Time-dependent effect of acute hypoxia on corticospinal excitability in healthy humans

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1HP2 Laboratory, Joseph Fourier University & CHU Grenoble, Grenoble, France; 2U1042, INSERM, Grenoble, France; 3Laboratoire de Physiologie de l’Exercice, Université de Lyon, Saint-Etienne, France; 4Laboratoire “Motricité, Interactions, Performance,” University of Nantes, Nantes, France; and 5Movement To Health (M2H) Laboratory, Euromov, Montpellier-I University, Montpellier, France

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Rupp T, Jubeau M, Wuyam B, Perrey S, Levy P, Millet GY, Verges S. Time-dependent effect of acute hypoxia on corticospinal excitability in healthy humans. J Neurophysiol 108: 1270–1277, 2012. First published June 13, 2012; doi:10.1152/jn.01162.2011—Contradictory results regarding the effect of hypoxia on cortex excitability have been reported in healthy subjects, possibly depending on hypoxia exposure duration. We evaluated the effects of 1- and 3-h hypoxia on motor corticospinal excitability, intracortical inhibition, and cortical voluntary activation (VA) using transcranial magnetic stimulation (TMS). TMS to the quadriceps cortex area and femoral nerve electrical stimulations were performed in 14 healthy subjects. Motor-evoked potentials (MEPs at 50–100% maximal voluntary contraction; MVC), recruitment curves (MEPs at 30–100% maximal stimulator power output at 50% MVC), cortical silent periods (CSP), and VA were measured in normoxia and after 1 (n = 12) or 3 (n = 10) h of hypoxia (FiO2 = 0.12). One-hour hypoxia did not modify any parameters of corticospinal excitability but reduced slightly VA, probably due to the repetition of contractions 1 h apart (96 ± 4% vs. 94 ± 4%; P = 0.03). Conversely, 3-h hypoxia significantly increased J) MEPs of the quadriceps muscles at all force levels (+26 ± 14%, +24 ± 12%, and +27 ± 17% at 50, 75, and 100% MVC, respectively; P = 0.01) and stimulator power outputs (e.g., +21 ± 14% at 70% maximal power), and 2) CSP at all force levels (+20 ± 18%, +18 ± 19%, and +14 ± 22% at 50, 75, and 100% MVC, respectively; P = 0.02) and stimulator power outputs (e.g., +9 ± 8% at 70% maximal power), but did not modify VA (98 ± 1% vs. 97 ± 3%; P = 0.42). These data demonstrate a time-dependent hypoxia-induced increase in motor corticospinal excitability and intracortical inhibition, without changes in VA. The impact of these cortical changes on physical or psychomotor performances needs to be elucidated to better understand the cerebral effects of hypoxemia.

motor cortex; magnetic stimulation; muscle

INTEGRITY OF THE BRAIN FUNCTION profoundly depends on oxygen availability, and reduced oxygen supply cannot be tolerated for long periods without critical cerebral consequences. Neurons mostly rely on oxidative metabolism for maintenance of ion homeostasis and membrane potential. They quickly sense reduced oxygen availability and consequently decrease their metabolic requirement and activity (Neubauer and Sønderram 2004). This may have functional consequences in healthy humans exposed to hypoxia, such as impaired cognitive performances (Virues-Ortega et al. 2004) or alterations in central motor command during fatiguing exercise (Amann et al. 2007; Goodall et al. 2010). Arguments in favor of hypoxia-induced perturbations of cerebral neuron activity also come from electroencephalographic recordings indicating reduced activity in hypoxia compared with normoxia both at rest (Ozaki et al. 1995) and during mental tasks (Papadelis et al. 2007).

