superimposed twitch
SpO_2	Peripheral arterial oxygen saturation
TB	Triceps brachii
TMS	Transcranial magnetic stimulation
TSI	Tissue saturation index
TTE	Time to exhaustion
VA	Voluntary activation
VA_{TMS}	Voluntary activation assessed with TMS
η_p^2	Partial eta-squared

Introduction

Repeated sprint ability (RSA) is characterized by the athlete's capacity to repeatedly produce maximal efforts for a short period of time (< 10 s) interspersed with incomplete (< 60 s) recovery and has been defined as an important factor of team-sport performance and intermittent activity efficiency (Girard et al. 2011).

Sprint repetition induces fatigue due to a complex interaction between muscular (peripheral) and neural (central) responses leading to an impairment of the neuromuscular function (Girard et al. 2011). Peripheral fatigue is usually described as a decrease in peak twitch force induced by electrical stimulation whereas central fatigue is characterized by a diminution of voluntary activation (VA) using the interpolated twitch technique (Shield and Zhou 2004). More recently, transcranial magnetic stimulation (TMS) has been used to calculate VA and this method provides additional information [e.g., motor evoked potential (MEP) or cortical silent period (CSP)] about the fatigue that occurs upstream of the motor cortex (Todd et al. 2016).

Collins et al. (2018) proposed that knee extensor neuromuscular fatigue throughout a RSA exercise mainly refers to peripheral impairments during the first five sprints (e.g., peak twitch diminution) but then relies on both peripheral and central perturbations. While the literature about RSA-related neuromuscular function predominantly focuses on the legs, researchers (Pearcey et al. 2016) have also investigated the impact of a RSA test on neuromuscular parameters of the elbow flexors since RSA with the upper limbs is of particular interest in multiple sport activities (e.g., kayak, judo, nordic skiing) and in some rehabilitation modalities. Using a determined number of sprints (i.e., 10), they concluded that arm-cycling sprints impacted neuromuscular function by increasing spinal excitability [e.g., increase in cervicomedullary motor evoked potentials (CMEP) from sprint 1 to sprint 10] and decreasing supraspinal excitability (e.g., decrease in MEP/CMEP ratio from sprint 1 to sprint 5). Gruet et al. (2013) also demonstrated that upper limbs were more sensitive to spinal adaptations compared to lower limb. Furthermore, muscle metabolism also elicits systemic perturbation that could influence oxygen transport, extraction and brain function (Calbet et al. 2009). Considering the smaller muscle mass and the differences in muscle typology (Koppo et al. 2002) involved with arm exercise compared to the legs, it may result in different systemic perturbation, highlighting limb specificities regarding the development of neuromuscular fatigue. There is a lack of information regarding what are the underlying mechanisms limiting RSA performed to exhaustion in the upper limbs.

In the last few years, repeated sprint training in hypoxia has received growing interest in light of a probable, although debated (Goods et al. 2015) optimization of the gains in terms of performance compared to repeated sprint training performed in normoxia (Brocherie et al. 2017). It is then likely that physiological adaptations induced by a single session in hypoxia are more prone to promote gains when repeated chronically. As a specificity, it has been shown that short intermittent bouts of sprints (15 × 5-s leg cycling/25-s passive recovery) combined with acute hypoxia (SpO_2 ~ 84%) induce greater decline in cerebral oxygenation, quadriceps muscle activation and cycling performance than in normoxia, but with no difference in the magnitude of quadriceps fatigue (Billaut et al. 2013). The authors suggested that the central nervous system regulated the development of peripheral muscle fatigue, acknowledging, however, that it was not possible to rule out a direct effect of O_2 desaturation on reducing motor output. Hence, from the only study exploring neuromuscular function pre–post a RSA test performed in hypoxia vs normoxia (Billaut et al. 2013), it is not possible to determine if the origin of fatigue differs and how far performance limitation is predominantly due to systemic, brain and/or muscle hypoxia. One way to evaluate the respective weight of localized vs systemic hypoxia in the genesis and the amount of exercise-induced fatigue would be to dissociate and combine these distinct environmental stressors during a session of RSA.

Localized hypoxia can be achieved by blood flow restriction (BFR) after the inflation of occlusion cuffs in the

proximal portion of the limbs (Willis et al. 2018). This technique has been used for training purposes in combination with low-load resistance exercise, to promote hypertrophy and increase muscle strength due to significant hypoxic stimuli and greater accumulation of metabolites in the exercising muscles (Scott et al. 2015). A study from Fatela et al. (2016) using electromyographic (EMG) indices showed that the use of BFR combined to resistance exercise could enhance muscle activity [e.g., increased EMG root mean square (RMS)] and may increase neuromuscular fatigue. The exact hypoxic response to BFR exercise is not well understood but preliminary evidence suggests that BFR may acutely (i) lead to enhanced hypoxia-inducible factor-1α-mediated cell signaling through an increase of its mRNA expression (Taylor et al. 2016) as classically seen in response to hypoxia (Maxwell 2005) and/or (ii) increase corticospinal excitability, possibly due to altered sensory feedback via group III and IV afferents (Brandner et al. 2015). Hemodynamic responses are known to differ between upper and lower limbs. For example, arm exercise is known to elicit larger increases in arterial blood pressure than leg exercise (Calbet et al. 2015) potentially inducing differences in response to BFR. Whether BFR in upper limbs may specifically modify arm-cycling performance, the amount of fatigue and/or its etiology after high-intensity arm-cycling sprints needs to be clarified. Also, it remains unknown if the combination of BFR plus hypoxia would have cumulative deleterious effects on RSA performance and neuromuscular function.

The purpose of this study was to determine the effects of repeated maximal intensity arm-cycling sprints on elbow flexor neuromuscular function when exercise is performed to exhaustion in normoxia vs. hypoxia and/or BFR. It was first hypothesized that arm-cycling performance would be more impacted under both hypoxia and/or BFR compared to normoxia. Second, it was hypothesized that during exhaustive exercise, BFR would predominantly affect peripheral parameters of fatigue due to the reduction in blood flow restraining the removal of muscle metabolites, while hypoxia would rather exacerbate central fatigue through a direct brain-hypoxic effect.

Materials and methods

Participants

Fourteen healthy volunteers (ten men and four women: age 26 ± 4 years; height 181 ± 6 cm; mass 76 ± 9 kg) provided written informed consent after being informed of the procedures and risks involved in the current study. All participants were physically active (at least 4 h of training per week), unacclimated to high altitude (no sojourn above 2000 m of altitude over the past 3 months) and completed the magnetic stimulation safety checklist for TMS. Two participants were excluded for TMS (one had a metal implant in the head and the other previously had a serious head injury) making 12 participants for TMS parameters only. Participants were asked to refrain from intense physical activity on the day before testing and to refrain from having a meal or drinking caffeinated beverages in the 2 h preceding the tests due to potential effects on exercise responses. This study was conducted according to the seventh revision of the Declaration of Helsinki (2013) and approved by the local ethics committee [CER-VD; protocol number: PB_2016-01,170 (138/15)].

