Brain Damage and Motor Cortex Impairment in Chronic Obstructive Pulmonary Disease: Implication of Nonrapid Eye Movement Sleep Desaturation
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INTRODUCTION
Patients with chronic obstructive pulmonary disease (COPD) present several neurological disorders that directly affect daily life. These disorders include cognitive dysfunction, which degrades quality of life by, for example, decreasing driving ability.1 In our laboratory, we previously showed that motor cortex impairment could be involved in COPD muscle weakness due to inadequate motor cortex activation.2

The origin of the cerebral dysfunction in patients with COPD remains unelucidated. The potential role of hypoxemia in triggering neuronal damage and dysfunction by cerebral oxygen deprivation has often been hypothesized.3 However, several studies have provided evidence of cerebral dysfunction in nonhypoxic COPD patients, indicating that hypoxemia per se is not the main factor.4–6 This observation is unsurprising because an adequate oxygen supply to the brain is permanently ensured through cerebrovascular oxygen (O2) reactivity. During hypoxemia or oxygen desaturation, cerebrovascular O2 reactivity prevents cerebral hypoxia by increasing cerebral blood flow (CBF) up to 200%.7,8 Consequently, the resting CBF is much higher in hypoxic than in nonhypoxic COPD patients and healthy controls.9,10 For the same reason, CBF increases in COPD during exercise-induced desaturation.11 This results in adequate cerebral oxygen delivery even in the case of hypoxemia.11 As a whole, these studies provide evidence that cerebrovascular O2 reactivity prevents brain hypoxia in COPD.

Unfortunately, cerebrovascular reactivity is impaired during nonrapid eye movement (NREM) sleep stages.12–15 Numerous studies have reported an unexpected absence of CBF modulation during NREM sleep (but not during rapid eye movement [REM] sleep) in individuals who experience NREM sleep desaturation.12–15 Indeed, by decreasing arterial saturation of oxygen (SaO2) artificially by 5% to 10%, Meadows et al.15 found a consistent CBF increase in wake states, whereas it tended to decrease during slow wave sleep in hypoxemia. Therefore, if the arterial oxygen content falls below the normal value during NREM sleep, it may not be compensated, potentially leading to neuronal injury.16

Nocturnal desaturation is frequent in nonhypoxic COPD patients. The prevalence of COPD patients who are normoxic while awake and who spend at least 30% of the total sleep time (TST) with a saturation of peripheral oxygen (SpO2) below 90% ranges from 38% to 70%.16,17–19 To the best of our knowledge, the prevalence of NREM sleep desaturation in COPD has never been specifically assessed. It is generally acknowledged that the deepest
An increase in serum S100B concentration has been described in a wide range of neurological disorders such as acute ischemic and traumatic brain injury and hypoxic brain damage. Serum S100B is considered as a surrogate biomarker for cerebral damage. An increase in serum S100B concentration has been described in a wide range of neurological disorders such as acute ischemic and traumatic brain injury and hypoxic brain damage. Serum S100B is considered as a surrogate biomarker for cerebral damage.

The aim of the study was twofold: to determine the prevalence of patients with COPD who are nonhypoxemic but experience nocturnal desaturation during NREM sleep; and to compare CNS injury and neuromuscular function in patients experiencing desaturation and those who are not during NREM sleep and assess the repercussions of desaturation on neural drive during maximal voluntary muscle contraction. We hypothesized higher levels of serum S100B associated with lower motor cortex activation and lower muscle strength in patients with COPD who experience desaturation during NREM sleep.

METHODS

Participants
The study was conducted between 2012 and 2014 at the Clinique du Souffle La Vallonie in Lodeve, France, and the Clinique du Souffle Les Clarines in Riom-es-Montagnes, France. Over this period, 1,213 patients taking part in a 4-w inpatient pulmonary rehabilitation program underwent a routine medical examination in the first days following admission, composed of anthropometric evaluation, resting pulmonary function assessment, resting blood gas assessment, the 6-min walk test, and polysomnographic sleep (PSG) recordings. After completion, patient records were screened to identify those patients who met the following criteria: between 40 and 80 y old, diagnosis of COPD with postbronchodilator forced expiratory volume in 1 sec (FEV1) between 30% and 90% of predicted values (corresponding to grades 2 and 3 of the Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification), resting partial pressure of oxygen (PaO2) between 60 and 80 mmHg, and an apnea-hypopnea index (AHI) lower than 15 events per hour. One hundred fifteen patients fulfilled these criteria and were thus selected for a study to determine the prevalence of NREM sleep desaturation in nonhypoxemic COPD patients (Figure 1).