Only a few studies have evaluated in healthy subjects the effect of hypoxia on motor corticospinal excitability as assessed with transcranial magnetic stimulation (TMS). After 10-min wash-in periods with inspiratory oxygen fraction (FIO2) from 0.16 to 0.10 and pulse oxygen arterial saturation (SpO2) from 93 to 74%, Goodall et al. (2010) reported no change in MEP amplitudes and CSP compared with normoxia, suggesting that corticospinal excitability and inhibition remained unaffected after some minutes of hypoxic gas inhalation. Conversely, after 20–30 min with FIO2 = 0.12 (SpO2 ~75%), Szubski et al. (2006) showed unchanged MEP amplitudes but reduced resting motor threshold (RMT) and shorter CSP compared with normoxia, suggesting that acute hypoxia may increase motor corticospinal excitability and decrease intracortical inhibition. Evaluation of motor corticospinal excitability by TMS after 3–5 days at 4,554 m (SpO2 ~84%) (Mischio et al. 2009) indicated higher RMT and lower short-interval intracortical inhibition as well as tendencies towards lower MEP and intracortical facilitation compared with normoxia. This suggests that prolonged hypoxic exposure in healthy subjects can lead to a hypoexcitability of both the excitatory and inhibitory cortical circuits. These differences between studies regarding the effects of hypoxia at rest on corticospinal excitability suggest that the length of exposure to hypoxia may be critical regarding its impact on cortex excitability and emphasize the need to further investigate the effect of hypoxia on corticospinal excitability. Moreover, the consequences of potential changes in corticospinal excitability and intracortical inhibition due to hypoxia on central motor command remain also to be clarified (Gandevia and Taylor 2006; Kalmar and Cafarelli 2006; Smith et al. 2007).

Therefore, the present study aimed to evaluate the effect of 1-h and 3-h hypoxic gas inhalation in healthy subjects on motor corticospinal excitability and inhibition and the effect of potential changes in corticospinal excitability on maximal voluntary activation (VA) assessed by TMS. One-hour hypoxic breathing encompasses most of the exposure durations used in previous studies investigating the neuromuscular effects of hypoxia at rest and during exercise (e.g., Goodall et al. 2010; Szubski et al. 2006). Three-hour hypoxic exposure corresponds to the earliest signs of acute mountain sickness including
symptoms such as headache and tiredness (Hackett and Roach 2001) that have been previously correlated to changes in cortex excitability (Miscio et al. 2009). We hypothesized that longer hypoxic exposure would induce greater impairment of both excitatory and inhibitory cortical circuits that would be associated with impaired VA level.

MATERIALS AND METHODS

Subjects. Fourteen healthy physically active male subjects were studied, 12 in the first part of the protocol (age: 35 ± 9 yr, body mass: 70 ± 9 kg, height: 176 ± 7 cm) and 10 in the second part (age: 37 ± 7 yr, body mass: 73 ± 7 kg, height: 180 ± 5 cm; no significant difference compared with Part 1, P > 0.05). Eight subjects performed both parts of the protocol. The study was approved by the local ethics committee and performed according to the Declaration of Helsinki. All subjects gave their written informed consent before participating in the study.

Experimental setup. This study was part of a larger project evaluating the effect of hypoxia on exercise-induced neuromuscular fatigue, and data measured before exercise only were used to assess the effect of hypoxia duration on motor corticospinal excitability and VA. The study protocol included two parts: the first part evaluated the effect of 1-h hypoxic exposure while the second part evaluated the effect of 3-h hypoxic exposure (Fig. 1A). In the first part of the protocol, subjects were evaluated on the same day before and after 1 h of hypoxic breathing. In the second part, subjects were evaluated on two occasions (at least 72 h apart) after either normoxic or hypoxic breathing, in a randomized, counterbalanced order. Hence, in both parts of the protocol, normoxic and hypoxic measurements were performed at the same time of the day ± 1 h to avoid the effect of diurnal variations in corticospinal excitability (Tamm et al. 2009).

The effect of hypoxia on motor corticospinal excitability, VA, neuromuscular transmission, and muscle contractile properties was assessed on the right quadriceps femoris muscle under isometric conditions. TMS was used to assess motor corticospinal excitability and intracortical inhibition from MEP and CSP measurements. Electromembrane nerve stimulation (ENS) was performed to measure neuromuscular transmission and contractile properties. VA was assessed with both ENS and TMS (see below).

