To the Editor:

The paper by MONTES DE OCA and CELLI [1] revisited the rather complex mechanisms leading to chronic hypercapnia in chronic obstructive pulmonary disease (COPD). The results confirm data in the literature indicating that arterial carbon dioxide tension (P_{a,CO_2}) is inversely related to forced expiratory volume in one second (FEV_1), and that the respiratory drive mouth occlusion pressure ($P_{0.1}$) and the resting tension-time index of the diaphragm (T_{tdi}) are both higher in normocapnic and hypercapnic COPD groups than in normal subjects [2–4].

What is new in this paper is the mechanistic interpretation of the data proposing that "baseline central drive in COPD is preserved and may have reached the upper limit of their drive". The authors "speculate that patients with severe COPD reach the top values of neuromuscular inspiratory drive". They propose that "hypercapnia occurs because there is a failure of the pump to wash out CO_2". Also new is the finding of quite high absolute values of T_{tdi} in both COPD patient groups during resting ventilation. In fact, nearly half of the COPD patients had a resting T_{tdi} at or considerably above the fatigue threshold of ~0.16 (fig. 4). This finding, which in itself is intriguing, supports the claim of a very high neuromuscular output in their COPD patients.

A closer look at the methods section shows that the transdiaphragmatic pressure (P_{di}) values fed into the T_{tdi} equation were "peak" P_{di} swing values rather than "mean" pressures, as the equation requires [5]. Since the time shape of P_{di} in inspiration is rather triangular, the peak values are about twice as high as the mean values. If instead of the peak, P_{di} is expressed as mean pressure, figure 2 of the paper will probably show mean T_{tdi} values of ~0.06 for normocapnic and 0.10 for hypercapnic subjects, quite in agreement with the data reported previously [4] and with the suggestion by BÉGIN and GRASSINO [2] that neural drive is not so inordinately high as to bring the muscles into fatigue.

The authors hypothesis proposing that COPD patients during resting breathing may have maximally activated respiratory centres is not realistic. The fact is that most resting hypercapnic COPD patients asked to voluntarily increase ventilation do so and are capable of decreasing P_{a,CO_2} [6, 7]. However, the effort can be held for only a short time because the muscles fail. It is unlikely that spontaneous neural drive at rest will ever drive the respiratory muscles to fatigue. This strategy is self-defeating.

We think that an alternative to the proposed mechanism of maximal drive and pump failure is that the neural output during resting breathing increases sufficiently to drive the ineffective breathing pump muscles near their fatigue threshold, where muscles could keep a sustainable rate of ventilation even at the expense of incurring chronic alveolar hypoventilation. This hypothesis was supported by the fact that we found none of >300 COPD patients in steady state to generate sufficient inspiratory pressure to bring the tension-time index of their inspiratory muscles at or above the fatigue threshold [2]. Our data also showed that ~30% of COPD patients in steady state live with chronic hypercapnia.

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REPLY

From the authors:

We reviewed with interest the letter by H. Folgering regarding our article entitled "*Mouth occlusion pressure, CO_2 response and hypercapnia in severe chronic obstructive pulmonary disease*". This response will help clarify some of their observations, and ultimately will prove that we agree, more than disagree, with the findings and interpretation of the study.

Firstly, H. Folgering incorrectly suggests that the resting mouth occlusion pressure ($P_{0.1}$) reported in the abstract is significantly different from the value shown in table 2. They are the same in both sections of the article, 2.7 ± 1.5 and 3.2 ± 2.1 cmH_2O, respectively.

Secondly, there is no question that resting lung volume (functional residual capacity (FRC)) is lower in control subjects compared with chronic obstructive pulmonary disease patients (COPD), but they were the same in eucapnic and hypercapnic patients. Contrary to the speculation of H. Folgering, experimental evidence indicates that increases in lung volume reduce $P_{0.1}$. This is analysed in detail by WHITELAW and DERENNE [1], which was quoted in

our discussion. The change is mainly due to a decrease in the pressure-generating capacity of the diaphragm as it flattens with hyperinflation. If anything, there was an intrinsic advantage favouring the control subjects (who should have had higher central drive, as their resting lung volume is lower). In contrast, the true "central driving pressure" is probably underestimated in the patients compared to control subjects, an argument that provides more strength to our findings. Because both the eucapnic and hypercapnic patients had similar lung volumes and $P0.1$, it is very difficult to accept the suggestions of H. Folgering that there may have been differences in compliance of the lung and thorax between the groups. Furthermore, we actually measured pleural pressure (P_{pl}), which again was similar in both groups, thereby negating any theoretical difference in compliance.

