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Cortical Implication in Lower Voluntary Muscle Force Production in Non-Hypoxemic COPD Patients

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1 **Title: Cortical implication in lower voluntary muscle force production in non-hypoxemic**
2 **COPD patients**

3

4 **Authors:** Francois Alexandre^{1,2}, Nelly Heraud², Nicolas Oliver², Alain Varray¹

5

6 ¹Movement To Health Laboratory, Euromov, University of Montpellier 1, Montpellier,
7 France. ²Clinique du Souffle La Vallonie, Fontalvie, Lodève, France

8

9 **Corresponding author:**

10 Francois Alexandre, Movement To Health (M2H), Euromov, University of Montpellier 1, 700
11 avenue du Pic Saint Loup, 34090 Montpellier, France. Phone: (+33) 434 432 632; Fax: (+33)
12 434 432 644; E-mail: francois.alexandre@fontalvie.fr

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26 **Abstract**

27 Recent studies have shown that muscle alterations cannot totally explain peripheral muscle
28 weakness in COPD. Cerebral abnormalities in COPD are well documented but have never
29 been implicated in muscle torque production. The purpose of this study was to assess the
30 neural correlates of quadriceps torque control in COPD patients.

31 Fifteen patients (FEV_1 54.1 ± 3.6 % predicted) and 15 age- and sex-matched healthy controls
32 performed maximal (MVCs) and submaximal (SVCs) voluntary contractions at 10, 30 and
33 50% of the maximal voluntary torque of the knee extensors. Neural activity was quantified
34 with changes in functional near-infrared spectroscopy oxyhemoglobin (fNIRS-HbO) over the
35 contralateral primary motor (M1), primary somatosensory (S1), premotor (PMC) and
36 prefrontal (PFC) cortical areas.

37 In parallel to the lower muscle torque, the COPD patients showed lower increase in HbO than
38 healthy controls over the M1 ($p < 0.05$), PMC ($p < 0.05$) and PFC areas ($p < 0.01$) during MVCs.
39 In addition, they exhibited lower HbO changes over the M1 ($p < 0.01$), S1 ($p < 0.05$) and PMC
40 ($p < 0.01$) areas during SVCs at 50% of maximal torque and altered motor control
41 characterized by higher torque fluctuations around the target.

42 The results show that low muscle force production is found in a context of reduced motor
43 cortex activity, which is consistent with central nervous system involvement in COPD muscle
44 weakness.

45

46 **Keywords:** Muscle Weakness, Near Infrared Spectroscopy, Neural Activity, Central Nervous
47 System, Peripheral Muscle Dysfunction, Quadriceps Force

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51 **Introduction**

52 Peripheral muscle dysfunction is very frequent in COPD and has major consequences. The
53 loss of muscle force in COPD patients has become a matter of heightened concern because it
54 implies exercise limitation [1], increased use of health care resources [2], and higher mortality
55 [3]. The involvement of muscle atrophy in this loss was established several years ago [4].
56 However, several elements point to the existence of other explanatory mechanisms. For
57 instance, a recent study reported that COPD patients exhibit a decline in muscle force even
58 when their muscle mass is comparable to that of healthy controls [5]. In addition, the lower
59 muscle force across GOLD stages (between GOLD I and IV) is not explained by smaller
60 muscle cross-sectional areas [6]. Therefore, other mechanisms should be explored to enhance
61 understanding of the pathophysiology of muscle weakness in COPD.

62 A decline in muscle force can be caused by alterations in the muscle and/or the nervous
63 system [7]. Interestingly, several studies have assessed the cerebral properties in COPD
64 patients and reported small cerebral vessel disease [8], gray matter deficits [9], white matter
65 lesions [9, 10] and neuronal dysfunction [11]. At a more functional level, COPD patients
66 exhibit lengthening peripheral [12] and central [13] nervous conduction times, alterations in
67 motor cortex excitability [14], and cognitive disorders [9, 10]. In contrast, the potential
68 repercussions over the central motor drive and muscle performance are unknown.

69 A few studies have evaluated muscle activation in COPD using the twitch interpolation
70 technique [15-17], an indirect assessment of the central motor drive. However, the results
71 were discrepant [15-17] and no definitive conclusions could be drawn. The discrepancies may
72 be explained by the poor sensitivity of this technique at near maximal force, which makes it
73 difficult to discriminate two populations during maximal voluntary contractions (MVCs) [18].
74 Thus, the question of nervous system involvement in COPD muscle weakness remains
75 unanswered.

76 An alternative to circumvent the limitations of twitch interpolation could be the use of
77 neuroimaging techniques. Force output is directly related to cortical activity as measured by
78 functional magnetic resonance imaging (fMRI) [19] and functional near infrared spectroscopy
79 (fNIRS) [20]. The fNIRS oxy- (HbO) and deoxy-hemoglobin (HbR) signals are strongly
80 correlated with the blood-oxygen-level-dependent (BOLD) fMRI signal, and they are widely
81 acknowledged to be reliable for functional cortical activity assessment in various conditions
82 [21-23]. In addition, fNIRS has been validated for the study of neural activity in a wide range
83 of populations, such as the elderly [23] and COPD [24], stroke [25], and obese patients [26]
84 during various motor tasks, including MVCs [26]. Whereas fMRI restricts body movement
85 within the enclosed chamber, fNIRS presents a high signal-to-noise ratio and relatively poor
86 sensitivity to motion artifacts, making it the more suitable for cortical activity assessment
87 during exercise [27, 28].

