Ventilation-perfusion alterations after smoke inhalation injury in an ovine model

TAKESHI SHIMAZU, TETSUO YUKIOKA, HISASHI IKEUCHI, ARTHUR D. MASON, JR., PETER D. WAGNER, AND BASIL A. PRUITT, JR. Ventilation-perfusion alterations after smoke inhalation injury in an ovine model. J. Appl. Physiol. 81(5): 2250–2259, 1996.—To study the pathophysiological mechanism of progressive hypoxemia after smoke inhalation injury, alterations in ventilation-perfusion ratio (VA/Q) were studied in an ovine model by using the multiple inert gas elimination technique. Because ethane was detected in expired gas of some sheep, we replaced ethane with krypton, which was a unique application of the multiple inert gas elimination technique when one of the experimental gases is present in the inspire. Severity-related changes were studied 24 h after injury in control and mild, moderate, and severe inhalation injury groups. Time-related changes were studied in controls and sheep with moderate injury at 6, 12, 24, and 72 h. Arterial PO2 decreased progressively with severity of injury as well as with time. In smoke-exposed animals, blood flow was recruited to low VA/Q compartment (0 < VA/Q < 0.1; 17.6 ± 10.6% of cardiac output, 24 h, moderate injury) from normal VA/Q compartment, (0.1 < VA/Q < 10). However, increases in true shunt (VA/Q = 0; 5.6 ± 2.5%, 24 h, moderate injury) and dead space were not consistent findings. The VA/Q patterns suggest the primary change in smoke inhalation injury to be a disturbance of ventilation.

Lung injury; severity-related changes; time-related changes; low ventilation-perfusion; krypton; gas chromatography-mass spectrometry

SMOKE INHALATION INJURY is one of the primary determinants of survival after major burns. Smoke inhalation injury by itself increases mortality of burn patients up to a maximum of 20% (21). Such injury has commanded wide clinical interest, but its pathophysiological mechanisms are not clearly defined (11).

To elucidate the mechanism of progressive hypoxemia after smoke inhalation injury, we have used the multiple inert gas elimination technique (MIGET) in an ovine model, which is reproducible and dose responsive (20). The MIGET, using gas chromatography (GC), was developed by Wagner et al. (26, 28) in 1974 to determine continuous distribution of ventilation-perfusion ratios (VA/Q). By use of this method, the true shunt (VA/Q = 0) and the low VA/Q (0 < VA/Q < 0.1) can be differentiated, enabling detailed analysis of the mechanism of respiratory impairment. The technique has been applied extensively in evaluation of respiratory pathophysiology (5, 10, 18, 24, 27). For smoke inhalation injury, however, there has been only one report of the use of MIGET in a small number of patients and animals (16). To perform MIGET by using sheep, we substituted krypton for ethane as one of the six gases because ethane as well as methane was detected in the expired gas. With krypton being present in trace amounts in the inspire (~1.1 parts/million in the atmosphere), this is a unique application of the MIGET. In the present study, we have characterized VA/Q changes after smoke inhalation injury in terms of severity-related and time-related alterations to obtain physiological information for use in respiratory management.

MATERIALS AND METHODS

Study design and animals. Forty-seven neutered male sheep weighing 22–50 kg (33.2 ± 5.6 kg) were used in this study. Severity-related changes were studied in 21 sheep consisting of 5 uninjured controls and 16 exposed individually to amounts of smoke that produced mild (n = 5), moderate (n = 5), or severe (n = 6) smoke inhalation injury in a previous study (20). Measurements were made 24 h after smoke exposure, when changes in cardiopulmonary function showed a distinct dose response.

Time-related changes were studied in 26 sheep. Moderate smoke inhalation injury was produced in 20 sheep, and measurements were made 6, 12, 24, and 72 h after smoke exposure in groups of 5. Six uninjured sheep were used as controls.

In conducting the research described in this report, the investigators adhered to the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and to the “Guide for the Care and Use of Laboratory Animals” [Department of Health, Education, and Welfare Publication no. (NIH) 85-23, revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20892].

Smoke exposure. Sheep were intubated, anesthetized with methohexitol sodium (9 mg/kg, Breval, Eli Lilly, Indianapolis, IN), and insufflated with a standard dose of smoke to produce mild, moderate, or severe injury. The sheep model has been described in detail elsewhere (20), but in summary it enables dose-dependent injury by insufflating the lungs with a certain volume of smoke under general anesthesia and intubation. Smoke was produced by burning 10 disposable underpads (Hosposable, Bound Brook, NJ) in a smoke generator. The smoke generator was a 32-gallon metallic container equipped with an air inlet, a dampered chimney, a window, and a smoke outlet. The smoke was administered at ambient temperature to avoid thermal injury of the airway and contained 10–14% oxygen, 3–8% carbon dioxide, 0.7–2.2% carbon monoxide, and other combustion products but no cyanide. The experimental sheep were individually exposed to smoke with a tidal volume of 30 ml/kg and breath hold of 5 s followed by 10 successive ventilations with room air, which
were defined as 1 unit of smoke exposure. The time required per unit was ~50 s. Mild, moderate, and severe injuries were induced by exposing sheep to 3, 9, and 12 units of smoke, respectively.

The sheep started breathing spontaneously soon after smoke exposure and were extubated and housed in climate-controlled facilities (at 74–76°F and a relative humidity of 40–50%) until cardiopulmonary function and VA/Q distribution were measured.

