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Esophageal manometry: a valuable tool for the comprehensive management of COVID-19-related hypoxic respiratory failure

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Abstract

The optimal management of respiratory failure related to SARS-CoV-2 infection is a subject of heated debates in the scientific community. The lack of solid scientific evidence, combined with the unclear pathophysiology of COVID-19 pneumonia, means that the modalities and duration of ventilator assistance often rely on subjective assessments of the doctor on call. In establishing a suitable respiratory support, it is essential to evaluate the degree of activation of the respiratory muscles as objectively as possible. Among the various methods of evaluating the inspiratory effort, measurement of the phasic variations of esophageal pressure (intended as a surrogate of pleural pressure) represents the gold standard. Esophageal pressure measurement can be implemented in a minimally invasive way in every patient category, does not require sophisticated devices, and provides objective data about respiratory muscle activity. In patients with ongoing COVID-19-related respiratory failure, esophageal pressure monitoring allows i) optimizing the type and settings of non-invasive ventilation, ii) providing objective support in the delicate choice of establishing invasive ventilation in cases in which such an indication is unclear, and iii) monitoring the clinical evolution of COVID-19 pneumonia to allow early interception of cases with progressive worsening of lung function. Esophageal manometry provides a complete and objective assessment of respiratory muscle activity. Its clinical use in patients with respiratory failure in the course of COVID-19 would allow clarifying some pathophysiological aspects of the disease and customizing ventilatory support according to the needs of specific patients.

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Introduction

The management of acute hypoxemic respiratory failure is challenging, starting with the choice of the most appropriate type of respiratory support. From this perspective, it may be difficult to define the most appropriate respiratory assistance for patients. In most cases, the decision to place an endotracheal tube and start an invasive mechanical ventilation still relies on the personal evaluation of the doctor on call.[1] Although the decision making can be simpler in extreme cases, wide-ranging intermediate conditions exist, and personal experience, background knowledge, and available data play essential roles in these cases.

This problem is particularly relevant in the context of the COVID-19 pandemic. SARS-CoV-2 infection, which causes COVID-19, has affected 114,140,004 people worldwide thus far, involving >2,535,520 deaths and high hospitalization rates.[2] Respiratory failure is the main cause of hospitalization in an intensive or semi-intensive environment. Post-mortem histological analysis of pulmonary parenchyma has shown that Acute Respiratory Distress Syndrome (ARDS) from COVID-19 (CARDS) is characterized by prolonged intracellular viral RNA persistence, morpho-functional alterations at the endothelial level resulting in micro- and macro-thrombosis, and the presence of dysmorphic pneumocytes that often form syncytia, whereas dif-

fuse alveolar damage (typical of classic acute respiratory distress syndrome) is less represented.[3]

One of the crucial aspects in deciding the proper management of patients with respiratory failure is evaluating the respiratory drive. The respiratory drive can be difficult to evaluate, primarily because there is no consensus on its definition. From a pathophysiological viewpoint, it corresponds to the discharge intensity of the respiratory centers; however, this definition is not highly applicable from a clinical viewpoint.[4] Assuming that the nervous transmission between the bulbar centers and respiratory muscles is intact, the respiratory drive is directly proportional to the respiratory effort. Jonkman *et al.* recently proposed defining the respiratory drive as an integral of the discharge time of the bulbar centers, starting from the measurement of respiratory effort, which is clinically more assessable.[5]

The importance of respiratory stress assessment is even more pronounced in patients with COVID-19 pneumonia. Despite having a profound oxygenation deficit, these patients often do not exhibit respiratory distress, a phenomenon called "happy hypoxemia" or, more appropriately, "silent hypoxemia".[6] Different from the classic ARDS, in which inspiratory effort and respiratory rate are similarly affected, SARS-CoV-2-related pneumonia presents a discrepancy between the respiratory drive (usually high) and respiratory rate (often only slightly increased).[7] It is reasonable to assume that one of the reasons for this difference is that, at least in the early disease stages, the mechanical properties of the respiratory system including the lungs are pseudo-normal.[8] This pseudo-normality has its foundation in the anatomo-pathological characteristics of COVID-19 pneumonia, which helps explain the deep hypoxemia in the presence of preserved respiratory mechanics and low lung recruitability that characterize the early disease stages.[9]