88 Given the numerous cerebral alterations in COPD that have never been linked with poor
89 muscle force production, the purpose of this study was to assess the fNIRS-neural correlates
90 of quadriceps contraction at maximal and submaximal intensity in COPD patients. We
91 hypothesized lower activity over motor cortical areas in COPD patients than healthy controls
92 during quadriceps contractions.

93

94 **Material and Methods**

95 *Subjects*

96 Fifteen COPD patients and 15 age- and sex-matched sedentary healthy subjects were recruited
97 for the study. The participation criteria for the COPD patients were forced expiratory volume
98 in the 1st second (FEV₁) between 30 and 80% of the predicted values, with no exacerbation or
99 weight loss in the month preceding the study. No patient had taken part in a rehabilitation
100 program in the previous 12 months. The non-inclusion criteria for the participants were an

101 inability to give written consent, inability to perform the experimental maneuvers, impaired
102 visual function, use of drugs known to impair brain function, current or past alcohol abuse,
103 and neurologic or neuromuscular disease. All participants gave written consent. Procedures
104 were approved by the local Ethics Committee (Comité de protection des personnes Sud Est
105 VI, number AU980) and complied with the principles of the Declaration of Helsinki for
106 human experimentation. The study was registered at www.clinicaltrials.gov as
107 NCT01679782.

108 *Design*

109 All participants underwent a medical examination, including evaluation of resting pulmonary
110 function, body composition and clinical parameters, before taking part in the study. The
111 protocol consisted of maximal and submaximal voluntary contractions of the knee extensors,
112 during which cortical activity was assessed non-invasively from changes in fNIRS signals
113 [22, 25]. The exercise protocol is presented in Figure 1. After determination of the dominant
114 leg, the participants performed a standardized warm-up of the knee extensors by repeating 20
115 submaximal voluntary contractions for 2 s every 5 s. They next performed three maximal
116 voluntary contractions (MVCs) and three submaximal voluntary contractions (SVCs) at 10,
117 30 and 50% of the maximal voluntary torque twice in random order. Each MVC lasted for 5 s
118 and two successive MVCs were separated by a 2-min resting period. Each SVC lasted for 20 s
119 and two successive SVCs were separated by a 1.5 min resting period. The random draw to
120 determine the order of the SVCs took place immediately after the three MVCs had been
121 performed and the target torques calculated. A last MVC was performed to ensure the absence
122 of neuromuscular fatigue at the end of the exercise testing.

123 *Mechanical recordings*

124 Subjects were comfortably seated on a dedicated ergometer for knee extensor testing
125 (Quadriergoforme, Aleo Industrie, Salome, France) with a 30° back inclination. Chair

126 adjustments were made to ensure that the foot, patella and coxofemoral articulation of the
127 dominant leg were in the same axis. The knee angle was set to 110° . The pelvis and the
128 proximal extremity of the patella were securely attached to the chair in order to minimize
129 movements of adjacent muscles. In addition, the head was supported by a neck brace to avoid
130 potential head motion. Torque of the knee extensors during the contractions was recorded
131 with a strain gauge torque sensor (Captels, Saint Mathieu de Treviers, France). The acquired
132 analog signal was converted into digital data (DA conversion) through an acquisition system
133 (Biopac MP100, Biopac Systems, Santa Barbara, CA, USA) and instantaneously relayed to a
134 screen to give visual feedback. During each MVC and each SVC, subjects were verbally
135 encouraged to ensure maximal muscle torque and to maintain the force requirement,
136 respectively. Before the SVCs, the target torque was clearly indicated to the subjects via the
137 computer monitor and they received visual feedback of their performance during the
138 contractions.

139 *Cortical activity assessment*

140 A continuous wave multichannel functional near-infrared spectroscopy (fNIRS) system
141 (Oxymon Mark III, Artinis, the Netherlands) was used at two wavelengths in the near-infrared
142 range (nominal wavelengths of 760 and 850 nm) to detect regional concentration changes in
143 oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) during cortical activation over cortical
144 motor areas. fNIRS is based on neurovascular coupling: when neural activity increases, the
145 increase in regional cerebral blood flow is ten times higher than the increase in regional
146 oxygen consumption. Thus, as the increase in regional cerebral blood flow greatly exceeds the
147 increase in oxygen consumption, neuronal hemodynamic concentration is closely coupled
148 with the increase in regional cerebral blood flow, which turns into local hyperoxygenation
149 [29] and subsequent increase in HbO with a decrease in HbR [30]. The fNIRS-measured
150 hemoglobin is comparable to the BOLD-fMRI signal and mainly reflects changes in cortical

