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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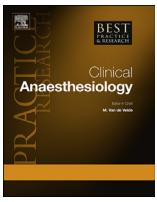

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The use of positive end expiratory pressure in patients affected by COVID-19: Time to reconsider the relation between morphology and physiology

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Coronavirus disease 2019 (COVID-19) is a new disease with different phases that can be catastrophic for subpopulations of patients with cardiovascular and pulmonary disease states at baseline. Appreciation for these different phases and treatment modalities, including manipulation of ventilatory settings and therapeutics, has made it a less lethal disease than when it emerged earlier this year. Different aspects of the disease are still largely unknown. However, laboratory investigation and clinical course of the COVID-19 show that this new disease is not a typical acute respiratory distress syndrome process, especially during the first phase. For this reason, the best strategy to be applied is to treat differently the single phases and to support the single functions of the failing organs as they appear.

Introduction

The recent outbreak of the respiratory illness caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1] has raised clinical and organizational concerns that culminated in the declaration of a pandemic on March 11, 2020 [2]. The World Health Organization has named the disease caused by the SARS-CoV-2 as coronavirus disease 2019 (COVID-19) [3].

Pathophysiology of COVID-19 relevant for anesthesiologists

COVID-19 is a new disease and only a part of the mechanisms that subtend its clinical course have been elucidated. The progression from the nasopharyngeal cavity to the lung alveoli is suspected to be at the base of the onset of the most severe form of the disease; however, quantification of the minimum viral load that allows the onset of the disease is not known.

The mechanisms of viral infection and replication are better characterized [4] also because the scientists have profited from previous knowledge on similar viruses. The passage from the cytopathic level to the alteration of tissue structure is again less understood, although is widely acknowledged that a key role is played by local and general immunologic mechanisms [5]. However, also here the balance between innate and adaptive immune systems during the course of the disease is a subject of discussion [6].

For the reasons previously listed, in absence of certainties about several important steps of the pathophysiology, research has proceeded by gathering information about patterns of presentation by the observation of affected patients and then started ordering them in a possible time sequence of events. Using this method, a recent systematic review [7] on 42 published articles revealed that three clinical stages can be identified: viral infection, pulmonary involvement with inflammation, and fibrosis. In all the stages, epithelial damage (inflammation and diffuse alveolar damage), microvascular damage (including thrombosis), and fibrinous pneumonia were co-existed; the presence of fibrotic patterns appeared after 3 weeks from the onset of the disease. An important message from the mentioned paper by Polak and coworkers [7] is that “the patients can present with more than one pattern, either simultaneously or consecutively.” As we can note later, this pathologic finding has important implications on the way we ventilate these patients.

Parallel to this histopathological investigation, since the beginning of the COVID-19 outbreak, intensivists have tried to associate lung morphology (studied by computed tomography (CT)) with the measurements of lung mechanics on these patients. In a widely diffused editorial [8], on the basis of the first evidence, Gattinoni and coworkers outlined the presence of two different paradigmatic patterns and labeled as “phenotypes”.

Among the first, they reported that the disease was characterized by a severe hypoxemia often associated with a near normal respiratory system compliance, whose clinical expression was very inhomogeneous, ranging from normal breathing ("silent" hypoxemia) or to remarkable dyspnea [8].

The observation of many cases of the disease made them able to sketch two different patterns labeled as phenotypes L and H. The characteristics of type L were low values of: elastance, low ventilation/perfusion ratio, low lung weight, and low recruitability. Radiological expression of type L is a pattern based on multiple ground-glass/crazy-paving opacities mainly in the subpleural region.

Instead, the characteristics of type H were high levels of: elastance, right-to-left shunt, lung weight, and recruitability [8]. Radiologically, this last phenotype resembles a classical patchy acute respiratory distress syndrome (ARDS) pattern.

The authors speculated that the clinical presentation of phase L was determined by an important hypoxemia deriving from a vasoplegic mechanism. In fact, a preliminary hypothesis made them ascribe this phenomenon to the loss of the hypoxic pulmonary vasoconstriction reflex, which is physiologically able to divert the blood flow away from the poorly ventilated areas; the absence of this reflex would cause a remarkable hyperperfusion of gasless tissue [9]. The mechanism beyond hypoxia during L-phase could be the virus blockade of the angiotensin-converting enzyme 2 (ACE-2) vascular receptors [10] or a more complex epithelial–endothelial crosstalk, responsible of the endothelial dysfunction and of a "proinflammatory"/"procoagulant" phenotype change in the endothelial cells [11]. In the attempt of compensating for the hypoxemia, the patient progressively begins hyperventilate up to 15–20 ml/kg[8], although in many cases, for the almost normal compliance, these patients do not complain about the presence of dyspnea. The tachypnea could be also caused by the viral neurotropism [12], direct affecting the respiratory centers.

