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Increased Ratio of Dead Space to Tidal Volume in Subjects With Inhalation Injury

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BACKGROUND: Inhalation injury increases morbidity and mortality in burn patients. Patients with inhalation injury present with large differences between end-tidal CO_2 pressure and P_{aCO_2}, an indirect measure of dead space. We aimed to investigate the relationships between increased dead space and inhalation injury outcomes. METHODS: This retrospective study included 51 adult subjects with burns and inhalation injuries. Demographics, size of burns, length of stay, ventilator days, blood gas results, end-tidal CO_2 pressure, presence of ventilator-associated pneumonia, and mortality data were collected. Modified Baux scores and ratios of alveolar dead space to alveolar tidal volume ($V_{D_{alv}}/V_{T_{alv}}$) were calculated. Independent *t* tests were used to compare mean $V_{D_{alv}}/V_{T_{alv}}$ of survivors to that of subjects who died and between subjects with and without pneumonia. The relationships between $V_{D_{alv}}/V_{T_{alv}}$ and ventilator days or modified Baux score were assessed with bivariate correlation analysis. RESULTS: Our population had a mean age of 52 y and an average burn size of 17.5%. The average length of stay and ventilator days were 12 d and 3.8 d, respectively. The mean modified Baux score was 87. The mean $V_{D_{alv}}/V_{T_{alv}}$ was 0.38. Ten subjects died, and 6 subjects had pneumonia. The $V_{D_{alv}}/V_{T_{alv}}$ of survivors was significantly smaller for survivors than for subjects who died (0.34 vs 0.52, $P = .03$). No significant difference was observed between subjects with and without pneumonia (0.36 vs 0.47, $P = .26$). $V_{D_{alv}}/V_{T_{alv}}$ correlated significantly with modified Baux score ($r = .524$, $P < .001$). CONCLUSIONS: Alveolar dead space ($V_{D_{alv}}/V_{T_{alv}}$) is easily calculated from P_{aCO_2} and end-tidal CO_2 pressure and may be useful in assessing severity of inhalation injury, the patient's prognosis, and the patient's response to treatment. *Key words: burn; inhalation injury; mortality; ratio of dead space to tidal volume; dead space fraction; modified Baux scores; total burn surface area.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Inhalation injury remains a significant cause of morbidity and mortality despite overall improvement in survival from burn injuries. The pathophysiology of inhalation injury involves direct, local injury to the tracheobronchial tree and humoral mediated derangements of the pulmonary microvasculature. The former results in respiratory epithelial sloughing, tracheobronchial hemorrhage, and airway occlusion. The latter results in inflammatory infiltrates, leaky capillaries, increased pulmonary lymph flow, and pulmonary edema.[1-3]

Early studies of inhalation injury detected impairments of pulmonary mechanics and ventilation-perfusion mismatch. In 1970, Garzon et al[4] reported on five patients with

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The authors have disclosed no conflicts of interest.

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smoke inhalation and detected reduced pulmonary compliance and increased work of breathing. Moylan et al[5] used ^{133}xenon scans to describe the ventilation-perfusion mismatch from air trapping secondary to small bronchiole obstruction in patients with inhalation injury.

Dead space (V_D), however, received little attention in the field of research on inhalation injury. Pruitt et al[6] made a passing comment about the elevated ratio of dead space to tidal volume (V_D/V_T) in patients with thermal injury and "progressive pulmonary insufficiency," but they did not specifically attribute the observation to patients with inhalation injury. Trunkey[7] repeated the observation without elaboration in 1978. Recently, Dries and Endorf[8] commented on increased dead-space ventilation associated with inhalation injury in their review on the topic.

In our burn unit, the bedside monitors display and record continuous end-tidal CO_2 pressure (P_{ETCO_2}) for our patients on ventilators. These data, along with ventilator settings, ventilator measurements, and blood gas results, are uploaded to the respiratory therapy flowsheets and stored in the electronic medical record. These flowsheets provide detailed records of patients' respiratory physiology. We noted abnormally wide differences between measured P_{aCO_2} on arterial blood gas results and P_{ETCO_2} in some of our patients with inhalation injury. This difference between P_{aCO_2} and P_{ETCO_2} can be used to calculate the alveolar dead space ($V_{D_{alv}}/V_{T_{alv}}$) as described by Hardman and Aitkenhead:[9,10]

$$\frac{V_{D_{alv}}}{V_{T_{alv}}} = \frac{P_{aCO_2} - P_{ETCO_2}}{P_{aCO_2}}$$

where $V_{D_{alv}}$ and $V_{T_{alv}}$ are the alveolar V_D and alveolar V_T, respectively. The normal $V_{D_{alv}}/V_{T_{alv}}$ in healthy adults is 0.15–0.35.