Approximately 30% of patients with CARDS develop, over time, a pulmonary pattern characterized by reduced compliance and high recruitment, with clinical, pathophysiological, and radiological characteristics closer to those of classic ARDS.[10] The transition is believed to be facilitated by intense respiratory muscular effort, linked to reflex stimulation of damaged lungs, to a SARS-CoV-2-mediated alteration in the sensitivity of the carotid glomus, and to complex alterations in bulbar breath-control centers.[7]

Evaluation of the respiratory effort

Several ways of evaluating respiratory effort are available in the clinical setting, each of which assesses the activity of the bulbar centers in a relatively indirect manner and is characterized by different applicability and invasiveness.

The simplest and most indirect way of assessing inhalation effort is through clinical examination. The respiratory rate, although extremely simple to determine, may not reflect the real extent of the inspiratory effort, especially in COVID-19 patients, because of the peculiar disease characteristics mentioned above.[5] The main clinical sign associated with increased respiratory load is phasic contraction of the sternocleidomastoid muscle.[11] However, this assessment has the disadvantage of being impossible to accurately quantify and objectify and may be difficult to perform in some patient categories [e.g., those with Non-Invasive Ventilation (NIV) with a helmet].

Ultrasound evaluation of the diaphragm is a promising method that is noninvasive, repeatable, and easily available in any care setting.[12,13] In COVID-19 patients, a reduced Diaphragm Thickening Fraction (DTF) at the time of hospitalization in the Intensive Care Unit (ICU) has been associated with an increased probability of NIV failure, and a DTF of > 21.4% has been associated with a statistically significant reduction in the probability of intubation ($p = 0.003$).[14] However, ultrasonography, by definition, has considerable variability depending on both the operator's experience and the patient's physical characteristics. Moreover, in the aforementioned study, a single ultrasound survey of the DTF has been performed, but regular monitoring over time would be potentially useful to clarify the relationship between clinical progress and patient outcomes.

In the setting of invasive ventilation, it is possible to monitor the patient's effort by calculating the airway pressure (Paw) drop in the first 100 ms of the inspiratory work (P0.1) and by quantifying the Paw change during a prolonged occlusion (DPocc).[15,16] These indices have the advantage of quantifying, in a technically simple, easily repeatable, and clinically applicable way, the inspiratory activity of the patient. Esnault *et al.* recently demonstrated that in patients with COVID-19, P0.1≥ 4 cmH_2O and DPocc < -10 cmH_2O measured on the first day of spontaneous ventilation are reliable predictors of respiratory function deterioration.[17] As the correlation of these indices with respiratory muscle activity has been demonstrated, their use for evaluating respiratory effort is fully justified.[15,18] The main limitation of P0.1 and DPocc lies in the need for closed respiratory circuits, which therefore presuppose invasive ventilation. In spontaneously breathing or noninvasively ventilated patients, such indices are not applicable.

One of the most direct methods for evaluating the respiratory drive is analyzing the Diaphragmatic Electrical Activity (EADi).[19] In the clinical field, this analysis is possible through the use of nasogastric probes equipped with electrodes positioned at the esophageal level, which provide an electromyographic trace of the phrenic nerves.[20] Studies have shown that the intensity of electrical activity is proportional to diaphragmatic muscle activation in both healthy volunteers and ICU patients, thus confirming the validity of the method in monitoring respiratory effort.[19,21] However, although the intrinsic limitations of EADi have negligible clinical impact, such as the inability to assess the activity of accessory respiratory muscles or the potential unreliability of the generated signals,[22] clinical monitoring of the EADi is only possible through specific ventilators (Servo-I/-U, Maquet), which strongly limits its usability.

