We report a complicated case of acute respiratory distress syndrome (ARDS) from severe sepsis, in which we measured the ratio of physiologic dead space to tidal volume ($V_D/V_T$) with volumetric capnography prior to, during, and after therapy with human recombinant activated protein C. Previous studies hypothesized that early in ARDS, elevated $V_D/V_T$ primarily reflects increased alveolar $V_D$, probably caused by pronounced thrombi formation in the pulmonary microvasculature. This may be particularly true when severe sepsis is the cause of ARDS. We repeatedly measured $V_D/V_T$ in a 29-year-old man with sepsis-induced ARDS over the course of activated protein C therapy. Treatment with activated protein C resulted in a pronounced reduction in $V_D/V_T$, from 0.55 to 0.27. Alveolar $V_D$ decreased from 165 mL to 11 mL (93% reduction). Activated protein C was terminated at 41 h because of gastrointestinal bleeding. When the measurement was repeated 29 h after therapy was discontinued, $V_D/V_T$ had increased modestly, to 0.34, whereas alveolar $V_D$ had increased to 71 mL, or 43% of the pre-activated-protein-C baseline measurement. Alveolar $V_T$ rose from 260 mL to 369 mL and decreased slightly after termination of activated protein C (336 mL). Over the course of activated protein C therapy there was a persistent decrease in alveolar $V_D$ and increase in alveolar $V_T$, even while positive end-expiratory pressure was reduced and respiratory-system compliance decreased. Thus, improved alveolar perfusion persisted despite signs of alveolar de-recruitment. This suggests that activated protein C may have reduced microvascular obstruction. This report provides indirect evidence that microvascular obstruction may play an important role in elevated $V_D/V_T$ in early ARDS caused by severe sepsis. Key words: acute respiratory distress syndrome; ARDS; activated protein C; alveolar dead-space; lung-protective ventilation; physiologic dead space; severe sepsis; single-breath test for carbon dioxide; volumetric capnography. [Respir Care 2010;55(5):617–622. © 2010 Daedalus Enterprises]
tion and pro-coagulation. Although a recent phase-2 study of patients with acute lung injury did not find a mortality reduction, administration of activated protein C significantly reduced \( V_{D}/V_T \) while increasing the plasma activated protein C level.\(^9\)

Physiologic dead space includes both airway (anatomic) and alveolar components, with the latter caused by alterations in pulmonary perfusion. The improvement in both plasma activated protein C and \( V_{D}/V_T \) was therefore attributed to improved microcirculation and better matching of ventilation to perfusion.\(^9\) Therefore, administration of activated protein C should cause a corresponding decline in alveolar \( V_D \). However, alveolar \( V_D \) was not reported in the aforementioned study.\(^9\) We present a case of severe sepsis-induced ARDS in which both \( V_{D}/V_T \) and alveolar \( V_D \) were measured over the course of therapy with activated protein C. Our report provides evidence supporting the hypothesis that microvascular obstruction is an important cause of increased alveolar \( V_D \) in sepsis-induced ARDS and can be reversed effectively with activated protein C.

**Case Report**

The patient was a previously healthy 29-year-old male who presented to the hospital with agitation and altered mental status, vomiting, and shortness of breath. In the emergency department he had a heart rate of 145 beats/min, blood pressure of 134/68 mm Hg, and a core temperature of 36.7°C. Initial blood analysis was notable for a white-blood-cell count of 34.5 \( \times 10^3/\mu \)L, hematocrit of 47%, creatinine of 2.3 mg/dL, blood urea nitrogen of 48 mg/dL, glucose of 42 mg/dL, and total bilirubin of 3.9 mg/dL.

His oxygen saturation (measured via pulse oximetry) was 80% while breathing room air with a frequency of 28 breaths/min. The patient was placed on a non-rebreathing oxygen mask at 10 L/min, which resulted in an arterial pH of 7.31, \( P_{aCO_2} \) of 31 mm Hg, \( P_{aO_2} \) of 105 mm Hg, and a base deficit of −10.5 meq/dL. An initial chest radiograph revealed extensive bilateral patchy infiltrates.