Monitoring. Sheep were studied at 24 h after smoke inhalation for evaluation of severity-related changes and at 6, 12, 24, and 72 h after smoke exposure, in groups of five, for time-related alterations. Before the measurements, arterial, peripheral, and central venous lines, a Swan-Ganz catheter (7-Fr, American Edwards Laboratories, Irvine, CA), and an esophageal balloon were inserted after induction of general anesthesia and intubation. Anesthesia was induced with methohexitol sodium and maintained with a-chloralose (0.05 g/kg, Calbiochem, La Jolla, CA), and the sheep were paralyzed with pancuronium bromide (0.03–0.04 mg/kg, Pavulon, Organon Pharmaceuticals, West Orange, NJ) (2). Chloralose and pancuronium bromide were administered with one-half of the initial dose as needed to maintain anesthetized and paralyzed conditions. After the placement of catheters, the animals were positioned prone and artificially ventilated. A volume-limited ventilator (Bear 2, Bear Medical Systems, Riverside, CA) with a tidal volume of 21 ml/kg was applied every 3 min to prevent atelectasis. Lactated Ringer solution was continuously infused at a rate of 1 ml·kg⁻¹·h⁻¹.

Central venous pressure and pulmonary arterial pressure were monitored with Statham P23Db transducers (Statham Instruments, Oxnard, CA), and systemic arterial pressure was monitored with a Hewlett-Packard 1290A quartz transducer (Hewlett-Packard, Waltham, MA). Respiratory indexes were monitored with a pneumotachograph (model 17212, Gould) for flow rate and tidal volume and a differential transducer (MP-451, Validine Engineering, Northridge, CA) for transpulmonary pressure. The position of the esophageal balloon was adjusted to reflect the negative intrathoracic pressure, and transpulmonary pressure was taken as the pressure gradient between the connector site of the endotracheal tube to the respiratory circuit and the esophageal balloon. These cardiopulmonary indexes were recorded continuously on two Hewlett-Packard four-channel recorders (model 7754A). Cardiac output was measured in triplicate by thermodilution technique (cardiac output computer, model 9520A, American Edwards Laboratories). Blood gas analysis was performed by using an IL 1303 pH/blood gas analyzer and 1L 282 CO₂-oximeter (Instrumentation Laboratories, Lexington, MA). Thermodilution cardiac output and arterial (Pao₂) and mixed venous (PvO₂) blood gas levels were measured every 30 min. The values measured at 2 h were taken as representative values when they were judged to be in stable condition from the traces of blood pressure, heart rate, and airway pressure as well as serial measurement of Pao₂ and cardiac output. The sigh modality was discontinued 30 min before the measurement of VA/Q, which requires gas-exchange equilibrium in the lung.

Static compliance of the lung was calculated from the following equation at end inflation (3): compliance = volume change/transpulmonary pressure.

Transpulmonary pressure (mouth pressure – intrapleural pressure) was measured with the differential transducer.

Measurement was made at end inflation by placing a prolonged pause before exhalation.

Pulmonary resistance (RL) was calculated from the following equation:

\[ R_L = \frac{\text{mouth pressure} - \text{intrapleural pressure}}{\text{flow rate}} \]

RL includes airway resistance plus pulmonary tissue resistance (3).

All the physiologic measurements including MIGET were made under mechanical ventilation with Fio₂ of 0.21.

Necropsies were performed on all sheep killed at the end of the experiments for histological examination.

MIGET. MIGET was performed according to the method described by Wagner et al. (26, 28) with some modifications. Modifications included replacement of ethane, as originally employed, with krypton and the use of GC-mass spectrometry (MS) instead of GC with flame ionization and electron-capture detectors.

The six gases used in this study were sulfur hexafluoride (SF₆), krypton, cyclopropane, diethyl ether, halothane, and acetone. Ethane was replaced with krypton because trace levels of ethane were detected in expired gas in some sheep, probably derived from fermentation in the rumen (7). Ethane and krypton have almost the same solubility and are equivalent for the MIGET method. However, the use of krypton necessitated mathematical compensation to correct the blood and expired gas samples for the natural occurrence of krypton (1.1 × 10⁻⁶ vol/vol) in air. Correction was made by subtracting the krypton level in the air (Pkr,0, measured) from that measured in expired gas samples (Pkr,m, PEKR,m = Pkr,m - Pkr,0). For blood samples, krypton level (Pkr,blood) was measured by using krypton-free nitrogen for extraction, as described in the original MIGET method, and then the contribution from the atmospheric krypton, i.e., the dissolved krypton (Pkr,2) from the atmosphere, was subtracted (Eq. 1). Pkr,2 was calculated by performing mass balance by using Pkr,0 and measured krypton solubility (S) according to Eq. 2. Use of corrected krypton values in the standard MIGET program is evaluated in the APPENDIX (model 7754A).
were taken in duplicate and were analyzed immediately by
delay in the mixing chamber. Blood and expired-gas samples
ranged from 3.1 (halothane) to 5.2% (SF6), values that are
comparable to those measured with the standard GC detector.
Expressed as the coefficient of variation (means ± SD) of the
GC-MS method for gas phase measurement, ranged from 0.46
(acetone) to 0.97% (SF6). The reproducibility in blood samples
from 0.9988 (CP, Act) to 0.9999 (Etr). The reproducibility in blood samples
from 0.9988 (CP, Act) to 0.9999 (Etr). The reproducibility in blood samples
from 0.9988 (CP, Act) to 0.9999 (Etr).

