Dealing With the CARDS of COVID-19

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The need to counter the global threat posed by coronavirus disease 2019 (COVID-19) has prompted unprecedented hi-speed sharing of clinical data, experience, and ideas geared to first understanding and then formulating an effective approach to treatment of the coronavirus disease-associated acute respiratory distress syndrome—let us call it “CARDS.” Consistent features have quickly emerged worldwide (1, 2). Clinically, cough, and malaise and myalgias usually precede by several days the first awareness of difficult breathing. Fever occurs inconsistently. Those at higher risk for deterioration are elderly and/or have preexisting hypertension, diabetes, and obesity—disorders that often compromise small blood vessels. Late phase thrombosis frequently occurs. Notably, patients present to hospital at any stage of their pulmonary illness and vary in responses to standard treatment. Sudden and rapid progression occurs frequently, whereas resolution of CARDS is typically slow.

Respiratory findings include high minute ventilation (Ve), impressive hypoxemia, and a radiologic picture that ranges from scant and peripheral “ground-glass infiltrates” in the earliest stage and in very mild cases, to atelectasis, edema, and consolidation that characterize more familiar forms of acute respiratory distress syndrome (ARDS) (3). Unlike routinely encountered cases of ARDS, respiratory system compliance remains relatively normal despite impressive hypoxemia, indicating flexible, gas-filled lungs until later and/or more advanced stages. This early flexibility explains why some hypoxicemic and spontaneously breathing patients appear quite comfortable, despite high ventilation requirements. If intubation is required, plateau and driving pressures are initially well below those that infringe on their upper limit thresholds for lung protection. Therefore, when a relatively large tidal volume is delivered, the strain of the tidal cycle may be tolerable, even though mechanical power is uniformly high. Standard approaches to addressing the hypoxemia of CARDS, such as using high positive end-expiratory pressure (PEEP) and prone positioning, do not work uniformly well in that early phase, and enforcing 6 mL/kg tidal volumes and higher PEEP values may be ill-advised. In some patients, such interventions improve oxygenation to varying degrees but worsen ventilation efficiency, breathing comfort, and overall clinical condition. The wide range of fatal outcomes reported in CARDS patients suggest an iatrogenic component; unexpected responses to standard guidelines for ventilator management indicate that PEEP tables, usual protocols and “open lung” targets for lung protection must be seriously rethought and their components selectively applied (4).

Despite an abundance of valuable demographic and clinical observations of the type just described, as well as elegant pathologic, molecular, and radiographic descriptions of COVID, they do not help enough—ICU clinicians remain insecure in making bedside decisions regarding lung protective ventilation. Understanding the time-dependent mechanisms that explain these confusing features is needed, but high-quality prospective investigations into organ-level pathophysiology have been difficult to come by, given the especially challenging demands of the current ICU environment. It is important, therefore, that the investigation reported in this issue of Critical Care Medicine by Mauri et al (5) receives close attention.

These data, which were single, time-stamped “snapshots” from 10 patients whose illness duration varied over a wide span, highlight the variability of lung unit recruitability and ventilation efficiency in response to the applied PEEP increment of 10 cm H2O (5–15). Extensive “reopening” of the CARDS lung, an event usually tied to bringing more functioning lung units into play, produced the expected improvement in ventilation homogeneity but made surprisingly inconsistent and often marginal improvements of Pao2/Fro2, and shunt. More importantly, “ventilation” efficiency did not parallel the often extensive recruitment (5). This disconnect between recruitment and response, which deviates markedly from that of routinely encountered ARDS, prompted the authors to conclude that ventilation to perfusion (V/Q) mismatching is likely to account for the unusually high estimated “dead space” they observed as well as the failure of PEEP-associated recruitment to dramatically boost oxygenation or to improve ventilation efficiency. I fully agree that V/Q mismatch contributes strongly and that high dead space is a characteristic of CARDS to measure and track. Yet, there are reasons to wonder whether, when, and why.

This small study involved patients with varying durations and severities of illness (5). Methodologies for noninvasively assessing lung inflation, lung unit perfusion and dead space approximation (by electrical impedance tomography) (6) and

Key Words: acute respiratory distress syndrome; coronavirus disease; coronavirus disease 2019; dead space; mechanical ventilation

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DOI: 10.1097/CCM.0000000000004427
the “ventilation ratio” (7), as well as recruitment estimation by the recently described recruitment to inflation ratio (8) lack precision and require additional validation. Exhaled capnography was not employed to confirm the assumed dead space by accepted bedside technique. Confirmatory real-time imaging of the pulmonary vasculature and right ventricle (e.g., by ultrasound and CT) would have been reassuring, but understandably was not performed. Despite these limitations, the conclusion that altered V/Q matching helps account for their data seems valid. The mix of mechanisms contributing to the impressive dead space, however, may differ at different time points in the evolution of CARDS.

