Defining "stable chronic hypercapnia" in patients with COPD: the physiological perspective

To the Editor:

We read with interest the "European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD" [1]. In recent years, several studies have attempted to improve outcomes by using home non-invasive ventilation in patients with end-stage COPD who suffer from chronic hypercapnic respiratory failure (CHRF). As noted in the guidelines, the definition of "stable chronic hypercapnia" following an acute exacerbation has historically been ambiguous, which has probably contributed to the inconsistent findings across clinical trials of home non-invasive ventilation [1].

From a physiological point of view, one may argue that the respiratory acidosis associated with chronic hypercapnia must be fully compensated to be considered "stable". In various prediction rules, equations and algorithms for diagnosing acid-base disorders by arterial blood gas analysis, respiratory acidosis is often stated to be fully compensated within 5 days [2]. This compensation involves an increase in the renal tubular reabsorption of bicarbonate, mainly in the proximal tubule and collecting ducts. This is partly based on findings from studies in dogs conducted in the 1950s and 1960s, which suggested that renal compensation to respiratory acidosis reached a near steady state within the first 6 days [3, 4]. However, a remarkable study by Schaefer *et al.* [5] indicated that a true steady state may take several weeks to develop [5]: they studied 21 healthy subjects in which respiratory acidosis was induced by exposure to a carbon dioxide-rich environment (inspiratory carbon dioxide fraction (F_{ICO_2}) 1.5%) for 42 days aboard a submarine. The authors found that full renal compensation was not reached until on average 24 days of exposure. In a more recent study on goats exposed to a hypercapnic environment (F_{ICO_2} 6.0%), full renal compensation was not reached until after 30 days [6].

To our knowledge, no studies have yet specifically investigated the time required for full renal compensation in patients with COPD. Based on data from the above-mentioned studies, we posit that a time period of several weeks is required before a state of "stable chronic hypercapnia" is likely to be present. Thus, we suggest that future studies on home non-invasive ventilation in CHRF be conducted on COPD patients who are at least 2 to 4 weeks out from their acute exacerbation event. Operationally, it would be reasonable to define recovery as the time when the patient is deemed clinically stable without severe decompensated acidosis (*e.g.* pH >7.30). This physiologically based definition of "stable chronic hypercapnia" should be considered when designing future clinical trials, as well as when interpreting results from previous and current studies on patients with CHRF.

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A time period of 2–4 weeks is required before a state of "stable chronic hypercapnia" is likely to be present following an acute COPD exacerbation http://bit.ly/2D4lOok

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From the authors:

We would like to thank C. Hedsund and co-workers for their commentary on the "European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD" [1]. We agree that the definition of "stable chronic hypercapnia" following exacerbation is challenging.

We also agree that physiological studies showed heterogeneous results in terms of the time to achieve a full compensatory bicarbonate renal retention when humans and animals have been exposed to a carbon dioxide-rich environment. However, these experimental studies may not fully recapitulate physiological changes that occur in COPD patients, for several reasons: First, alveolar ventilation is dynamic and there are considerable physiological changes that occur from wakefulness to sleep, and also from activity to rest. This very probably impacts on the time course of compensatory bicarbonate renal retention. Secondly and similarly, this would also refer to the condition of recurrent exacerbation, *i.e.* "revolving door" COPD phenotype. Thirdly, co-existing acute or chronic pre-existent renal failure would substantially impact on the speed and capability of bicarbonate retention. Finally, loop diuretics are frequently used to treat peripheral oedema that is a typical clinical finding in patients with COPD and chronic hypercapnic respiratory failure [2]. However, oedema is not only related to cor pulmonale or congestive heart failure, but also to carbon dioxide-related vasodilation; here, loop diuretics may cause bicarbonate retention, which in turn may worsen hypercapnia and, as consequence, oedema [3].

Thus, the optimal definition of "stable chronic hypercapnia" is still unclear. We also feel that a time period of approximately 2–4 weeks following exacerbation is the minimum required to define a stable respiratory condition. This is not only based on the experimental studies as described by C. Hedsund and co-workers, but also due to clinical conditions, *i.e.* medical treatment of exacerbation (corticosteroids and/or antibiotics) or mechanical ventilation. However, this is arbitrary, and in our opinion the time required to achieve a clinically stable condition after a COPD exacerbation may be variable and not precisely predictable and sometimes may last considerably longer than 2–4 weeks, depending on the clinical individual context.

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The definition of "stable chronic hypercapnia" following COPD exacerbation is challenging
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