Measured Versus Estimated Dead-Space Ventilation in ARDS: Does It Matter? Perhaps

Nearly two decades ago, Nuckton and colleagues[1] published their seminal study demonstrating that physiologic dead space fraction (V_D/V_T) was independently associated with mortality in ARDS.[1] This and other studies of dead space were facilitated by the availability of indirect calorimetry and volumetric capnography that have made expired CO_2 collection easy. Its ready availability opened the door for numerous studies that have consistently demonstrated the importance of measuring V_D/V_T in furthering our understanding of ARDS pathophysiology,[2,3] as well as assessing the effects of pharmacologic therapies,[4] prone positioning,[5] PEEP, and recruitment maneuvers.[6,7] More recently, V_D/V_T was found useful in predicting the effectiveness of extracorporeal carbon dioxide removal that allows for "ultra-protective ventilation."[8]

Unfortunately, neither widespread availability of user-friendly technology, nor the wealth of data demonstrating the importance of measuring dead space in ARDS, has translated into widespread adoption in clinical management. Rather the momentum has steadily shifted toward relying upon indirect estimations of V_D/V_T using the Harris-Benedict equation for determining CO_2 generation per minute ($\dot{V}_{CO_2}$) and hence the derivation of fractional concentration of expired CO_2 ($F_{\overline{E}CO_2}$) and thus partial pressure ($P_{\overline{E}CO_2}$).[9]

A practical motivation for using noncapnographic estimates of V_D/V_T is the ability to analyze large prospective and retrospective studies that otherwise would be unavailable for assessing the impact of dead-space ventilation. Yet reluctance to routinely measure V_D/V_T in ARDS appears grounded in a perception that volumetric capnography is (unreasonably) expensive or that it requires an inordinate amount of training, neither of which I have found to be true. Nonetheless, indirect estimations using either the Harris-Benedict equation or the ventilatory ratio appear to possess a reasonable approximation for assessing mortality risk in ARDS.[9,10] Whether indirect estimates of V_D/V_T are accurate enough for monitoring syndrome progression and recovery, titrating PEEP, or judging the impact of other therapies has not been determined.

In the current issue of the Journal, Dianti and colleagues[11] have begun to address this issue. Using an ARDSNet database that measured V_D/V_T using volumetric capnography,[12] the investigators compared direct capnograhic measurements of both physiologic and alveolar dead space to estimates based on the Harris-Benedict equation. The primary objective was to evaluate the level of agreement between direct measurements and indirect estimates of dead space and its subsequent impact on predicting the reduction of driving pressure (ie, plateau pressure – PEEP) during extracorporeal carbon dioxide removal. The secondary outcome was to evaluate the strength of association between V_D/V_T and 60-d mortality with each technique.

The investigators reported that anticipated reductions in driving pressure with extracorporeal carbon dioxide removal using estimated V_D/V_T produced "reasonable agreement" with those based on measured dead space.[11] While this is a welcome result in terms of pursing ultra-protective ventilation, it was overshadowed by another finding that calls into question the reliability of estimated V_D/V_T in assessing mortality risk. Only a modest correlation was found between estimated and measured V_D/V_T, so that values derived from the Harris-Benedict equation overestimated measured V_D/V_T by 0.05. Most of the error was attributed to underestimation of $\dot{V}_{CO_2}$ resulting in falsely lower $F_{\overline{E}CO_2}$ and $P_{\overline{E}CO_2}$, and hence falsely elevated V_D/V_T. In contrast, another study using estimated V_D/V_T found that it underestimated measured V_D/V_T.[5]

It is important to emphasize that under pathologic conditions $\dot{V}_{CO_2}$ deviates from CO_2 production and represents CO_2 excretion. This occurs due to complex, intertwined, dynamic factors such as variations in cardiac output, distribution of systemic and pulmonary perfusion, and the body's enormous capacity to store CO_2. Over 20 years of measuring dead space in patients with ARDS, I have observed that $P_{\overline{E}CO_2}$ can fluctuate by 3–9 mm Hg over relatively brief periods (eg, 5–30 min). This in turn can introduce errors of 10–20% if blood gas procurement does not coincide with expired gas collection. Furthermore, when performing indirect calorimetry in a clinic setting, I have also encountered large, transient fluctuations in $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ apparently caused by minor events (eg, muscle spasm

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in the lower extremities) without any overt signs of patient discomfort. These observations underscore the scientific necessity of simultaneously monitoring for relative $P_{\overline{E}CO_2}$ stability both before and during arterial blood sampling. Moreover, it emphasizes the vulnerability of estimated $\dot{V}_{CO_2}$ to error because it is unrelated to the actual and sometimes unstable conditions of CO_2 excretion present when arterial blood gases are obtained.

The consequence of such vulnerability to error was present in the study by Dianti and et al[11] and manifested as a failure of estimated V_D/V_T to predict mortality risk. This finding is at odds with previous studies.[9,13] Whereas Dianti and colleagues[11] speculated that the combination of low mortality and small sample size may have reduced statistical power to detect a relationship between estimated V_D/V_T and mortality risk, I suggest a more nuanced interpretation.

Subjects enrolled into prospective therapeutic ARDS trials are recognized as having lower mortality compared to the general ARDS population.[14] This stems from the necessity to exclude subjects with certain comorbidities and clinical presentations (eg, perceived moribund condition) that would interfere with detecting the presence of a "therapeutic signal." The database used for the current study is a salient example given the extraordinarily low 60-d mortality of 19%; this is also reflected in a relatively low mean V_D/V_T of ≤ 0.58 over 3 study days.[12] In our previous dead-space studies of subjects with ARDS managed with either traditional or lung-protective ventilation (and not enrolled into prospective therapeutic trials), a $V_D/V_T \geq 0.60$ was associated with a significantly higher mortality risk, with odds ratios of 4.28 (95% CI 1.74–9.97) and 3.08 (95% CI 2.18–4.33), respectively ($P < .001$).[15,16]

Thus, in these particular subjects with ARDS, the error caused by estimating $\dot{V}_{CO_2}$ using the Harris-Benedict equation was enough to produce a positive bias that falsely elevated mean V_D/V_T above this nodal point. This might help explain why estimated V_D/V_T failed to be associated with mortality risk. Whether this type of error might occur only in those with inherently lower mortality risk remains an open question. Regardless, clinicians and researchers alike should be cognizant of the vulnerability to error that estimated V_D/V_T measurements pose and temper both their interpretations and conclusions accordingly.

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