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Non-invasive mechanical ventilation in myasthenic crisis outside intensive care unit setting: a safe step? Response

We thank Di Costanzo et al. [1] for their interest in our article describing a 20-year experience on 90 patients with myasthenic crisis (MC) undergoing non-invasive ventilatory support (NIV) in the general ward [2]. The comments require attention and might point out the following key question: can NIV be performed safely and successfully in MC outside the intensive care unit (ICU) setting?

NIV outside ICU is becoming a rapidly growing occurrence. More than 20 years ago, a multicenter randomized controlled study called YONIV trial showed that, in moderately acidotic chronic obstructive pulmonary disease (COPD) patients, early NIV application in general ward setting could be safe and effective in reducing the need for intubation and in-hospital mortality, opening up new perspectives on NIV treatment outside ICUs [3]. In the following years, a series of studies have confirmed the benefit of early NIV treatment in general ward in the context of COPD exacerbations [4–5]. More recently, in the course of SARS-CoV-2 outbreaks, shortage of ICU beds led clinicians to deliver NIV to patients with COVID-19 ARDS (CARDS) outside ICUs, showing a reduction in the need of endotracheal intubation in about 60% of cases [6].

NIV application outside ICU is an intriguing issue and the respiratory failure due to neuromuscular diseases remains a controversial indication for NIV ventilatory support, due to high risk of failure and to lack of prospective studies that validate its use. However, studies have suggested that NIV could be used in MC, showing a success rate of 38% in avoiding intubation [7].

MG is characterized by fluctuating skeletal muscle weakness and fatigability reduced by rest. The weakness may involve the respiratory muscles, as demonstrated by the "myasthenic pattern" highlighted by dynamic respiratory tests such as maximal voluntary ventilation [8]. Manifest MC is a severe event with rapid onset; approximately 20% of MG patients experience MC in their lifetime, typically within the first 2 years of the diagnosis [2,7].

Considering this physiologic mechanism behind ventilatory failure in MG, early NIV treatment started at the onset of inspiratory fatigue, before diaphragmatic weakness and hypoventilation are established, could potentially prevent the development of severe respiratory failure and the need of endotracheal intubation. In this context, NIV could act as resting therapy for inspiratory muscles that had reached the threshold fatigue, through the reduction of pressure pleural swings during tidal ventilation and consequently mitigating the inspiratory effort. Given that, the most recent literature supports the notion that NIV might provide sufficient and useful respite to eligible patients until fast-acting procedures as plasma exchanges and other immunomodulating therapies exert their effect [2,7].

The main question addressed by Di Costanzo et al. [1] cannot be fully answered for several reasons. First, the retrospective nature of the study cannot allow definitive conclusions, although the current understanding of MC, including treatment and outcome, up to now is only retrospective [2,7,9–12]. Di Costanzo et al. [1] should consider that in our study, we reviewed all patients admitted to our Neurological ward falling into the definition of Class V of Myasthenia Gravis Foundation of America, therefore in need of ventilator support by definition [2,7]. One the main findings of our study was the low rate of NIV failure; indeed, only 37.7% of MC required endotracheal intubation and MV [2]. The difference from the large work by Neumann et al. [7] can be partly explained by the different severity of the enrolled population and probably by the early use of NIV. This result is not new since previous works already suggested that early NIV treatment could reduce the need for intubation and MV in the course of MC [9–12]. Indeed, in our general ward, NIV is started when patients exhibit respiratory muscle impairment recorded by functional tests, before the gas exchange impairment takes place.

As a second point, we know that the information about general ward health care-team and patients monitoring system is crucial to validate the results, but these assessments were beyond the scope of our work. There might be heterogeneity of settings capable of delivering NIV within a single hospital and certainly the experience and the skills of the medical and nursing staff is of great importance in obtaining the best results from the application of NIV.

Third, a suitable assessment of upper respiratory muscles involvement is missing in our retrospective study. Previous trials by Lizzaraga et al. [9] and by others [10–12] suggested that bilevel positive airway pressure ventilation might be recommended also in MC with significant bulbar weakness. The presence of bulbar weakness is a critical point in considering the appropriate setting for patients monitoring, due to the high risk of aspiration, sudden respiratory deterioration and NIV failure. Furthermore, careful clinical assessment aimed at evaluating the patient's airway mucus clearance capacity and the level of pressure support required to obtain adequate minute ventilation are essential in

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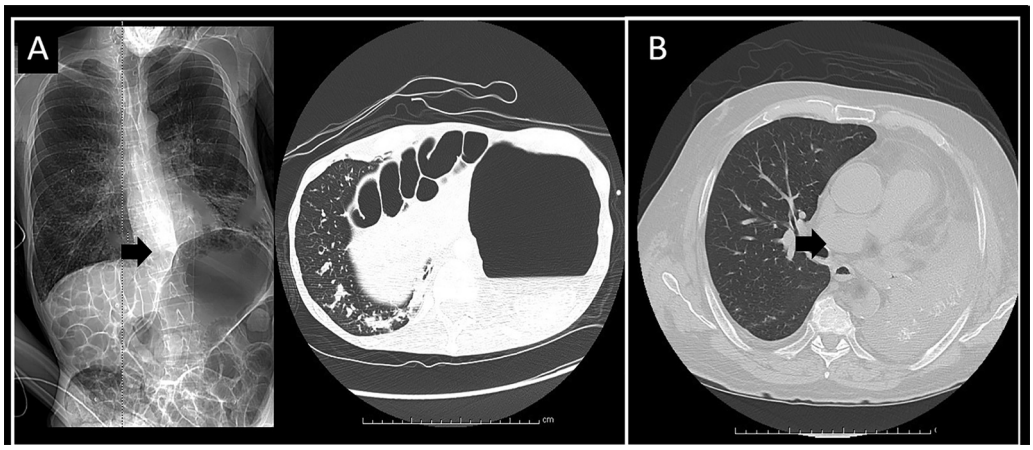

Fig. 1. **A.** Chest x ray and CT scan showing a MG patient who developed abdominal distension after NIV trial. Notice (arrow) how abdominal distension compresses the diaphragm and could act as precipitating factor of sudden respiratory deterioration if respiratory muscles are working on the fatigue threshold. **B.** CT scan showing occlusion of the right main bronchus with ipsilateral lung atelectasis (arrow) in patients with ineffective cough due to expiratory muscles weakness.

discriminating the appropriate setting for patient management. Indeed, airways occlusion due to mucus retention, but also gastroparesis and abdominal distension caused by high levels of pressure support, can act as a trigger for sudden respiratory arrest in neuromuscular diseases (Fig 1).

We believe these clinical aspects should be kept in mind in the selection of myasthenic patients with MC possibly undergoing a NIV trial. Our study may suggest a perspective in the field of MC treatment; the NIV delivery before hypoventilation is established could be another “bullet to fire” in MC treatment and early application in a skilled general ward might positively influence the outcome and timing of recovery in selected patients. These results obviously should be confirmed by large multicenter prospective study.

Declaration of competing interest

None of the co-authors and myself have financial/personal interest or belief that could affect their objectivity, or the source and nature of that potential conflict.

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