Reviewer’s report

Title: Specific motor cortex hypoexcitability and hypoactivation in COPD patients with peripheral muscle weakness

Version: 1 Date: 12 Sep 2019

Reviewer: Wendy Darlene Reid

Reviewer's report:

Introduction

The introduction provides good background information and the flow is logical. However, the paragraph structure needs to be revised.

Methodology

No major concerns related to methodology. The authors addressed both the use of a figure of 8 coil and the number of participants excluded within the limitations section appropriately. Some clarification should be added however:

Line 85-87: The participants were systematically familiarized with maximal voluntary contractions, femoral nerve stimulation and transcranial magnetic stimulation the day before the protocol. Can the authors elaborate on what was meant by familiarization? Were they explained what the tasks would be? Were they given physical training doing MVCs, stimulation etc?

Line 110-112: One pulse was delivered on the femoral nerve every 10 s, with the intensity beginning at 50 mA and increasing from 10 mA until no further increase in twitch mechanical response and M-wave amplitude occurred. Should this read increasing by 10 mA? Ie. in 10 mA increments?

Was the femoral nerve stimulation and TMS at rest performed with the same body positioning as the MVC testing position? This will influence excitability and the details should be included.

Results

Line 222-223: Moreover, they also exhibited significantly higher Hmax latency (t37=2.94, p<0.01) and silent period duration (t37=3.33, p<0.001) than controls. This should state "longer silent period duration" instead of "higher."

Lines 236-237: The data are presented in Figures 2a and 2b. Both QMVC and QPt were significantly lower in COPDMW compared with the COPDNoMW and control groups (F2,57=10.73, p<0.001 and F2,57=4.46, p<0.01, respectively).

As an ANOVA was performed, the authors should first state whether there was an overall significant effect of group and then discuss the comparisons to improve transparency of results. This should be done for all group comparisons. (This was demonstrated in the Table however so perhaps it is okay).
Regarding comparisons, the authors need to explicitly state when there was an overall difference between the three groups or when some comparisons were a pooled two group comparison (lines 209-211). These two types of comparisons were described in the Statistical analyses section. However, there is a lack of clarify for some statements in the Results - "Hmax latency was significantly higher in the two COPD groups compared with controls (F2,36=4.26, p<0.05), but the central motor conduction time was not different between the three groups (p=0.33)." These data are also pooled for the COPD patients in Table 1. Was an ANOVA performed followed by post hoc analyses to determine differences?

Discussion

Some of the statements in the Discussion should be qualified. The following statement is too all encompassing.

"In sum, because higher corticospinal inhibition and impaired neuromuscular transmission are unlikely to be involved in the reduced quadriceps strength of the patients with muscle weakness, the most likely mechanism responsible for muscle weakness, and thus for reduced voluntary activation, is decreased excitation from the brain, which is supported by the observation of lower gray matter density in the motor cortex (precentral gyrus) in COPD"

Suggest to break the sentence up into two parts and have the first sentence end after "…reduced quadriceps strength of the patients with muscle weakness,": The second part of this sentence negates the contribution of peripheral muscle factors i.e. atrophy, myopathic changes, contributing to muscle weakness. Thus, the second part of the sentence should be qualified accordingly to include some reference to the contribution of peripheral muscle factors contributing to weakness.

One of the next statements should be placed in a greater context as well. -
"In the current study, the weak patients had lower resting PaO2 levels. However, the implication of this result in the reduced cortical activation is unlikely, since hypoxemia is not a sufficient condition to induce cerebral hypoxia, due to the cerebrovascular reactivity that compensates any reduction in PaO2 by an increase in cerebral blood flow [51]."

Cerebrovascular reactivity may compensate for a reduction in PaO2 by an increase in cerebral blood flow in some individuals but to make this blanket statement for your sample of COPD patients is unfounded. Cerebral vascular disease and hypoxemia are considered to be major factors that can contribute to cognitive impairment and regional brain changes in people with COPD.1-4


4. Reference 22 from the authors' paper
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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