We undertook this study to estimate the prevalence of increased $V_{D_{alv}}/V_{T_{alv}}$ in patients with inhalation injury and its possible relationship with morbidity and mortality associated with inhalation injury.

QUICK LOOK

Current knowledge

Early studies of inhalation injury detected impairments of pulmonary mechanics and ventilation-perfusion mismatch. Dead space, however, received little attention in the field of research on inhalation injury.

What this paper contributes to our knowledge

Our results indicate that the ratio of alveolar dead space to alveolar tidal volume ($V_{D_{alv}}/V_{T_{alv}}$) was often increased in subjects with inhalation injury. In our population, $V_{D_{alv}}/V_{T_{alv}}$ was higher in subjects who died and in those who suffered acute kidney injury, and $V_{D_{alv}}/V_{T_{alv}}$ correlated moderately with total body surface area of burn and modified Baux Score.

Methods

Subjects

This retrospective study was approved by the University of Iowa Institutional Review Board. We queried the University of Iowa Hospital admission database for subjects with a diagnosis of inhalation injury using StarMaker software (Park Street Solutions, Naperville, Illinois). All patients admitted to our burn center and diagnosed with inhalation injuries from January 2000 to January 2016 were included in this study. Pediatric patients and patients who were misdiagnosed and did not have inhalation injuries were excluded from the study. Smoke inhalation injury was defined as evidence of epithelial damage below the vocal cords on bronchoscopy.

Data Collection

Data on the following characteristics were abstracted from the medical records of adult subjects diagnosed with inhalation injuries: age, sex, height, weight, body mass index, total body surface area, total body surface area of burn, date and time of burn, date and time of admission, history of lung disease, smoking status, carboxyhemoglobin, presence of ventilator-associated pneumonia (VAP) or acute kidney injury during the hospital stay, arterial blood gas results, P_{ETCO_2}, ventilator settings and records, date and time of liberation from the ventilator, and vital signs.

We used the collected data to derive the following variables: Baux score (age + total body surface area of burn), modified Baux score (age + total body surface area of burn + 17),[11] CO_2 gap ($P_{aCO_2} - P_{ETCO_2}$), and $V_{D_{alv}}/V_{T_{alv}}$.[9,10] The CO_2 gap was calculated using arterial blood gas results from a sample that had been drawn within 20 min of a recorded P_{ETCO_2} reading. Many subjects had multiple gap results because of their long period of ventilator support. Thus, we considered all P_{ETCO_2} and P_{aCO_2} available in the medical record. P_{ETCO_2} was captured and stored by the monitor at a frequency of 30–120 min. P_{aCO_2} from arterial blood gas was recorded on admission and as needed depending on the attending physician preference or based on the patient condition. The time at which the arterial blood gas specimen was obtained was recorded for the results in the medical record. We reasoned that the result of the arterial blood gas would not be available to the physician or respiratory therapist until 10–20 min after the blood draw to account for transportation to the lab, completion of the lab analysis, and reporting the results.

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Therefore, even if ventilator changes were made based on the lab results, we thought the P_{aCO_2} was an accurate estimate for at least 20 min from the time of the blood draw. $V_{D_{alv}}/V_{T_{alv}}$ was calculated using the maximum difference between P_{aCO_2} and P_{ETCO_2}. Ventilator days were calculated using the date and time of ventilator liberation.

Statistical Analysis

Descriptive statistics were obtained. Independent *t* tests and nonparametric Mann-Whitney tests were used as appropriate. Bivariate correlation was performed to assess the association between $V_{D_{alv}}/V_{T_{alv}}$ and other variables. Multivariate linear regression analysis was performed to assess the impact of smoking and chronic lung disease on the association between $V_{D_{alv}}/V_{T_{alv}}$ and other variables. Statistical analysis was performed using SPSS 25.0 (IBM SPSS, Armonk, New York). Significance was considered at $P < .05$.

Results

Subject Characteristics

A total of 57 patients diagnosed with inhalation injuries were identified. After review of their medical records, we excluded 6 patients: 3 were pediatric patients, 1 patient had 2 medical record numbers and required merging the data into a single case, and 2 patients who were misdiagnosed and did not have inhalation injuries.