Solubilities of the inert gases were measured individually
in each animal according to the original method (26). Solubilities
of SF6, cyclopropane, halothane, ether, and acetone were 0.00090 ± 0.00015, 0.00908 ± 0.00175, 0.0583 ± 0.0137, 0.268 ± 0.0353, 1.408 ± 0.117, and 50.2 ± 7.15 (SD) ml gas, each ml blood of 1 mmHg at 40°C, respectively. The
solubility of krypton ranged from 0.0061 to 0.0118 ml gas, 100
ml blood of 1 mmHg, but there was no significant correlation
with the hematocrit (r^2 = 0.02, P = 0.33).

Ninety minutes after the induction of anesthesia, the sigh
modality and lactated Ringer infusions were discontinued and
a lactated Ringer solution containing the six inert gases was
infused at a rate of 0.1 ml·kg^-1·min^-1. After 30 min, when
equilibrium of gas exchange was reached, arterial and mixed
venous blood were drawn anaerobically into preweighed
heparinized syringes (30 ml, matched, glass, Becton-Dickinson)
simultaneously. Mixed expired gas was taken from a
temperature-controlled copper coil (OD = 4.49 cm, length = 6,400 cm) ~1 min after blood sampling, compensating for the
delay in the mixing chamber. Blood and expired-gas samples
were taken in duplicate and were analyzed immediately by MS.
Representative VA/Q distributions were then calculated on
a VAX-11780 (Digital Equipment) computer. The original
program, developed for use with MIGET employing a GC, was
modified only for subroutines that handle error terms to fit
for our system (computer display of peak area and experimental
error). In principle, the duplicate data sets were used to
average the VA/Q parameters (i.e., moments, predicted PaO2,
and so on). If residual sums of squares of the best fit exceeded
16.8, the data were not used because the chance of this
happening is only 1% (see Table 6 for degree of freedom of 6)
when residual sums of squares of the best fit are >16.8 (15).

To avoid the effect of acetone in the heparin, we used heparin
that was reported to be free of acetone (heparin sodium
infusion, Upjohn, Kalamazoo, MI) and tested a vial from each
lot before use to confirm it to be free of acetone (14).

Statistical analysis. Data were displayed as means ± SD. Multiple comparisons of cardiopulmonary indexes were
made by one-way analysis of variance (Tukey’s and Bonferroni’s tests) (6). VA/Q results were examined by multivari-
ate analysis to compare fractional blood flow to the four major
compartments among different groups (see Figs. 3 and 5,
Tables 3 and 5) because each fractional blood flow cannot be
independent from the others and, as such, univariate analy-
alysis will cause the probability of type I error to be higher for
each analysis than the selected level of significance used (17).
Significance was assigned when P < 0.05.

RESULTS

The animals regained spontaneous breathing soon
after smoke insufflation, and breathing was supported
by an Ambu-bag until they were extubated. The sheep
usually started walking within 10 min after smoke
exposure. Peak carboxyhemoglobin (HbCO) levels im-
mediately after smoke exposure were 51.4 ± 9.8% in
the mild-injury group, 64.4 ± 6.8% in the moderate-
injury group, and 73.2 ± 5.7% in the severe-injury
group (Table 1). In the time-related study groups, peak
HbCO levels ranged from 61.2 ± 11.7 to 67.2 ± 3.0%. At
6 h after exposure, HbCO levels were 20.2 ± 2.3%,
suggesting that the cardiopulmonary indexes at this
period are more or less affected by HbCO (Table 1).

Table 1. Blood carboxyhemoglobin levels

<table>
<thead>
<tr>
<th>Severity-related study</th>
<th>Peak</th>
<th>At Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.8 ± 1.4</td>
<td>5.7 ± 1.7</td>
</tr>
<tr>
<td>Mild-injury group</td>
<td>51.4 ± 9.8</td>
<td>52.2 ± 0.94</td>
</tr>
<tr>
<td>Moderate-injury group</td>
<td>64.4 ± 6.8</td>
<td>51.1 ± 1.4</td>
</tr>
<tr>
<td>Severe-injury group</td>
<td>73.2 ± 5.7</td>
<td>58.8 ± 1.3</td>
</tr>
<tr>
<td>Time-related study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.0 ± 1.3</td>
<td>5.9 ± 1.5</td>
</tr>
<tr>
<td>6-h group</td>
<td>67.2 ± 3.0</td>
<td>20.2 ± 2.3</td>
</tr>
<tr>
<td>12-h group</td>
<td>61.5 ± 8.7</td>
<td>7.4 ± 1.4</td>
</tr>
<tr>
<td>24-h group</td>
<td>64.5 ± 5.6</td>
<td>5.8 ± 0.96</td>
</tr>
<tr>
<td>72-h group</td>
<td>61.2 ± 11.7</td>
<td>5.0 ± 0.87</td>
</tr>
</tbody>
</table>

Values are means ± SD. Peak carboxyhemoglobin (HbCO) in %
was measured in venous samples at end of smoke exposure. At
measurement, HbCO was measured in arterial samples at allocated
time. HbCO levels of arterial blood are 1–3% higher than those of
simultaneously drawn venous samples.
the changes were significant in the severely injured group. However, the severe-injury group showed no significant changes compared with the control in cardiac index (P > 0.10), pulmonary arterial pressure (0.10 > P > 0.05), total peripheral resistance index (P > 0.10), or pulmonary vascular resistance index (P > 0.10).