Study design

A preliminary session was first conducted to familiarize participants with sprint exercise on the arm cycloergometer, and with neuromuscular function evaluation (NME) procedures. Individual pressure inducing total brachial artery occlusion was also assessed during this session following 15 min of seated rest (see description below).

At least 3 days after the preliminary session, four experimental sessions (3–4 days apart) were performed for each subject in a randomized order (to limit potential training effect) at a similar time of the day and under standard environmental conditions (temperature 24 ± 2 °C, relative humidity 41 ± 5%, and barometric pressure 731 ± 4 mmHg) in a normobaric hypoxic chamber (ATS Altitude, Sydney, Australia) located in the laboratory at an altitude of 380 m (Lausanne, Switzerland). At the beginning of each session, electrical muscle stimulation (EMS), electrical nerve stimulation (ENS) as well as TMS sites and intensities were assessed to allow the elbow flexors of the right arm to be investigated (see Fig. 1a for an overview). A standardized isometric warm-up was completed with repetitions of 5-s isometric contractions/5-s rest with intensities self-adjusted by the participant to progressively reach maximal voluntary contraction (MVC) during the last three trials. After a subsequent 6-min recovery period, participants performed the NME (see Fig. 1b). After another 6-min recovery period, participants engaged in a repeated arm-cycling sprint ability test (aRSA) to exhaustion. The aRSA test was conducted under either normoxia (NOR), normoxia with BFR (N_{BFR}), hypoxia (HYP, with an inspired fraction of oxygen $FiO_2 = 0.13$) or hypoxia with BFR (H_{BFR}, $FiO_2 = 0.13$). The FiO_2 of 0.13 was chosen based on the previous literature showing no impact on single sprint performance but changes in cerebral oxygenation (Smith and Billaut 2010). Post-NME was measured 2 min after aRSA. This 2-min period was standardized between the end of the aRSA and the beginning of the post-test to adjust the setup. TMS, ENS and EMS to assess corticospinal excitability, and peripheral fatigue were achieved during NME. In addition, arterial (SpO_2), pre-frontal cortex (PFC) and biceps brachii (BB) oxygenation (using

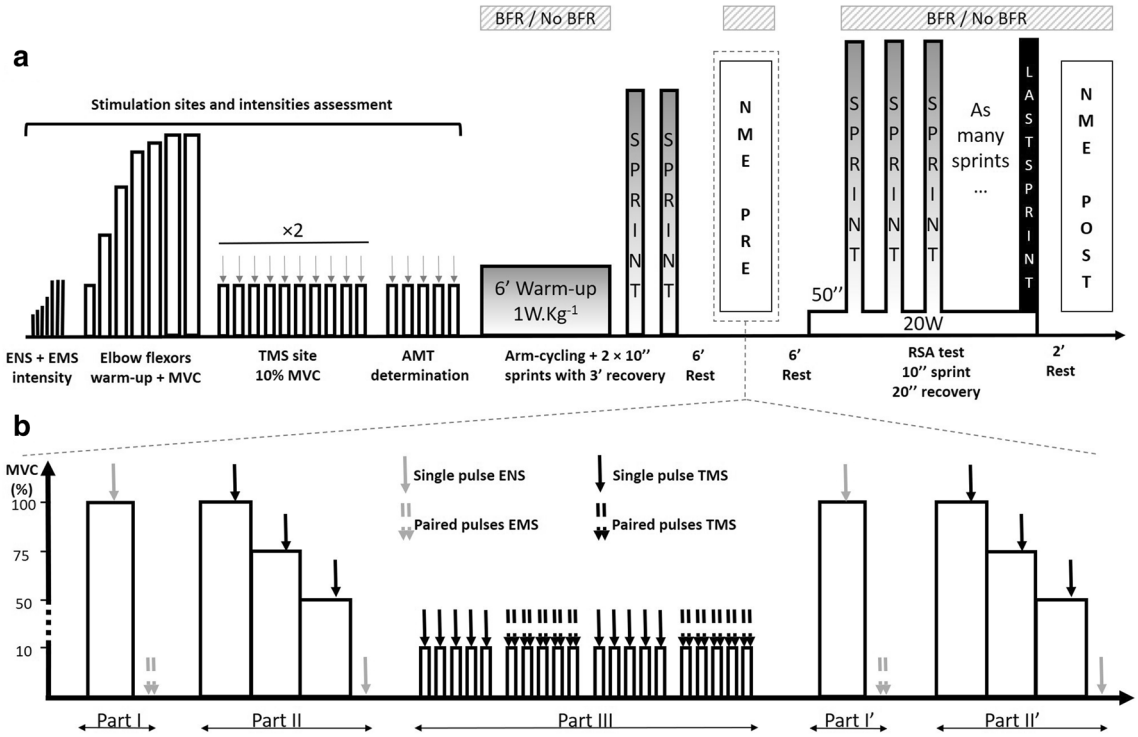

Fig. 1 **a** Protocol overview. **b** Details on neuromuscular function evaluation (NME) performed PRE and POST exercise. *AMT* active motor threshold, *aRSA* arm-cycling repeated sprint ability, *BFR* blood flow restriction, *EMS* electrical muscle stimulation, *ENS* electrical nerve stimulation, *MVC* maximal voluntary contraction, *TMS* transcranial magnetic stimulation

near-infrared spectroscopy) were monitored and EMG signals of the BB and triceps brachii (TB) muscles were measured continuously throughout sessions. Each session lasted ~ 120 min and was executed in a single semi-blinded fashion, as participants were naïve regarding altitude level but were not blinded for the blood flow restriction conditions.

Experimental session

EMG, stimulation sites and intensity assessment

Electromyography recordings EMG signals of the BB and TB muscles were recorded during the whole session with three pairs of bipolar silver chloride surface electrodes (10-mm diameter, Type 0601000402, Contrôle Graphique, France), the reference electrode being placed on the elbow. The recording electrodes were secured lengthwise to the skin over the muscle belly following SENIAM recommendations, with an inter-electrode distance of 20 mm. A low resistance (< 5 kΩ) between the two electrodes was verified after shaving, gently abrading the skin and cleaning it with isopropyl alcohol. Electrode positions were marked using permanent marker during the first session to ensure a reproducible position through subsequent visits. EMG and force signals were amplified, analog-to-digitally converted, band-pass filtered (10–500 Hz, input impedance = 200 MH, common mode rejection ratio = 85 dB, gain = 1000) and recorded at a sampling rate of 2 kHz using BioAmp (octal bio-amplifier ML138, ADInstruments, Bella Vista, Australia) and PowerLab system (16/35, ADInstruments,). Data were stored and analyzed offline with LabChart 8 software (ADInstruments).

