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EDITORIAL

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Bronchodilators and mechanical ventilation in COPD patients

Emptying, pumping or both?

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Acute exacerbation in patients affected by chronic obstructive pulmonary disease (COPD) worsens airway obstruction and thereby produces a further rise in airflow resistance and dynamic hyperinflation. As a consequence, elevated airway resistance and intrinsic positive end-expiratory pressure (PEEPi) increase the load faced by the respiratory muscles, while hyperinflation reduces the force generation capacity of the diaphragm by shortening its fibres [1].

Pharmacological treatment, acting directly on the bronchial smooth muscle (beta$_2$-agonists, anticholinergic agents and xanthines) [2] and reducing the inflammatory process (steroids and antibiotics) [3], may decrease airway obstruction and hyperinflation, thereby diminishing the mechanical load imposed on the respiratory muscles and improving diaphragmatic function. Unfortunately, during an episode of acute pump failure medical therapy works in about only 30% of the patients admitted to the ICU [4].

When the force-load balance is altered to a level such that respiratory muscle fatigue occurs, spontaneous breathing is no longer sustainable and mechanical ventilation is required. The ventilator acts as an extra pump put in series to the respiratory muscles and assumes the work of breathing entirely or in part, thereby reversing the unfavourable force-load balance. Furthermore, by reducing inspiratory effort, improving breathing pattern and correcting abnormal arterial blood gas tensions, mechanical ventilation may determine an improvement in respiratory muscle function through the mechanisms of rest, mechanical advantage due to reduced hyperinflation, better oxygenation and normalisation of acidosis.

As bronchodilators are a primary component of the treatment of COPD exacerbation [5, 6], they should not be discontinued when acute respiratory failure develops and mechanical ventilation is initiated. While steroids [7], xanthines [8] and antibiotics are usually parenterally administered, beta$_2$-agonists are more effectively and safely given via a small volume nebuliser (SVN) or a metered-dose inhaler (MDI) connected to an appropriate spacer, even in mechanically ventilated patients [9].

Mouloudi and co-workers [10], in the paper published in this issue of the journal, studied nine patients within 72 h of the institution of ventilation. They found that 600 μg of salbutamol delivered using MDI reduced airway resistance and PEEPi by an average of approximately 20% and 25%, respectively, in eight of the nine (88%) subjects. Their data qualitatively and quantitatively confirm the results of previous studies performed on mechanically ventilated COPD patients [11, 12, 13].

It is interesting to observe that, in contrast to that described for the "acute" patients, only approximately 25–30% of stable COPD patients have significant bronchodilation, defined as an increase in the forced expiratory volume in 1 s (FEV_1) of 12% or more or 200 ml or more, after administration of beta$_2$-agonists or anticholinergics. As a matter of fact, COPD is defined according to the major international guidelines "as a disease characterised by the presence of irreversible or only partially reversible airflow obstruction" [5, 6]. The different degree of bronchodilation in the acute and chronic set-

tings might depend on a more pronounced sensitivity to the drug during the acute phase since, during an episode of exacerbation, COPD has many histological features in common with asthma [14], which by definition is usually characterised by a significant response to bronchodilators.

The lack of sensitivity of FEV_1 in assessing functional improvement after a reversibility test in stable "poorly reversible" COPD patients has very recently been a matter of study. Maesen and co-workers [15] found that measurements of airway resistance and work of breathing were more likely to reveal changes in airway calibre than FEV_1 and this may be because the early airway collapse and subsequent airway decline due to the forced expiratory manoeuvre cause underestimation of "real" bronchodilator effect. However, as a matter of fact, we still do not know whether inhaled bronchodilators work beyond the acute phase in these mechanically ventilated COPD patients but, if so, they might be useful in the process of discontinuing mechanical ventilation, usually quite difficult in COPD patients. In this group of patients airway resistance and PEEPi have been shown to account for approximately 80% of the global burden [16]. Extrapolating the results of the study by Mouloudi et al. [10], inhaled $beta_2$-agonists would reduce the load imposed on the respiratory muscles by approximately 15–20%, an amount that might be crucial in determining successful weaning. Indeed, in our experience sustained bronchodilator therapy may help to facilitate and accelerate the weaning process, although this has never been systematically tested.

