Dead Space in ARDS: Die Hard

Physiologic dead space (V_D), which is defined as the fraction of tidal volume (V_T) that does not participate in gas exchange, provides information about the efficiency of lung gas exchange. In critical care, the most common approach to measuring V_D/V_T is volumetric capnography, which reports CO_2 elimination as a function of expired V_T, and V_D/V_T is calculated using the Enghoff modification of Bohr's equation: $V_D/V_T = (P_{aCO_2} - P_{\bar{E}CO_2})/P_{aCO_2}$, where P_{aCO_2} is the partial pressure of CO_2 in arterial blood and $P_{\bar{E}CO_2}$ is a measure or an estimate of mixed-expired partial pressure of CO_2.[1-6] The Enghoff equation is influenced by large shunt fractions present in ARDS, and the result is a good global index of the efficiency of lung gas exchange.[2,3,5,7] Increased dead space is independently associated with an increased risk of death in subjects with ARDS.[2] This association has been found in the era of lung-protective ventilation,[6] at different stages of ARDS,[8] using different measurement techniques,[9,10] and in subjects with ARDS diagnosed using the Berlin definition.[11]

In this issue of Respiratory Care, Kallet et al[12] present the results of an observational study in 685 subjects with ARDS managed with lung-protected ventilation, with V_D/V_T measurements forming part of clinical management. Calculating V_D/V_T using the Enghoff-Bohr equation from mean expired CO_2, they found that V_D/V_T was generally elevated in subjects with aspiration or pneumonia, who had higher values than those with non-pulmonary sepsis or trauma. Although the magnitude of V_D/V_T elevation differed between etiologies, V_D/V_T in non-survivors was consistently higher than in survivors and correlated directly with the number of failing organs. The highest values of V_D/V_T were found in subjects with severe ARDS according to the Berlin classification, and V_D/V_T was the strongest predictor of mortality, with a 22% increase in the risk of death for every 0.05 increase in V_D/V_T.

The study by Kallet et al[12] represents a step forward in establishing the clinical value of V_D/V_T, showing that this parameter can potentially be used to personalize care for mechanically ventilated patients. Dead space in patients with ARDS must be understood as a physiomarker of severity, and management should aim to protect the lung from overdistention while maximizing recruitment to avoid further increases in V_D/V_T.

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ARDS is a broad term encompassing a heterogeneous group of severe diseases with acute onset that affect the lung parenchyma and impair respiratory system mechanics, manifesting with bilateral pulmonary infiltrates and loss of lung volume with hypoxemia refractory to high concentrations of oxygen.[13] Two major types of injury can lead to ARDS: direct injury to the lung epithelium and indirect injury resulting from direct inflammation or disruption of the vascular endothelium. The differentiation between the 2 categories is based on clinical information, although they are distinct in terms of respiratory mechanics, pathologic findings, radiographic appearance, genetic risk, and protein biomarkers.[14] The study by Kallet et al[12] shows that they are also distinct in terms of V_D/V_T values. These findings should be interpreted in light of the recent finding by Luo et al[15] that despite lower severity of illness and fewer organ failures, subjects with direct ARDS had similar mortality to subjects with indirect ARDS and that factors previously associated with mortality during ARDS were associated with mortality only in direct ARDS. Thus, it seems that the distinct features of ARDS resulting from direct and indirect lung injury may differentially affect risk prediction and clinical outcomes. In another recent study comparing the molecular phenotypes of direct versus indirect ARDS, Calfee et al[16] found that direct lung injury in humans is characterized by more severe lung epithelial injury and less severe endothelial injury, whereas indirect lung injury is characterized by more severe endothelial injury and less severe epithelial injury. These authors concluded that the heterogeneity of ARDS should be taken into account to design better clinical trials. Unfortunately, neither of these studies measured dead space.

Interestingly, the response to treatment also differs between the 2 types of ARDS. One of the main objectives of

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lung-protective ventilation in ARDS is to achieve maximum lung recruitment while using low V_T. Increased PEEP, recruitment maneuvers, and prone positioning result in much greater improvements in oxygenation, respiratory mechanics, or radiologic infiltrates in subjects with indirect ARDS than in those with direct ARDS.[14,17,18] Several studies have failed to show a clear effect of PEEP on V_D/V_T[19-23]. Variations in V_D/V_T and its partitions resulting from PEEP largely depend on the type, degree, and stage of lung injury. When PEEP results in global lung recruitment, physiologic V_D and alveolar V_D decrease; when PEEP results in lung overdistention, physiologic V_D and alveolar V_D increase. Unfortunately, these results, found mostly in well-designed experimental models of ARDS, have not been reproduced in human subjects with ARDS.[24] To assess of the influence of systematic respiratory mechanics tests on clinical management, a recent study compared physiological parameters associated with clinical outcomes by comparing their value before and after performing the tests.[25] After the tests, the oxygenation index, airway pressure, and driving pressure improved, but V_D/V_T remained unchanged.[25] The reason for the attenuated effect of the intervention on V_D/V_T might be wide variation in individual responses. Kallet et al[12] also found only minor differences in V_D/V_T between mild and moderate ARDS, highlighting the importance of the response to PEEP in early stages of the disease for the prognosis. An increase in oxygenation with incremental PEEP is associated with better outcome in terms of Berlin classification,[13,26] so in the rigid framework of this classification, the patient could not be moved to a different category from the initial allocation.

Since physiology is one of the foundations of critical care, Goligher et al[27] applied the precision medicine paradigm to extracorporeal CO_2 removal for ultraprotective ventilation in ARDS. Interestingly, they demonstrated that V_D/V_T and static compliance determine the effect of extracorporeal CO_2 removal on driving pressure and mechanical power. They concluded that measuring V_D/V_T can be used to enrich clinical trials by selectively enrolling patients with a predicted treatment response.

Many voices are calling for changes in conventional ICU practice toward precision medicine to improve both physiological and clinical outcomes and to maximize cost-effectiveness.[28,29] Continuous monitoring of physiologic signals, including V_D/V_T, and point-of-care data might lay the groundwork for precision critical care. In mechanically ventilated patients, it is important to monitor respiratory variables (oxygenation, mechanics, and V_D/V_T) to track respiratory changes and to prevent ventilator-induced lung injury or avoid further lung deterioration.[5,30-32] Currently, big data techniques make it possible to store, manage, and analyze the huge volumes of multidimensional data generated in the ICU, so that advanced signal processing and computing techniques can transform volume to value.[33,34] Whether adding V_D/V_T values to the clinical data available in ICUs will detect unseen patterns and/or provide valuable tools for decision making to improve outcomes in ARDS remains to be seen.

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