Peripheral muscle and nerve stimulation For both EMS and ENS, square-wave pulses (respectively, 100 µs and 200 µs duration) were delivered via high-voltage constant-current stimulators (DS7A; Digitimer, Hertfordshire, UK). Single ENS was delivered percutaneously to the brachial plexus via a 20-mm diameter cathode electrode (Ag–AgCl, Controle Graphique Medical, Brie-Comte-Robert, France) pressed into the supraclavicular fossa and a 50 × 90-mm anode gel pad electrode (Dura-Stick Plus, DJO Global, Vista, USA) placed on the acromion. ENS intensity started at 10 mA and was incremented by steps of 10 mA every 5 s up to the maximal amplitude of BB *M*-wave was reached. Stimulation intensity corresponding at 130% of this latter was used thereafter.

Since ENS to the brachial plexus also recruits the antagonist muscle, paired-pulse EMS (10 Hz) was used instead to obtain the force response of the BB. It was delivered percutaneously via a 45 × 45-mm cathode pad gel electrode (Dura-Stick Plus, DJO Global, Vista, USA) placed over the

BB motor point found using a stimulator pen (Compex SA, Ecublens, Switzerland) and a 50 × 90-mm anode gel pad electrode (Dura-Stick Plus, DJO Global) positioned over the bicipital tendon (2–3 cm proximal to the elbow). Initially, EMS intensity was set at 20 mA, and was augmented by step of 10 mA every 5 s to reach the maximal amplitude of force response. Again, 130% of the defined optimal intensity was used for the whole experiment.

Transcranial magnetic stimulation A magnetic stimulator (Magstim BiStim^2, The Magstim Company, Dyfed, UK) was used to stimulate the motor cortex during voluntary isometric elbow flexion. Single and paired (3-ms interspaced) TMS pulses were delivered with a circular coil (135-mm outside diameter) held tangentially to the skull. Participants wore a swim cap, secured to the skin, on which lines were drawn between the preauricular points and from nasion to inion to identify the vertex. Every 1.5 cm from 3 cm anterior to 3 cm posterior to the vertex was demarcated along the nasal–inion line and also to 2 cm left from this line. At each point, a stimulus was delivered at 50% of maximal stimulator power output during 5-s isometric elbow flexion at 10% MVC. The optimal stimulus site was defined as the one eliciting the largest MEP in the BB and a MEP as small as possible in the TB. The position was drawn directly on the swim cap to ensure reproducibility of the stimulus throughout the session. The optimal TMS site was defined for each session.

The active motor threshold (AMT) was defined from multiple sets of contractions (6 × 5 s on/10 s off) at 10% MVC during which participants received a TMS starting at 25% of maximal stimulator output and increasing by 5% after each set, up to the specific intensity eliciting at least four MEP visually recognizable and ≥ 50 µV out of the six contractions in the BB (Forman et al. 2015). The intensity for eliciting MEP during PRE and POST neuromuscular evaluations was set at 140% of AMT to avoid underestimating evoked responses (Temesi et al. 2014). Short-interval intracortical inhibition (SICI) indices were obtained by administrating two TMS pulses interspaced by 3 ms during contractions at 10% MVC. The first (conditioning) stimulation was set at 70% of AMT and the second (test) stimulation was 140% of AMT.

Arm-cycling position and dynamic warm-up

Participants sat upright, with hips and knees flexed at 90° in front of a cycloergometer (Excalibur, Lode, Groningen, The Netherlands) mounted on a table and equipped with hand grips. The crankset center was on the same level as the chest and arms were nearly straight and shoulders at 90° when the grips reached the further point. Participants were authorized to use their feet to stabilized body position. Participants performed a 6-min bout on the cycloergometer at 1 W/kg. After a 3-min resting period, they subsequently performed two maximal sprints for 10 s, interspaced again with a 3-min recovery. During each sprint, the cycloergometer was set in 'Wingate' mode and the torque factor (i.e., resistance) was set at 0.4 Nm/kg (adjusted from pilot testing). Strong verbal encouragements were given during the sprints to promote maximal efforts.

Arm repeated sprint ability test

The aRSA test consisted of a repetition of 10-s sprints interspersed with 20 s of active recovery (20 W) up to task failure (i.e., volitional stop or inability to maintain a cadence > 70 rpm). Participants were instructed to go "as hard as you can" from the start of every sprint. The mean power of the first sprint of the aRSA test had to reach at least 95% of the best sprint performed during the warm-up to limit any pacing strategies.

Neuromuscular function evaluation

Participants were in a similar position as described above but the right arm was positioned in an isometric ergometer equipped with a strain gauge (Captels, St. Mathieu deTreviers, France) with the shoulder and elbow flexed at 90° allowing measurement of the force evoked or produced voluntarily by the elbow flexors.

As described in Fig. 1b, NME was separated into three distinct parts. It consisted of (I) a supramaximal single-pulse ENS delivered during a brief MVC of the elbow flexors and a paired-pulse EMS delivered 3 s after MVC to assess elbow flexor contractile properties; (II) a voluntary contraction of the elbow flexors with TMS at different torque levels without rest between them (i.e., MVC, followed directly by 75% and 50% MVC all in a continuous way, refer to Mira et al. (2017) for methodology of the technique) to assess corticospinal excitability, CSP, and cortical VA. A single ENS was then delivered 3 s after the last contraction to assess sarcolemma excitability; (III) 20 contractions at 10% of MVC force (3-s on/3-s off) with TMS, where contractions 1–5 and 11–15 were superimposed by a single-pulse TMS to measure MEP and contractions 6–10 and 16–20 superimposed by paired-pulse TMS to assess SICI (Rothwell et al. 2009). Parts I and II were then performed again (I′ and II′, respectively) to complete the testing procedure. This testing procedure lasted ~ 4 min.

Near-infrared spectroscopy measurements

Tissue saturation index was estimated in the BB (TSI_{BB}) and the PFC (TSI_{PFC}) throughout testing sessions using 3 × 2 wavelength (760 and 850 nm) multichannel continuous wave NIRS systems based on spatially resolved spectroscopy (respectively, Portamon and Portalite, Artinis Medical

Systems, the Netherlands) with 30, 35, 40 mm optode distance (between receiver and transmitters). The probes were secured on the skin using double-sided tape and covered to prevent ambient light from disturbing the optode. Elbow flexor muscle oxygenation was assessed from the left BB, and the left PFC oxygenation was assessed between Fp1 and F3 locations according to the international 10–20 EEG system. Data were recorded continuously at the maximum frequency for each device (10 Hz for Portamon and 50 Hz for Portalite) and filtered at 10 Hz with a fourth-order low-pass zero-phase Butterworth filter (cutoff frequency 0.2 Hz).

