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Mini-Review

Controversial Aspects of Static Respiratory Compliance and D-Dimer in COVID-19 Associated ARDS

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ABSTRACT

Clinical outcomes in COVID-19 associated acute respiratory distress syndrome may be influenced by respiratory system mechanics, CT scan findings, oxygenation variables and biomarkers. Low respiratory system compliance and high plasmatic D-dimer were associated to higher mortality rate in a subgroup of COVID-19 patients. Our purpose is to review the impact of respiratory compliance and plasmatic D-dimer in COVID-19 associated acute respiratory distress syndrome according to recent literature. Increased D-dimer concentration in COVID-19 patients is a strong predictor of worse outcome while static respiratory compliance is not. Combined evaluation of both enhances the prediction of mortality in COVID-19 related ARDS.

Keywords: COVID-19; ARDS; D-Dimer; Static respiratory compliance

ABBREVIATIONS

ARDS: Acute Respiratory Distress Syndrome; CRS: Respiratory System Compliance; CT: Computed Tomography; PEEP: Positive End Expiratory Pressure

INTRODUCTION

COVID-19-associated Acute Respiratory Distress Syndrome (ARDS) has a phenotypic heterogeneity widely described in recent literature. It appears to have a worse outcome than ARDS from other causes with a mortality rate ranged between 15% and 94% when intensive care admission and mechanical ventilation are required [1-3].

Different respiratory system mechanics, CT scan findings, oxygenation variables and biomarkers may have implications for patient outcomes.

We performed a prospective observational study on mechanical ventilated patients to examine the functional and morphological characteristics of COVID-19 associated ARDS. Lung morphology and respiratory mechanics in COVID patients largely matched those of classical ARDS but a subgroup of patients with low static compliance and higher D-dimer concentration had higher mortality compared to other COVID patients.

The purpose of this manuscript is to present the controversial aspects of the patho-physiological and clinical characteristics of COVID-19 associated ARDS and to review our study findings according to recent literature.

COMPLIANCE AND SEVERITY OF COVID-19 ASSOCIATED ARDS

Quantitative analysis of CT scan of adult ARDS patients showed that in severe ARDS, the amount of lung tissue that is still accessible to ventilation may be assimilated to the amount of normal lung tissue of a six-years old healthy child. These data led to the concept of "baby-lung" to describe the one of the most relevant aspect of the pathophysiology of ARDS.

Static Compliance of Respiratory System (Crs), calculated as idal volume (mL) divided by plateau pressure (cmH_2 O) minus Positive End-Expiratory Pressure (PEEP) (cmH_2O), characterizes lung units that receive the gas volume and it is expression of the baby lung [4]. In other words, decreased respiratory compliance also largely reflects the degree of lung volume loss.

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Before the COVID-19 era, low compliance of the respiratory system was considered as important parameter used in clinical practice to identify a subgroup of patients affected by severe ARDS. The initial draft of the Berlin definition of severe ARDS also included a low respiratory system compliance (<40 mL/cmH_2O) as well as paO_2/FiO_2 ratio (<100 mmHg), quantity of chest radiograph opacities, PEEP of at least 10 cmH_2O and high minute ventilation standardized at $PaCO_2$ of 40 mmHg (>10 L/min). However, these ancillary variables did not enhance predictive validity since they identified a subgroup of patients with identical mortality to the simpler severe ARDS category identified by PaO_2/FiO_2 of 100 mmHg or less. Under these circumstances, the final Berlin definition did not included Crs is an additional physiological measurement [5].

During the COVID era, again more attention was focused on compliance and the hypothesis of different phenotypes of ARDS for different therapeutic implications.

Unusual finding of COVID-19 related ARDS was severe hypoxemia despite compliance higher than classical ARDS and two different phenotypes of COVID-19 pneumonia were described by Gattinoni and colleagues.

One, supposed to be more common during the early stage of COVID-19 disease (Type L), characterized by with lower elastance (higher compliance), Ventilation-To-Perfusion (VA/Q) ratio, lung weight and recruitability. In this case, hypoxemia was supposed to be mainly related to the loss of hypoxic vasoconstriction resulting to a large shunt fraction with a very low amount of non-aerated tissue. Low lung weight was suggested by a predominant pattern of sub-pleurical ground glass opacities at CT-scan and nearly normal amount of gas in the lung resulting to nearly normal compliance and consequently low recruitability.