Typical V˙A/Q patterns after various levels of smoke inhalation injury are shown in Fig. 2. Controls (Fig. 2A) had sharp peaks of ventilation and perfusion at V˙A/Q = 1, suggesting good V˙A/Q matching, whereas bimodal ventilation distribution would primarily be attributable to relatively large tidal volume setting of the ventilator. Figure 2B shows an example of mildly injured animals that had minimal hypoxemia (Pao2, of 85 Torr), but peaks of ventilation and perfusion near one were wider and true shunt (V˙A/Q = 0) was observed. Moderate injury (Fig. 2C) produced further V˙A/Q mismatching as hypoxemia became more severe with development of low V˙A/Q (0 < V˙A/Q < 0.1). In this example, 6.2% of the cardiac output perfused unventilated parts of the lung (true shunt). In the severely injured sheep (Fig. 2D), the low V˙A/Q developed further and 42% of the cardiac output perfused the low V˙A/Q, whereas there was little increase in shunt flow in this example.

V˙A/Q patterns of blood flow were bimodal distribution in almost all the animals exposed to moderate and severe injuries. We did not observe any wide unimodal blood flow distribution pattern extending over normal and low V˙A/Q compartments that would explain moderate or severe hypoxia, whereas relatively wide unimodal distribution was frequently observed in mildly hypoxic sheep, as shown in the example of Fig. 2B.

Severity-related changes in V˙A/Q values are summarized in Table 3. V˙A/Q distribution was divided into four major compartments: true shunt (V˙A/Q = 0), low V˙A/Q (0 < V˙A/Q < 0.1), normal V˙A/Q (0.1 < V˙A/Q < 10), and high V˙A/Q (V˙A/Q > 10) (Fig. 3). Fractional blood flows to the four compartments are shown as percent cardiac output. In the controls, 98.4% of the cardiac output went to the normal V˙A/Q compartment. Blood flow to the normal compartment decreased progressively as the injury became more severe, whereas flows to the shunt and low V˙A/Q compartment increased reciprocally. These changes were significant in the moderate- and severe-injury groups. The high V˙A/Q compartment showed no significant changes.

Table 3 also shows progression of the overall V˙A/Q mismatch (dispersion) expressed as the second moments of ventilation and blood flow distributions, log SDV˙, or rdispersion of perfusion (log SDQ˙) increased significantly with time as hypoxia was developed further and 42% of the cardiac output went to the disturbance of oxygenation, relationships between Pao2 and shunt flow (S in Fig. 3; %cardiac output), flow to the low V˙A/Q compartment decreased at all (P > 0.10).
compartment (L in Fig. 3) and shunt plus low V̇A/Q̇
compartment (S+L in Fig. 5) were studied with linear
regression analysis. Blood flow to L had good correlation
with measured PaO₂ (PaO₂ = 92.2 - 106.6L; r² = 0.692;

with measured PaO₂ (PaO₂ regression analysis. Blood flow to L had good correlation with measured PaO₂ (PaO₂ = 92.2 - 106.6L; r² = 0.692;)

Table 3. Severity-related changes in V̇A/Q̇ indexes at 24 h

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Mild Injury</th>
<th>Moderate Injury</th>
<th>Severe Injury</th>
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<tbody>
<tr>
<td>Shunt [%]</td>
<td>0.4 ± 0.5</td>
<td>0.5 ± 0.8</td>
<td>5.6 ± 5.5</td>
<td>11.7 ± 9.5</td>
</tr>
<tr>
<td>Low V̇A/Q̇ [%]</td>
<td>0.4 ± 0.8</td>
<td>0.7 ± 0.9</td>
<td>17.6 ± 10.6</td>
<td>36.9 ± 4.7</td>
</tr>
<tr>
<td>Normal V̇A/Q̇ [%]</td>
<td>98.4 ± 0.9</td>
<td>91.3 ± 7.2</td>
<td>76.4 ± 9.3</td>
<td>50.8 ± 9.8</td>
</tr>
<tr>
<td>High V̇A/Q̇ [%]</td>
<td>0.8 ± 0.4</td>
<td>0.5 ± 0.4</td>
<td>0.3 ± 0.4</td>
<td>0.6 ± 0.9</td>
</tr>
<tr>
<td>Mean Q̇ [L/min]</td>
<td>0.06 ± 0.21</td>
<td>0.73 ± 0.23</td>
<td>0.43 ± 0.33</td>
<td>0.23 ± 0.12</td>
</tr>
<tr>
<td>Log SDQ̇ [L/min]</td>
<td>0.76 ± 0.14</td>
<td>1.37 ± 0.42</td>
<td>1.75 ± 0.48</td>
<td>2.52 ± 0.37</td>
</tr>
<tr>
<td>Mean V̇e [L/min]</td>
<td>3.35 ± 1.41</td>
<td>2.42 ± 0.59</td>
<td>2.20 ± 0.46</td>
<td>3.70 ± 2.42</td>
</tr>
<tr>
<td>Log SDV̇e [L/min]</td>
<td>1.40 ± 0.56</td>
<td>1.14 ± 0.30</td>
<td>1.05 ± 0.29</td>
<td>1.09 ± 0.43</td>
</tr>
<tr>
<td>Vo/VT [%]</td>
<td>33.9 ± 7.0</td>
<td>39.3 ± 3.1</td>
<td>41.7 ± 4.9</td>
<td>45.2 ± 14.9</td>
</tr>
</tbody>
</table>

Values are means ± SD; V̇A/Q̇, ventilation-perfusion ratio. *Blood
flow (Q̇) to true shunt (V̇A/Q̇ = 0); + Q̇ to low V̇A/Q̇ compartment
(0<V̇A/Q̇ < 0.1); S to normal V̇A/Q̇ compartment (0.1<V̇A/Q̇ < 10);
+Q̇ to high V̇A/Q̇ compartment (10<V̇A/Q̇); a-d are expressed as
percentage of cardiac output. †Mean Q̇ (L/min) or ventilation (V̇;
l/min) on logrithmic scale (9); ‡second moment of Q̇ distribution
(logSDQ̇) or ventilation distribution (logSDV̇) (9, 23); §dead space
dead space (VD)-to-tidal volume (VT) ratio. See text for details.