151 gray matter hemodynamic [22]. The fNIRS optodes were held by a cap fixated by several
152 bands surrounding the subject's head. A total of nine channels were positioned over the
153 contralateral primary motor (M1), primary somatosensory (S1), premotor (PMC) and
154 prefrontal (PFC) cortical areas in accordance with the modified EEG 10-10 system [31]
155 (Figure 2a). The source-detector spacing was set to 3.5 cm. During probe placement, Oxysoft
156 software (V6.0, Artinis, the Netherlands) allowed real time assessment of the quality of the
157 fNIRS signal for each channel based on the light source power level and the receiver gain.
158 Hemoglobin concentrations were corrected by implementing a specific differential pathlength
159 factor ($4.99 + 0.067 \times \text{age}^{0.814}$), in order to convert the concentration changes in HbO and
160 HbR to μM units [32]. The fNIRS signal was low-pass filtered (finite impulse response) using
161 a cut-off frequency of 0.7 Hz. The sampling rate was set at 10 Hz. To avoid systemic bias, we
162 also monitored the pulsed arterial oxygen saturation (SpO_2) in a restricted group of patients
163 ($n=12$). The oximetry probe (Weinman, Hamburg, Deutschland) was placed on the index
164 finger and the participants were asked to keep their hand motionless throughout the
165 experiment.

166 *Data analysis*

167 During MVCs, maximal quadriceps torque (Q_{MVC}) was calculated over the highest 500-ms
168 plateau of torque during the best trial of the three MVCs.

169 During SVCs, task matching was evaluated by averaging and comparing the mean performed
170 torque versus the target torque. In addition, during each SVC, the motor control was assessed
171 from the fluctuations around the target. An inaccuracy index ($\text{Inaccuracy}_{\text{index}}$) was calculated
172 and represents the RMS (root mean square) of the difference between produced and target
173 torques during the 20 s of submaximal voluntary contractions expressed as a percentage of the
174 target torque [33]. The normalization by the target torque is necessary because the torque
175 variability is known to be proportional to the torque level [34].

176 Changes in cortical activity were determined from HbO variations as previously described
177 [25]. HbO signals with artifacts or a too-low signal-to-noise ratio were marked and excluded
178 from the analyses under a visual pre-processing analysis [35]. During the best trial of the three
179 MVCs and of the more accurate SVCs at 10, 30 and 50% of Q_{MVC} , the area under the curve of
180 HbO normalized over time was used as an index of neural activity (Figure 2b).

181 The data, taken from the four channels over the M1 area, the two channels over the S1 area,
182 and the two channels over the PMC area were averaged, resulting in the overall response of,
183 respectively, the M1, S1 and PMC areas.

184 Before the beginning of exercise testing, resting HbO was calculated for each cortical area
185 over a 2-min resting period, respecting the same analysis process as aforementioned.

186 *Statistical analysis*

187 All statistical analyses were performed using Statistica software (StatSoft, Inc., version 6.0,
188 Tulsa, OK, USA). All data were examined for normality using a Shapiro-Wilk test.
189 Differences in subject characteristics and variables recorded during MVCs were tested
190 between controls and patients using an unpaired Student's t-test. Absence of neuromuscular
191 fatigue was tested using a two-way analysis of variance (ANOVA) with group as between-
192 subject factor (COPD and controls) and condition (before and after exercise testing) as within-
193 subject factor. The $Inaccuracy_{index}$ and HbO recorded during SVCs were tested using a two-
194 way ANOVA with group as between-subject factor and torque level (10, 30 and 50% of
195 Q_{MVC}) as within-subject factor. Analysis of covariance (ANCOVA) with adjustment for Q_{MVC}
196 was used to ensure that the difference in HbO between patients and controls was not due to a
197 difference in muscle torque between the groups. Task compliance during SVCs was tested
198 with a three-way ANOVA with group as between-subject factor and condition (target versus
199 performed) and torque level (10, 30 and 50% of Q_{MVC}) as two within-subject factors. The
200 underlying assumptions of ANOVA were checked using a Levene test (homogeneity of the

201 variance) and a Mauchly test (sphericity of the variance). When the ANOVA F ratio was
202 significant ($p < 0.05$), the means were compared by a LSD post-hoc test. Data are reported as
203 means and standard error of the mean (SE).

204

205 **Results**

206 *Subject characteristics*

207 The subject characteristics are given in Table 1. Consistent with the matching, no difference
208 in the gender ratio or age was observed between patients and controls. Weight, body mass
209 index and fat-free mass index exhibited no significant differences ($p > 0.05$). According to the
210 Voorrips questionnaire [36], the level of physical activity was comparable for patients and
211 controls ($p = 0.64$).

212 *Control of absence of desaturation and fatigue during exercise testing*

213 SpO₂ remained stable for all patients during both MVCs and SVCs. The mean Δ SpO₂ was
214 0.01 ± 0.12 % during MVCs ($p = 0.98$) and 0.017 ± 0.19 % during SVCs ($p = 0.98$).

215 Absence of neuromuscular fatigue was checked by changes in Q_{MVC} after the protocol. Both
216 patients and controls exhibited no significant differences in Q_{MVC} (condition and interaction F
217 ratio ranged from 0.17 to 1.10, p ranged from 0.31 to 0.68).

218 *Maximal voluntary contractions*

219 Q_{MVC} was significantly lower by 24.8% in COPD patients compared with controls ($131.9 \pm$
220 16.6 and 175.4 ± 24.9 Nm, respectively, for patients and controls, $t = 2.5$, $p < 0.05$).