In a second step, we compared the neuromuscular function between patients with COPD with and without NREM sleep desaturation. Over a 6-mo period, a total of 29 consecutive patients underwent additional blood sampling and neuromuscular assessment. Patients were not eligible for neuromuscular assessment if they were unable to give written consent or perform the experimental maneuvers, were on medication known to impair brain function, or had impaired visual function, a pacemaker, current or past alcohol abuse, an exacerbation in the past 4 w, or neurologic or neuromuscular disease. Procedures were approved by the local Ethics Committee (Comité de protection des personnes Sud Est VI, number AU980) and complied with the principles of the Declaration of Helsinki for human experimentation. The study was registered at www.clinicaltrials.gov as NCT01679782.

Design
All tests were completed within the first week after admission. All participants were first evaluated for anthropometric parameters, resting pulmonary function, resting blood gases, the 6-min walk test, and polysomnographic sleep (PSG) recordings. The patients eligible for neuromuscular assessment were then probed and underwent medical examination after giving written consent. These patients were familiarized with the neuromuscular tests on the first day. Blood samples were collected the next day at patient wake-up, and between 6:30 and 7:30. The neuromuscular tests took place in the morning. The design of the neuromuscular tests is detailed in the Protocol section.

Measurements

Pulmonary function test
Diagnosis and staging of COPD were based on spirometry (V6200 Autobox, Sensormedics Corp., Yorba Linda, CA, USA). Measurements included forced vital capacity (FVC) and FEV1. The presence of persistent airflow obstruction and thus COPD was defined by a postbronchodilator FEV1/FVC ratio < 70%. The FEV1 values were compared with the predicted values of Quanjer et al.31

Figure 1—Flow diagram of the trial. The patients were assessed for eligibility at the beginning of a 4-w inpatient pulmonary rehabilitation program. All tests were completed within the first week following admission.
Blood gas analysis
Blood gases (PaO\textsubscript{2} and partial arterial pressure of carbon dioxide (PaCO\textsubscript{2})) collected from the radial artery were measured in the resting patients while they breathed room air, using a blood gas analyzer (ABL 825, Radiometer Medical, Bronshoj, Denmark).

Polysomnographic sleep recordings
PSG was performed using standard techniques and manually analyzed according to the latest guidelines of the American Academy of Sleep Medicine.\textsuperscript{32} Stage epoch classification and SpO\textsubscript{2} were exported at 1 Hz in a text file. Then the percentage of SpO\textsubscript{2} below 90% during NREM sleep was analyzed with an automatic routine developed in MATLAB (MATLAB 8.0, The MathWorks, Inc., Natick, MA, USA). Patients who spent more than 10% with SpO\textsubscript{2} below 90% during NREM sleep were classified as NREM sleep desaturators (NREM\textsubscript{des}), and non-NREM sleep desaturators otherwise (NREM\textsubscript{nondes}), according to published data giving evidence of cognitive dysfunction for similar levels of desaturation.\textsuperscript{33}

Exercise-induced desaturation
Exercise-induced desaturation was assessed during a 6-min walk test,\textsuperscript{34} which was performed indoors along a 15-m corridor following the current international recommendations.\textsuperscript{35} The SpO\textsubscript{2} was monitored throughout the test with a digital pulse oximeter (Nonin Medical, Inc. Minneapolis, MN, USA).

S100B measurement
Blood serum was obtained by centrifuging the blood samples for 10 min at 4,000 rpm and was kept frozen at −80°C until studied. Serum samples were analyzed for human S100B using commercial enzyme-linked immunosorbent assay kits (EMD Millipore, Billerica, MA, USA). S100B concentrations are expressed in pg/mL and the limit of detection was 2.74 pg/mL. More details on S100B measurement can be found in the supplemental material.