Following emergency intubation the patient was admitted to the medical intensive care unit, where both bronchoscopy with bronchoalveolar lavage and blood cultures were done. Both bronchoalveolar lavage fluid and blood samples were positive for methicillin-resistant *Staphylococcus aureus*. Also on the day of admission, an abdominal/pelvic computed tomogram revealed a large thrombus that extended from the right renal vein to the inferior vena cava. Therefore, the suspected source of ARDS was septic emboli from the deep-vein thrombosis. This suspicion was confirmed when subsequent chest radiographs, taken over the next 2 days, revealed extensive cystic changes in the left lower lobe. Initial antibiotic coverage included ceftriaxone, vancomycin, and trimethoprim-sulfamethoxazole. Five hours after admission, the patient developed septic shock that required both phenylephrine (267 \( \mu \)g/min) and norepinephrine (3 \( \mu \)g/min) to maintain a mean arterial blood pressure > 60 mm Hg. Approximately 10 h after admission, activated protein C was started at 24 \( \mu \)g/kg/h.

Lung-protective ventilation was initiated, using the ARDS Network protocol,\(^10\) with volume-control ventilation at a set frequency of 30 breaths/min, a delivered \( V_T \) of 577 mL (6.5 mL/kg predicted body weight), and a positive end-expiratory pressure (PEEP) of 10 cm H\(\text{O}\), which produced an end-inspiratory plateau pressure of 27 cm H\(\text{O}\). These initial ventilator settings resulted in an arterial pH of 7.28, a \( P_{aCO_2} \) of 38 mm Hg and a \( P_{aO_2} \) of 80 mm Hg, on an inspired oxygen fraction (\( F_{IO_2} \)) of 0.50 (\( P_{aO_2}/F_{IO_2} \), 160 mm Hg). As septic shock and ARDS worsened, the arterial pH decreased further, to 7.11, and the PEEP and \( F_{IO_2} \) requirements rose to 14 cm H\(\text{O}\) and 0.90, respectively, to sustain a \( P_{aO_2} \) above 60 mm Hg. This in turn required a further reduction in \( V_T \), to 500 mL (5.6 mL/kg predicted body weight), to maintain plateau pressure under 30 cm H\(\text{O}\). Patient-ventilator synchrony ultimately required continuous infusions of fentanyl (100 \( \mu \)g/h), midazolam (2 mg/h), and vecuronium at 5.5 mg/h.

Several measurements of \( V_{D}/V_T \) were made to assist ventilator management during the first 3 days of ARDS while the patient was managed on volume-control ventilation. Measurements of mixed expired carbon dioxide partial pressure (\( P_{E CO_2} \)) and \( V_{D}/V_T \) were made with an automated volumetric capnograph and pulmonary mechanics monitor (NICO, Respironics, Wallingford, Connecticut).\(^11\) Active humidification was used, and the apparatus dead space of the ventilator circuit was minimized, to approximately 15 mL, which included the dead space of the NICO monitor’s Capnostat CO\(\text{2}\)/flow sensor.\(^11\) The Capnostat sensor and NICO monitor were used only to obtain dead-space measurements, and were removed from the ventilator circuit afterwards.

An arterial blood sample was obtained when \( P_{E CO_2} \) stabilized (change of no more than ± 1 mm Hg over 5 min).\(^11\) \( V_{D}/V_T \) was calculated by the NICO monitor, which uses the Enghoff modification of the Bohr equation\(^12\):

\[
V_{D}/V_T = (P_{aCO_2} - P_{E CO_2})/P_{aCO_2}
\]

In addition, the NICO monitor incorporates the Fletcher single-breath technique to determine the airway and alveolar components of physiologic dead space and carbon dioxide excretion (\( V_{CO_2} \)) (Fig. 1).\(^13\) Alveolar \( V_T \) (to perfused alveoli) was calculated as:

\[
\text{Expired } V_T - [V_T \times (V_{D}/V_T)]
\]