Thirdly, the observations regarding the $P0.1$ and the $\Delta P0.1$/arterial carbon dioxide tension $\Delta(P_{a,CO_2})$ suggests some confusion regarding methodology. We reported baseline $P0.1$ in cmH_2O, whereas the change in $P0.1$ as CO_2 rises is reported in cmH_2O (pressure) over change of $CO_2 \times$ time (torr $\times$ min). The same is true for the ventilatory response (minute ventilation (V'_E)), which is reported in litres over the same change in $CO_2 \times$ time. The values that we found are within the range of those reported by READ [2] in the initial study and by other authors [3–9].

Fourthly, once more H. Folgering takes a theoretical consideration and uses it as an argument against our findings. All of his reasonings regarding the potential difference introduced by starting patients and control subjects at similar levels of CO_2 are interesting, but highly speculative and without experimental support. If his argument were correct (that control subjects and eucapnic patients are stimulated earlier and more intensely by the relatively high CO_2 at the beginning of the run), the $\Delta P0.1$/end tidal carbon dioxide tension (P_{ET,CO_2}) slopes had to have been different. Quite to the contrary, the response in all three groups was similar (see table 2), thereby negating the theoretical considerations discussed by H. Folgering. In addition, the Read technique has been used by all the authors quoted in our study, whereas there is extremely little data from studies in patients validating the steady-state technique. Finally, we would like to suggest that H. Folgering review the paper published by DE TROYER *et al.* [10] who using electromyography without CO_2-stimulation, documented increases in neuromuscular drive in eucapnic and hypercapnic COPD patients. Contrary to the beliefs of H. Folgering, we consider the $P0.1$ an underutilized test of central drive, and we may be doing the test a disfavour by expressing theoretical reasons why it may not be good. This is somewhat disturbing as we have no other simple, reliable and validated test of central drive, an area that requires intense research. Central drive and its rhythmic consequence is the equivalent of cardiac rhythm. We are light years behind our cardiologist colleagues because we are looking for the perfect test.

We apologize that we did not reference the work of SCANO *et al.* [11]. This was involuntary as we did not find it in our search. On the other hand, we would like to congratulate H. Folgering for bringing it to our attention, as it argues against his own arguments. That work, even though it had a small number of patients (n=17), totally supports our findings and renders all of the worries of H. Folgering somewhat meaningless. Our argument is precisely that patients with hypercapnic COPD do not have a decreased central drive, and that this is not different from eucapnic patients. Therefore, the hypercapnia is "not" a consequence of an adaptive hypoventilatory state. We do not disagree that the increased central drive cannot be translated by the muscles into more effective ventilation, and it is in this sense that we state that patients have reached their "maximal drive". Indeed, we are very pleased that our definition of "neuroventilatory (not neuromechanical, as stated by H. Folgering) coupling failure" is supported by the findings reported by SCANO *et al.* [11].

We are also honoured that P. Begin and A. Grassino have commented on our results. Their comments once again, do help clarify some of the issues surrounding the topic. Basically, we agree with work by A. Grassino, who together with J. Sorli showed similar CO_2 responses in hypercapnic and eucapnic COPD patients. We disagree with the interpretation that hypercapnia results from an adaptive strategy by the pump to prevent fatigue. If this were so, then the central drive should be different. Nevertheless, this letter does point out two issues.

Firstly, the diaphragmatic tension-time index (T_{tdi}) values of our patients were high because we used peak transdiaphragmatic pressure (P_{di}) rather than mean P_{di}, but they were similar in eucapnic and hypercapnic patients. Whether mean or peak P_{di} is used, the results show a similar degree of respiratory muscle load in the two groups. We believe this argues against "adaptation" as a reason for hypercapnia. If the hypercapnic had "adapted", we would have expected a difference in T_{tdi} and, more importantly, a difference in $P0.1$ or pleural occlusion pressure 0.1/s after onset of inspiration ($P_{pl,0.1}$) as drive was increased during CO_2 rebreathing.

Secondly, rather than proposing that resting patients are functioning at a "maximal" drive, the theory we would like to argue is that hypercapnic patients are not "underdriven". Furthermore, our results, those of SCANO *et al.* [11], and those of DE TROYER *et al.* [10] indicate that eucapnic and hypercapnic COPD patients have an increased drive that responds to CO_2.

It is reassuring that the available evidence (including the study referred to by H. Folgering), indicates that, in stable hypercapnic COPD patients, central drive is well preserved, and that an adaptive decrease in ventilatory drive is not the cause of the increased CO_2.

Finally, we would like to express our gratitude to H. Folgering, P. Bégin and A. Grassino for their thought-provoking comments, and we hope that this scientific exchange in the *European Respiratory Journal* stimulates our quest to find answers to all of these interesting questions.

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