Torque and electromyography recordings
Maximal quadriceps torque was studied during isometric maximal voluntary contractions (MVCs) of the dominant leg with hip and knee angles set at 90° and using the same settings as previously described.\textsuperscript{2} The surface electromyography (EMG) signal of the vastus medialis was recorded using bipolar, silver chloride, surface electrodes. The surface EMG signal was amplified (>1000) and recorded at a sampling frequency of 4096 Hz (Biopac MP100, Biopac Systems, Santa Barbara, CA, USA).

Neuromuscular excitability and activation
Peripheral nerve stimulation was used to measure peripheral voluntary activation (peripheral VA), muscle contractility (peak twitch), muscle excitability (M-wave), and spinal excitability (H-wave). The femoral nerve of the dominant leg was stimulated with a constant-current, high-voltage stimulator (DS7AH, Digitimer, Hertfordshire, UK). A recruitment curve was performed at rest to determine which intensities to use during the protocol to elicit maximal M-waves (M\textsubscript{max}) and H-waves (H\textsubscript{max}).

Transcranial magnetic stimulation was used to measure cortical voluntary activation (cortical VA) and corticospinal excitability. Single transcranial magnetic stimulation (TMS) pulses of 1-ms duration were delivered over the motor cortex using a Magstim 200 (Magstim Co., Whitland, UK). A recruitment curve was performed during voluntary contraction at 10% of the maximal quadriceps torque in order to determine the maximal intensity.\textsuperscript{36} The intensity at which the highest motor-evoked potentials (MEP) was observed was then used during the protocol to assess cortical VA and corticospinal excitability.

More details on the peripheral nerve and transcranial magnetic stimulation procedures are provided in the supplemental material.

Protocol
The neuromuscular tests consisted of four MVCs of the knee extensors, each separated by 2 min of recovery (Figure 2). Participants were asked to maintain maximal effort for at least 4 sec. A double pulse at 100 Hz was delivered at the M\textsubscript{max} intensity over the femoral nerve during the force plateau of the first two MVCs (superimposed doublet) and 2 sec after relaxation (control doublet), according to the twitch interpolation.
A single transcranial magnetic stimulation pulse was delivered to the motor cortex to elicit MEPs during the force plateau of the last two MVCs. Three single pulses at Mmax intensity or Hmax intensity separated by 10 sec were delivered twice among MVCs to elicit Mmax and Hmax at rest, respectively (see Figure 2 for more details). After the MVCs, three submaximal voluntary contractions (SVCs) with visual feedback were performed at 50% and 30% of MVC. A single transcranial magnetic stimulation pulse was delivered during the force plateau of each SVC to elicit superimposed twitch responses at 30% and 50% of MVC. Then the transcranial magnetic stimulation resting twitch was determined by extrapolation of the linear regression between voluntary force and the superimposed twitch evoked at 30%, 50%, and during MVC.  

Data Analysis
Maximal quadriceps torque (Qmax) was selected as the highest torque plateau of 500 ms from the four MVCs. Muscle contractile properties were evaluated by the quadriceps peak twitch (Qpt) from the highest twitch response induced by femoral nerve stimulation at rest. Muscle excitability was determined as the highest Mmax peak-to-peak amplitude induced by femoral nerve stimulation at rest. Spinal excitability was determined as the highest Hmax peak-to-peak amplitude normalized with respect to muscle excitability (i.e., Hmax/Mmax).

The amount of neural drive to the muscle was quantified by the root mean square of the vastus medialis EMG signal (EMG RMS) during the highest torque plateau of 500 ms normalized with respect to muscle excitability (i.e., EMG RMS/Mmax). Peripheral VA was calculated via femoral nerve stimulation according to the twitch interpolation technique as follows:

Peripheral VA (%) = \[1 - ((\text{superimposed doublet})/\text{(control doublet)}) \times 100\]

Motor cortex activation (cortical VA) was calculated via transcranial magnetic stimulation. Because the relationship between superimposed transcranial magnetic stimulation twitch and voluntary force is not linear for intensities below 25% of MVC (reduced cortical and spinal excitability at low force levels), the transcranial magnetic stimulation resting twitch was estimated by extrapolation of the linear regression between voluntary force and the superimposed twitch evoked at 30% of MVC, 50% of MVC, and during MVC. The cortical VA was calculated as follows:

Cortical VA (%) = \[1 - ((\text{superimposed twitch})/\text{(estimated resting twitch)}) \times 100\]

Corticospinal excitability was assessed by the amplitude of the maximal MEP induced by transcranial magnetic stimulation during MVCs, normalized with respect to muscle excitability (i.e., MEP/Mmax). The cortical silent period (CSP) duration was measured as the time between MEP onset and the return of voluntary EMG activity. The central motor conduction time (CMCT) was calculated from the delay between the stimulus artifact and MEP onset.