Cardiorespiratory parameters

Arterial oxygen saturation (SpO_2) was recorded continuously during the session by pulse oximetry at the ear lobe (Radical-7, Masimo Corporation, Irvine, CA, USA).

Blood flow restriction

Narrow (3 cm wide) nylon specialized cuffs were applied to the most proximal portion of the arms. The cuff pressure was regulated by a rapid cuff inflator system (E20 Hokanson, Bellevue, WA, USA). At the beginning of the familiarization session, the cuffs were inflated to 50 mmHg and pressure was slowly raised until the arterial flow was no longer detected during inflation. The pulse (arterial blood flow) was detected using a hand-held bidirectional Doppler probe (Linear probe L12-5L60N; Software EchoWave II 3.4.4, Telemed Medical Systems, Milano, Italy) placed on the brachial artery. This operation was performed two to three times and resting arterial occlusion pressure was set as the mean cuff pressure at which a pulse was not present. Then 45% (95.4 ± 11.9 mmHg) of this value was used during the BFR conditions as recommended by Loenneke et al. (2014). The cuffs were inflated during the dynamic warm-up, 5 s prior to the beginning of neuromuscular testing and 5 s before the first sprint of the aRSA test with a 6-min wash-out period between them.

Data analysis

All the data were analyzed blinded. SpO_2 and TSI were averaged, respectively, over a period of 5 and 10 s at the end of the 20-W period before the first sprint and during the last sprint of the aRSA test. Maximal force was measured during part II of the NME as the maximal force before any TMS stimulation (Fig. 1b). The amplitude of the *M*-wave was measured from the superimposed single-pulse ENS during MVC (M_{SUP}) and in relaxed muscles 3 s after the contraction (M_{max}). EMG root mean square (EMG_{RMS}) was calculated during MVC over a 500-ms period before TMS delivery and normalized using M_{SUP}.

MEPs of the BB were recorded using TMS superimposed on maximal (MEP_{100}) or submaximal (75%, 50%, e.g., MEP_{50}) contractions and were normalized by M_{SUP}. SICI was normalized by MEP obtained on the same level of contraction (i.e., 10%). CSP was manually analyzed as the time between the TMS delivery and the return of prestimulation EMG activity.

Force amplitude for paired EMS at 10 Hz (Db10) was determined as the maximal force measured after paired EMS in relaxed muscle 3 s after the end of MVC. VA_{TMS} was quantified by measuring force responses to TMS. Superimposed twitch (SIT) amplitude evoked during contractions at 100, 75, and 50% MVC, and the *y*-intercept of the linear regression between SITs and voluntary force allowed to quantify the estimated resting twitch (ERT). When linear regression was not linear ($R^2 < 0.9$), ERT was excluded and VA_{TMS} was not calculated for the considered set of contractions. Hence, one subject was excluded from VA_{TMS} measurements, otherwise, R^2 were acceptable permitting VA_{TMS} to be determined in 11 subjects using the equation:

$$VA_{TMS} = \left[1 - \left(SIT \times ERT^{-1}\right)\right] \times 100.$$

The number of sprints was defined as the total sprints performed by the subject before exhaustion, no cutoff (e.g., $\%P_{max}$) was applied and the best sprint (mean power over 10 s) during the aRSA test was calculated.

Statistical analysis was performed on the raw values for sprint performance indices (number of sprints and mean power output of the best sprint) whereas delta (Δ) values were used between PRE and POST, expressed in percentage of PRE to evaluate the effect of altitude and/or occlusion on MVC force, EMG_{RMS}, VA_{TMS}, Db10, M_{max}, MEP, SICI, SpO_2 and TSI.

Statistical analysis

All statistical procedures were completed on Statistica v10 (Statsoft, Tulsa, OK, USA). Grubbs test was used to determined potential outliers and when such a value was detected, it was deleted. If more than one data was determined as outliers or missing for the same period of analysis (i.e., PRE or POST), participants were excluded of the variable analysis (cf. parameters of the *F* value).

Normality of the distributions and homogeneity of the variances were confirmed using Shapiro–Wilk normality tests and the Levene's tests, respectively. Two-way ANOVAs (altitude × occlusion) with repeated measures were performed to evaluate the effect of an aRSA performed in different conditions on performance, MVC force, EMG_{RMS}, VA_{TMS}, Db10, M_{max}, MEP, SICI, SpO_2 and TSI. Post hoc Tukey's tests were applied to determine a difference if the ANOVA revealed a significant main or interaction effect.

Statistical significance was set at $P < 0.05$. Effect sizes are reported as partial eta-squared (η_p^2) for ANOVAs [with interpretation thresholds fixed at 0.02, 0.13, 0.26 for, respectively, small, medium and large (Cohen 1988)]. All data are presented as mean ± SD.

Two additional statistical analyses were performed. Since their results are not the main focus of the study but may be of interest for some readers, they are depicted in electronic supplementary material (ESM) to not overload the article. (1) Two-way ANOVAs (altitude × occlusion) with repeated measures were performed on PRE values only to evaluate the acute effect of altitude and occlusion before the start of the fatiguing test (see results in ESM I); and (2) *T* tests for dependent samples were performed on data PRE/POST aRSA test in NOR condition only to describe variables evolution in terms of absolute values rather than delta in this "control" condition (see results in ESM II).

Results

Performance and saturation indices

As shown in Fig. 2a, occlusion had a significant effect on aRSA test performance decreasing the number of sprints (10 ± 4 in BFR vs. 13 ± 7 without BFR, $F_{(1,13)} = 9.73$, $P < 0.01$, $\eta_p^2 = 0.43$). Altitude also affected performance, (9 ± 3 sprints in hypoxia vs 14 ± 6 in normoxia, $F_{(1,13)} = 14.30$, $P = 0.002$, $\eta_p^2 = 0.52$). Altitude × occlusion interaction did not reach significance but tended to show an attenuation of BFR effect when combined with hypoxia ($F_{(1,13)} = 3.41$, $P = 0.09$, $\eta_p^2 = 0.21$). The same result occurred when considering the total work (time × mean power, not presented here).