The most accurate way of assessing inspiratory effort is to measure the esophageal pressure (Pes) swing.[23] Pes can be assessed minimally invasively and offers the advantage of providing objective and continuous data about respiratory activity. Further, it is applicable to all patients, regardless of the presence and type of ventilatory support.

As Pes is correlated with pleural pressure, the patient's spontaneous muscle activity, aimed at lowering pleural pressure to create the incoming airflow to the alveoli, results in a Pes drop:[23] the greater the variation of Pes, the greater the central activation of the respiratory muscles.[24] From Pes, it is possible to calculate, at any time (t), the pressure generated by the respiratory muscles (Pmus) through the following equation:

$$Pmus = V(t) * Ecw - \Delta Pes(t)$$

where V is the tidal volume, Ecw is the elastance of the chest wall, and DPes is the variation in Pes from baseline.[25] If not previously calculated, Ecw can be estimated as 4% of the predicted vital capacity.[26]

In addition to directly quantifying the inspiratory effort, Pes allows calculating the transpulmonary pressure (PL), which is the pressure applied at every moment of the inspiratory work on the walls of the alveoli. PL is calculated by subtracting, at any time, Pes from Paw (PL = Paw – Pes).[23] In spontaneously breathing patients with hypoxic respiratory failure, it is particularly impor-

tant to consider the variation of PL within the same respiratory work, which better reflects the lung inhomogeneities that account for the Pendelluft phenomenon.[27] The PL swing is known as the Dynamic PL (DPL).

Growing evidence shows that DPL may play an important role in the development of lung damage during respiratory failure. The high muscle activation in these cases results in a high PL swing, which, in turn, entails increased blood flow to the lung, alveolar damage, and ultimately increased pulmonary edema.[28] This process represents the pathophysiological basis of Patient Self-Induced Lung Injury (P-SILI).[29] As it has been suggested that P-SILI has a nonnegligible role in the clinical evolution of COVID-19 pneumonia, early recognition and prevention could play a key role in the treatment of this condition.[30]

Currently, there is no scientifically proven evidence on the best management of respiratory failure in COVID-19 patients. Clinical experience and current guidelines suggest implementing a step-up therapy with high-flow nasal cannulas and NIV in cases in which hypoxemia does not resolve with conventional oxygen therapy through nasal cannulas or facial masks.[31,32] Orotracheal intubation may be considered if clinical conditions do not improve or worsen after 2h of NIV.[33] In most cases, the choice of intubation is based on easily obtainable bedside clinical parameters, such as peripheral oxygen saturation, respiratory rate, and arterial blood gas.[34] However, current evidence suggests that these parameters do not have sufficient predictive power in discriminating which patients may benefit from noninvasive respiratory support.[35] Moreover, the histopathological nature of the disease itself makes the clinical evaluation of respiratory fatigue misleading. These factors make the timing of intubation a subject of heated debates. Some authors propose early establishment of controlled mechanical ventilation to abolish intense muscle activity and reduce the possible impact of P-SILI on disease progression.[36,37] Conversely, invasive ventilation and orotracheal intubation inevitably have mechanical, inflammatory, and infectious adverse effects, globally known as Ventilator-Associated Events (VAEs). VAEs result in increased duration of mechanical ventilation in the ICU and increased hospital stays and, consequently, increased morbidity and mortality.[38] On the basis of these observations, Tobin *et al.* recommended a reasoned approach to the establishment of controlled ventilation, based on a careful assessment of the patient's clinical state and the pathophysiological mechanisms of the underlying pathology.[39]

Pes monitoring may play a pivotal role in the management of COVID-19-related respiratory failure. To our knowledge, although the evaluation of inhalation effort through Pes measurement has been proposed several times, no specific studies have assessed the impact of such an evaluation on patient management.[10,37]

In our opinion, the use of Pes should be scientifically validated and implemented in clinical practice in at least three areas.