Statistical Analysis
All statistical analyses were performed using Statistica software (StatSoft, Inc., version 6.0, Tulsa, OK, USA). All data were examined for normality using a Shapiro-Wilk test. Differences between NREMDes and NREMnoDes patients were studied using unpaired t-tests for parametric data, and nonparametric Mann-Whitney U tests otherwise. The required sample size for the sub-study was calculated on the level of voluntary activation (main outcome), based on a between-groups difference of 20%. With a 5% significance level and a power of 90%, the required sample size was ten per group. Data are reported as mean and standard deviation (SD) or median and quartiles (lower and upper quartiles labeled respectively by Q1 and Q3) in the case of nonparametric statistics. The significance level was set at P ≤ 0.05.

RESULTS

Prevalence of NREM Sleep Desaturation
The main characteristics of the NREMnoDes and NREMDes patients are depicted in Table 1. The NREMDes group was composed of 59 patients (51.3% of the study sample), meaning that over half of the patients with COPD spent more than 10% of NREM sleep time with SpO2 below 90%. Mean SpO2 during NREM sleep was 92.9 ± 1.51% in the NREMnoDes patients versus 88.9 ± 1.96% in the NREMDes patients (P < 0.001). There was no significant difference between the NREMDes and NREMnoDes patients regarding age (P = 0.78), weight (P = 0.98), body mass index (BMI; P = 0.71), FEV1 (P = 0.32), FEV1/FVC (P = 0.13), blood gases (P = 0.15 and P = 0.98 for PaO2 and PaCO2, respectively) or AHI (P = 0.81).

Subsample Characteristics and Blood Sample Analysis
The NREMdes and NREMnoDes patients who took part in the neuromuscular tests (n = 29) did not exhibit any significant differences regarding age, weight, BMI, FEV1, FEV1/FVC, blood gases, or time to desaturate during exercise (Table 2). The total sleep time, arousal index, and AHI were also comparable between groups (P = 0.26, 0.97, and 0.92, respectively). Serum levels of S100B were significantly higher in the NREMDes compared with NREMnoDes patients (P = 0.028). The values were 45.1 [Q1: 37.7, Q3: 62.8] versus 32.9 [Q1: 25.7, Q3: 39.5] pg.mL−1 in the NREMDes and NREMnoDes patients, respectively (Figure 3).

Quadriiceps Torque and Voluntary Activation
The data are presented in Figure 4. There were no significant differences on Qmax (P = 0.58) or Qpt (P = 0.48) between the NREMDes and NREMnoDes patients. Qmax values were 101.1 ± 39 and 110.9 ± 61 Nm, and Qpt values were 41 ± 20 and 37 ± 16 Nm, for the NREMDes and NREMnoDes patients, respectively. Conversely, peripheral VA was significantly lower in the NREMDes patients (90.7 ± 7.6 versus 95.9 ± 3.3%, P = 0.022). The cortical VA was also decreased in the NREMDes group compared with NREMnoDes and was 89.5% [Q1: 85.8, Q3: 93.6] versus 94.1% [Q1: 93.6, Q3: 96.8], respectively (P = 0.03, Figure 4B).

Electrophysiological Data
The data are presented in Table 3. EMG RMS/Mmax and MEP/Mmax were significantly lower in the NREMDes compared with NREMnoDes.
with NREM\textsubscript{noDes} patients ($P = 0.031$ and $P = 0.03$, respectively). Mmax amplitude ($P = 0.08$), Hmax/Mmax ($P = 0.66$), CSP ($P = 0.28$) and CMCT ($P = 0.88$) were not significantly different between groups.

**DISCUSSION**

The major findings of the study were that more than half of the nonhypoxemic COPD patients spent more than 10% of NREM sleep time with SpO\textsubscript{2} below 90%, and the nonhypoxemic COPD patients who spent more than 10% of NREM sleep time in desaturation had reduced motor cortex activation and excitability during maximal voluntary contractions and higher serum S100B concentrations.