In this model proposed by Gattinoni [8] in March, the transition to phase H can be caused by two possible mechanisms. If the patient is still breathing spontaneously, a combination of deep negative intrathoracic pressure and increased lung permeability (due to inflammation) brings to a patient self-induced lung injury (P-SILI) [13]. If the patients are already mechanically ventilated, the reason of worsening can be a ventilator-induced lung injury (VILI) [14] determined by a pattern of ventilation that is no more appropriate for the by-now edematous lungs, characterized by a higher lung weight than normal, which through a high superimposed pressure creates dependent atelectasis and reduction of the space available for ventilation ("baby lung") [15]. The H-phase shares similar features with ARDS; for this reason, as in ARDS, the further stage in the evolution of COVID-19 can be characterized by a fibrotic evolution [16]. Two recurring components of the disease are trombofilia [17–19] and altered immune response [20]. The tendency to thrombophilia is associated with poor prognosis [21].

The progressive accumulation of clinical and radiological evidence, although maintaining intact the value of the difference between the L and the H phenotypes, has brought to observation also the presence of intermediate patterns between the two. Robba and co-authors [22] reported the presence of transitional phenotypes characterized by the appearance of inhomogeneously distributed atelectasis and peri-bronchial opacities.

The association of these morphological aspects with the time sequence of the disease has even reawakened the debate on the correctness of the usage of term "phenotype" (as univocal external expression of a disease) in favor of the term "stage" of the disease [11]. The debate will continue, but the presence of morphological elements of different phases of inflammation in the same patient, in the same time, or in the temporal sequence speak in favor of stating that the COVID has one phenotype constituted by different stages [23] (by definition, a "full disease phenotype incorporates the abnormal phenotypes realized at each stage of the disease course") [23].

Aspects of PEEP physiology that are relevant for the management of COVID-19

Nowadays, the application of positive end expiratory pressure (PEEP) is finalized both to contribute to the maintenance of acceptable gas exchange (specifically blood oxygenation) and to position the pressure–volume loop during ventilation in a range that minimizes tidal excursions (in order to reduce atelectotrauma and volu-/baro-trauma [24]). In fact, the direct effect of PEEP is to keep a definite amount of gas inside alveoli throughout expiration, thus maintaining them open, constituting a buffer for gas exchange, avoiding cyclic opening and closing [25].

The search for the "best PEEP" has been at the center of a debate that has inflamed scientific literature over the past 40 years. It is now accepted that in order to achieve the best combination between respiratory mechanics, oxygenation, hemodynamics, and lung protection, it is necessary to accept a compromise [26].

Therefore, the ways to titrate and to monitor the effects of PEEP are different and highly dependent on the goals that the healthcare provider wishes to pursue. In general, they can be classified in physiological and morphometric methods. Physiological methods make use of different portions of the lung pressure–volume curve [27], compliance of the respiratory system [28], gas exchange parameters [29,30], or transpulmonary pressure [31]. Morphometric methods are based on imaging technology as CT [32] and electrical impedance tomography [33].

The idea that the lung is inherently inhomogeneous even in healthy conditions [34] has as logical consequence the fact that, instead of having only one critical opening (or closing) pressure, it presents a continuous distribution of them along the pressure/volume curve: the mechanical implication is that recruitment (and de-recruitment) phenomena must be considered distributed stochastically all over the curve [35].

For the hysteretic characteristics of the pressure–volume curves, the opening pressures do not correspond to the closing pressures. This implies that the maneuvers for opening the lung, the so-called "recruitment" maneuvers [36] should reach higher pressures than the ones successively maintained with PEEP. Moreover, PEEP as a procedure to prevent lung collapse should be considered an aid to an expiratory event and inefficient per se to recruit the lung thoroughly [26]. For this reason, the application of PEEP should be anticipated by a recruitment maneuver.

Recruitment can be quantified as the amount of nonaerated lung tissue that becomes aerated after a recruitment maneuver and can be measured as an absolute quantity (grams, milliliters) or as incremental proportion. In fact, a key concept that progressively has funneled through different studies is that the effectiveness of PEEP application depends on the type and distribution of lung injury. If the lung presents a diffuse loss of aeration, it behaves almost as a single compartment and the risk of lung over-inflation from PEEP application is low [37]; on the contrary, if the loss of aeration is focally distributed the system becomes multi-compartmental and can exhibit opposite response to the increment of intrathoracic pressure, resulting in a significant risk of over-inflation, if high PEEP levels are used [37]. These effects of PEEP on lung parenchyma are mirrored by the significant hyperinflation that focal ARDS pattern can exhibit after lung recruitment, while lungs with diffuse and patchy aeration loss respond with a significant recruitment without relevant hyperinflation [38].