P < 0.01; n = 47), whereas PaO₂ and S did not show

P < 0.01; n = 47), whereas PaO₂ and S did not show close correlation (r² = 0.228). On the other hand, S+L showed significant correlation with PaO₂ (PaO₂ = 93.9 - 94.7S+L); r² = 0.749; P < 0.01; n = 47; Fig. 5). These results suggest that development of low V̇A/Q̇ is the primary

Fig. 2. Typical ventilation-perfusion ratio (V̇A/Q̇) distributions at 24 h after exposure to various extents of smoke injury. A: control animals had sharp peaks of ventilation and perfusion at V̇A/Q̇ = 1, whereas bimodal ventilation distribution would primarily be attributable to relatively large tidal volume setting. B: peaks of ventilation and perfusion became broader and true shunt (V̇A/Q̇ = 0) was observed in a mildly injured example. C: moderate injury produced further V̇A/Q̇ mismatch with development of low V̇A/Q̇ (0 < V̇A/Q̇ < 0.1) and moderate true shunt. D: in a severely injured sheep, low V̇A/Q̇ developed further, but true shunt was minimal. Note that illustrations correspond to 4 different representative sets of data derived from a single animal in each category studied. PaO₂, arterial PO₂; PaCO₂, arterial PCO₂; V̇e, minute ventilation; CO, cardiac output; Vo/VT, dead space (VD)-to-tidal volume (VT) ratio. See text for details.
pairs), indicating that hypoxemia is adequately explained by V\(\dot{A}\)/Q\(\dot{A}\) mismatch mechanism. Cardiac output (CO in Fig. 2A) measured by thermodilution method and MIGET-derived cardiac output for the 47 sheep in this study also showed fairly good correlation [CO (inert gas) = 0.97 ± 0.75CO (measured with Swan-Ganz catheter method), \(r^2 = 0.58\), \(P < 0.01\)].

DISCUSSION

Main findings. Severity-related and time-related changes after smoke inhalation injury were very similar. Progressive hypoxemia, lower lung compliance, and higher airway resistance were noted as the severity of injury increased. The observed hypoxemia and changes in ventilatory mechanics suggest substantial changes in V\(\dot{A}\)/Q\(\dot{A}\) distribution, findings confirmed by the MIGET. The changes in V\(\dot{A}\)/Q\(\dot{A}\) distribution after smoke inhalation injury, in terms of severity-related and time-related progression, were characterized by development of low V\(\dot{A}\)/Q\(\dot{A}\) (0 < V\(\dot{A}\)/Q\(\dot{A}\) < 0.1), explaining the observed hypoxemia. Increase in true shunt (V\(\dot{A}\)/Q\(\dot{A}\) = 0) was not a consistent finding and was statistically significant only in the severely injured group (Fig. 3), although occasional individual animals in other groups developed moderate shunt flow. These results suggest that the development of hypoxemia after smoke inhalation injury was primarily attributable to increased perfusion of the low V\(\dot{A}\)/Q\(\dot{A}\).

Critique of methods. Validity and limitations of the method we employed to compensate for the atmospheric krypton were evaluated in the APPENDIX. In summary, prior correction by subtraction of partial pressure of inspire from arterial partial pressure, mixed expired gas partial pressure, and mixed venous partial pressure produced no error in normal or injured lungs of animals breathing room air (Table 6).

There might also be an argument that, even if the animals are producing ethane, measurement of the retention and excretion of the naturally produced ethane would be enough and that any methane production could be separated from ethane on a GC. However, natural ethane is not usable in this particular situation due to lack of separation from methane because both ethane and methane were detected in expired gas. Furthermore, when we say ethane was detected in expired gas, what we are really saying is that a peak appeared where ethane normally appears. We cannot be certain that this is ethane as opposed to some other