Both SVN and MDI have been proven to induce significant reduction in airway resistance and dynamic hyperinflation, but MDI potentially offers advantages such as reduced risk of contamination and flow sensor damage, ease of administration, dose reliability and, possibly, cost reduction [9]. With MDI, however, adequate deposition of the drug in the lung may be affected by several technical aspects, including the ventilator settings. In in vitro studies end-inspiratory pause, duty cycle (Ti/Ttot), flow rate and tidal volume (V_T) have been proposed as important determinants of the amount of drug actually delivered [17]. A previous work by Moloudi et al. excluded the possibility that an end-inspiratory pause of a few seconds could enhance the effect of the drug [18]. The study published in this issue of the journal [10] demonstrates that the response to salbutamol, delivered via MDI during controlled mechanical ventilation at constant flow, is not improved when V_T and Ti/Ttot of the breath following drug administration are increased by 50%. Minimising the importance of these manipulations, the work by Mouloudi makes the use of MDI in ventilated COPD patients more appealing because it is more applicable.

What is the reason for these discrepancies between in vitro and in vivo studies? It should be kept in mind that bench studies measure the quantity of drug inhaled and not its actual deposition and the amount of drug reaching the lungs does not necessarily mean actual bronchodilator response. The rise in inhaled drug observed using a larger V_T in bench studies is, therefore, not necessarily followed by increased bronchodilatation. It has been shown that 4 puffs of albuterol (90 μg/puff) can produce the same decay in airway resistance as 28 puffs in COPD patients, because of the limited airway reversibility of this population or the down-regulation phenomenon [19]. In the study by Mouloudi et al.[10] six puffs of salbutamol (100 μg/puff) were used. This dose, as suggested by the authors, might have produced maximal broncodilatation, which prevented any further beneficial effect being gained from V_T manipulation. In addition, it should be remembered that in vitro studies have shown an increase in drug delivery for a V_T greater than 500 ml [17]. In Mouloudi's study [10] the so-called "normal" V_T ranged from 450 to 660 ml, the mean being 582 ml. The authors ascertained the lack of positive effects when V_T was increased, but could not exclude drawbacks due to V_T reduction.

Like most of the previous in vivo studies, Mouloudi et al. [10] performed their investigation in subjects invasively ventilated in controlled mode (CMV). Forms of partial ventilatory support are preferred nowadays whenever possible and this is particularly the case for COPD patients, at least after the initial 12–24 h [20]. Fink et al. [17] observed that albuterol delivery in vitro was not different using total (CMV) or partial (A/C and PSV) forms of mechanical ventilatory assistance. By minimising the importance of some ventilatory settings (i.e. end-inspiratory pause, V_T, inspiratory time and duty cycle), the works of Mouloudi et al. [10–18] indirectly support the concept that the efficacy of the bronchodilator administered via MDI can be extended to the assisted ventilatory modes. If proven, this would increase the use of bronchodilators via MDI in the ICU. Indeed, non-invasive mechanical ventilation has been proven to be an effective treatment in acute respiratory failure due to COPD exacerbation [4] and, in our opinion, the possibility of delivering bronchodilators via MDI during this ventilatory mode deserves future investigation.

In summary, should we start thinking that beside pumping, emptying is also a major goal to achieve in mechanically ventilated COPD patients? To date we have scientific evidence that both mechanical ventilation and bronchodilators are important weapons that we have to use in these critically ill patients. While, in several studies, the choice of different strategies of mechanical ventilation have been shown to have an impact on the outcome, facilitating for example the process of weaning while reducing complications [20], we have no data concerning the use of bronchodilators. It is nevertheless surprising that in the most important randomised clinical trials [20, 21, 22, 23] comparing different

methods of weaning, there is no mention at all of the inhalation therapy, if any, that the patients were receiving. If, as suggested by Mouloudi's study [10], the delivery of salbutamol may reduce the global burden of the respiratory pump by about 20%, this may profoundly influence, at least in COPD patients, the weaning results, so that some of the previously reported data may need to be reconsidered. It is time, therefore, to design randomised and controlled clinical studies to assess whether bronchodilators, besides having a physiological effect, may also influence survival, duration of mechanical ventilation and ICU stay and the related costs.

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