Subjects refrained from physical exercise on the two days prior to the tests, refrained from drinking caffeinated beverages on test days, and were required to sleep for at least 7 h the night before the tests and to have their last meal at least 2 h prior to the tests. Subjects sat on a custom-built quadriceps chair with the right hip angle set at 90° and knee joint angle set at 100° of flexion. A noncompliant strap connected to a strain gauge (Captels, St Mathieu de Treviers, France) was attached around the subject’s shank, 3–5 cm above the tip of the lateral malleoli. The subjects were firmly secured to the chair with noncompliant straps to minimize body movement. Subjects were at rest for at least 20 min before the first measurements, permitting skin preparation and electrode placing. Subjects inhaled the gas mixtures (normoxic with FIO2 = 0.21 or hypoxic with FIO2 = 0.12) delivered by an Altitrainer 200 (SMTEC, Nyon, Switzerland) via a face mask and were blinded for the gas mixture composition. This FIO2 level is equivalent to an altitude of ∼4,100 m and induced arterial desoxygenation in healthy subjects comparable to values typically observed in hypoxic respiratory patients at sea level.

Neurophysiological evaluations summarized in Fig. 1B included the following stages: 1) electromyographic (EMG) electrodes placement, 2) determination of ENS intensity, 3) measurement of maximal voluntary force (~10 submaximal warm-up knee extensions followed by 2 MVC, 1 min apart), 4) determination of the optimal TMS site, 5) determination of the optimal TMS intensity (recruitment curve), 6) two MVCs followed by supramaximal ENS to assess knee extensors contractile properties, and 7) assessment of peripheral (with ENS) and cortical (with TMS) VA. The whole procedure lasted for ∼1 h. In Part 1 of the protocol, all measurements from stage 5 to stage 7 were repeated after 1 h of hypoxic gas inhalation. In Part 2 of the protocol,

Fig. 1. Description of the study protocol (A) and the neurophysiological evaluations (B). A: normoxic/hypoxic exposure and neurophysiological evaluations (hatched square) in Parts 1 and 2 of the protocol. B: after setting electromyographic recording and electrical femoral nerve stimulation (ENS), maximal voluntary and evoked quadriceps responses were measured, the optimal transcranial magnetic stimulation (TMS) site was determined (in Part 1, the optimal TMS site was defined in normoxia only and kept the same in hypoxia), TMS at different stimulator intensities were performed to establish the optimal intensity, and peripheral and cortical maximal voluntary activation levels were assessed (see MATERIALS AND METHODS). MVC, maximal voluntary contraction.
all neurophysiological evaluations were performed identically after 3 h of normoxic or hypoxic breathing.

ENS. ENS was delivered percutaneously to the femoral nerve by a cathode electrode (20-mm diameter) pressed in the femoral triangle, 3–5 cm below the inguinal ligament. The anode, a 5 × 10-cm gel pad electrode (Compex, Ecublens, Switzerland), was located over the gluteal fold. For both single and paired stimulations (see below), square wave pulses (1-ms duration) were produced via a high-voltage (maximal voltage 400 V) constant-current stimulator (Digitimer DS7, Hertfordshire, UK). For all stimulus modalities, stimulation intensity corresponded to 150% of the optimal intensity (range 38–95 mA), i.e., the stimulus intensity at which the maximal amplitude of both twitch force and concomitant quadriceps muscle M-wave were reached. Supramaximal ENS was delivered 1) 2 s after the MVCs with paired stimulations at 100 Hz (10-ms interstimulus interval) and 2) during and 2 s after the last MVC of the four-contraction sets for VA assessment (see below) and M-wave measurement with single stimulations (see Fig. 1B).