Descriptive statistics for the population are presented in T1,AQ:E Table 1. The population was composed of 31 men (61%); 24 subjects were known cigarette smokers (47.1%), and 12 had a history of COPD (23.5%). The mean subject age was 52.3 y. The average burn size was 17.5%, and the average modified Baux Score was 86.8. The mean length of stay and mean ventilator days were 11.9 d and 3.8 d, respectively. The mean carboxyhemoglobin was 6.4 among the 34 subjects for whom it was measured. $V_{D_{alv}}/V_{T_{alv}}$ ranged from 0.05 to 0.97; the average was 0.38, slightly above the normal range. On average, $V_{D_{alv}}/V_{T_{alv}}$ was not significantly different between smokers and nonsmokers (0.46 ± 0.21 vs 0.34 ± 0.25, respectively; $P = .39$), subjects presenting with chronic lung diseases (including COPD) or not (0.40 ± 0.24 vs 0.36 ± 0.23, respectively; $P = .75$), or subjects who developed ARDS ($n = 9$; 17.6%) assessed on the basis of the Berlin Criteria[12] or not (0.37 ± 0.23 vs 0.39 ± 0.20, $P = .70$). ARDS was determined using the Berlin Criteria because a definitive clinical diagnosis of ARDS was noted in the medical records of only 5 subjects.

Ten subjects died (19.6%), and 41 survived (80.4%). Six subjects suffered VAP (11.8%), but they all survived. Thirteen subjects developed acute kidney injury (25.5%); 6 died, and 7 survived.

Table 1. Subject Characteristics

Variables	Data
Age, y	51 (52.3 ± 16.1)
Male	31 (60.8)
Body mass index, kg/m^2	50 (32.3 ± 10.2)
Chronic lung disease (including COPD)	12 (23.5)
Smoker	24 (47.1)
Length of stay, d	51 (11.9 ± 15.0)
Total body surface area burned, %	51 (17.5 ± 25.2)
Baux score	51 (69.8 ± 26.8)
Modified Baux score	51 (86.8 ± 26.8)
Carboxyhemoglobin, %	34 (6.42 ± 5.6)
Ventilator days	45 (3.8 ± 5.67)
$V_{D_{alv}}/V_{T_{alv}}$	41 (0.38 ± 0.22)
Ventilator mode	
CPAP	1 (2)
Pressure control	15 (29.4)
Pressure-regulated volume control	5 (9.8)
Pressure support	1 (2)
Synchronized intermittent mandatory ventilation	15 (29.4)
Synchronized intermittent mandatory ventilation with pressure support	1 (2)
Volume control	1 (2)
Unknown	1 (2)
PEEP, cm H_2O	45 (6.0 ± 1.7)
Tidal volume, mL/kg	44 (0.54 ± 0.12)
P_{aO_2}	49 (191.2 ± 132.7)
P_{aCO_2}	49 (44.5 ± 1.4)
F_{IO_2}	44 (0.80 ± 0.26)
P_{aO_2}/F_{IO_2}	44 (263.9 ± 170.1)
Presence of infiltration on chest radiograph	15 (29.4)
ARDS[12]	
No	34 (66.7)
Mild	3 (5.9)
Moderate	4 (7.8)
Severe	2 (3.9)
Missing data	8 (15.7)
Ventilator-associated pneumonia	6 (11.8
Acute kidney injury	13 (25.5
Mortality	10 (19.6

Data are presented as *n* (%) or mean ± SD.
$V_{D_{alv}}/V_{T_{alv}}$ = ratio of alveolar dead space to alveolar tidal volume

$V_{D_{alv}}/V_{T_{alv}}$ and Outcomes

For our analysis on $V_{D_{alv}}/V_{T_{alv}}$ and outcomes, only 41 subjects had appropriate P_{ETCO_2} and P_{aCO_2} measurements to make the calculations. In the other 10 cases, either P_{ETCO_2} or P_{aCO_2} was not available. As shown in Table 2, the mean $V_{D_{alv}}/V_{T_{alv}}$ was significantly lower in subjects who survived compared to that of subjects who died. Similarly, the mean $V_{D_{alv}}/V_{T_{alv}}$ was significantly higher in subjects who suffered acute kidney injury than in those who did not have acute

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Table 2. $V_{D_{alv}}/V_{T_{alv}}$ and Outcomes

Outcome	Yes	No	*P*
Survival	0.34 ± 0.20	0.52 ± 0.24	.03
Acute kidney injury	0.51 ± 0.27	0.34 ± 0.19	.031
Ventilator-associated pneumonia	0.47 ± 0.31	0.36 ± 0.20	.26

Data are presented as mean ± SD. Independent *t* tests were performed to assess differences.
$V_{D_{alv}}/V_{T_{alv}}$ = ratio of alveolar dead space to alveolar tidal volume

kidney injury. No significant difference was observed in $V_{D_{alv}}/V_{T_{alv}}$ between subjects with and without VAP.