The other phenotype (Type H) was characterized by high elastance (lower compliance), right-to-left-shunt due to more non aerated tissue for increased edema and high lung weight and lung recruitability similar to classical ARDS.

Based on differences in compliance and recruitability of Type L and H patients, different strategies of ventilation were proposed without any strong evidence [6].

The tendency of higher compliance in COVID-19 related ARDS was supported by Chiumello et al. that showed a higher compliance (49.9 ml/cmH_2O *vs.* 39 ml/cmH_2O, p=0.03) and lung gas volume in 32 COVID-19 ARDS patients compared with a cohort of 2 historical ARDS patients matched for PaO_2/FiO_2. Conversely, these findings were not confirmed in other studies where COVID-19 related ARDS compliance observed in ventilated patients with a lower median range similar to non-COVID 19 ARDS [8,9]. We conducted a prospective observational trial of 301 patients with COVID-19 ARDS finding a median range of compliance of 41 ml/cmH_2O (33-52), 28% more than a cohort of unrelated COVID-19 ARDS (32 ml/cmH_2O (25-43), p<0.0001). However only 6% of patients had compliance greater than 95th percentile of classical ARDS group implying that patients with COVID-19 associated ARDS and patients with classical ARDS could not be distinguished [10]. Grasselli et al. documented a compliance heterogeneity with a range from 24 to 49 ml/cmH_2O that became narrow (from 27 to 41 ml/cm H2O) in studies with more than 100 patients. In addition, when the analysis was restricted to the studies that reported median values of Crs, only 21% of the 75th percentile values were higher than 50 ml/cm H_2O. Data reported were also comparable to those of LUNG SAFE study, where compliance varied from 37 to 28 ml/cm H_2O in mild and severe ARDS respectively.

Furthermore, a recent secondary analysis of LUNG SAFE study investigated the distribution of compliance phenotypes in non-Covid ARDS and their relationship with mortality. Among the 1000 patients included in the analysis, only 12% had "preserved" compliance (>50 ml/cm H_2O) and most of patients had Crs<40 ml/cmH_2O with intra-hospital mortality of 45% *vs.* 32%, respectively (p<0.05). In the multivariable logistic regression analysis lower compliance was an independent risk factor for mortality even if without a clear transition threshold. Another important finding was the lack of relationship between degree of hypoxemia and compliance, with moderate to severe hypoxemia present in a significant proportion (43%) of patients with preserved Crs [11].

The stronger predictively of PaO_2/FiO_2 ratio compared to compliance was also confirmed in a Spanish study with a total of 742 patients describing outcomes in COVID-ARDS according to different model analysis. The first model stratified population as mild, moderate and severe ARDS based on the Berlin criteria; the second model stratified patients as having normal or low Crs (<50 ml/H_2O). The study showed that while stratifying patients according to oxygenation criteria allowed predicting the probability of being discharged alive from ICU, stratification according to values of compliance did not predict outcome [12].

Another recent multicenter observational study demonstrated that nor Crs, Crs/Ideal Body weight or a decrease of compliance between day 1 and day 14 during invasive ventilation, were predictors of survival or breathing without assistance or ventilator free days. However, Pplat was strongly associated with patient outcomes [13].

Conversely, some studies showed a correlation between low compliance and worse outcome in term of mortality and ventilator free days [14,15].

The linear regression model of ProVent-COVID study, conducted in 553 patients in the Netherlands, identified low compliance at day-1 of invasive ventilation a factor independently associated with less ventilator free days and higher 28-day mortality as well as higher age, male gender, lower arterial pH, higher heart rate, higher tidal volume.

D-DIMER

Many studies demonstrated extra-pulmonary implication of SARS-COV2 infection and its multi-systemic involvement, especially cardiovascular, renal, gastrointestinal and central nervous system implications and hematological alteration.

The most common reported hematological alteration is a hypercoagulability state with a high incidence of Disseminate Intravascular Coagulation (DIC), Pulmonary Intravascular

Coagulation (PIC), Venous Thromboembolism (VTE), Pulmonary Embolism (PE), and Arterial Thrombosis (ischemic stroke, myocardial infarction, limb ischemia).

Increased D-dimer is the most common finding in hypercoagulable state and his correlation to severity of disease and mortality is known [16].

In two systematic reviews, higher level of D-dimer was found in non-survivors as well as in patients with severe COVID-19 patients than in those with mild-moderate disease [17,18] High level of D-dimer represents an early abnormality during DIC that is an independent risk of mortality in suspected infection or sepsis [19,20].