Mean power output of the best sprint (Fig. 2b) was impacted by occlusion ($F_{(1,13)} = 7.65$, $P = 0.02$, $\eta_p^2 = 0.37$), but was not impacted by altitude ($F_{(1,13)} = 2.70$, $P = 0.12$) or altitude × occlusion ($F_{(1,13)} = 0.07$, $P = 0.79$). The decrease in MVC force after exercise was not impacted by occlusion ($F_{(1,11)} = 3.39$, $P = 0.09$), altitude ($F_{(1,11)} = 2.37$, $P = 0.15$), or altitude × occlusion ($F_{(1,11)} = 3.03$, $P = 0.11$). Data are presented in Table 1.

Figure 3 shows that ΔSpO_2 and ΔTSI_{PFC} from the end of the warm-up to the end of aRSA were not impacted by occlusion ($F_{(1,13)} = 0.45$, $P = 0.51$ and $F_{(1,13)} = 2.12$, $P = 0.17$, respectively), altitude ($F_{(1,13)} = 2.92$, $P = 0.11$ and $F_{(1,13)} = 0.17$, $P = 0.69$, respectively) or altitude × occlusion ($F_{(1,13)} = 2.21$, $P = 0.51$ and $F_{(1,13)} = 0.17$, $P = 0.68$, respectively).

ΔTSI_{BB} was not impacted by occlusion compared to without BFR ($F_{(1,13)} = 1.43$, $P = 0.25$) but decreased with altitude (−7.6 ± 6.8% vs. +1.3 ± 7.1% in normoxia, $F_{(1,13)} = 35.8$, $P < 0.01$, $\eta_p^2 = 0.73$). The interaction altitude × occlusion was significant ($F_{(1,13)} = 5.61$, $P = 0.03$, $\eta_p^2 = 0.30$) and the post hoc analysis showed different evolution in NOR (+1.9 ± 8.6%) vs. HYP (−10.3 ± 7.4%, $P < 0.01$, $d = 1.52$) and vs. H_{BFR} (−4.8 ± 5%, $P = 0.02$ $d = 0.96$).

Peripheral indices

An example of raw data from typical subjects is presented in Fig. 4. ΔM_{max} from PRE to POST exercise was more impacted with BFR (−9.4 ± 1.9%) compared to without BFR (+0.8 ± 2.0%, $F_{(1,13)} = 14.03$, $P < 0.01$, $\eta_p^2 = 0.52$) but was not affected by altitude ($F_{(1,13)} = 0.98$, $P = 0.34$) or altitude × occlusion ($F_{(1,13)} = 0.23$, $P = 0.64$).

ΔDb10 was significantly greater from PRE to POST exercise in occlusion conditions (−40.8 ± 4.7% vs. −27.9 ± 4.5% without BFR, $F_{(1,13)} = 10.73$, $P < 0.01$, $\eta_p^2 = 0.45$) but was not impacted by altitude ($F_{(1,13)} = 3.43$, $P = 0.09$) or altitude × occlusion ($F_{(1,13)} = 1.01$, $P = 0.37$).

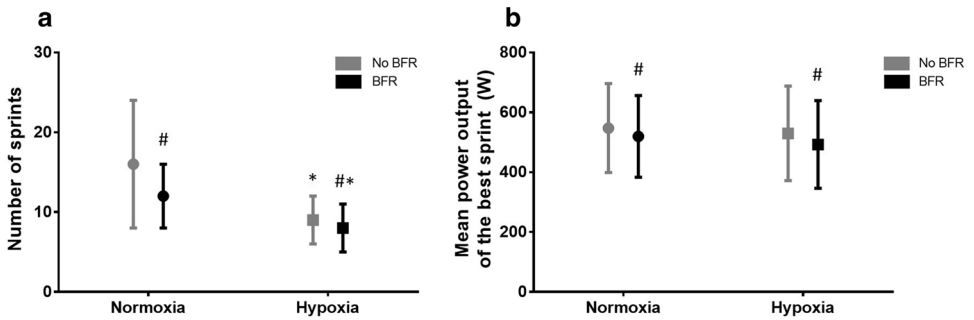

Fig. 2 Performance on the arm-cycling repeated sprint ability test depending on the condition: normoxia without blood flow restriction (NOR), normoxia with BFR (N_{BFR}), hypoxia without BFR (HYP) and hypoxia with BFR (H_{BFR}). **a** Number of sprints completed until exhaustion. **b** Best single sprint performance as mean power output over the 10-s period. Hash indicates a significant main effect of occlusion and asterisk indicates a significant main effect of altitude. Statistical significance set at $P < 0.05$

Table 1 Effects of an arm-cycling repeated sprint ability test to task failure on elbow flexors, saturation index, and neuromuscular function under different combination of hypoxia and blood flow restriction

	Conditions				Factors		
	NOR	N_{BFR}	HYP	H_{BFR}	Altitude	Occlusion	Altitude × occlusion
					P value	*P* value	*P* value
Performance							
TTE (s)	460 ± 220	340 ± 100	250 ± 70	220 ± 70	**0.002**	**0.008**	0.088
Sbest (W)	547 ± 149	520 ± 137	530 ± 158	493 ± 147	0.124	**0.0160**	0.786
ΔMVC (%)	− 16.5 ± 9	− 10.5 ± 12.1	− 11.1 ± 10.4	− 9.8 ± 11.1	0.152	0.093	0.110
Peripheral indices							
ΔM_{max} (%)	0.5 ± 14.6	− 11.6 ± 10.9	1.1 ± 6	− 7.2 ± 12.3	0.339	**0.002**	0.643
ΔDb10 (%)	− 29.3 ± 23.2	− 46.5 ± 19.8	− 26.6 ± 18	− 35 ± 19.8	0.087	**0.006**	0.332
Central indices							
ΔVA_{TMS} (%)	− 3.4 ± 2.8	− 1.3 ± 3.3	− 3.5 ± 6.7	− 4.0 ± 5.6	0.352	0.627	0.360
ΔEMG_{RMS} (%)	18.2 ± 26.5	18.5 ± 18.9	7.8 ± 20.9	− 0.8 ± 20.2	**0.048**	0.538	0.588
ΔMEP_{100} (%)	20 ± 36.4	7.2 ± 11.4	2.6 ± 17.7	− 5.9 ± 13.9	**0.051**	0.182	0.742
ΔMEP_{75} (%)	23.2 ± 33.8	8.8 ± 15.5	− 0.3 ± 21.8	− 4.6 ± 17.1	**0.028**	0.130	0.580
ΔMEP_{50} (%)	15.7 ± 27.2	12.9 ± 12.3	4.7 ± 25.3	− 8.7 ± 10.1	**0.030**	0.072	0.52
ΔCSP_{100} (%)	− 1.7 ± 8.3	5.3 ± 14.9	3.8 ± 6.2	8.1 ± 11.1	0.097	0.064	0.702
ΔCSP_{75} (%)	− 2.5 ± 9.4	3.9 ± 13.5	4.0 ± 9.0	3.7 ± 8.7	0.200	0.327	0.240
ΔCSP_{50} (%)	− 5.4 ± 10.4	0.6 ± 11.4	− 1.1 ± 8.0	1.9 ± 6.2	0.310	0.130	0.487
ΔSICI (%)	4.3 ± 16.6	7.5 ± 20.3	6.6 ± 21.3	− 3.1 ± 18.6	0.407	0.579	0.211