Table 4. Time-related changes in selected cardiopulmonary indexes

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Control</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_{A\dot{O}_2}), Torr</td>
<td>101 ± 6.3</td>
<td>89.7 ± 9.2</td>
<td>78.0 ± 12.6†</td>
<td>68.8 ± 9.2†</td>
<td>63.5 ± 11.6†</td>
</tr>
<tr>
<td>(P_{A\dot{O}_2}), Torr</td>
<td>38.7 ± 4.0</td>
<td>34.0 ± 2.5</td>
<td>34.2 ± 2.4</td>
<td>33.8 ± 3.3</td>
<td>32.6 ± 2.0*</td>
</tr>
<tr>
<td>(P_{A\dot{O}_2}), Torr</td>
<td>34.1 ± 4.1</td>
<td>32.2 ± 2.8</td>
<td>33.8 ± 5.1</td>
<td>33.8 ± 3.3</td>
<td>37.3 ± 9.3</td>
</tr>
<tr>
<td>(pH)</td>
<td>7.516 ± 0.023</td>
<td>7.480 ± 0.046</td>
<td>7.544 ± 0.031</td>
<td>7.524 ± 0.035</td>
<td>7.504 ± 0.073</td>
</tr>
<tr>
<td>Cardiac index, l/min</td>
<td>4.10 ± 0.72</td>
<td>4.8 ± 0.83</td>
<td>4.00 ± 0.89</td>
<td>4.00 ± 0.55</td>
<td>4.5 ± 1.40</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>157 ± 21.3</td>
<td>167 ± 31.6</td>
<td>168 ± 22.8</td>
<td>175 ± 9.4</td>
<td>166 ± 26.7</td>
</tr>
<tr>
<td>(P_{pa}, Torr)</td>
<td>14.1 ± 1.2</td>
<td>14.9 ± 4.8</td>
<td>18.5 ± 8.1</td>
<td>18.4 ± 4.7</td>
<td>23.4 ± 2.7*</td>
</tr>
<tr>
<td>(P_{\text{peak}}, \text{cmH}_2\text{O})</td>
<td>4.5 ± 1.1</td>
<td>5.9 ± 0.8</td>
<td>8.6 ± 2.1</td>
<td>9.3 ± 3.6†</td>
<td>13.8 ± 3.6†</td>
</tr>
<tr>
<td>Cst, ml/cmH(_2)O</td>
<td>180 ± 49</td>
<td>138 ± 30</td>
<td>138 ± 55</td>
<td>110 ± 27</td>
<td>75 ± 22†</td>
</tr>
<tr>
<td>Rcl, cmH(_2)O·s·l(^{-1})</td>
<td>10.3 ± 2.3</td>
<td>12.4 ± 1.8</td>
<td>19.1 ± 10.5</td>
<td>19.4 ± 10.5</td>
<td>37.2 ± 14.0†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Only significant difference from control is marked, although Bonferroni test was made for all possible pairs of means, i.e., for 10 comparisons. * \(P < 0.05\), † \(P < 0.01\), significantly different from control (1-way ANOVA).
hydrocarbon, and it may indeed be more than one gas, although we could avoid this problem partly by using MS as the detector. If this were the case, then with different gases having different solubilities, we would have a very complex situation to understand the behavior of the "ethane" peaks. All of these uncertainties are to be avoided by using krypton even if compensation for atmospheric krypton is necessary.

Pathophysiology. In reports of other acute respiratory insufficiencies, flows to the true shunt and to the low V˙A/Q make variable contributions to hypoxemia, reflecting the specific pathophysiology of the disease (27). Increased true shunt occurs in oleic acid-induced lung edema with little or no increase in the low V˙A/Q (5, 18, 24). Schone et al. (18) reported that oleic acid-injured dogs developed significant shunt at postinjury day 1, with resolution of the shunt by day 7, whereas animals that developed supplicative bronchopneumonia after repeated bronchial lavage showed low V˙A/Q. In the present study, inflammatory changes were observed in all the animals, and every animal with smoke inhalation showed a certain amount of perfusion to the low V˙A/Q, although some were <5% of flow. Gas emboli produce hypoxemia mainly attributable to low V˙A/Q (10), whereas other acute injuries show combinations of shunt and low V˙A/Q.

Changes in physiological dead space were somewhat similar to those of the shunt; some animals showed substantial increase in dead space and PACO₂, but this was not a consistent finding. Robinson et al. (16) have reported increased high V˙A/Q and dead space ventilation soon after smoke exposure, and Stollery et al. (22) suggested that increased dead space ventilation was responsible for respiratory failure at a later stage in a small subset of burn patients with inhalation injury. As Nunn (13) has pointed out, physiological interpretation at the higher end of the V˙A/Q scale is not as clear as that at the lower end. The high V˙A/Q cannot be evaluated without consideration of peak inspiratory pressure and PACO₂, because the measured perfusion of the high V˙A/Q is influenced by the tidal volume setting of the ventilator and such perfusion can occur even in control animals (Fig. 2). Peak inspiratory pressure was significantly elevated in the severely injured group at 24 h (Table 2) and in moderately injured animals at 24 and 72 h (Table 4), in many cases, with hypercapnia. In the present study, even though mean values did not change significantly, increased dead space and high V˙A/Q were observed in some of the moderately and severely injured animals and were associated with hypoxemia. These findings suggest that extensive small-airway occlusion caused by smoke inhalation diverted the inspired gas to alveoli, with good compliance, leading to the increased high V˙A/Q and dead space ventilation. The findings could also be interpreted that the increased airway resistance facilitated both gas trapping and lung hyperinflation, thereby resulting in the development of regions with high V˙A/Q and increased dead space.

Development of the low V˙A/Q, and especially of very low V˙A/Q (V˙A/Q ≤ 0.01; Fig. 2), characterized both severity-related and time-related V˙A/Q alterations after smoke inhalation injury. Such deviation of V˙A/Q from 1 (normal) to 0.01 (low) can be caused by either an increase in perfusion or a decrease in ventilation or probably by both. The V˙A/Q patterns suggest a disturbance of ventilation, such as airway constriction, obstruction by secretions, pulmonary edema, or some other cause of partial atelectasis, because a 100-fold increase in perfusion to a lung unit with normal V˙A/Q seems physiologically unlikely, if not impossible. This may be rephrased that it is unlikely that after moderate or severe injury 20–40% of the cardiac output goes to lung units that were virtually not perfused in control conditions. This interpretation of airway impair-
ment is consistent with histological findings (8, 12, 20; Fig. 6). Such low $V_{A}/Q$ is very unstable at higher inspiratory oxygen concentration ($F_{I O_{2}}$) and is easily converted to true shunt, which should be noted in the respiratory management of patients with smoke inhalation injury (4, 19).