First of all, as a parameter for monitoring the adequacy of NIV: NIV is one of the cornerstones of the ongoing treatment for respiratory failure in COVID-19 patients.[40,41] However, there are no clear indications for the type of interface to be used, treatment to be set (*i.e.*, continuous positive airway pressure vs. pressure support NIV), setting of ventilatory parameters, and timing of the therapy cycles. If the choice of the interface type depends on the tolerability of the patient, availability of resources, and expertise of the center, the optimization of other aspects can benefit from Pes monitoring. As the reduction of the Pes swing reflects the satisfaction of the patient's ventilatory requests, it can be assumed that setting an appropriate level of positive end-expiratory pressure and the eventual support pressure can be based on the benefits in terms of Pes changes. Similarly, the choice to start an NIV cycle after a temporary interruption can be guided not only by clinical laboratory parameters but also by monitoring the patient's effort. Finally, monitoring the activity of the respiratory muscles can be useful to discriminate which patients are not responsive to NIV, even after optimization attempts. From this perspective, Tonelli *et al.* have shown that, in patients with respiratory failure not related to COVID-19, a reduction in Pes swing < 10 cmH_2O after 2 h of NIV is an early and accurate predictor of NIV failure at 24 h.[42]

In addition to that, the use of Pes should be scientifically validated and implemented as an evaluation parameter for the need to establish invasive ventilation, in addition to the clinical parameters already suggested by previous reports and that are normally used: as early as March 2020, Gattinoni *et al.* suggested measuring the Pes swing to determine which patients are at a major risk of developing P-SILI and thus may benefit from early controlled ventilation. The authors proposed a Pes of 15 cmH_2O as a threshold value beyond which endotracheal intubation should be considered.[10,43] Definitive studies on the effectiveness of this strategy are still lacking, and there is no scientific validation of such a threshold value. In the context of the scientific diatribe inherent in the timing of establishment of mechanical ventilation, which mainly concerns patients without a clear indication for endotracheal intubation, objective evaluation of the patient's inhalation effort through Pes monitoring should be integrated with other clinical laboratory parameters.

The use of Pes should be scientifically validated and implemented as an indirect marker of the clinical evolution of CARDS as well: In early-onset pneumonia of COVID-19, pseudo-normal compliance indicates that ventilatory demands are met through an increase in tidal volume rather than respiratory rate. In cases in which the disease progresses toward an ARDS-like phenotype (characterized by low compliance), ensuring the same tidal volume is necessary for the generation of a greater inspiratory effort, which results in an increased Pes swing. By monitoring Pes, it may be possible to intercept this transition early. A typical example may be a patient whose ventilatory requests are no longer satisfied by a previously targeted and effective treatment and whose inhalation effort is progressively incremental. A possible confirmation of this hypothesis could allow the early introduction of invasive, controlled, and protective ventilation only when it is actually necessary.

Lastly, the use of Pes should be scientifically validated and implemented as a clinical tool for guiding the transition from controlled to assisted ventilation and for optimizing sedation and ventilatory support to facilitate weaning from mechanical ventilation: This topic is beyond the scope of this work and will not be discussed here.

Conclusions

In conclusion, Pes monitoring, besides being crucial in the management of protective ventilation and in the prevention of ventilator-induced lung injury, allows an easy and objective evaluation of the respiratory work of patients with respiratory failure. Its potential in this field has been the subject of an increasing number of scientific studies in recent years. Considering the clinical and histopathological characteristics of COVID-19 pneumonia, the scarcity of available data, and the requirement for commitment of health resources, it seems necessary to develop an objective and physiology-guided approach to the management of this condition. In this sense, evaluation and monitoring of Pes can offer a clinically usable foothold to guide ventilatory support, especially when clinical features and laboratory data seem discordant. This tool opens interesting scenarios to better clarify the complex pathophysiology of COVID-19 pneumonia and simultaneously offers great potential to customize and optimize the ventilatory support of

affected patients. We hope that its use will become increasingly common in clinical practice.

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