Data are presented as delta from PRE to POST exercise (except for time to exhaustion and the best sprint performance). Values are presented as mean (SD)

Statistical significance was set at $P < 0.05$ and is highlighted by bold type

NOR normoxia without blood flow restriction, N_{BFR} normoxia with blood flow restriction, *HYP* hypoxia without blood flow restriction, H_{BFR} hypoxia with blood flow restriction, *TTE* time to exhaustion, *Sbest* best sprint performed (in mean power), *MVC* maximal voluntary contraction force, M_{max} maximal *M*-wave, *Db10* force evoked by a 10 Hz doublets, VA_{TMS} voluntary activation assess by TMS, EMG_{RMS} EMG root mean square, MEP_{100} MEP_{75}, MEP_{50} motor evoked potential, respectively, during MVC, submaximal contraction at 75 and 50% of MVC, CSP_{100}, CSP_{75}, CSP_{50} cortical silent period, respectively, during MVC, submaximal contraction at 75, and 50% of MVC, *SICI* short-interval intracortical inhibition during contraction at 10% MVC

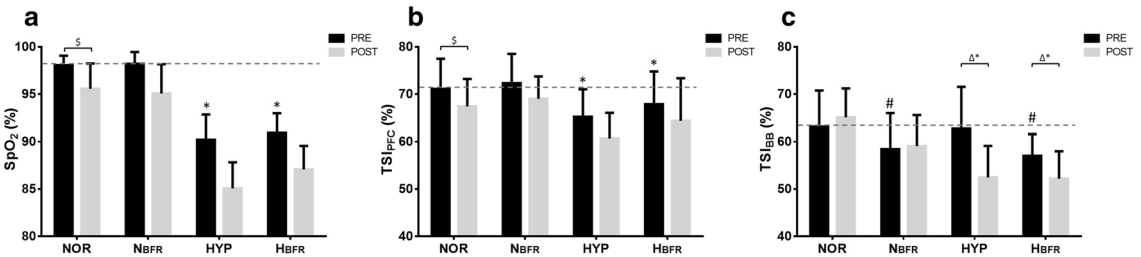

Fig. 3 Arterial and tissue oxygenation PRE and POST arm-cycling repeated sprint ability test. **a** Peripheral arterial oxygen saturation (SpO_2). **b** Tissue saturation index of the biceps brachii (TSI_{BB}). **c** Tissue saturation index of the pre-frontal cortex (TSI_{PFC}). Dotted lines help referring to values observed in control (NOR) condition PRE exercise. Dollar indicates a significant main effect of time, hash indicates a significant main effect of occlusion, asterisk indicates a significant main effect of altitude and delta square indicates a significant main effect of altitude on the delta from PRE to POST aRSA test. Statistical significance set at $P < 0.05$

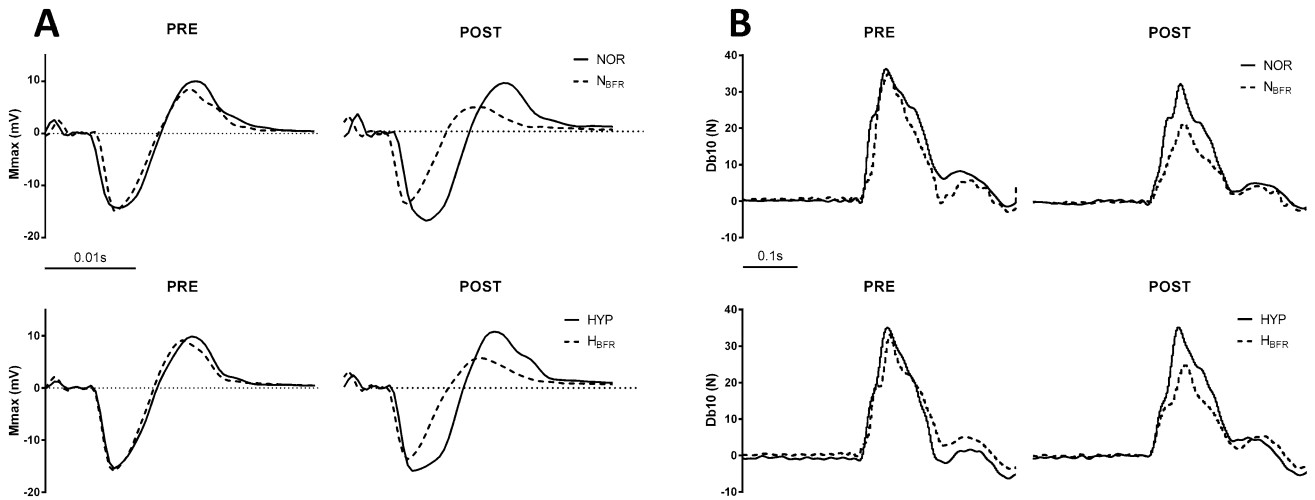

Fig. 4 Peripheral fatigue indices PRE and POST arm-cycling repeated sprint ability test performed in four conditions: normoxia without blood flow restriction (NOR), normoxia with BFR (N_{BFR}), hypoxia without BFR (HYP), and hypoxia with BFR (H_{BFR}). **a** Amplitude of the *M*-wave (M_{max}) measured from the relaxed muscles 3 s after maximal voluntary contraction. **b** Force amplitude for paired electrical muscle stimulation at 10 Hz (Db10) in relaxed muscle 3 s after maximal voluntary contraction. Presented as raw data from a typical subject

Central indices

ΔVA_{TMS} from PRE to POST exercise was not impacted by any factors (occlusion: $F_{(1,10)}=0.25$, $P=0.62$; altitude: $F_{(1,10)}=0.95$, $P=0.35$; altitude × occlusion: $F_{(1,10)}=0.92$, $P=0.36$).

ΔEMG_{RMS} was not impacted by occlusion ($F_{(1,10)}=0.41$, $P=0.54$) or altitude × occlusion ($F_{(1,10)}=0.31$, $P=0.59$) but was significantly less increased with altitude ($+3.5\pm4.2\%$ in hypoxia vs. $+18.3\pm4.1\%$ in normoxia, $F_{(1,10)}=5.09$, $P=0.05$, $\eta_p^2=0.34$).