\( V_{D}/V_T \) was measured at baseline, prior to initiation of activated protein C, and again at 2, 19, 45, and 70 h after...
Borrowing from the Enghoff method, the arterial PCO2 is used to signify mean alveolar PCO2 across all lung zones, and forms the horizontal line at the top of the figure (for conceptual purposes this is expressed as the mean fractional concentration of alveolar carbon dioxide \(F_{ACO2}\)). The area subtended by mean \(F_{ACO2}\), the slope of Phase III, and the continuation of the line bisecting the slope of Phase II form area \(Y\), which represents the alveolar \(V_D\). The sum of areas \(Y\) and \(Z\) represents the physiologic \(V_D\). The subtraction of physiologic \(V_D\), from the expired \(V_T\) allows the estimation of the volume received by perfused alveoli (alveolar \(V_T\)).

Fig. 1. The Fletcher technique\(^{13}\) for measuring dead-space fraction, and its subcomponents of airway dead space \(V_D\) and alveolar \(V_D\), is based on the single-breath test for carbon dioxide. The horizontal axis represents expired tidal volume \(V_T\), and the vertical axis represents the fractional concentration of expired carbon dioxide \(F_{ECO2}\). The \(F_{ECO2}-V_T\) curve has 3 phases, which are depicted in the upper panel. Phase I, in which the expired volume contains no CO2, represents pure airway \(V_D\). Phase II is the rapid upstroke in \(F_{ECO2}\), that indicates the mixing of alveolar gas from fast-emptying lung units (ie, those with short time constants) with airway \(V_D\). Phase III represents pure alveolar gas and is known as the alveolar plateau. The steepness in the upward slope of Phase III represents unequal emptying of alveolar units with different time constants. In the lower panel, Area X represents the volume of expired CO2. To calculate airway \(V_D\), the expired capnogram is mathematically manipulated to create a 2-compartment model of a single airway and single alveolus. This is achieved by extending the slope of Phase III backwards where it crosses a perpendicular line drawn to bisect the slope of Phase II. Those lines form triangles of equal area (p and q), which creates distinct airway and alveolar compartments. This in turn allows the calculation of airway \(V_D\) (area 2). The remaining portion of the expired capnogram represents the \(V_T\) distributed to both perfused and unperfused alveoli. Borrowing from the Enghoff method,\(^{12}\) the arterial \(P_{CO2}\) is used to signify mean alveolar \(P_{CO2}\) across all lung zones, and forms the horizontal line at the top of the figure (for conceptual purposes this is expressed as the mean fractional concentration of alveolar carbon dioxide \(F_{ACO2}\)). The area subtended by mean \(F_{ACO2}\), the slope of Phase III, and the continuation of the line bisecting the slope of Phase II form area \(Y\), which represents the alveolar \(V_D\). The sum of areas \(Y\) and \(Z\) represents the physiologic \(V_D\). The subtraction of physiologic \(V_D\), from the expired \(V_T\) allows the estimation of the volume received by perfused alveoli (alveolar \(V_T\)).
alveolar $V_D$ include the effects of activated protein C on macro and microthromboemboli, as well as the effects of PEEP on alveolar recruitment and alveolar ventilation.

In regards to pulmonary vascular obstruction, it has long been recognized that embolization of both large and small pulmonary vessels is a prominent feature of severe ARDS.14-16 A wide variety of pulmonary vascular lesions have been described, and these tend to develop in stages.17 Relevant to our report, the first week of lung injury (the early exudative phase) is characterized by acute endothelial injury resulting in capillary engorgement and diffuse microthrombi. Tomashefski et al17 described 2 types of microthrombi: those found in the capillaries and small alveolar wall arteries, consisting of dense hyaline clots formed from platelets and fibrin; and those predominantly located in the small pre-acinar and large intra-acinar arteries. This is consistent with Vieillard-Baron’s18 observation that in ARDS the site of pulmonary vascular obstruction tends to be focused in the distal vessels. Macrothrombi in the larger pulmonary arteries have been found in all stages, but tend to be more prominent in the intermediate and later stages of ARDS.17

