Systemic steroids in severe forms of COPD exacerbations: a question of balance?

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Systemic steroids in mechanically ventilated COPD: the absence of obvious benefit should make prescription the exception http://ow.ly/spRFx

Chronic obstructive pulmonary disease (COPD) is a lung disorder with systemic inflammatory-related consequences, for which there is no cure. Beside tobacco cessation (of which the beneficial effects are many), the only available therapeutic interventions in COPD target exercise-related dyspnoea and exacerbations. There is extensive solid evidence to support the use of bronchodilators and pulmonary rehabilitation to address these clinically relevant issues [1]. The corpus of data supporting the beneficial effects of pulmonary rehabilitation is vast and has been built through the years by several convergent studies from independent investigators [2]. It is widely acknowledged that locomotor muscles are dysfunctional in COPD [3], and also widely acknowledged that rehabilitation in COPD improves exercise tolerance, decreases the rate of exacerbations, ameliorates quality of life and might prolong survival in certain contexts (*e.g.* after an exacerbation of the disease) [2, 4, 5]. Exercise training (or re-training) is a major driver of the success of pulmonary rehabilitation in COPD. Thus, the current state of the evidence suggests that patients with COPD who want to tackle their disease should quit smoking, inhale bronchodilating substances, be they associated or not with corticosteroids, and seriously think about rebuilding the strength and endurance of their meagre quadriceps. To do so, exercise is needed, but so is an adequate balance between muscle anabolism and muscle catabolism.

It is at this point that this editorial connects with the article that it accompanies, although through a contorted route. In this issue of the *European Respiratory Journal*, Abroug *et al.* [6] report data that are first of their kind on the effects of systemic steroids in patients admitted to an intensive care unit (ICU) and requiring ventilatory support for a severe, life-threatening exacerbation of COPD. In an open-label, randomised trial of 217 patients, Abroug *et al.* [6] observed no difference between patients receiving standard care or standard care plus 1 $mg \cdot kg^{-1}$ of prednisone, in terms of ICU mortality, the rate of noninvasive ventilation failure, the duration of mechanical ventilation or the ICU length of stay. How are these observations relevant to our quadriceps story? Because systemic steroids are classically known to tip the balance between muscle anabolism and muscle catabolism toward the side of catabolism [7], resulting in a loss of muscle mass, possibly involving myostatin upregulation [8]: proximal muscle weakness is among typical features of hypercorticism [9, 10]. Yet, a great many critically ill patients exhibit increased catabolism as a consequence of their acute state, with both locomotor muscle and respiratory muscle the clinical victims of this aggression [11, 12]: preserving muscle mass is a major clinical concern for all intensivists. Systemic steroids can be beneficial in some of these clinical situations if they effectively interrupt an

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inflammatory process. If this is not the case, however, they do have the capacity to bring more harm than remedy. In patients with severe COPD experiencing an exacerbation, an early study of the effects of nutritional support [13] showed a negative nitrogen balance in all the patients where it was calculated. There was a statistically significant inverse correlation between nitrogen balance and the cumulative dose of methylprednisolone received, and between handgrip strength and nitrogen balance [13]. Corticosteroids are listed among the factors of striated muscle dysfunction during acute respiratory failure of COPD [14] and negative relationships between muscle strength and the cumulative dose of steroids received for COPD exacerbations have also been reported [15]. In COPD patients who have been intubated and are mechanically ventilated, the occurrence and severity of ICU-acquired myopathy (documented by electrophysiological studies and biopsies) has been related to the dose of systemic steroids received [16], with consequences as severe as prolonged mechanical ventilation and prolonged hospital stay. Of note, systemic steroids in ICU patients (COPD notwithstanding) can increase the risk of ICU-acquired polyneuromyopathy, directly or by contributing to hyperglycaemia, an independent risk factor of this entity [17] is an obvious cause of quadriceps atrophy and weakness. The ''steroid–COPD–ICU–muscle'' picture is thus rather gloomy: it is then only a small step to conclude that having received systemic steroids during a severe exacerbation will not help a COPD patients who survive the ICU stay (and fortunately this is the majority, with in-hospital mortality of acute respiratory failure of COPD lower than that of many other causes of respiratory failure [18, 19]) start and achieve a successful rehabilitation. This would be a lesser problem if the said steroids had major other benefits. The study by ABROUG *et al.* [6] suggests that this is not the case in the most severe category of COPD exacerbations, those that require ventilatory assistance.