221 The regional HbO during MVCs is shown in Figure 3. Compared with controls, patients
222 showed significantly lower HbO changes over M1 ($t = 2.1$, $p < 0.05$), PMC ($t = 2.3$, $p < 0.05$) and
223 PFC ($t = 3.1$, $p < 0.01$). In contrast, HbO changes during MVCs were comparable between
224 patients and controls over S1 ($t = 0.3$, $p = 0.74$).

225 *Submaximal voluntary contractions (SVCs)*

226 Task matching during SVCs was checked by comparing the performed torque with the target
227 torque (Figure 4). No significant differences were found between performed and target
228 torques for patients or controls at the three submaximal torque levels (F ranged from 0.31 to
229 2.22, p ranged from 0.15 to 0.74). In contrast, the Inaccuracy_{index} was significantly higher in
230 patients compared with controls for all submaximal torque levels (F=7.99, p<0.001). At 10,
231 30 and 50% of Q_{MVC}, the Inaccuracy_{index} was 7.04 ± 0.59 vs 5.15 ± 0.62 , 4.6 ± 0.44 vs $3.46 \pm$
232 0.58 , and 4.83 ± 0.47 vs 3.69 ± 0.78 in patients and controls, respectively.

233 The regional HbO as a function of torque level is shown in Figure 5.

234 Over the M1 area, HbO was significantly increased compared with resting values, from 30%
235 of Q_{MVC} in controls (p<0.001) and from 50% of Q_{MVC} in patients (p<0.01). Compared with
236 controls, patients showed significantly lower HbO changes at 30% and 50% of Q_{MVC}
237 (respectively, p<0.05 and p<0.01).

238 Over the S1 area, HbO was significantly increased compared with resting values, from 50%
239 of Q_{MVC} in controls (p<0.001). In patients, HbO did not change significantly whatever the
240 submaximal torque (p ranged from 0.34 to 0.49). In addition, at 50% of Q_{MVC}, HbO changes
241 were significantly lower in COPD patients than in controls (0.26 ± 0.09 vs 0.59 ± 0.18 μM ,
242 p<0.05).

243 Over the PMC area, HbO was significantly increased compared with resting values, from 30%
244 of Q_{MVC} in patients and controls (systematically p<0.01). Compared with controls, patients
245 showed lower HbO changes at 50% of Q_{MVC} (0.25 ± 0.13 vs 0.72 ± 0.12 μM , p<0.01).

246 Over the PFC area, HbO was significantly increased compared with resting values, at 50% of
247 Q_{MVC} in patients and controls (systematically p<0.05). There was no difference in HbO
248 changes between patients and controls for any submaximal torque level (F ranged from 0.75
249 to 0.9, p ranged from 0.35 to 0.53).

250 The impact of the patients' lower absolute torque values compared with controls on HbO
251 changes was checked using an ANCOVA. Consistently with respect to Figure 6 and adjusting
252 for Q_{MVC} , HbO remained significantly lower over M1 at 30% and 50% of Q_{MVC} in patients
253 compared with controls (all $p < 0.05$). Similarly, the observed effects in HbO changes over the
254 S1, PMC and PFC areas were unaffected when Q_{MVC} was added as a covariable: HbO
255 changes remained significantly lower over the S1 and PMC areas in patients at 50% of Q_{MVC}
256 (all $p < 0.05$), but comparable between the patients and controls over the PFC area (F ranged
257 from 0.01 to 2, p ranged from 0.17 to 0.99).

258

259 **Discussion**

260 The present study is the first to assess the neural correlates of quadriceps contractions in
261 COPD patients. The main findings were lower HbO changes over the M1, PMC and PFC
262 areas during maximal voluntary contractions in the COPD patients compared with controls. In
263 addition, the COPD patients showed lower HbO changes than controls over the M1 area at
264 30% and 50% of Q_{MVC} and over the S1 and PMC areas at 50% of Q_{MVC} . Last, the COPD
265 patients exhibited greater torque fluctuations around the target than controls.

266 The COPD patients exhibited 24.8% lower muscle force than healthy controls. This is
267 consistent with the usual torque deficit reported in the literature in moderate COPD patients,
268 which ranges from 20% to 30% [37]. The neural correlates of quadriceps torque were
269 simultaneously recorded with the non-invasive neuroimaging fNIRS technique [22, 25] over
270 major cortical areas for movement generation. Our results show smaller HbO increases over
271 the M1, PMC and PFC areas in the COPD patients during MVCs. These results cannot be due
272 to oxygen desaturation because the exercise did not induce SpO_2 changes. Similarly, it may
273 not be explained by lower resting cerebral blood flow due to resting blood gases abnormalities
274 because cerebrovascular reactivity to hypoxemia (increase in cerebral blood flow when PaO_2

275 decreases) is preserved in COPD [38, 39]. According to the neurovascular coupling principle
276 (as previously explained in the methods section), the data thus obtained with the fNIRS
277 technique suggest a smaller local hyperoxygenation at the cortex in COPD patients compared
278 with healthy controls. These results support lower neural activity in these patients, which
279 would explain the decreased voluntary torque via reduced cortical motor output, and is
280 coherent with the cerebrovascular damage and gray matter deficit described in the literature
281 [8,9].