As shown in Table 1, exercise-induced adaptations in MEP were not affected by occlusion (e.g., ΔMEP_{75}: $F_{(1,9)}=2.78$, $P=0.13$) or altitude × occlusion (e.g., ΔMEP_{75}: $F_{(1,9)}=0.33$: $P=0.58$) but exercise-induced increase in corticospinal excitability was significantly lower with altitude (e.g., ΔMEP_{75}: $-2.4\pm4.2\%$ in hypoxia vs. $+16\pm5.9\%$ in normoxia, $F_{(1,9)}=6.78$, $P=0.03$, $\eta_p^2=0.43$).

ΔCSP from PRE to POST exercise was not impacted by any factors during contractions at 100, 75 or 50% MVC. The same was observed for SICI.

Discussion

The purpose of this study was to determine the effects of systemic hypoxia and/or localized hypoxia induced by BFR on performance and neuromuscular function adaptations induced by an arm-cycling RSA test. The main finding is that the number of sprints performed was similarly decreased when exercise is performed under hypoxia ($FiO_2=0.13$) and/or moderate BFR (45% of resting full ischemia). Regarding the neuromuscular function, BFR impacted the peripheral compartment, specifically leading to an impairment of the muscle excitation–contraction coupling. Contrarily, hypoxia led to lower corticospinal excitability compared to normoxia, potentially indicating an incapacity of the corticospinal pathway to adapt to fatigue as in normoxia.

aRSA test performance

The number of sprints performed to exhaustion decreased both with altitude and occlusion without any clear cumulative effect, indicating that both hypoxic stressors negatively impacted the ability to repeat arm-cycling sprints. It has been shown that partial occlusion impacts muscular endurance during low-load resistance training (up to 40% of 1RM), decreasing the number of repetitions completed at a given intensity (Wernbom et al. 2006). To our knowledge, this is the first study demonstrating such a diminution when repeated sprints are performed with BFR in the arms. Regarding the impact of hypoxia on RSA performance, the topic is more widely documented and the decreased number of sprints performed was expected (Girard et al. 2017). It is yet to determine if the mechanisms responsible for the decrease in the number of sprints are similar for the two modalities.

The mean power of the best sprint performed during each session was lowered by occlusion but not by altitude, leading to speculation that BFR immediately negatively impacts the ability of the neuromuscular system to produce maximal force (cf. MVC, Db10). This could be, at

least partly, related to PRE-exercise lower levels of muscle oxygenation with BFR (refer to ESM I), which is not visible with altitude only. These observations reinforce the assumption that hypoxia per se does not impact short isolated sprint performance (Girard et al. 2017).

Oxygen saturation indices

At the end of the aRSA test, both SpO_2 and TSI_{PFC} decreased in similar ways from warm-up level, no matter the condition. However, since both variables were impacted negatively at rest by altitude (see ESM I), it is likely that the level of deoxygenation at the end of exercise was exacerbated with hypoxia (Fig. 3a). In addition, TSI_{BB} decreased with altitude whereas no changes were noticed in normoxia. It means that despite not being affected by altitude at rest, muscular oxygenation imbalance was exacerbated with altitude compared to normoxia. This implies that the vascular system was not able to match the muscular demand in oxygen during exercise in hypoxic conditions. This supports previous studies that have demonstrated no peripheral vasodilation during leg cycling repeated sprint in hypoxia (Willis et al. 2017). However, further researches are needed regarding the question of peripheral vasodilatation during intermittent supramaximal exercise in hypoxia in the upper limb as the present results do not allow us to investigate this hypothesis. Interestingly, while impacting muscle oxygenation at rest, BFR had no major additional effect during exercise (Fig. 3c). This could be explained by the fact that muscle activity during aRSA test could induce an increase of intramuscular pressure that may reach levels high enough to impede blood flow by itself, therefore, bypassing the effect BFR may have had. This is well known with isometric contractions (Sadamoto et al. 1983) and also occurs during dynamic isolated exercise at 50% of 1RM (Wernbom et al. 2006). It should also be noted that the current study used 45% of the pressure corresponding to total occlusion at rest as recommended by Loenneke et al. (2014) to promote muscle adaptation during resistance training and previously used on lower limb muscle during high-intensity repeated sprint exercise (Willis et al. 2018). It has been shown that during a dynamic exercise, arterial pressure and muscular vasodilation are correlated with the exercise intensity (Saltin et al. 1998). Therefore, in this study, it is likely that supramaximal exercise intensity induced vasodilatation and an increase in arterial pressure sufficient to counteract the action of BFR on tissue oxygenation parameters. Taken together, these results show different oxygenation perturbations regarding the tissue and the use of BFR or hypoxia.

Neuromuscular parameters

No matter the condition, the aRSA test induced comparable changes in MVC from PRE to POST (mean ΔMVC of $-12 \pm 10.7\%$ over conditions, see ESM II for absolute responses on NOR condition only). Note that the tendency towards lower impact of BFR on ΔMVC could be partially related to the fact that BFR already has an effect at rest (i.e., before the fatiguing exercise, see ESM I), therefore, limiting the possible range of force decrease. These results are in accordance with the previous literature showing similar force decrement in the elbow flexors (−9%) after a set of ten repeated sprints in normoxia without BFR (Pearcey et al. 2016). In the present study, despite a lower number of sprints performed in hypoxia and/or BFR condition, the decrease in MVC seems to be consistent, indicating a similar global level of fatigue. Thus, only the rate of fatigue seems to be accelerated rather than its amounts as shown by the shorter TTE (Table 1). After a set of fifteen 5-s leg cycling sprints performed either in normoxia or hypoxia, Billaut and Buchheit (2013) observed similar peripheral fatigue (−54.3% in peak twitch) whereas central indices were more impacted in hypoxia (VA: −3.4% in normoxia and −6.7% in hypoxia; EMG_{RMS}: −7.6% in normoxia and −15.7% in hypoxia). The authors concluded that muscle recruitment and performance were regulated by the central nervous system to restrict the peripheral fatigue generated. However, only systemic hypoxia was used in that previous study. Accordingly, it is unknown if the fatigue etiology would be different depending on local and/or systemic hypoxic stresses.