Between the lines, we understand that knowing the morphology of lung injury or applying a recruitment maneuver, it is possible to predict the response by lung parenchyma to the application of PEEP.

Clinical implications for COVID management

As with many other researchers, we believe that COVID-19 is a specific disease [39] composed of different phases that require specific treatments and aware that treating COVID-19 as a "standard" ARDS may lead to adverse outcomes.

As previously discussed, the patients affected by COVID-19 might arrive to the observation of intensivists with a composite lung pattern. In our experience, it is very rare that a patient with a pure L phenotype is admitted to intensive care if not for other reasons (decompensation of another organ system). As described by Robba et al. [22], very often they present a transitional pattern or a frank ARDS-like phenotype H. These last can become more frequent if the hospital organization has a systematic delay in admitting the patient from the ward to the intensive care unit. The problem of deciding the level of PEEP follows the decision to start a positive pressure ventilation, often after hours already spent ventilating with high-flow oxygen.

The most advantageous level of PEEP for a COVID-19 patient is related to the extension and typology of lung injury. Different research letters have warned against the use of unneeded high PEEP [40,41] and advocate the use of a personalized approach, tailored to the effective phase of COVID-19 [16,42].

When the possibilities of executing a lung CT are limited, an alternative way to assess the potential for recruitment is the computation of recruitment-to-inflation (R/I) ratio [43]. Using this method, Beloncle et al. [44] studied a series of 25 patients with COVID-19 and observed 64% highly recruitable and 36% poorly recruitable. The authors concluded that the use of R/I ratio was useful in PEEP titration procedure and could help in the prevention of the harmful effect of unnecessary high PEEP. In a small series of 12 patients, Pan et al. [45] were able to assess that the 83% of their patients were poorly recruitable and that recruitability changed when modifying body position.

Summarizing the recommendation of literature

In Gattinoni's phenotype L [8], corresponding to Robba's phenotype 1[22]: lung compliance is nearly normal; lung CT shows subpleural ground-glass patterns together with other high-perfusion areas. Mechanism of hypoxia is the altered distribution of lung perfusion. Low to moderate levels of PEEP should be applied. The rationale behind moderate PEEP levels is the possibility (to be tested case by case) to divert pulmonary blood flow from impaired to non-damaged lung areas. If high PEEP is used in this phase, the recruiting effect will be minimal and the impairment of hemodynamics will be substantial, requiring additional fluid and vasopressors.

In Robba's transitional phenotype 2, atelectasis appears and it is inhomogeneously distributed [22]. The authors advocate the use of moderate to high PEEP in relation to the likely higher potential for recruitment in comparison with phenotype L/1. Of potential help is the measure of the potential for recruitment by computing the R/I ratio or by the method that is more suitable in the single units.

In Gattinoni's phenotype H [8], corresponding to Robba's phenotype 3, in this condition, the strategies developed for the management ARDS should be used: protective ventilation using low tidal volumes and choice of PEEP according to accepted international guidelines [22,46]. In the late COVID phase H/3, when a fibrotic pattern is established, the response to recruitment and to PEEP are thought to be lower than at the beginning of the course of the disease.

Conclusion

In summary COVID-19 is a new disease with different phases that can be catastrophic for subpopulations of patients with cardiovascular and pulmonary disease states at baseline. Appreciation for these different phases and treatment modalities, including manipulation of ventilatory settings and therapeutics, has made it a less lethal disease than when it emerged earlier this year. Different aspects of the disease are still largely unknown. However, laboratory investigation and clinical course of the COVID-19 show that this new disease is not a typical ARDS process, especially during the first phase. For this reason, the best strategy to be applied is to treat differently the single phases and to support the single functions of the failing organs as they appear.

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Declaration of competing interest

Dr Kaye serves on the Speakers Bureau for Merck, Inc.

Practice points

- Coronavirus disease 2019 (COVID-19) is a new disease with different phases that can be catastrophic for subpopulations of patients with cardiovascular and pulmonary disease states at baseline.
- Appreciation for these different phases and treatment modalities, including manipulation of ventilatory settings and therapeutics, has made it a less lethal disease than when it emerged earlier this year.

Research agenda

- Laboratory investigation and clinical course of the coronavirus disease 2019 (COVID-19) show that this new disease is not a typical acute respiratory distress syndrome process, especially during the first phase, thus more thorough investigations and studies are needed.
- Further studies are needed to assess what is the best strategy to be applied to treat the single phases and to support the single functions of the failing organs as they appear.

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