TMS. A magnetic stimulator (Magstim 200; The Magstim, Dyfed, UK) was used to stimulate the motor cortex. Single TMS pulses of 1-ms duration were delivered via a concave double-cone coil (110 mm diameter; maximum output 1.4 T) positioned over the vertex of the scalp and held tangentially to the skull. The coil was slightly moved (following sagittal and coronal planes) to preferentially activate the left motor cortex (contralateral to the right leg) until eliciting the largest MEP in the rectus femoris with only a small MEP in the biceps femoris during knee extensions at 20% MVC and with a stimulation intensity of 70% of the maximal stimulator power output. The optimal stimulation site was rigorously marked over the scalp to ensure reproducibility of the stimulation conditions for each subject throughout the entire experimental day. Then, following 3 min of rest and at each measurement time point (i.e., in normoxia and in hypoxia), stimulations during brief (~4 s) knee extensions at 50% MVC, i.e., the force level inducing the largest MEP on the quadriceps muscles (Sidhu et al. 2009), were performed at 30, 40, 50, 60, 70, 80, 90, and 100% of the maximal stimulator power output, with four trials for each stimulation intensity (10-s separated contractions at the same intensity, 30-s separated series of 4 contractions; stimulation intensities of the series were randomized). The stimulation intensity that elicited the largest rectus femoris MEP with small MEP of biceps femoris (amplitude <10% of maximal rectus femoris M-wave) was selected for subsequent VA assessment. After another 3 min of rest, VA assessment consisted of four sets of four brief (~4 s) contractions at 100, 75, 50, and 100% MVC, with 10 s of rest between contractions and 30 s between series (Sidhu et al. 2009). TMS was delivered on the first three contractions, and ENS (single stimulation) was delivered during and 2 s after the last contraction (Fig. 1). Strong verbal encouragements were given during MVCs, and real-time visual feedback of target torque levels was provided via custom software (Labview 8; National Instruments, Austin, TX) on a computer screen throughout the experiment.

EMG recordings. The EMG signal was recorded from the right vastus lateralis, rectus femoris, vastus medialis, and biceps femoris muscles (as a surrogate for antagonist hamstring muscles) with four pairs of silver chloride surface electrodes of 20 mm diameter (Universal ECG electrode, Control Graphic Medical, Brie Comte Robert, France) during ENS and TMS. Low resistance (<5 kΩ) between the two electrodes was obtained by shaving, light abrasion of the skin, and cleaning with alcohol. Recording electrode locations were based on SENIAM recommendations (Hermens and Freriks 1997) with an interelectrode distance of 20 mm. The reference electrode was fixed over the patella. The positions of the EMG electrodes were marked with indelible ink on the first experimental day to ensure that they were placed in the same location at subsequent visits. EMG signals were amplified and band-pass filtered (5 Hz–1 kHz) using BioAmp and PowerLab systems (ADInstruments, Bella Vista, Australia), recorded at a sampling rate of 2 kHz, and stored on a computer for subsequent analysis.

Arterial saturation. SpO2 and heart rate (HR) were measured continuously using a pulse oximeter (Pulsox 300; Konica Minolta, Osaka, Japan) placed on the forefinger.

Data analysis. MEP peak-to-peak amplitudes of quadriceps muscles during TMS superimposed on submaximal and maximal contractions were normalized to peak-to-peak amplitudes of the M-waves during single ENS delivered on relaxed muscle 2 s after the MVC. The duration of the CSP was determined as the interval from stimulation to the time at which poststimulus EMG activity exceeded, for at least 100 ms, ±2 SD of the prestimulus EMG calculated as the averaged signal over the 500 ms preceding the stimulation (Goodall et al. 2010). Because similar results were obtained for all quadriceps muscles, the averaged MEP amplitudes and CSP values from the vastus lateralis, rectus femoris, and vastus medialis were calculated in each condition and used for further analysis.

Peripheral VA was assessed using twitch interpolation technique (Merton 1954). Briefly, the force produced during a superimposed single twitch (TwQs) delivered at peak force during the MVC was compared with the force produced by a single ENS delivered on relaxed muscle 2 s after the MVC (TwQp), and peripheral VA (%) was calculated using the equation: \[1 - \left(\frac{\text{TwQs}}{\text{TwQp}}\right) \times 100\]. Cortical VA was quantified by measurement of the force responses to TMS. Because motor cortex and spinal cord excitability increase during voluntary contractions, it is necessary to estimate rather than directly measure the amplitude of the resting twitch evoked by motor-cortex TMS (Todd et al. 2003). The mean superimposed twitch (SIT) amplitude evoked during contractions at 100, 75, and 50% MVC was calculated, and the y-intercept of the linear regression between the mean SITs and voluntary force was used to quantify the estimated resting twitch (ERT) (Goodall et al. 2009; Sidhu et al. 2009; Todd et al. 2003). Cortical VA (%) was then calculated using the equation: \[1 - \left(\frac{\text{SIT}}{\text{ERT}}\right) \times 100\]. The reliability of this method for the determination of cortical VA for the knee extensors has been described recently (Goodall et al. 2009; Sidhu et al. 2009).