282 During the submaximal voluntary contractions, we found a smaller HbO increase in the
283 patients over the three main cortical areas of the frontal lobe involved in the execution and
284 control of visual-motor tasks [40], at 30 and 50% of Q_{MVC} over the M1 area, and at 50% over
285 the PMC and S1 areas. These results complete and support the findings of Vivodtzev et al.
286 [17], who indirectly showed lower activation in COPD for comparable submaximal force
287 levels with the twitch interpolation technique. In parallel to the altered neural activity, we
288 found an increase in the inaccuracy index for submaximal torque levels in the COPD patients
289 compared with controls, indicating greater torque fluctuations around the target in patients.
290 Such torque fluctuations, known as dysmetria, are classic signs of lesions in the cerebellum
291 [41], a subcortical area whose main function is the control and coordination of movement and
292 whose output travels to motor and premotor cortex [42]. Interestingly, the dysmetria reported
293 in the patients did not impact the task matching, as they were able to reach the required target
294 (mean values). Hence, to summarize, the COPD patients were able to reach the desired target
295 at submaximal intensities but with lower motor drive and high fluctuations, indicating less
296 efficient motor control.

297 Given the difference in absolute torque value between the COPD patients and controls, we
298 sought to ensure that the lower neural activity did not result from the lower muscle torque
299 developed by the patients. As shown in Figure 6, for any given absolute torque value,

300 increases in HbO were always about twice lower in the patients over M1. This agrees with the
301 analysis of covariance, which indicated that adjusting for maximal voluntary torque had no
302 impact on the difference in HbO changes between the COPD patients and controls. Taken
303 together, these results provide new insight into the functional limitations in COPD patients, as
304 the lower neural activity (lower increase in HbO) cannot be explained by either lower muscle
305 torques or a lack of patient motivation or cooperation.

306 "In a previous study, Higashimoto et al. [24] recorded neural activity over the PFC area
307 during a whole-body exercise that induced an increase in dyspnea score in both COPD
308 patients and controls during testing, with the increase being higher in COPD. The authors
309 reported a clear tendency toward smaller HbO changes in the COPD patients compared with
310 healthy controls, although it did not reach the significance threshold. In addition, they
311 reported correlations between the increase in dyspnea score and the increase in PFC activity
312 during the exercise testing. These results raised the possibility of lower neural activity during
313 whole-body exercise in COPD that might have been hidden by the greater increase in
314 dyspnea-induced PFC activation [24]. Our findings are consistent with and complete the
315 results of Higashimoto et al. [24], because a local exercise carried out without any dyspnea
316 confirmed that the COPD patients had lower cortical activity."

317 Several factors have been suggested to explain the cerebral alterations in COPD but the exact
318 mechanisms remain unclear. These factors notably include inflammation, oxidative stress,
319 hypoxemia and vascular disease [43]. In accordance with other studies [10], we report
320 cerebral alterations in stable non-hypoxemic COPD patients, ruling out a determining role for
321 hypoxemia. Understanding the mechanisms of the brain impairment in COPD patients has
322 become a major issue. Our results provide new insight into the extrapulmonary effects of
323 COPD on the brain and suggest new directions for research in order to optimize treatment for
324 muscle force recovery in COPD. Further, they suggest the interest of early physical activity

325 for COPD patients, given the potential effects of exercise on cerebral plasticity and
326 neuroprotection [44], although this has yet to be specifically investigated in COPD.

327

328 In summary, COPD patients showed lower HbO changes over cortical motor areas during
329 maximal and submaximal voluntary contractions of the knee extensors. This impairment was
330 associated with a decrease in the maximal voluntary torque and altered motor control. The
331 results provide the first evidence that the knee extensors of patients with stable moderate
332 COPD cannot be optimally driven by the brain. Our findings highlight a lower motor cortex
333 activity during quadriceps contraction in COPD and are consistent with an involvement of the
334 central nervous system in the COPD quadriceps torque impairment. To optimize muscle force
335 recovery in COPD patients, interventions targeting neuroprotection and neuroplasticity must
336 be strongly considered.

337

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343

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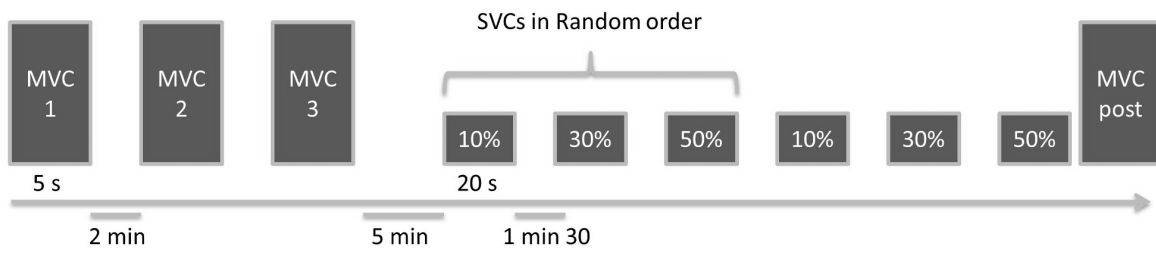
460 **Figures**

461

462 **Figure 1.** Experimental Design. MVC: Maximal Voluntary Contraction, SVC: Submaximal

463 Voluntary Contraction.

464



465

466 **Figure 2.** Measurement of cortical activity by functional near-infrared spectroscopy (fNIRS).