A previous study on $V_{A}/Q$ changes after smoke inhalation reported by Robinson et al. (16) was consistent with our results regarding the mechanism of hypoxemia. They measured $V_{A}/Q$ distribution in 5 patients with evidence of smoke inhalation (association of skin burn was not clear) at 24, 48, and 72 h after injury and in 10 rabbits (5 controls and 5 smoke inhalation) at 6 h after smoke exposure. They reported that early alterations of ventilation and perfusion resulted from increased high $V_{A}/Q$ and dead space ventilation, whereas late alterations were characterized by significantly increased perfusion of low $V_{A}/Q$ compartments and notably absent true intrapulmonary shunting. They did not describe very low $V_{A}/Q$ ($V_{A}/Q < 0.01$), which would be attributable to high $F_{I O_{2}}$ ($0.51 \pm 0.07$ at 24 h) employed to maintain $P_{A O_{2}}$ in the patients, although use of positive end-expiratory pressure was not clearly stated. They observed that predicted $P_{O_{2}}$ values were systematically higher than measured ones in clinical cases and suggested increased postpulmonary shunt resulting from increased bronchial blood flow as the mechanism of such discrepancy. However, their speculation was based primarily on four measurements on day 1. They observed predicted $P_{O_{2}}$ was higher than measured $P_{O_{2}}$ in three of four cases, the probability of which would be 32%.

Fig. 6. Photomicrograph of a sheep lung 24 h after mild smoke inhalation injury. Sloughed respiratory epithelial cells and inflammatory cells are occluding an airway. Note early vascular congestion and septal thickening (S) extending from blocked airway. Alveolar spaces are essentially normal. Hematoxylin and eosin stain, $\times 1,020$ = print magnification, $\times 325$ = original magnification.

Table 6. Comparison between prior correction and correct kernel in 3 conditions of sheep data

<table>
<thead>
<tr>
<th></th>
<th>Sheep 204, Normal ($F_{I O_{2}} = 0.21$)</th>
<th>Sheep 141, Injured ($F_{I O_{2}} = 0.21$)</th>
<th>Sheep 171, Injured ($F_{I O_{2}} = 1.0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{c}$ (krypton)</td>
<td>0.04658</td>
<td>0.35188</td>
<td>0.44439</td>
</tr>
<tr>
<td>$E_{c}$ (krypton)</td>
<td>0.1779</td>
<td>0.01409</td>
<td>0.01836</td>
</tr>
<tr>
<td>RSS</td>
<td>0.0696</td>
<td>0.106</td>
<td>0.0178</td>
</tr>
<tr>
<td>Log $SD_{V}$</td>
<td>1.96</td>
<td>2.59</td>
<td>1.21</td>
</tr>
<tr>
<td>Log $SD_{V}$</td>
<td>0.78</td>
<td>0.74</td>
<td>0.83</td>
</tr>
<tr>
<td>Shunt (%)</td>
<td>0.0</td>
<td>0.1</td>
<td>37.9</td>
</tr>
<tr>
<td>$Q$ in low $V_{A}/Q$, %*</td>
<td>1.3</td>
<td>39.9</td>
<td>39.9</td>
</tr>
<tr>
<td>$V$ in high $V_{A}/Q$, %†</td>
<td>8.4</td>
<td>4.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Dead space, %</td>
<td>13.0</td>
<td>45.1</td>
<td>53.5</td>
</tr>
<tr>
<td>Predicted $P_{A O_{2}}$, Torr</td>
<td>97.0</td>
<td>49.6</td>
<td>83.6</td>
</tr>
<tr>
<td>$P_{I}/P_{V}$</td>
<td>0.0056</td>
<td>0.0075</td>
<td>0.062‡</td>
</tr>
</tbody>
</table>

$R_{c}$, corrected retention; $R_{c}$ (Eq. A4), $R_{c}$ according to Eq. A4 (prior correction); $R_{c}$ (Eq. A5), $R_{c}$ according to Eq. A5 (correct kernel); $E_{c}$, corrected excretion; $E_{c}$ (Eq. A4), $E_{c}$ according to Eq. A4 (prior correction); $E_{c}$ (Eq. A5), $E_{c}$ according to Eq. A5 (correct kernel); $R_{c}$ (krypton); $R_{c}$ (krypton), $E_{c}$ (krypton); $E_{c}$ (krypton); RSS, residual sum of squares of best fit to data (15); $P_{I}$, inspired partial pressure; $P_{V}$, mixed venous partial pressure; *fractional $Q$ to low $V_{A}/Q$ ($0 < V_{A}/Q < 0.1$) compartment; †fractional $V$ to high $V_{A}/Q$ ($V_{A}/Q > 10$) compartment; ‡way $O_{2}$ is produced from air by suppliers of 100% $O_{2}$ concentrates krypton severalfold, as these data show.
(4C1 + 4C0)/2^4 = (4 + 1)/16 = 0.31). In this study, we did not see a statistically significant difference between predicted and measured PaO2, even with paired t-test (P = 0.063). Abdi et al. (1) measured bronchial blood flow in a sheep model of smoke inhalation and reported that bronchial circulation was 1% or less of cardiac output in normal condition but that it approached 5% of cardiac output after inhalation. Bronchial arterial occlusion in that sheep model resulted in reduced lung lymph flow and lung edema after inhalation injury, but oxygenation (PaO2/FIO2) was not significantly different; in fact, those with occluded bronchial artery had a tendency to have a lower PaO2/FIO2 value. Therefore, it would not be necessary to introduce bronchial blood flow in the pathogenesis of hypoxemia after inhalation injury, whereas the possibility of diffusion limitation to oxygen or an increase of intrapulmonary oxygen consumption cannot totally be ignored. However, in this study hypoxemia was adequately explained by VA/Q mismatch mechanism.