Nonetheless, the presence of a large thrombus in this patient’s right renal vein and inferior vena cava complicates the pathophysiologic interpretation. Smaller thrombi generated from this source may have formed emboli in the larger pulmonary arteries. As computerized tomographic pulmonary angiography was not done in this patient, we cannot rule out the presence or relative contribution of pulmonary arterial macrothrombi to the elevation in alveolar $V_D$. However, when the initial dead-space measurements were made, the central venous pressure was 15 mm Hg while the total PEEP was 15–16 cm H2O (12 mm Hg). The fact that this patient had an extrapulmonary source of ARDS, which typically is characterized by a higher degree of airway pressure transmission to the pleural space, along with a relatively high respiratory-system compliance ($C_{RS}$) of 38 mL/cm H2O, suggests that central venous pressure reflected some degree of airway pressure transmission to the pleural space. If a substantial

<table>
<thead>
<tr>
<th>Table 1. Pulmonary Gas Exchange and Mechanics During Treatment With Activated Protein C</th>
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<tbody>
<tr>
<td>Before Activated Protein C Therapy</td>
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<tr>
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<tr>
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<tr>
<td>$V_D/V_T$ physiologic</td>
</tr>
<tr>
<td>$V_D$ alveolar (mL)</td>
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<td>$V_D$ airway (mL)</td>
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<td>$V_D$ expired (mL)</td>
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<td>$V_T$ alveolar (mL)</td>
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<td>$\dot{V}CO_2$ (mL/min)</td>
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<tr>
<td>PEEP (cm H2O)</td>
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<td>PEEP total (cm H2O)</td>
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<td>$P_{plat}$ (cm H2O)</td>
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<td>Mean $P_{mean}$ (cm H2O)</td>
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<tr>
<td>$C_{RS}$ (mL/cm H2O)</td>
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<td>f (total breaths/min)</td>
</tr>
<tr>
<td>$T_I$ (s)</td>
</tr>
<tr>
<td>$V_R$ (L/min)</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mm Hg)</td>
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<tr>
<td>$P_{ECo_2}$ (mm Hg)</td>
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<tr>
<td>Oxygenation index</td>
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<tr>
<td>$P_{aco2}/P_{aO_2}$ (mm Hg)</td>
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$V_D$ = dead space volume
$V_T$ = tidal volume
$\dot{V}CO_2$ = carbon dioxide excretion
PEEP = positive end-expiratory pressure
PEEP total = total PEEP at the alveolar level, measured during an end-expiratory pause and representing the absolute pressure
ND = no data available
$P_{mean}$ = plateau pressure
$P_{mean}$ = airway pressure
$C_{RS}$ = compliance of the respiratory system
f = respiratory frequency
$T_I$ = inspiratory time
$V_R$ = minute ventilation
$P_{ECo_2}$ = mixed expired carbon dioxide partial pressure
$P_{aco2}$ = fraction of inspired oxygen
Fig. 2. Changes in physiologic dead-space fraction (VD/VT) and its sub-components, airway VD/VT and alveolar VD/VT, at 5 time points before, during, and after activated protein C therapy. The baseline measurement was just prior to initiation of activated protein C therapy. Both physiologic and alveolar VD/VT declined in tandem during therapy. Activated protein C was discontinued after 41 h because of bleeding. Approximately 29 h after activated protein C was stopped, alveolar VD/VT had increased from 0.02 to 0.14, but it never approached its initial value of 0.29. Also note that the initial increase in physiologic VD/VT after activated protein C therapy started was due to changes in airway VD/VT, probably attributable to a VT decrease that was necessary to achieve the lung-protection target, as well as a radical reduction in inspiratory time (0.47 s), which limited gas diffusion.