467 a) fNIRS optode placement. Three receivers (black circles) and seven emitters (white circles)

468 were set over the scalp, resulting in 9 measured channels. The crosses represent the reference

469 points used to target primary sensory (CP₃ - CP₁), primary motor (C₃ - C₁), premotor (FC₁ -

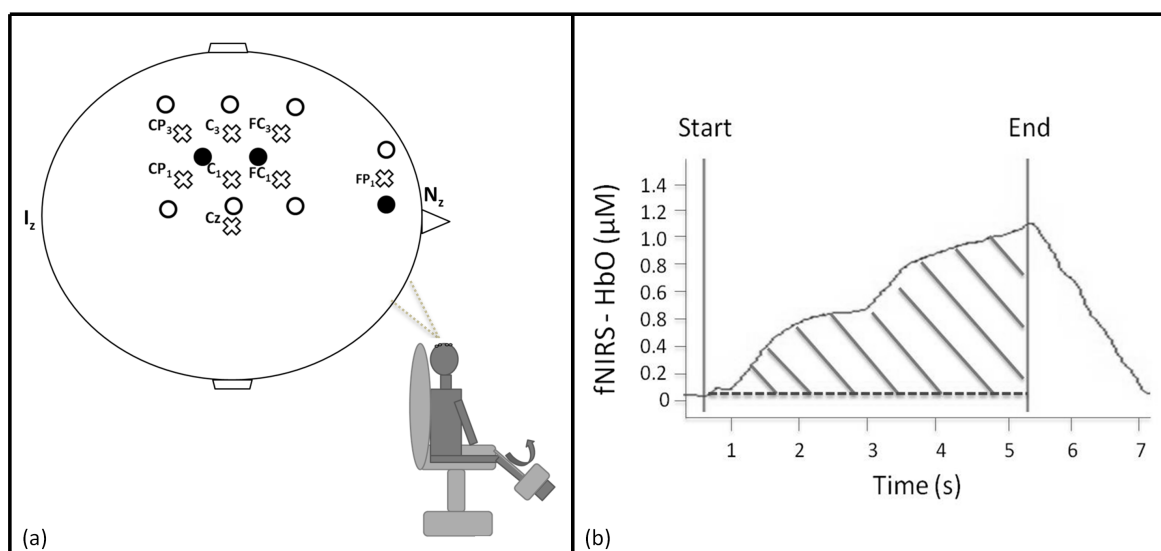
470 FC₃) and prefrontal cortical areas (FP₁) according to the modified international EEG 10-10

471 system. I_z: Inion, N_z: Nasion.

472 b) Example of a functional near-infrared spectroscopy oxyhemoglobin signal (fNIRS-HbO)

473 during a maximal voluntary contraction in one subject. Hatched area represents the area under

474 the curve of HbO (as index of neural activity).