Length of stay and ventilator days correlated weakly, but not significantly, with $V_{D_{alv}}/V_{T_{alv}}$ (r = 0.276 and 0.281, respectively; $P = .08$). No correlation was observed between $V_{D_{alv}}/V_{T_{alv}}$ and body mass index, P_{aO_2}, or the P_{aO_2}/F_{IO_2} ratio. As shown in Figure 1, both total body surface area of burn size and modified Baux score correlated moderately but significantly with $V_{D_{alv}}/V_{T_{alv}}$ (r = 0.606 and 0.524, respectively; $P < .001$). Multivariate regression analysis indicated that being a smoker, presenting with a history of chronic lung disease or presenting with ARDS did not affect the association between burn size and modified Baux scores with $V_{D_{alv}}/V_{T_{alv}}$ (data not shown).

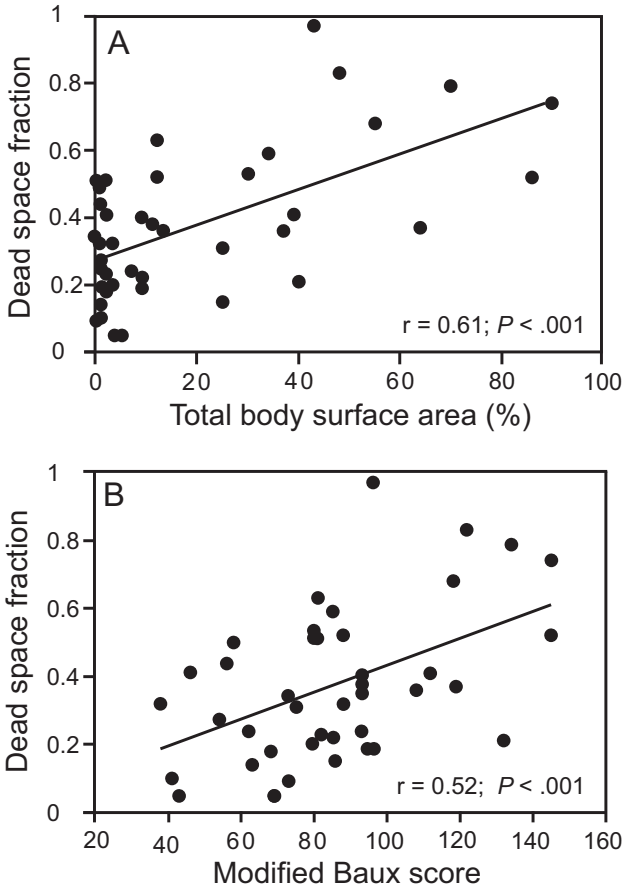

Fig. 1. Ratio of alveolar dead space to alveolar tidal volume ($V_{D_{alv}}/V_{T_{alv}}$) correlates with (A) total body surface area of burn and (B) modified Baux score.

Discussion

This was a retrospective review of subjects with inhalation injury from a single institution. Detailed physiologic data were available from the electronic medical records, particularly continuous P_{ETCO_2} measurements and laboratory results. These data allowed for the easy calculation of $V_{D_{alv}}/V_{T_{alv}}$. $V_{D_{alv}}/V_{T_{alv}}$ is another measure of respiratory physiology and is often increased in patients with inhalation injury. We calculated the alveolar dead space because the equation uses the P_{ETCO_2} rather than the mixed expiratory CO_2 that is used in the Enghoff modification of the Bohr equation. The latter requires extra apparatus on the ventilator and cumbersome calculations. In this study, subjects who died and subjects who suffered acute kidney injury presented with significantly increased $V_{D_{alv}}/V_{T_{alv}}$ values.

Early studies on inhalation injury noted the impaired ventilation and marked ventilation-perfusion mismatch in many of these patients.[5,7] Pruitt et al[6] mentioned increased V_D/V_T in burn subjects with inhalation injury and "progressive pulmonary insufficiency," but they did not elaborate on the finding. They used the terms "progressive pulmonary insufficiency" instead of "shock lung" from the Vietnam era. Their description of progressive pulmonary insufficiency resembles ARDS, which was not a commonly used term at that time.