Peak forces measured during MVC (before the magnetic stimulation) and TwQs, MEPs, CSPs, M-wave, and VA were calculated as the averaged values obtained during the four sets of contractions (see Fig. 1) performed at each time point. Peak force during paired ENS at 100 Hz on relaxed muscles was also measured at each time point.

Statistical analyses. Normality of distribution and homogeneity of variances of the main variables were confirmed using a Skewness-Kurtosis normality test and the Levene’s test, respectively. In both parts of the protocol, two-way \(\text{FIO}_2\) (normoxic 0.21 or hypoxic 0.12) × force contraction level (50, 75, 100% MVC) or stimulation intensity (30–100% of the maximal stimulator output) ANOVA with repeated measures was performed for each dependent variable. Post hoc Fisher tests were applied to determine a difference between two mean values if the ANOVA revealed a significant main effect or interaction effect. Relationships between changes in MEP, CSP, VA, and SpO2 were also determined by Pearson product correlation. For all statistical analyses, an alpha level of 0.05 was used as the cut off for significance. All descriptive statistics presented are mean values ± SD.

RESULTS

Part I: effects of 1-h hypoxic breathing. SpO2 was 98 ± 1% in normoxia and 83 ± 5% after 1 h of hypoxia (main \(\text{FIO}_2\) effect: \(F_{(1,11)} = 127.2, P < 0.001\)). HR was 65 ± 8 bpm in normoxia and 69 ± 10 bpm after 1 h of hypoxia (\(P = 0.98\)). MEP amplitudes during contractions at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output are shown in Fig. 2A. No significant difference was observed between normoxia and hypoxia (\(P = 0.93\)).

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Similar optimal TMS intensities were determined in normoxia (70 ± 10%) and after 1 h of hypoxic breathing (73 ± 8%; P = 0.19). MEP amplitudes during contractions at 50, 75, and 100% MVC with the optimal TMS intensity are shown in Fig. 3A. No significant difference was observed between normoxia and hypoxia (P = 0.78). Similarly, no significant difference was observed in CSP during contractions at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output (Fig. 4A; P = 0.49) and during contractions at 50, 75, and 100% MVC with the optimal TMS intensity (Fig. 5A; P = 0.36).

Peak forces during maximal voluntary and evoked contractions, M-wave amplitudes as well as cortical and peripheral VA, are shown in Table 1. Peak forces during MVC (main FIO₂ effect: $F_{(1,11)} = 7.0, P = 0.02$) and paired ENS at 100 Hz (main FIO₂ effect: $F_{(1,11)} = 11.4, P = 0.006$) were significantly reduced after 1 h of hypoxic breathing compared with normoxia while no significant change in peak force during TwQP (P = 0.13) was observed. M-wave amplitudes (P > 0.20 for all quadriceps muscles) and peripheral VA (P = 0.48) did not differ significantly between normoxia and hypoxia. Cortical VA, however, was significantly reduced in hypoxia compared with normoxia (main FIO₂ effect: $F_{(1,11)} = 5.8, P = 0.03$).

**Part 2: effects of 3-h hypoxic breathing.** SpO₂ was 96 ± 1% in normoxia and 86 ± 5% after 3 h of hypoxia (main FIO₂ effect: $F_{(1,9)} = 45.1, P < 0.001$). HR was 75 ± 13 bpm in normoxia and 80 ± 18 bpm after 3 h of hypoxia (P = 0.41). MEP amplitudes during contractions at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output were shown in Fig. 2B. MEP amplitudes were significantly higher in hypoxia compared with normoxia (main FIO₂ effect: $F_{(1,63)} = 7.1, P = 0.03$). Similar optimal TMS intensities were determined in normoxia (60 ± 10%) and after 3 h of hypoxic breathing (63 ± 9%; P = 0.19). MEP amplitudes during contractions at 50, 75, and 100% MVC with the optimal TMS intensity are shown in Fig. 3B. MEP amplitudes were significantly higher in hypoxia compared with normoxia (main FIO₂ effect: $F_{(1,36)} = 10.3, P = 0.01$). Also, CSP were significantly longer in hypoxia compared with normoxia during contractions at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output (Fig. 4B; main FIO₂ effect: $F_{(1,63)} = 6.3, P = 0.04$) and during contractions at 50, 75, and 100% MVC with the optimal TMS intensity (Fig. 5B; main FIO₂ effect: $F_{(1,36)} = 8.1, P = 0.02$).