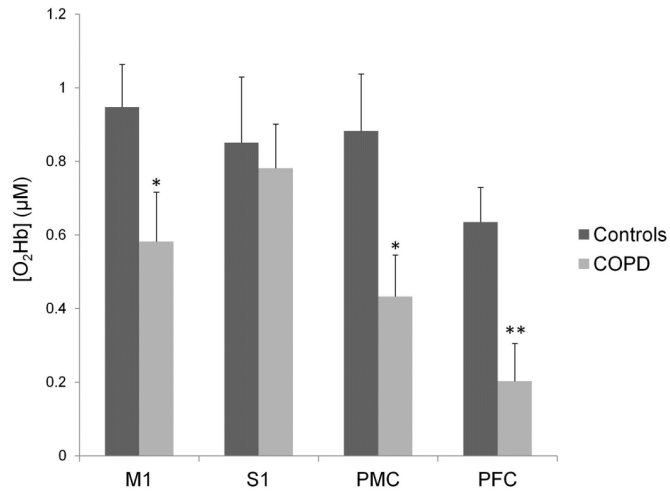


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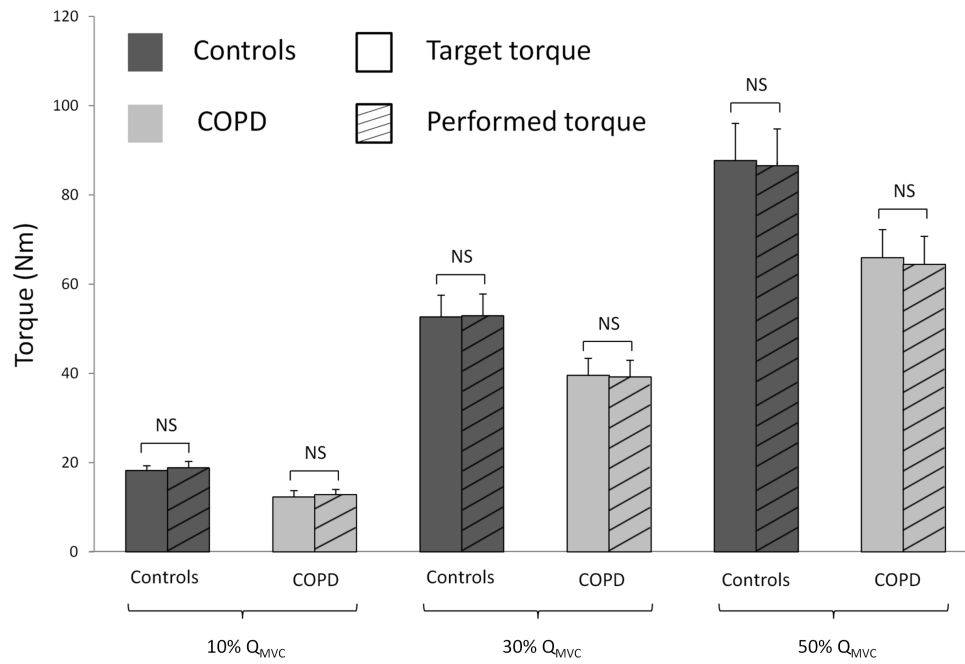
478 **Figure 3.** HbO changes during maximal voluntary contractions over primary motor (M1),
479 primary sensory (S1), premotor (PMC) and prefrontal (PFC) cortex areas. * $p < 0.05$ and ** p
480 < 0.01 significantly different from controls.



481

482 **Figure 4.** Performed torque versus target torque during submaximal voluntary contractions at
483 10, 30 and 50% of maximal quadriceps torque (Q_{MVC}). NS: Non-significant difference
484 between target and performed torque.

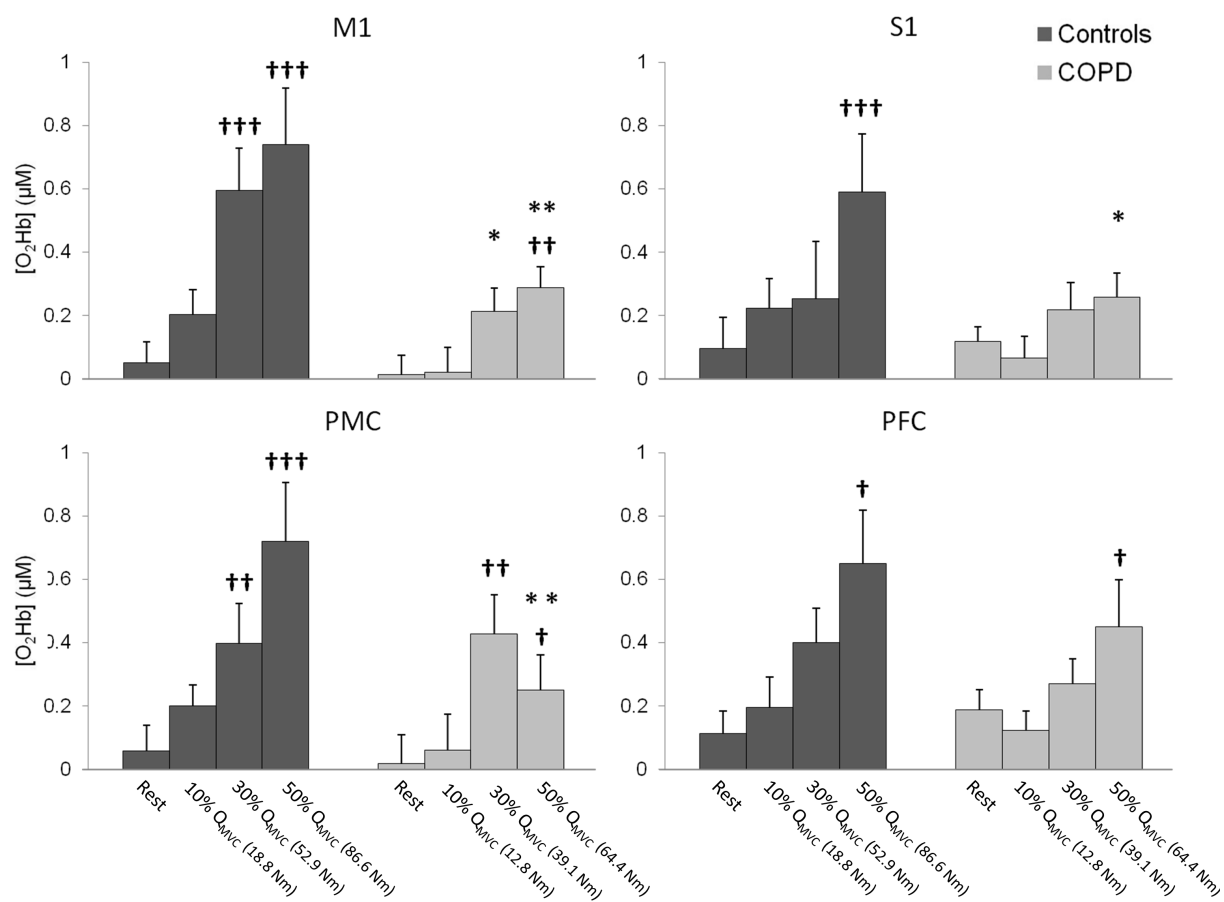
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487 **Figure 5.** HbO changes during submaximal quadriceps contractions as a function of % of
 488 maximal quadriceps torque (Q_{MVC}) over primary motor (M1), primary sensory (S1), premotor
 489 (PMC) and prefrontal (PFC) cortex areas. Values in parenthesis on the x axis indicate the
 490 mean torque performed at the given % of maximal quadriceps torque. Significant differences
 491 from rest: † $p < 0.05$ †† $p < 0.01$ and ††† $p < 0.001$. Significant differences between controls
 492 and patients: * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

