

We thank the Referees for the revision of our manuscript. Here below you find the point to point answers to their comments.

Reviewer's code: 04334222

This mechanism, however, besides being physically limited, leads to an increment in DH and intrinsic end-expiratory alveolar pressure, adding an increasing threshold load on the inspiratory muscles, which become functionally weaker, and eliciting dyspnoea. In advanced chronic obstructive pulmonary disease, bronchodilators and lung volume reduction surgery do not usually reverse expiratory flow limitation, but they appear to be useful because they often allow expiratory flow limitation to occur at a lower absolute lung volume, thus reducing dynamic pulmonary hyperinflation and limiting exertional dyspnoea.

The Reviewer is right saying that in many clinical situations the priority is not abolishing EFL but rather decreasing dynamic hyperinflation. Indeed it is well known that in COPD patients bronchodilators do not abolish EFL, rather a substantial part of their beneficial effect is due to a reduction of the operating volume, secondary to an increase of the maximal expiratory flows (Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. *Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur Respir J. 1998;12(4):799-804*). Note that in this way bronchodilators reduce PEEPi (Dal Vecchio L, Polese G, Poggi R, Rossi A. *"Intrinsic" positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. Eur Respir J 1990, 3, 74-80*). To the contrary, application of an external PEEP do not reduce hyperinflation, but neither does increase it, if PEEPi is secondary to the presence of flow-limitation (Natalini G, Tuzzo D, Rosano A, et al. *Effect of external PEEP in patients under controlled mechanical ventilation with an auto-PEEP of 5 cmH₂O or higher. Ann Intensive Care. 2016;6(1):53*). If pharmacological bronchodilating treatment is limited, as in ARDS patients (Bassford CR, Thickett DR, Perkins GD. *The rise and fall of β -agonists in the treatment of ARDS. Critical Care 2012, 16:208*), the effects of EFL should be managed by carefully adjusting ventilator settings. A short paragraph, together with 3 new references, has been added to the text, dealing with these issues.

Reviewer's code: 00502932

Very good review of this important and overlooked aspect of mechanical ventilation. I believe the article would be greatly enhanced by inclusion of some illustrations, for example diagrams showing the techniques for detection of EFL via NEP, and ZEEP in the mechanically ventilated subject. Step-by-step instructions might also be useful.

We agree with the suggestion of the Reviewer. A figure illustrating the effect of NEP application in a non flow limited and in a flow limited patient was added. The idea of adding step by step instruction is also interesting, but this addition would lengthen excessively the editorial, and probably would distract the reader from the main purpose of this editorial, that is to explore the effects of EFL in ICU patients and the possibility that EFL by itself has a role in the genesis in ventilator-induced lung injury.

Reviewer's code: 03189996

The manuscript (MS) by Drs. Koutsoukou and Pecchiari reviews the phenomenon of expiratory flow-limitation (EFL) in ventilated patients. Major part of the MS is devoted to the pathophysiology and assessment in ARDS patients which is expected. However, other diseases heralded by ventilatory impairment are briefly discussed, namely COPD, heart failure, along with the effects of

positioning and anesthesia. The MS is well balanced and offers a solid overview to a somewhat educated reader.

No straightforward clinical recommendations are made and thus the clinical message of the MS could be limited. It does not seem that this was the primary aim of the authors. An almost sole example of a “hidden” second-handed message is on page 8 – “A PEEP of 10 cmH₂O abolished EFL... [ref 34].” Indeed, it seems that “PEEP 10” is the new “PEEP 5” as was previously deemed to represent a “physiologic PEEP”.

The Referee is right when saying that we did not give straightforward clinical recommendations. In the absence of randomized clinical trials specifically aimed to investigate the effect of abolishing EFL in mechanically ventilated patients, no recommendation can be given. Though there are some clues pointing toward a role of EFL in the development of ventilator-induced lung injury, a clear demonstration is lacking. Moreover, we are aware that ICU patients, in particular ARDS patients, are complex patients, and interventions focused on one aspect of the disease can be uninfluential regarding the prognosis because other factors have a greater effect on the outcome, and in this situation to give precise indications is risky without randomized trials. Actually, in our intentions, this editorial should help stimulating both preclinical and clinical research to investigate the role played by EFL in the pathogenesis of ventilator-induced lung injury.

The only recommendation I may have is replacing the word “enhanced” with “compromised” on P7 end of first paragraph. While you certainly mean that FRC is reduced by anesthesia and in other scenarios, i.e. the reduction is enhanced, an inexperienced reader may wrongly assume that FRC is enhanced as this word (i.e. FRC) immediately precedes the verb.

Done