Peak forces during voluntary and evoked contractions, M-wave amplitudes as well as cortical and peripheral VA, are shown in Table 1. No difference was observed between normoxia and hypoxia (all P > 0.05).

Hypoxia-induced changes in MEP or CSP did not correlate with changes in VA or SpO₂ (all r² < 0.15 and P > 0.05).
When comparing the effect of 1 and 3 h of hypoxic breathing in the eight subjects having performed both parts of the protocol, 3-h hypoxia induced significantly larger increase in MEP amplitudes during contractions at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output (main FIO₂ effect: $F_{(1,49)} = 6.9, P = 0.03$) and during contractions at 50, 75, and 100% MVC with the optimal TMS intensity (main FIO₂ effect: $F_{(1,14)} = 8.2, P = 0.02$) compared with 1-h hypoxia. Changes in CSP were also larger after 3 h compared with 1-h hypoxic breathing at 50% MVC with TMS intensities from 30 to 100% of the maximal magnetic stimulator output (main FIO₂ effect: $F_{(1,49)} = 6.5, P = 0.04$) while a tendency toward larger increase during contractions at 50, 75, and 100% MVC with the optimal TMS intensity was observed (main FIO₂ effect: $F_{(1,14)} = 2.7, P = 0.10$). No other difference was observed between responses to 1- and 3-h hypoxic breathing.

**DISCUSSION**

In the present study, we used the recently described methods based on quadriceps (i.e., a major locomotor muscle) responses during TMS (Goodall et al. 2009; Sidhu et al. 2009) to evaluate the effects of 1- and 3-h hypoxic exposure on motor corticospinal excitability and cortical VA. MEP amplitudes as well as CSP were significantly increased after 3 h of hypoxic exposure only, indicating a time-dependent effect of hypoxia on corticospinal excitability. These changes in corticospinal excitability after 3 h of hypoxia were not accompanied by any change in cortical VA and MVC.

**Methodological aspects.** We defined the optimal TMS site and intensity during submaximal contractions that are known to radically increase cortical excitability compared with muscles in a relaxed state, rather than setting the TMS intensity based on the resting motor threshold, because all subsequent MEP, CSP, and VA measurements were performed during voluntary contractions. This is nevertheless inconvenient as it requires numerous submaximal voluntary contractions (~50) that may be demanding for the subjects and even lead to some degree of fatigue despite the rest periods set between contractions and stages of the neurophysiological evaluations. In the first part of the protocol, when neuromuscular evaluations were repeated twice before and after 1 h of hypoxic breathing, we observed a slight but significant force reduction for MVC and paired ENS at 100 Hz (Table 1), suggesting some neuromuscular fatigue. Because acute hypoxia (from minutes to hours) has been clearly shown to have no significant effect on MVC (Perrey and Rupp 2009), we believe that the force reduction observed after 1-h hypoxia only is likely the consequence of the numerous contractions performed at 50% MVC during the neuromuscular evaluations. Such a high percentage of MVC
Hypoxia and Cortex Excitability

Table 1. Mechanical and EMG quadriceps responses during maximal voluntary or evoked contractions as well as maximal peripheral and cortical voluntary activation levels in normoxia and after 1 h (Part 1) or 3 h (Part 2) of hypoxic breathing

