Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

COVID-19 pneumonia: Therapeutic implications of its atypical features

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In a recent systematic review and meta-analysis, Reddy *et al.* [1] refuted the presence of "phenotypes" in patients with COVID-19 Acute Respiratory Distress Syndrome (C-ARDS), given that the distribution in their respiratory system compliance was near-Gaussian rather than bimodal. Consequently, they concluded that no change in conventional lung-protective ventilation strategies is warranted in C-ARDS, compared to standard ARDS. In the accompanying editorial, Schultz *et al.*, supporting the same conclusion, warned: "we should always take a cautious approach when interpreting small case series, and we should change practice only on the basis of firm evidence" [2].

Historically, the advances in clinical medical research have been driven by two different approaches: (a) *physiological*, in which the research focus is to identify the physiological phenomenon underlying a specific clinical condition, usually tested on a restricted cohort of extensively studied individuals; and (b) *epidemiological/statistical*, in which the study hypothesis is tested in a large number of individuals, in order to confirm or reject a set of prespecified clinical outcomes on a probabilistic ground.

The debate on *typical* or *atypical* ARDS for COVID-19 respiratory failure is an example that reflects these two different approaches. The relevance of this controversy, however, is not merely academic but carries important practical implications, which may affect patient outcomes.

Ashbaugh *et al.*, pertaining to the generation of the physiological approach, fully described the main features of ARDS based on a cohort of twelve individuals [3]. In that landmark paper, the authors referred to the following clinical features to define the presence of ARDS: refractory hypoxemia, (*i.e.*, the inability to maintain 100 mmHg of arterial blood oxygenation even when breathing at 100% oxygen); reduced respiratory compliance, and bilateral and patchy lung infiltrates on chest X-ray.

The great fortune of ARDS as an entity is deeply related to the birth of the intensive care units, a unique highly technological environment where these patients could be kept alive. Therefore, despite being a syndrome, ARDS became the "intensive care disease". Indeed, regardless of its origin, the physiological and clinical features of patients with ARDS are similar and require a similar symptomatic approach: *mechanical ventilation*, whose ultimate goal is to "buy time" while the underlying disease is reversed.

Because mechanical ventilation is a symptomatic therapy, the "best" mechanical ventilation treatment is the one that corrects life-threatening symptoms, such as severe hypoxemia, without contributing to further lung damage. Decades of basic, translational, and clinical research led to a simple conclusion: to decrease stress and strain. This can be achieved by applying a near-normal tidal volume of 6 $mL.kg^{-1}$ [4] to prone-positioned patients with moderate-severe disease [5], thus allowing a more even distribution of stress and strain throughout the lung parenchyma [6]; and applying a moderate-high PEEP [7], according to the 'open-lung' concept [8]. These indications are the core of lung protective strategies, although the use of high PEEP is controversial, and proved harmful when set above 15 cmH_2O [9].

In this context, in 2019 a new disease spread from China across the globe, leading to clinical conditions that, in several cases, fulfilled the ARDS criteria (hypoxemia and bilateral chest x-ray infiltrations) [10]. COVID-19 pneumonia is a specific disease with a well-defined etiology, and whose pathogenetic mechanisms are being progressively deciphered. During the first wave of the pandemic, the immediate reaction of the intensive care community was to apply a standard "lung protective strategy", which includes low tidal volume and prone positioning. Due to the severity of hypoxemia, high PEEP was often used [11], as recommended by some authorities [12], and the COVID-19 Sepsis Surviving Campaign guidelines [13].

Unfortunately, because of the number of cases and the enormous strain on healthcare resources, little time for a careful understanding of COVID-19 pathophysiology and its possible implications for treatment was available. Indeed, the common clinical feature since the beginning of the pandemic – so common as to be also reported by the media – was the striking hypoxemia (with PaO_2/FiO_2 as low as <100 mmHg, as the refractory hypoxemia defined by Ashbaugh) in patients whose lungs were easy to ventilate, even at low airway pressures. Data from the lung CT scans performed in the early stages of COVID-19 disease showed high lung-gas volume and fraction of normally aerated

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tissue [14] despite the presence of severe hypoxemia. This is in sharp contrast with the typical ARDS, in which the hypoxemia is correlated with the size of the "baby lung". The COVID-19 disease is characterized by ARDS with an "adult-size lung", and its main characteristic is the uncoupling between lung mechanics/gas volume and gas exchange.

The simultaneous presence of near-normal gas volumes (whose respiratory system compliance is a surrogate) and severe hypoxemia implies that the mechanisms underlying a decreased oxygenation in COVID-19 are different from the intrapulmonary right-to-left shunt, which is the primary cause of hypoxemia in typical ARDS. Briefly, there is growing evidence that the mechanisms of hypoxemia in COVID-19 are perfusion alterations with loss of hypoxic vasoconstriction, embolism, and, more relevant, the opening of intra-bronchial shunts, whose presence has been documented in pathological samples [15]. The lack of intrapulmonary shunt (*i.e.,* atelectasis/consolidation) in early C-ARDS is incongruous with the use of high PEEP levels, whose effect will be detrimental to the hemodynamic and renal function.

The studies summarized in the meta-analysis by Reddy *et al.* reported, however, respiratory mechanics values similar to the typical ARDS, implying that C-ARDS is also associated with low gas volumes and a "baby lung" [1].

So, how can we reconcile these observations with those reporting impressive dissociations between respiratory mechanics (near-normal compliance and low non-aerated lung tissue) and the degree of hypoxemia [16,17]? Two possible reasons may account for this discrepancy. First, the respiratory system compliance usually reported in the literature is measured at "clinical PEEP", which may lead to a substantial bias. Indeed, even a subject with healthy lungs (and expected normal compliance) would show low compliance if measured at high PEEP. Therefore, the condition in which respiratory system compliance is measured may lead to a severe underestimation of its actual value in the presence of near-normal lung gas volume. Second, the patients included in large trials are studied at different stages of COVID-19 disease. Over time, if the course of the disease is not modified by treatment, the evolution of the lung toward fibrosis is almost unavoidable, with associated decreased respiratory system compliance.

In COVID-19 disease, the incidence of pneumothorax and pneumomediastinum are far more commonly reported than in typical ARDS, both in spontaneously breathing patients and in those undergoing mechanical ventilation [18]. It was previously reported that high-volume ventilation, even in spontaneously breathing subjects, leads to significant lung damage [19], and this process was recently defined as Patient Self-Induced Lung Injury (P-SILI) [20]. During COVID-19 disease, two concomitant processes may occur simultaneously: the natural progression of the disease and the presence of P-SILI dictated by an excessive respiratory drive and associated elevated stress and strain. It is astonishing the paucity of data relative to the esophageal (*i.e.*, pleural) pressure measurements, albeit a high tidal esophageal pressure should indicate sedation and controlled mechanical ventilation in COVID-19 patients at this stage.

Regardless of the discussion on whether COVID-19 disease is typical ARDS or not, the optimal treatment for COVID-19 disease is likely to be better identified when the following variables are assessed and measured: tidal volume, lung gas volume, and esophageal pressure (and the derived lung mechanics calculated). From this perspective, a small study enrolling a reduced number of individuals in which an extended set of measures is collected may provide more relevant information than large observational studies or a big randomized trial.

Conflicts of interest

None for issues related to this article.

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