This study has one major merit, which is to provide novel and long awaited clinical data on an important issue. It is, however, not devoid of drawbacks and limitations, and points to issues of consideration by future studies. First, with respect to sample size calculations, we should question whether the goal is attainable. Indeed, this trial was designed to have 80% power to detect a 12% decrease in ICU mortality, *i.e.* from 22% to 10%, corresponding to a 55% relative reduction. This is enormous. Not many interventions can claim to reduce mortality rates to such a level. In fact the study was underpowered, as it was stopped early, and cannot preclude a 40% relative reduction in ICU mortality, which is also quite massive and rather unrealistic. A second issue is whether the study should be so restrictive in its patient population. Indeed, patients treated for a COPD exacerbation with systemic steroids in the 30 days prior to screening were excluded. These 160 excluded patients represent a significant number relative to the 217 included in the trial. Is it reasonable to exclude such patients when they represent an important portion of those seen routinely in the ICU? Future trials may wish to include patients who had a treated exacerbation, if the trial is to have wide value for clinical practice. In addition, it may be worthwhile to reconsider the 74 patients excluded because of evidence for pneumonia when 25% of the included patients had an unidentified cause for their AECOPD. The third issue relates to the statistical analysis in view of the small study size, which led to some imbalances in the groups. Indeed, the patients randomised to prednisone were older than the control patients by 2 years and had COPD for 2 years longer. A 2-year age difference is not negligible in terms of mortality among 70-year old COPD patients, while a longer COPD duration reflects a history of more exacerbations, which is also related to higher mortality risk during an exacerbation [20]. A statistical analysis that adjusts for these and other factors may provide a somewhat more accurate estimate of the effect, albeit power will remain an issue. Finally, the open-label nature of the randomised trial can be problematic. While the authors correctly point out the absence of bias from reporting hard end-points such as death, open-label trials can induce imbalances in other treatments prescribed specifically because of the ''openness'' of the intervention, and could affect the outcome. While this did not turn out to be the case in this trial, antibiotics could very well have been given differentially to patients who did not receive the trial prednisone, and could affect mortality. It is unclear how the results of such a trial would then be interpreted.

In spite of these limitations, the study by ABROUG *et al.* [6] must be taken as what it is, namely a stern, well-founded warning against the routine (and at times ''instinctive'') prescription of systemic steroids in COPD patients needing acute ventilatory support. Indeed, beyond the nitrogen and the anabolism–catabolism balances discussed above, and that this study does not directly address, what the results of ABROUG *et al.* [6] show is that the risk–benefit balance of systemic steroids in this indication is negative, not only because there is no clear benefit to weight but also because there is some weight on the risk plate of the scale with severe hyperglycaemia occurring more often in the ''prednisone'' group. This side-effect has already been reported as clouding the benefits of systemic steroids in less severe COPD exacerbations [21] and is of particular concern in the general management of the critically ill [22]. It is true that further studies are needed, including trials with a more robust design and perhaps even large-scale, well-designed observational studies, before definitive conclusions are drawn. Meanwhile, treatment guidelines could be reviewed and clinicians should exert caution and discernment. They should prescribe systemic steroids in ICU-managed COPD patients only if they have a particular reason to do so and not let themselves be driven by the

momentum of habit. Hopefully, sticking to *primum non nocere* in this instance will make it easier for those patients to benefit, after their ICU stay, from what there is actual evidence for, namely efficient exercise training in the context of pulmonary rehabilitation.

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