<table>
<thead>
<tr>
<th>Part</th>
<th>MVC, kg</th>
<th>Db100, kg</th>
<th>TwQp, kg</th>
<th>RF, Mmax, mV</th>
<th>VL, Mmax, mV</th>
<th>VM, Mmax, mV</th>
<th>Periph., Mmax, mV</th>
<th>Cortical, Mmax, mV</th>
<th>%VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td></td>
<td></td>
<td></td>
<td>RF</td>
<td>VL</td>
<td>VM</td>
<td>Periph.</td>
<td>Cortical</td>
<td></td>
</tr>
<tr>
<td>Normoxia</td>
<td>74.0 (8.9)</td>
<td>28.5 (2.5)</td>
<td>16.8 (2.2)</td>
<td>8.6 (2.9)</td>
<td>14.6 (4.1)</td>
<td>8.9 (3.2)</td>
<td>92.1 (5.6)</td>
<td>95.6 (4.2)</td>
<td></td>
</tr>
<tr>
<td>1-h Hypoxia</td>
<td>68.5 (12.0)*</td>
<td>26.8 (3.1)*</td>
<td>16.4 (2.9)</td>
<td>8.1 (2.6)</td>
<td>15.1 (4.0)</td>
<td>9.1 (3.1)</td>
<td>91.2 (5.4)</td>
<td>93.6 (4.2)*</td>
<td></td>
</tr>
<tr>
<td>Part 2</td>
<td></td>
<td></td>
<td></td>
<td>RF</td>
<td>VL</td>
<td>VM</td>
<td>Periph.</td>
<td>Cortical</td>
<td></td>
</tr>
<tr>
<td>Normoxia</td>
<td>76.0 (10.4)</td>
<td>18.8 (1.9)</td>
<td>17.1 (2.6)</td>
<td>9.0 (2.2)</td>
<td>16.4 (3.0)</td>
<td>12.8 (3.5)</td>
<td>92.4 (4.1)</td>
<td>97.5 (1.0)</td>
<td></td>
</tr>
<tr>
<td>3-h Hypoxia</td>
<td>72.2 (8.8)</td>
<td>17.9 (1.3)</td>
<td>15.7 (1.8)</td>
<td>8.5 (2.3)</td>
<td>15.0 (2.6)</td>
<td>12.6 (4.0)</td>
<td>92.2 (4.8)</td>
<td>96.6 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD). MVC, maximal voluntary contraction; Db100, paired stimulation at 100 Hz; TwQp, potentiated single twitch; Mmax, M-wave amplitude; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VA, maximum voluntary activation; Periph., VA obtained from femoral nerve stimulation; Cortical, VA obtained from cortical stimulation. *Significantly different from normoxia (P < 0.05).
all et al. 2010) as well as personal observations (unpublished data) regarding cortex oxygenation assessed with near-infrared spectroscopy in healthy subjects inhaling a hypoxic gas mixture at rest indicated that the kinetics of cortex deoxygenation response is noticeably longer than arterial blood deoxygenation, requiring >20–30 min to reach a steady state. Also, recent animal studies regarding brain oxygenation under hypoxemic conditions emphasize the specificity of brain tissue oxygenation response to hypoxemia, with, for instance, some cerebral reoxygenation being observed over the course of a 1-h stable periodic pattern of hypoxemia (Almendros et al. 2010). Therefore, the specific pattern of cerebral tissue deoxygenation under hypoxemic conditions could contribute to a time-dependent effect of hypoxic breathing on cortex excitability.

Functional consequences of changes in corticospinal excitability. Increased motor corticospinal excitability after 3 h of hypoxia did not induce changes in MVC or VA. This is in accordance with previous results showing changes in motor corticospinal excitability in healthy humans exposed to hypoxia for ~30 min without concomitant changes in force production and VA during brief MVCs (Szukszbi et al. 2006). These results as well as the reduction in cortical VA observed after 1 h of hypoxic exposure without changes in MEP amplitudes and CSP durations underline that cortex excitability and suboptimal output from the motor cortex during voluntary contractions reflect, at least in part, distinct mechanisms (Taylor and Gandevia 2001). It remains to be evaluated whether the effect of 3 h of hypoxia on corticospinal excitability may have functional consequences during intense sustained cerebral activation such as during physical exercise or demanding psychomotor tasks.

In conclusion, the present results demonstrate that acute hypoxia has a time-dependent effect on corticospinal excitability, as evidenced by significant increases in MEP and CSP after 3 h but not after 1 h, of hypoxic breathing. These changes suggest an increase in motor cortex excitability and intracortical inhibition after 3 h of hypoxic exposure. However, these changes had no impact on maximal force production and voluntary activation. Further investigations are needed to clarify the impact of these motor corticospinal changes on physical or psychomotor performances, in particular during intense sustained cerebral activation such as during physical exercise or demanding psychomotor tasks, to better understand the cerebral effects of hypoxemia.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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