Alterations in regional ventilation, perfusion, and shunt after smoke inhalation measured by PET

DONNA BETH WILLEY-COURAND, R. SCOTT HARRIS, GAETANO G. GALLETTI, C. A. HALES, ALAN FISCHMAN, and JOSE G. VENEGAS. Alterations in regional ventilation, perfusion, and shunt after smoke inhalation injury were evaluated through the use of positron emission tomography. Five lambs were imaged before and 1, 2, and 4 h after receiving 100 breaths of cotton smoke. Utilizing a recently developed model of $^{13}$N tracer kinetics (3), we evaluated changes in ventilation, perfusion, shunt, and regional gas content in nondependent, middle, and dependent lung zones. The data demonstrated a progressive development of regional shunt in dependent (dorsal) regions in which perfusion remained the highest throughout the study. These findings, together with decreasing regional ventilation and fractional gas content in the dependent regions, correlated with decreasing arterial PaO$_2$ values over the course of the study. A negative correlation between regional shunt fraction and regional gas content in dependent and middle regions suggests that shunt was caused by progressive alveolar derecruitment or flooding. 

Deaths secondary to smoke inhalation may occur acutely at the scene of the fire or days later as acute respiratory distress syndrome with development of complicating pneumonia (7, 8). Alterations in diffusion capacity, ventilation ($V_A$), and perfusion ($Q$) have been considered as explanations for the progressive hypoxemia seen in the most seriously injured (12, 15). Studies of extravascular lung water accumulation have suggested that increases in interstitial fluid volume in the early hours postinjury may result from dilutional hypoproteinemia after fluid resuscitation or later in the clinical course as burn edema begins to mobilize (11, 14, 16, 20).

Studies of delay have allowed only global estimates of alterations in $V_A$ and $Q$. Delayed clearance after intravenous injection of $^{133}$Xe in the early postinjury period have been shown to correlate with later development of more extensive parenchymal disease (12, 15). Abnormalities in $^{133}$Xe clearance are thought to be related to underperfusion of well-ventilated space or from impairment of $V_A$ to well-perfused regions. Pulmonary function tests, revealing changes in both large and small airway resistance to gas flow with maintenance of relatively normal lung volumes, seem to support the latter explanation (15). Analysis of $V_A/Q$ using multiple inert gas elimination technique (MIGET) by Robinson et al. (17) demonstrated that in the first 24 h after smoke inhalation the development of shunt and low $V_A/Q$ regions was negligible, but there was increased $V_A$ to poorly perfused (high $V_A/Q$) regions. By 72 h postinjury when hypoxemia was detected, there was a marked increase in blood flow to low $V_A/Q$ regions, yet there was still negligible true shunt detected. Shimazu et al. (19), however, demonstrated that both severity-related and time-related hypoxemia resulted from the development of low $V_A/Q$ regions and, less consistently, from shunt. Thus the question of whether early $V_A/Q$ mismatch results from alterations in $V_A$ or $Q$ remains.

Positron emission tomography (PET) analysis of $V_A/Q$ is different from MIGET in that it allows for the determination of regional rather than global alterations in lung function. By measuring the distribution of the positron-emitting radioisotope nitrogen-13 ($^{13}$NN) activity after bolus injection during apnea, an estimation of regional lung Q ($Q_R$) as well as an assessment of local shunt fraction ($Q_S/Q_R$) can be made (see accompanying paper, Ref. 3). With the resumption of $V_A$, the rate of radiolabeled tracer removal can be corrected for regional shunt to estimate regional $V_A$. Additionally, changes in regional gas content can be assessed by analyzing changes in regional lung density in PET transmission scans. Thus PET allows for a quantitative assessment of the distribution and extent of injury and the corresponding alterations in physiology resulting from smoke inhalation. This study used PET to characterize the contribution of alterations in...
\( V_a, Q_R, \) and \( Qs/Q_R \) to the development of hypoxemia in the early hours after smoke inhalation.