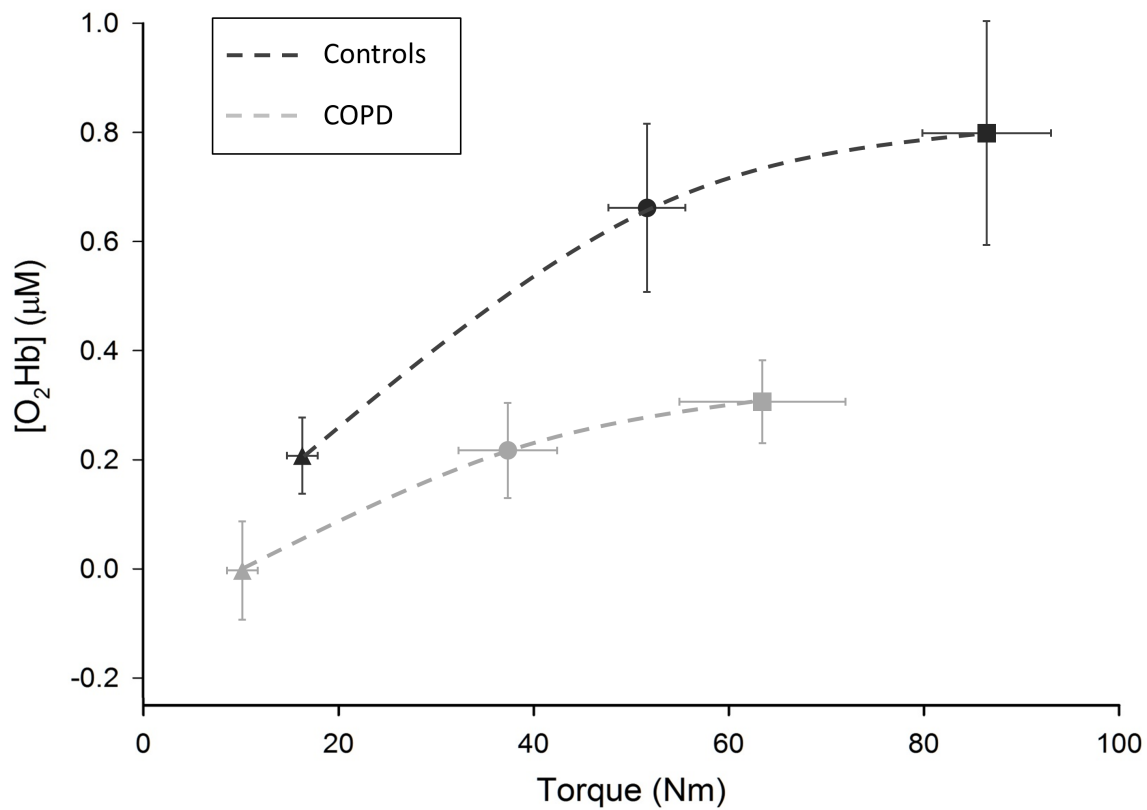
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496 **Figure 6.** HbO changes over M1 as a function of absolute torque value at 10 (triangular
497 shape), 30 (circular shape) and 50% (square shape) of the maximal voluntary torque.



498

499

Table 1. Characteristics of the subjects included in the study

	Control (n=15)	COPD (n=15)	p-value
Gender M/F	10/5	10/5	
Age yrs	61 (2.9)	62.8 (2.5)	NS (0.64)
Weight kg	75.8 (3.3)	72.8 (4.2)	NS (0.57)
BMI kg.m ⁻²	25.8 (1)	25.3 (1.3)	NS (0.76)
FEV ₁ L	3.1 (0.2)	1.5 (0.2)	<0.001
FEV ₁ % pred	104.5 (3)	54.1 (3.6)	<0.001
FEV ₁ /FVC	73.1 (1.1)	49.7 (2.4)	<0.001
FFM kg	55.3 (3)	53.9 (3)	NS (0.73)
FFMI kg.m ⁻²	18.6 (0.5)	18.8 (0.7)	NS (0.92)
Voorrips AU	7.4 (1.25)	6.5 (1.35)	NS (0.64)
PaO ₂ mmHg		72.9 (2.8)	
PaCO ₂ mmHg		37.4 (1.4)	

500 BMI: Body Mass Index, FEV₁: Force Expiratory Volume in 1 s, FVC: Force Vital Capacity, FFM: Fat-Free
501 Mass, FFMI: Fat-Free Mass Index. NS: no significant difference between controls and COPD patients.
502 Values are mean (SE).

503