Peripheral and central fatigue are known to both be partly accountable for the decrease of MVC force after leg cycling sprints (Girard et al. 2011) and arm-cycling sprints (Pearcey et al. 2016). The present study showed a similar decrease in Db10 from PRE to POST (−29.8% in NOR) in line with previous results of Pearcey et al. (2016) in normoxia in the same muscle group (−27.6% for peak twitch with a 5-s delay between the end of the sprint and the measurements). However, this decrease in Db10 was exacerbated in the present BFR conditions. Also, sarcolemma excitability was well preserved in NOR and HYP conditions while M_{max} decreased when exercise was performed with BFR. Together, these observations underline a BFR-induced-specific fatigue etiology through challenging peripheral perturbations. A decrease in Db10 suggests that peripheral fatigue occurred at and/or beyond the sarcolemma and could partly relate to impairments in the muscle excitation–contraction coupling potentially due to an intracellular accumulation of H^+ (Bishop et al. 2004) although debated (Allen et al. 2008), a reduction in blood lactate removal (Thomas 2004) and a phosphocreatine breakdown (Glaister 2005). The known effect of BFR developing an accumulation of muscle metabolites (Loenneke et al. 2011), which is strongly related to the

onset of peripheral fatigue (Kirkendall 1990), could explain the higher decrease of ΔDb10 under BFR conditions. In the literature, M_{max} impairment is explained by the change in ion concentrations across the muscle membrane. During ecological exercise, protecting mechanisms prevent a loss of excitability [refer to Allen et al. (2008) for a review of the mechanisms involved]. However, the use of BFR is known to induce muscular damages (Umbel et al. 2009) leading to sarcolemmal permeability (Wernbom et al. 2012) and, therefore, could imbalance the ion distribution across the sarcolemma explaining the diminution of M_{max}. The link between sarcolemmal excitability and sarcolemmal permeability has been previously reported during exercise (Piitulainen et al. 2008). It is likely that BFR impacts peripheral factors at rest not only due to tissue deoxygenation but also because of an impairment of the metabolite's removal per se during exercise.

As a global index of central fatigue, the present study showed a decrease of VA_{TMS} after exhaustive dynamic exercise of the elbow flexors in normoxia without BFR (refer to ESM II for details). Comparable VA_{TMS} decrements were observed whatever the condition. Exercising with hypoxia can lead to cerebral perturbation and exacerbated central fatigue (Goodall et al. 2010). It looks like the present experimental conditions were not constraining enough to aggravate the diminution of VA measurements in comparison to normoxia. The reason might be the relatively moderate systemic hypoxic stimulus used ($FiO_2 = 0.13$) compared to other studies [e.g., Goodall et al. (2010), $FiO_2 = 0.10$] and the moderate muscle mass involved in the task (i.e., arms vs. legs) preventing SpO_2 to decrease towards critical values for the central nervous system [e.g., 85–90% vs ~ 75–80% for Goodall et al. (2010) to fully activate motoneurons]. Hence, with higher systemic constrains, these authors reported an exacerbated central fatigue with less peripheral fatigue for a similar decrease in MVC (i.e., modified fatigue etiology compared to normoxia) what could, however, explain the tendency of altitude to limit the decrease in ΔDb10 force in the current study.

MEP amplitude in the BB tended to increase from PRE to POST aRSA test in normoxic conditions at 100, 75 or 50% of the MVC. Pearcey et al. (2016) showed that during the first five sprints, MEP amplitude decreased before returning to resting values after the tenth sprint. However, participants stopped the exercise before exhaustion maybe preventing them to increase MEP value even higher than the resting values. In another study (Fernandez-del-Olmo et al. 2013), MEP amplitude at 75 and 50% of MVC increased after a set of two 30-s Wingate test. It has been hypothesized that the increase in MEP could be an adaptation from the corticospinal pathway to compensate for a decrease of force production due to peripheral fatigue (Gruet et al. 2013). In hypoxia, MEP did not increase as in normoxia. This indicates lower exercise-induced excitability of the motor cortex in hypoxia compared to normoxia and potentially incapacity of the corticospinal pathway to adapt as in normoxia. Similar results were observed for ΔEMG_{RMS} during MVC in the BB with lower increases in hypoxia compared to normoxia potentially indicating an incapacity of the central nervous system to adapt fully during acute hypoxic exposure. Those results can be related to the effect of hypoxia on TSI_{PFC} leading to lower cerebral oxygenation levels and altered corticospinal excitability (although these perturbations are not marked enough to impact more global central indices such as VA). In the present study, BFR did not induce any measurable central adaptations in comparison to without BFR as observed by Brandner et al. (2015), who mentioned the potential impact of BFR on III and IV afferents that would modulate corticospinal excitability. This might be explained by the relatively low pressure used to elicit BFR and the specificity of the exercise (as discussed above in the "Oxygen saturation indices" section), therefore, limiting the impact of BFR on sensory feedback. No differences were found regarding the impact of an aRSA test performed with or without altitude and occlusion on SICI results, suggesting that neither hypoxia and/or BFR would impact directly intracortical inhibition through $GABA_A$ receptor activity. In accordance with previous studies measuring neuromuscular parameters after locomotive tasks in normoxia (Jubeau et al. 2014), CSP was not lengthened after aRSA test neither by occlusion nor altitude suggesting that intracortical inhibition through $GABA_B$ receptors activity was not impacted at exhaustion. Despite a moderate specific impact of altitude on fatigue etiology, evidences converge to consider that exercising within hypoxia rather than normoxia or BFR challenges predominantly central parameters and it can be hypothesized that this effect would be exacerbated with lower FiO_2 level than in the present study.

Methodological considerations

As a limitation, neuromuscular function was not able to be assessed immediately at the end of the aRSA tests. We must acknowledge that this could have induced some underestimation regarding both the peripheral (Froyd et al. 2013) and central parameters of fatigue (Mira et al. 2017). Further research should definitively explore the time course of recovery of the neuromuscular function after high-intensity exercise coupled with different hypoxic stressors. However, the time between exhaustion and post-exercise neuromuscular tests was strictly standardized to 2 min as previously used in the literature (Jubeau et al. 2017) to ensure similar testing conditions no matter the session.

Conclusion

The number of sprints performed during an aRSA test and the decline in the ability to produce force after exercise decrease to a similar extent when exercise was performed under hypoxia and/or moderate BFR. However, fatigue etiology differs depending on hypoxic modalities. BFR specifically led to an impairment of the muscle excitation–contraction coupling probably due to an immediate muscle deoxygenation and impairment in metabolite removal ability during exercise, whereas hypoxia predominantly impacted corticospinal excitability in line with lower levels of cerebral oxygenation, potentially indicating incapacity of the corticospinal pathway to adapt to fatigue as in normoxia. Further investigations are needed to understand the recovery time course of central and peripheral components and the potential exacerbated impact of higher systemic/localized hypoxic doses on fatigue etiology.

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Author contributions GPM, FB, NP, and TR designed the study methodology. AP and SW collected the data and analyzed the results. AP, SW, and TR drafted the article. All authors reviewed and revised the work. All authors reviewed the final article and approved it for submission.

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Compliance with ethical standards

Conflict of interest AP was supported by a doctoral research grant from University Savoie Mont Blanc and the French Conseil Savoie Mont Blanc. The authors declare that they have no conflict of interest.

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