**MATERIALS AND METHODS**

**Animal Preparation**

The study was approved by the Massachusetts General Hospital Subcommittee on Research Animal Care. Five Hampshire lambs weighing 11.5–14.8 kg (mean 13 ± 1.4 kg) were anesthetized with sodium pentothal (250–300 mg bolus) and orally intubated with a 7.5-mm ID endotracheal tube. They were mechanically ventilated with inspired oxygen fraction \((F_{I_{02}})\) of 0.50, inhalation-to-exhalation ratio of 1:2, positive end-expiratory pressure of 5 cmH\(_2\)O, rate of 10 breaths/min, and tidal volume of 18 ± 2 ml/kg adjusted to establish a baseline arterial \( PCO_2 \) > 35 < 45 Torr (Harvard Apparatus, Millis, MA). A Swan-Ganz catheter was placed in the left femoral vein (Edwards Swan Ganz-CCO/SvO\(_2\) 8.0 Fr; Baxter Healthcare, Irvine, CA) to provide continuous measurements of cardiac output and pulmonary artery pressure. The distal port of the catheter was used for delivery of intravenous fluid (0.9 NS) at a maintenance rate for the duration of the study. The right femoral artery was cannulated for pressure monitoring and collection of arterial blood gas samples. Hemoglobin profiles and blood-gas analysis were measured by using the IL482 co-oximeter system and the 1620 pH/blood gas analyzer (Instrumentation Laboratory, Lexington, MA). Anesthesia was maintained for the duration of the study by use of intravenous sodium pentothal (500 mg/h) via a right femoral vein catheter. Animals were paralyzed with pancuronium (4 mg) before the start of inhalation. Physiological parameters marking the start of inhalation were determined for eucapnia by using a modified anesthesia breathing circuit and ventilator (Fig. 1). Immediately after the smoke exposure, arterial blood gas and carboxyhemoglobin levels were measured. Collection of PET images and physiological parameters was then conducted 1, 2, and 4 h after the smoke inhalation exposure. At the conclusion of the study, the animal was euthanized with an intravenous injection of saturated potassium chloride.

**Experimental Setup**

The experimental apparatus included a single-ring PET camera, polymerase chain reaction 1, a mechanical ventilator, a rebreathing circuit, and an infusion system described in detail previously (2, 22). \( ^{13}NN \) (half life of ~9 min) was dissolved in previously degassed saline (0.1–0.2 μCi/ml). A sample of the \( ^{13}NN \)-labeled saline was collected to assess its specific activity before intravenous injection.

**Imaging Protocol**

A rapid-transmission scan was performed, and animal position was adjusted so as to maximize the cross-sectional area of the lungs in the imaging plane. This resulted in a transverse image plane at the apex of the heart just above the diaphragm. After optimization of animal position in the camera, a high-quality transmission scan was acquired to be used for correction of gamma ray energy attenuation by body tissues and supporting structures as well as to calculate regional gas content. Image acquisition during the transmission scan was conducted for 15 min during breathing and was gated by using an electrical signal from the mechanical ventilator marking the start of inhalation. Physiological parameters measured included heart rate, systemic and pulmonary arterial pressures, cardiac output (\( Q_T \)), and airway opening pressure. Measurements of pH, gas tensions, hemoglobin, carboxyhemoglobin, and oxygen saturation values were obtained from arterial blood samples. These parameters were measured before each PET scan as described below.

**VA Emission Scan Series**

Starting with a tracer-free lung, mechanical \( V_a \) was interrupted at end exhalation, and a bolus of \( ^{13}NN \)-labeled saline solution was infused immediately into the superior vena cava. Bolus volume was selected on the basis of the specific activity of the infusate to produce images with consistent number of counts per voxel. Simultaneously with the start of infusion, collection of six consecutive images was initiated, each with a scanning time of 10 s. At the end of the sixth image, mechanical \( V_a \) was resumed, and four additional consecutive images, each with a scanning time of 30 s, were collected as the tracer washed out from the lungs. Collection of these emission scans was not gated by the ventilator. A sample of the infusate was collected to assess its specific activity.

After collection of a \( V_a/Q \) emission scan series in control conditions, the sheep was exposed to inhalation of 100 breaths of cotton smoke generated by using a modified bee smoker (Bee Keeper, Woburn MA). The smoke was delivered at the same \( V_r \) and frequency (10 breaths/min) as previously determined for eucapnea by using a modified anesthesia breathing circuit and ventilator (Fig. 1). Immediately after the smoke exposure, arterial blood gas and carboxyhemoglobin levels were measured. Collection of PET images and physiological parameters was then conducted 1, 2, and 4 h after the smoke inhalation exposure. At the conclusion of the study, the animal was euthanized with an intravenous injection of saturated potassium chloride.

