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COPD exacerbation and diaphragmatic dysfunction: Conditions with mutual influence influencing outcomes?

To the Editor:

The article by Antenora *et al.*[1] provides new data on a particularly relevant topic: the assessment of diaphragmatic dysfunction (DD) using ultrasound. To date, no previous study has assessed the prevalence of DD in COPD patients admitted to hospital for acute exacerbations.

We found this article interesting both because of the relevance of the topic and because of the peculiarity of the sample. However, several points warrant attention.

First, it seems that Antenora *et al.*[1] ascribe DD mainly to exacerbations: '*During severe AECOPD, progressive development of dynamic hyperinflation causes a change in the geometry of the chest wall and diaphragm [...] thus exposing the diaphragm to dysfunction [...]*'[1]

But, as diaphragm function was assessed only on admission to hospital, with no further evaluation before or after resolution of the exacerbation, it appears difficult to determine whether the DD was related to the exacerbation *per se* or to a chronic pre-existent state or even to both overlapping conditions.

It would have been interesting to demonstrate the improvement of the dysfunction during the resolution of the exacerbation to corroborate the authors' statement. Furthermore, it would have been worthwhile to have monitored the DD afterwards, under conditions of complete clinical stability, to assess its possible reversibility. Moreover, functional data, gathered under the corresponding clinical conditions, would have been useful to correlate functional impairment (especially hyperinflation) and DD.

However, as the only factor significantly associated with DD was the use of systemic steroids and, as steroid-induced myopathy takes time, it seems more probable that a chronic condition with previous prolonged steroid administration rather than an acute event would have contributed to generating DD.

Accordingly, it would have been useful to investigate the systemic exposure to steroids (type, duration and dose) to gain an understanding of their role. Probably, the cumulative effects of both acute and chronic conditions may be implicated in the origin of DD.

The second point concerns the impact of DD on non-invasive ventilation (NIV) failure. Antenora *et al.* found DD to be an independent risk factor associated with NIV failure. It is plausible that DD represents a critical factor in determining a patient's clinical outcome, but the authors make no mention of the possible underlying mechanisms and do not specify details of the probable relationship between DD and NIV failure.

Concerning the ultimate cause of NIV failure, the authors mention several conditions but little evidence to suggest a direct link with DD evident (i.e. haemodynamic instability or electrocardiographic abnormalities or mask intolerance).

Furthermore, no details are provided on NIV modes and parameters. Were all the patients treated with same modes, parameters and interfaces? These details would have been provided insight into the role of DD and other possible factors, influencing NIV outcome.

A challenge for future research would be to investigate the ability of DD, assessed also under conditions of clinical stability, to predict the risk of severe exacerbations requiring hospitalization and mortality.

Potentially, ultrasonographic assessment of the diaphragm, like quadriceps muscle,[2] could represent an opportunity for future risk stratification.

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From the Authors:

We read with great interest the letter by Schreiber and Esquinas, whose thoughtful and constructive remarks related to our work allow us to revisit and expand some points.

Indeed, our study did not assess the pre-existence of DD in the patients in the study. Notwithstanding, the following considerations seem to indicate that dysfunction was mainly linked to the acute condition of our patients with COPD. First, we have chosen the change in thickness lower than 20% during inspiration to identify DD, namely a condition very close to paralysis.[1] Second, previous studies conducted on severe or very severe COPD patients during clinical stability did not recognize a significant difference in diaphragmatic function as assessed by ultrasound (US) when compared with healthy controls.[2] Third, most patients in our present study showed a meaningful improvement of the diaphragmatic US indices during recovery of their exacerbation (unpublished data), which suggests a causal relationship between acute lung impairment and DD. Finally, we are now conducting a physiological study on a similar

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population to assess the link between DD and mechanical derangement of the lung. Preliminary data show that static intrinsic positive end-expiratory pressure and end-expiratory lung volume increase while lung elastance decreases when acute exacerbation occurs in COPD patients with DD as compared to those without.

With regards to the role of steroids in shattering diaphragm function, studies conducted on animal models showed conflicting data concerning the damage on the diaphragmatic muscle structure following systemic steroid administration.[3,4] To date, there are no studies on humans, even though the activation of muscle proteolysis and decreased protein synthesis through the downregulation of Insuline-like growth factor 1 (IGF-1) could be a plausible mechanism responsible for steroid-induced myopathy.[5] In our opinion, the role of US to assess acutely developed DD in the management of Acute Exacerbation of COPD (AECOPD) requiring NIV is the most important message from our study.

With regards to the second point raised, we have to clarify that severe haemodynamic instability and major contraindications to NIV, including interface intolerance, were listed among the exclusion criteria in our study. Indeed, none of the patients required amine administration or major fluid support from the time of enrolment. Moreover, as we have specified in our discussion, the reasons for the exceeding NIV failure are not completely understood, whereas severe expiratory flow limitation and excessive hyperinflation might have played a critical role in uncoupling patient ventilatory efforts and mechanical ventilation.

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