**Prevalence of NREM Sleep Desaturation**

The prevalence of O\textsubscript{2} desaturation during sleep is thought to be in the range of 38% to 70% in nonhypoxemic COPD patients, and our data are consistent with this range.\textsuperscript{17–19} In the current
study, we used a cutoff of only 10% of the NREM sleep time, with SpO₂ below 90% to diagnose NREM sleep desaturation. As NREM sleep desaturation has never been specifically assessed in COPD, our choice was dictated by the criteria used to diagnose desaturation during TST. Although no clear consensus exists, a percentage of the TST with SpO₂ below 90% is frequently cited in the literature. We opted for a 10% criterion with SpO₂ below 90% as it has classically been used to study brain impairment.

This study is the first to assess the prevalence of NREM sleep desaturation in COPD. Although it is indisputable that the deepest O₂ desaturation occurs during REM sleep, a few studies have observed NREM sleep desaturation in patients with COPD who experience nocturnal desaturation. Our results are consistent with these observations and provide further evidence that O₂ desaturation during sleep is not restricted to REM sleep in COPD.

It should be noted that the mechanisms responsible for NREM desaturation cannot be determined from our results, although the phenomenon seems unlikely to be explained by obstructive sleep apnea (OSA). Indeed, patients with severe OSA were excluded, and the AHIs were comparable in the two groups of patients with and without NREM sleep desaturation. Furthermore, the mechanisms are unlikely to involve the levels of diurnal PaO₂, given the absence of diurnal PaO₂ differences between the groups. This result is unsurprising because PaO₂ changes during sleep are not correlated with the diurnal PaO₂ levels in COPD. Two important candidates to explain desaturation during sleep in COPD, especially during REM sleep, are alveolar hypoventilation and ventilation-perfusion mismatching. Their potential implication in NREM sleep desaturation remains to be investigated.

**Effect of NREM Sleep Desaturation on Neuronal Damage and Neuromuscular Function**

The second purpose of the study was to assess the repercussions of NREM sleep desaturation on neuronal damage and neuromuscular function. To do so, serum S100B, an easy-to-use and cost-effective biomarker of neuronal damage, was analyzed in a subgroup of patients with COPD. The ability of serum S100B to detect brain impairment was recently confirmed in COPD and found to be associated with hippocampal atrophy and impaired cognitive function. In the current study, we observed a higher S100B concentration in patients with NREM sleep desaturation, but without having the possibility to localize the impaired brain areas. The higher serum S100B concentrations could be linked to confounding factors other than NREM sleep desaturation, such as decreased sleep quality or sleep deprivation. Importantly, we did not find any differences between the patients who did and did not experience desaturation during NREM sleep regarding TST and the arousal index.
The functional repercussions of neuronal damage can be numerous. We chose to focus specifically on neuromuscular function and its effect on maximal quadriceps strength, as peripheral muscle weakness is one of the main deleterious systemic effects in COPD. By stimulating the motor cortex, we observed lower MEP/M amplitude in the NREMDes patients during maximal voluntary contractions. The MEP/M amplitude reflects both spinal and cortical excitability. In the current study, the comparable H-reflex amplitude observed in the NREMDes and NREMnoDes patients indicates that the lower MEP/M could not be attributed to lower spinal excitability and thus is mainly explained by reduced motor cortex excitability. Furthermore, the reduced cortical excitability was associated with lower motor cortex activation as well as lower quadriceps motor unit activation (as measured by peripheral VA and EMGrms/M). These results support the hypothesis that patients with COPD who experience NREM sleep desaturation have reduced neural drive reaching the quadriceps muscle during MVC because of motor cortical output failure.

Impaired neural drive to the quadriceps has been a controversial topic in COPD. One study reported lower activation at the muscle level in patients with COPD compared with healthy controls, whereas others did not. More recently, we found lower cortical activity through neuroimaging assessment in patients with COPD during MVCs. By using the neuroimaging technique, it was not possible to infer that the lower cortical activity resulted in lower cortical output. In the current study, we assessed the cortical motor output with a more direct approach by stimulating the motor cortex. Our results confirm that cortical output is impaired in COPD but that it mainly concerns those patients with NREM sleep desaturation, as the values of voluntary activation reached by the NREMnoDes patients (around 95%) were substantially similar to those of healthy subjects reported in other studies. In addition, our data suggest that the discrepancies in previous studies might be explained by differences in the number of patients with COPD who experience NREM desaturation, which was not taken into account in previous works.