Pulmonary Intravascular Coagulopathy (PIC), a novel pulmonary specific vasculopathy, was also observed in autopsies of COVID-19 patients. PIC is associated to pulmonary inflammation and lead to microthrombi in alveolar capillarities and small arterioles.

Because filling defects were not fully occlusive, PIC is probably related to thrombosis more than emboli [21,22].

Pulmonary artery embolism, is probably most common thrombotic complication, reported from 9% up to 21% in a large series of autopsies either fatal fulminant or peripheral (10% *vs.* 11% of non-survivors, respectively) [23,24].

A multicenter French study compared coagulation parameters between a group of COVID-19 ARDS and non-COVID ARDS patients finding significant differences in thrombotic complications, mainly pulmonary embolisms (17%), despite anticoagulation as an early complication at ICU admission (<7 days of ICU). Significantly higher ICU mortality in patients with PE compared to whom without PE was reported [24].

DISCUSSION

In our study concentrations of D-dimer less or equal than the observed median values of the whole population (1880 ng/mL [IQR 820-6243] were related to normal lung perfusion while concentrations of D-dimer>1880 ng/mL had perfusion scans consistent with the presence of thrombi or emboli.

Moreover, when values of compliance were coupled to values of D-dimers, study population was divided in 4 groups. 28-days mortality rate was significantly higher in a subgroup of patients with low compliance and high D-dimer compared to other groups.

All these data led to the hypothesis that intermediate dose and empiric full dose of anticoagulation has been evaluated as new strategies of treatments in critically ill COVID-19 patients. However, a recent study comparing standard-dose (40 mg daily) with intermediate dose (1 mg/kg daily) of anticoagulation in ICU patients affected by COVID-19, did not show any differences in outcome in term of arterial and venous thrombosis, extracorporeal oxygenation treatment and 30-day mortality (45.7% *vs.* 44.1%; p=.70) [25].

An international multiplatform randomized clinical trial over 1000 critically ill patients, did not document any improvement on survival or days free of organ support, although therapeutic anticoagulation reduced numerically major thrombotic events. The same study also showed the probability of inferiority of empiric full dose treatment around 89% although no increased major bleeding events were observed. Authors hypothesized exacerbations of alveolar hemorrhage during high dose of anticoagulation exacerbated by pulmonary inflammation [26].

Recent literature on COVID-19 focused the attention on respiratory static compliance and its possible implications for patient clinical management. Based on evidence, COVID-19 related ARDS did not differ significantly from other causes ARDS in term of static respiratory compliance ranging in a wide spectrum of values.

The heterogeneity of Crs may be due to different selection of study population in term of sample size considering that all the studies including conspicuous number of patients affected by COVID-19 ARDS showed a minor tendency to differ from classical ARDS.

Moreover, different compliance phenotypes may be expression of different time of the same disease. Indeed, some patients with a phenotype L at early stage of disease may improve, other may evolve to type H potentially due to the worsening of viral infection itself or patient self-inflicted lung injury.

CONCLUSION

Another important collateral finding is the absence of prediction of severity respiratory failure in relatively higher compliance. In summary, static respiratory compliance is not a strong predictor of outcome in COVID-19 ARDS and different mechanisms may play a role to cause severe hypoxemia such as intravascular pathology. High plasmatic level of D-Dimer may support the hypothesis of thrombotic or embolic complications as cause of incremented dead alveolar space.

However, coagulation system is a host defense response against bleeding, injury, and also the infectious agents such as viruses. Activation of the coagulation system following a viral invasion aims to eliminate the etiological agent by causing a clot. Coagulation and innate immunity use common pathways to counteract the damage and invasion of viruses, such as factors involved in the onset of coagulation and pro inflammation. This inflammation, following activation of coagulation, is a possible cause of elevated D-dimer levels following an infectious agent.

The lack of evidence about the beneficial effect of higher anticoagulation target on mortality in severe critically ill COVID-19 supports the hypothesis that D-Dimer that may reflect not also major thrombotic complications but more generally intense inflammation and cytokines storm, both mirror of severity of disease.

Increased D-dimer concentration in COVID-19 patients is a strong predictor of worse outcome while static respiratory compliance is not.

However, according to our study, a combined evaluation of compliance and D-Dimer level enhances the prediction of mortality in COVID-19 related ARDS.

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