Further research into inhalation injury elaborated on the role of large-volume fluid resuscitation and systemic inflammatory mediators in the pathophysiology of inhalation injury. Peitzman et al[13] reported increased extravascular lung water in subjects with inhalation injury who died of sepsis. In 1996, Darling et al[14] implicated large-volume fluid resuscitation in worsening pulmonary compliance in subjects with inhalation injury.

The role of systemic inflammatory mediators in secondary pulmonary injury in burns was identified by Rue et al[15] in 1993. They discovered that inflammatory mediators from cutaneous burns circulate via the bloodstream and damage the lungs. Secondary lung injury in inhalation injury was concisely summarized in reviews by Cancio and colleagues in 2005[1] and 2007.[16] In the latter review, the authors confirmed that the ventilation-perfusion mismatch in inhalation injury is not a shunt.[1]

In more recent studies, investigators identified increased V_D/V_T in subjects with ARDS. Nuckton et al[17] used the Enghoff modification of the Bohr equation to calculate the V_D/V_T in 179 subjects and reported that V_D/V_T predicted

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mortality. In 2014, Kallet et al[18] studied V_D/V_T in subjects with acute lung injury and ARDS and found that V_D/V_T rose early during the disease and was associated with increased mortality.

These studies suggest that increased V_D/V_T is associated with a variety of pulmonary disorders and is not unique to inhalation injury. Possible mechanisms for the increased V_D include hyperexpansion with reduced alveolar capillary flow or reduced pulmonary vascular flow secondary to endothelial damage.[19] Another plausible mechanism is incomplete expiration due to "dynamic hyperexpansion" with auto-PEEP as described by Rees and colleagues.[20]

In this study, increased V_D/V_T was associated with mortality and acute kidney injury, but not with ARDS, which is a potential confounding factor. These results suggest that the systemic effects of burn injuries on inhalation injury play a role in increasing V_D/V_T. One could propose that larger burn sizes generate more inflammatory mediators and require larger volumes of fluid resuscitation. The former might cause more distal organ injury, and the latter would increase extravascular lung water. Both mechanisms have been implicated in lung injury and mortality in patients with inhalation injury. In our study, the moderate correlation between $V_{D_{alv}}/V_{T_{alv}}$ and modified Baux Score, in which burn size is a significant factor, may be caused by either or both of these mechanisms. The stronger correlation between burn size and $V_{D_{alv}}/V_{T_{alv}}$ might discount age as a factor and favor the magnitude of the burn injury. Additionally, increased $V_{D_{alv}}/V_{T_{alv}}$ did not correlate with P_{aO_2}, suggesting that the increase in $V_{D_{alv}}/V_{T_{alv}}$ is more likely associated with impaired ventilation and not oxygenation. This study, however, does not provide sufficient evidence to reach that conclusion.

The stronger association between $V_{D_{alv}}/V_{T_{alv}}$ and acute kidney injury compared to the association between $V_{D_{alv}}/V_{T_{alv}}$ and VAP suggests systemic rather than local pulmonary mechanisms.

Our study has several limitations. First, the data were acquired with a retrospective chart review, which introduces a risk of bias due to poor documentation or missing data. Second, our sample size was small. Finally, only 6 subjects had VAP, and all of them survived. This group likely skewed the results in favor of survivors. Despite these limitations, our study suggests patterns of complex pathology in subjects with burns and inhalation injury, although the conclusions we can draw from our results are limited.

Conclusions

This study supports the feasibility and ease of calculating the alveolar V_D/V_T from continuous P_{ETCO_2} and P_{aCO_2} measurements, both readily available at the bedside in a burn unit with modern monitors. Although we do not know how using $V_{D_{alv}}/V_{T_{alv}}$ may improve patient care, previous studies suggest that extravascular lung water may play a role, thus, diuresis or high PEEP may be beneficial.[15] Conversely, lung-protective strategies and reduced PEEP may reduce V_D and improve patient outcomes. Additionally, in our population, $V_{D_{alv}}/V_{T_{alv}}$ was significantly higher in subjects who died and in subjects with acute kidney injury. Finally, $V_{D_{alv}}/V_{T_{alv}}$ correlated with total body surface area of burn and modified Baux score. Considering all that we learned from this study, we suggest that calculation of $V_{D_{alv}}/V_{T_{alv}}$ might be useful to assess inhalation injury severity, outcomes, and response to treatment. This study paves the way for future prospective studies assessing the association between $V_{D_{alv}}/V_{T_{alv}}$ and outcomes.

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