In conclusion, VA/Q alterations after smoke inhalation injury were characterized by the development of low VA/Q. Both severity-related and time-related progressive hypoxemia after inhalation of smoke were attributable to this change in the distribution of pulmonary ventilation and perfusion; increase in true shunt in that sheep model resulted in reduced lung flow in a sheep model of smoke inhalation and reported that bronchial blood flow was 1% or less of cardiac output in normal condition but that it approached 5% of cardiac output after inhalation. Bronchial arterial occlusion in that sheep model resulted in reduced lung lymph flow and lung edema after inhalation injury, but oxygenation (PaO2/FIO2) was not significantly different; in fact, those with occluded bronchial artery had a tendency to have a lower PaO2/FIO2 value. Therefore, it would not be necessary to introduce bronchial blood flow in the pathogenesis of hypoxemia after inhalation injury, whereas the possibility of diffusion limitation to oxygen or an increase of intrapulmonary oxygen consumption cannot totally be ignored. However, in this study hypoxemia was adequately explained by VA/Q mismatch mechanism. As Table 6 shows, prior correction by subtraction of PaO2 from PaO2, mixed expired gas partial pressure (PiO2), and mixed venous partial pressure (Pi) allow use of the standard MIGET program by using the kernel retention (R) = excretion (E) = λ/(λ + VA/Q), where λ is the partition coefficient of the gas, or should the kernel be modified to reflect PiO2 (krypton) > 0, thus using measured PaO2, PiO2, and Pi without prior subtraction?

The correct kernel equation for PiO2 (krypton) > 0 is

\[ R = \frac{E}{\lambda + \frac{\dot{V}_i}{\dot{Q}}} \] (A1)

where \( \dot{V}_i \) is the ventilation of krypton in the inspirate. This comes from mass balance considerations

\[ \dot{V}_i \cdot Pi - VA \cdot PA = \lambda Q (PA - PV) \]

where PA is alveolar pressure and Q is blood flow. If one uses the closely related kernel

\[ R = \frac{E}{\lambda + \frac{\dot{V}_A/Q}{\dot{Q}}} \] (2A)

and then subtracts Pi from PaO2, PiO2, and PiO2 to enable use of the usual MIGET algorithm, this correction would be algebraically perfect

\[ R_e = \frac{Pa - Pi}{PV - Pi} \] (3A)

\[ = \frac{Pa/PV - Pi/PV}{1 - Pi/PV} \] (3A)

\[ = \left( \frac{\lambda + \frac{\dot{V}_i}{\dot{Q}} \cdot (Pi/PV)}{\lambda + \frac{\dot{V}_A/Q}} \right) \left( 1 - (Pi/PV) \right) \]

\[ = \frac{\lambda + (\dot{V}_i/Q) \cdot (Pi/PV) - \lambda (Pi/PV) - (\dot{V}_A/Q) (Pi/PV)}{\lambda + \dot{V}_A/Q} \] (4A)

where \( R_e \) is corrected retention and use of Eq. 3A with the standard MIGET algorithm would be accurate as a result. Now, the remaining question is, How much error is caused by use of algorithm (Eq. 3A) when the proper consideration of inspired krypton requires Eq. A1, not Eq. A2?

Here

\[ 3A_e = \frac{Pa - Pi}{PV - Pi} \]

\[ = \left( \frac{\lambda + (\dot{V}_i/Q) \cdot (Pi/PV)}{\lambda + \dot{V}_A/Q} \right) \left( 1 - (Pi/PV) \right) \]

\[ = \frac{\lambda + (\dot{V}_i/Q) \cdot (Pi/PV) - \lambda (Pi/PV) - (\dot{V}_A/Q) (Pi/PV)}{\lambda + \dot{V}_A/Q} \] (5A)

\[ = \left( \frac{\lambda + (\dot{V}_i/Q) - (\dot{V}_A/Q) (Pi/PV)}{\lambda + \dot{V}_A/Q} \right) \left( 1 - (Pi/PV) \right) \]

\[ = \frac{\lambda + [\dot{V}_i/Q - (\dot{V}_A/Q) (Pi/PV)] (Pi/PV)}{\lambda + \dot{V}_A/Q} \] (5B)

We answered this question in three examples of data collected in the present study: 1) normal lungs, FIO2 = 0.21; 2) injured lungs, FIO2 = 0.21; and 3) injured lungs, FIO2 = 1.00. To do this, we calculated Vc from either Eq. A1 or Eq. A2. VA/Q compartment by VA/Q compartment, with knowledge of \( \dot{V}_i/Q \) and VA/Q for each compartment from the oxygen and carbon dioxide calculation parts of the MIGET program, as well as measured values of PiO2/PV. The results are summarized in Table 6. As Table 6 shows, prior correction by subtraction of PiO2 from PaO2, PiO2, and PiO2 produces no error in normal or injured lungs of animals breathing room air. With animals breathing 100% oxygen, there is a minor perturbation of the results (shown in sheep 17), but the effects are clinically insignificant and are less than the natural variability in data due to technical errors or minor alterations in physiological state over time.

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REFERENCES