Alveolar recruitment with PEEP can also affect VD/VT. In ARDS, alveolar VD is inversely proportional to both PEEP and CRS, and is indicative of the contribution of intrapulmonary shunt to VD/VT. Therefore, PEEP titration over the time course of the dead-space measurements may have contributed to the observed changes in alveolar VD. We were intrigued by the fact that alveolar VT continued to increase despite decreased PEEP (from 14 cm H2O to 5 cm H2O) and a corresponding 21% decrement in CRS (from 38 mL/cm H2O to 30 mL/cm H2O). This suggests that some degree of alveolar de-recruitment was also occurring. This finding further suggests that increased pulmonary perfusion may have been affected to a larger extent by decreased microvascular obstruction secondary to activated protein C therapy. The fact that alveolar VD increased after discontinuation of activated protein C also may reflect ongoing microvascular obstruction from an increasingly pro-coagulation state, relative to increasing shunt from alveolar de-recruitment, as PEEP and CRS remained stable.

Although the patient had a very high minute-ventilation requirement, dynamic gas-trapping was not an important contributor to alveolar VD, as the measured intrinsic PEEP was only 1–2 cm H2O above applied PEEP and did not change substantially during the measurement period. The minor degree of intrinsic PEEP measured in this patient was consistent with values found in patients on lung-protective ventilation during the original ARDS Network study.

This complicated case of severe, sepsis-induced ARDS provides further indirect evidence that pulmonary vascular obstruction may be a substantial source of alveolar VD contributing to elevated VD/VT. Treatment with activated protein C was associated with a rapid and almost complete elimination of alveolar VD and a 142% increase in alveolar VT. This marked decrease in alveolar VT also has been observed when heparin is administered preemptively to patients undergoing cardiac surgery, a situation known to cause inflammation and promote pulmonary microvascular thrombosis. It is also consistent with the findings of substantial improvements in pulmonary perfusion observed within 48 h when streptokinase is administered to patients with severe ARDS.

However, the impressive response in alveolar VD to activated protein C demonstrated in this case may be exaggerated somewhat by the fact that sepsis-induced ARDS apparently resulted from an extraordinarily large abdominal venous thrombus. Even though indirect signs of a substantial pulmonary embolus were absent in this case, we could not conclusively exclude the possibility. Thus, changes in alveolar VD observed in this case may not be as pronounced in ARDS not associated with sepsis, and in particular septic emboli (eg, pneumonia, aspiration, or trauma).

This case also demonstrates the utility of volumetric capnography in the management of severe ARDS, particularly in the era of lung-protective ventilation. In general, VD/VT is largely independent of VT in the range 8–13 mL/kg. However, when VT is adjusted to a sub-physiologic level, airway VD assumes a relatively larger fraction of VT. Under circumstances when severe reductions in inspiratory time are necessary to achieve elevated minute ventilation demand, as occurred in this case, both airway and alveolar VD may increase as there is less time for alveolar gas diffusion and mixing. This becomes more complicated during PEEP titration, as VD/VT decreases with lung recruitment, but rises again when pulmonary over-distention increases alveolar VD.

As illustrated in this complex case, attempting to implement lung-protective ventilation requires numerous ad-
justments to promote lung recruitment, maintain adequate acid-base balance, and minimize ventilator-associated lung injury. These adjustments often have divergent effects upon $V_{D}/V_T$ and pulmonary gas exchange function. This can obfuscate the assessment of adjustments to mechanical ventilation, particularly in the context of hemodynamic instability. Having the ability to make sophisticated measurements of pulmonary function may assist in clinical decision making under such circumstances.

In summary, this case report provides indirect evidence supporting the hypothesis that activated protein C reduces $V_{D}/V_T$ through decreased alveolar $V_D$ by a reduction in pulmonary vascular microemboli. In addition, our report illustrates the utility of volumetric capnography in the management of patients with severe ARDS.

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