Maximal muscle torque depends in part on the ability to activate the muscle. In addition, as the relationship between peripheral VA and torque is curvilinear, small modulations in peripheral VA induce much larger QMVC changes at near-maximal contraction intensities. For example, it was shown that a 5.7% increase in peripheral VA induced a 20.4% increase in QMVC. Conversely, a 3% decrease in peripheral VA caused by neuromuscular fatigue has been associated with a 11% decrease in QMVC. Therefore, the relatively low peripheral VA for NREMDes compared with NREMnoDes patients (average of 5.2% less) should have expressed a greater loss of strength in these patients than the average of 9% (nonsignificant) strength reduction (101 versus 111 Nm, P = 0.58). The finding that the NREMDes patients reached the same torque level as the NREMnoDes patients could be explained by low statistical power, or it may suggest a compensatory mechanism(s). Concerning the first explanation, it is important to note that the SD of the QMVC data are in accordance with those of other studies. In addition, the current QMVC data are far from the level of statistical significance and we calculated the a posteriori number of subjects needed to obtain 90% statistical power (400 participants). These observations are in accordance with a limited experimental effect, if proven. Any potential compensatory mechanism is unlikely to be linked to a difference in intrinsic muscle capacity (due to higher muscle mass or contractility) because QPt was comparable between groups. Muscle torque at a joint is the result of contributions from both agonist and antagonist muscles. In a condition of decreased agonist torque (due to lower cortical activation), any lower torque developed by the antagonist knee flexor muscles during maximal quadriceps contraction in the NREMDes group could account for the comparable resultant torque; that is, comparable QMVC. Unfortunately, the antagonist activity was not assessed in this study, but this hypothesis is supported by a study carried out by Simoneau et al. These authors reported no differences in the resultant maximal torque of the dorsiflexors in elderly subjects compared with young subjects, despite a 40% decrease in agonist maximal torque. This was explained by an activation of the antagonist planar flexor muscle during maximal dorsiflexion that was almost twofold lower in the elderly, showing that in some circumstances maximal voluntary torque can apparently be preserved despite a significant decrease in agonist torque.

Study Limitations
Serum S100B, which was used as a marker of CNS injury, has the advantage of being a strong, sensitive, and easy-to-use marker of neuronal damage. However, although S100B is a marker of cerebral damage, it does not inform the location of the damage and cannot be used to localize the impaired brain areas. Computed tomography and MRI are likely to provide

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Values are means (standard deviation) or median [Q1, Q3 quartiles] in the case of non-parametric statistics. CMCT, central motor conduction time; CSP, corticospinal silent period; EMGrms, root mean square of the vastus medialis electromyogram; MEP, motor-evoked potential; Mmax, maximal M-wave. 


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useful complementary information on the cerebral damage in patients with COPD experiencing desaturation during NREM sleep.

We did not directly assess the cerebrovascular O₂ reactivity during sleep. Therefore, although our results are highly consistent with an effect of NREM sleep desaturation on brain impairment, the occurrence of brain hypoxia during NREM sleep in the patients experiencing desaturation could only be inferred from the literature data. A study to address the effect of correcting NREM sleep desaturation on serum S100B levels and motor cortex impairment would address this limitation.

CONCLUSION
NREM sleep desaturation is far from negligible as it concerns approximately one of two patients with moderate to severe COPD and a resting PaO₂ between 60 and 80 mmHg. The patients with COPD who experience desaturation during NREM sleep exhibited an elevated level of a biomarker of CNS injury (i.e., serum S100B) and lower neural drive during quadriceps MVCs due to impaired cortical motor output. The observation that quadriceps muscle weakness was not more marked in the patients who experience desaturation suggests the existence of compensatory mechanisms whose nature and origin remain to be determined. Overall, the results are consistent with an involvement of NREM sleep desaturation in triggering CNS injury and decreasing neural drive to the quadriceps in COPD. The prevention of NREM sleep desaturation may well be an important clinical perspective to promote cerebral plasticity in COPD. Further studies are needed to determine the extent to which reversing neural activity is beneficial for the maximal voluntary force and functional capacity of patients with COPD.

REFERENCES

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