How do we square the results from this interesting study with the emerging clinical, radiologic, and pathologic database that surrounds CARDS? There would appear several pieces to achieving a satisfying explanation that could inform better practice: 1) the vasocentric root cause of CARDS; 2) the time course of CARDS evolution; and 3) the enhanced potential for inadvertently adverse patient-ventilator interactions. What follows is one potential way to put the pieces together.

Lung injury may originate from either side of the alveolar-capillary interface. In simplest terms, COVID-19 appears to have a special affinity for the interior lining of the vasculature throughout the body, exerting most damage in those organs that are best perfused (9). Because the lung receives the entirety of the cardiac output, its rich vascular bed is “hit” hard and early. This endothelium-avid virus initiates an endovasculitis that promotes thrombogenesis (10, 11) and disrupts regulating mechanisms (e.g., hypoxic vasoconstriction) that normally keep perfusion closely matched to lung unit ventilation.

At first, breakdown of the interface between gas and blood remains incomplete and regional; atelectasis and consolidation are relatively minor components. Fluid leakage is largely confined to the interstitium, resulting in CT-defined “ground glass” infiltrates scattered in the periphery and irregularly distributed “crazy paving” patterns of septal thickening (3). Disrupted V/Q matching is predisposed to worsen with elevations of mean airway pressure. By over expanding the alveoli that are already open, PEEP redirects their blood flows through channels with impaired vasoregulation, a dysfunctional property shared by any newly recruited units at all stages of CARDS. Therefore, although some atelectasis reversal does occur, lung expansion and recruitment lack normally expected improvements of gas exchanging efficiency. Simultaneously, PEEP elevates mechanical power and ventilator-induced lung injury (VILI) risk through units made vulnerable by COVID (12). During this initial phase, relative lack of atelectasis and consolidation seem strangely disassociated from labored breathing, high Ve, and severe hypoxemia. Dead space created by the endothelial V/Q dysregulation and by in situ thrombogenesis in small pulmonary blood vessels would seem to explain this paradox best (13).

Over time, the clinical picture may progress to a more conventional pattern of ARDS, even when ventilation is optimally managed. But the clinical course may worsen precipitously as high transpulmonary pressures (generated by ventilator and/or patient effort), intolerable tidal strains, and high breathing frequencies apply and concentrate VILI-inducing mechanical power onto a functioning “baby lung” that shrinks as it sustains injury (14). Increasing transmural vascular stresses and blood flows promote edema as well. Importantly, the assault on the alveolar barrier proceeds from both sides of the membrane and that these injury mechanisms of viral invasion, vascular stress, and VILI are mutually reinforcing.

Unchecked infection itself and superimposed VILI eventually complete the breakdown of the gas-blood barrier. The inflamed lungs then become heavy, edematous, atelectatic and may have parenchymal hemorrhages. Shed cellular debris and inflammatory products might even lead, if you are a believer, to a “cytokine storm” that complements (via the bloodstream) the viral compromise already ongoing in other systemic organs (15). Under these conditions, responses to PEEP and proning align better with expectations. Dead space in advanced CARDS is due not only to disrupted V/Q matching and shunting of venous blood through airless tissue but also to extensive pulmonary microthrombi (8). Viral invasion with thrombogenic consequences simultaneously affects tissues of the entire body. Consequently, the products of thrombolysis (e.g., D-dimers) rise to high levels, even when strokes, venothromboses of large vessels, and pulmonary emboli are not clinically detected (but do occur frequently).

What does all this mean for lung protective ventilation? How do we play this high stakes CARDS game? In a nutshell: 1) At all stages, limit the tidal “transpulmonary pressure and mechanical power”; 2) Intervene early to interrupt forceful inspiratory efforts and excessive flows of gas and blood through the lung; 3) To avoid extending the dead space in the milder early phase after intubation, err on the side of lower PEEP; 4) Reduce oxygen demands to limit the VILI-inducing ventilation, mechanical power, and blood flow (for this, extracorporeal real membrane oxygenation may be needed); and 5) Follow trends in CO2 elimination efficiency.

CARDS is an urgent, puzzling, and menacing problem whose optimal management must be better understood and implemented. Following this admittedly unproven mechanistic paradigm just set out, dead space is a logical marker worthy of tracking. This work by Mauri et al (5) helps solidify a viable conceptual framework for personalized ventilation of this disease.

REFERENCES

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