**Data Analysis**

**Image processing**. PET data were corrected for camera sensitivity and for tissue attenuation. The gating scheme yielded two images corresponding to the first and second half of the breathing cycle. Given that inspiratory time of the ventilator was set at 30% of the breathing cycle, the first gated image captured all inspiration and the initial rapid phase of exhalation, and the second gated image captured the slower last phase of exhalation in which lung volume is close to functional residual capacity. This second gated transmission scan was used for attenuation correction of the emission scans collected during apnea, whereas the sum of the two gated transmission scans was used for attenuation correction of the images collected ungated during breathing in the area of the lungs in the imaging plane. This resulted in a transverse image plane at the apex of the heart just above the diaphragm.
washout. Image reconstruction was then performed with a convolution back-projection algorithm by using a Hanning filter to yield an effective spatial resolution of 10 mm determined from the width at one-half height of a point source image. Resulting images consisted of an interpolated matrix of 159 \times 159 \text{ voxels} of dimension 2 \times 2 \times 10 \text{ mm}.

Lung field masks were defined from the transmission scans taken in control conditions and 1 h after exposure to smoke. The masks were divided into three regions of interest (ROIs) [nondependent (ND), middle (M), and dependent (D)] each of approximately equal number of voxels. The average volume of imaged lung corresponded to 104 ml or \(\sim 12\%\) of a lung volume for a sheep of this size. Tracer kinetics data was obtained for each ROI from the respective average regional activity per voxel for each of the sequential PET images (Fig. 2).

After bolus injection, \(^{13}\text{NN}\) was transported through the pulmonary vascular bed while the animal was held in apnea. Because of the preferential solubility of \(^{13}\text{NN}\) in gas relative to blood, radioactive gas readily diffused into gas-filled alveoli and remained there until \(V_{\text{A}}\) was reinstituted. Because \(^{13}\text{NN}\) did not have a preferential solubility in nonaerated alveoli, a peak activity was reached soon after injection but then diminished during apnea, reflecting intrapulmonary shunt.

A nonlinear model described in detail in the accompanying paper (3) was used to analyze the tracer kinetics data of each ROI. Briefly, the model assumed that each ROI was made of a nonaerated compartment (in which blood flow was pure shunt) and an aerated and ventilated compartment. The model was implemented in the SIMULINK software package (The MathWorks, Natick, MA) and fitted to the regional kinetics data of each ROI. A nonlinear model described in detail in the accompanying paper (3) was used to analyze the tracer kinetics data of each ROI. Briefly, the model assumed that each ROI was made of a nonaerated compartment (in which blood flow was pure shunt) and an aerated and ventilated compartment. The model was implemented in the SIMULINK software package (The MathWorks, Natick, MA) and fitted to the regional kinetics data of each ROI.

Fig. 2. Tracer kinetics curves for the dependent (D), middle (M), and nondependent (ND) regions of interest (ROIs) at control conditions (A) and after 4 h of smoke inhalation exposure (B). Positron emission tomographic (PET) images correspond to a transmission scan with voxel values proportional to tissue density (left) and 2 emission scans taken at the point of peak tracer concentration (middle) and at the end of the apneic period (right). In the hot color scale of these scans, white represents the highest density or tracer activity (\(-160\%\) of the mean represented by red) and black represents zero activity. Note the similarity of the 2 emission scans in control conditions and the disappearance of tracer from the D region 4 h after smoke inhalation exposure, consistent with the development of regional shunt and the increase in tissue density in that region.
tracer kinetics data by use of a nonlinear identification tool-
kit (Cambridge Control, Cambridge, UK) modified to include
the time averaging inherent to PET imaging. This analysis
yielded estimates of regional Q fraction relative to cardiac
output (Qo/Qt), regional shunt fraction (Qs/Qo), and
regional specific VA (sVA) of the aerated compartment for
each ROI (Fig. 2). In all animals studied, activity in ND
regions stayed constant or slightly increased during breath
hold. Shunt in these ND regions was thus presumed to be
negligible. In several animals, a semilog plot of regional
activity vs. time clearly demonstrated departure from a
single exponential washout model. For those cases, the
model was modified to include two independent subcom-
partments with different specific VA rates, sVA1 for the
"fast" subcompartment and sVA2 for the "slow" subcom-
partment. An effective regional index of sVA in those
regions was calculated as a Q-weighted average of the two
subcompartments sVA

\[
sVA = \frac{QsV_1 + QsV_2}{Q_1 + Q_2}
\]

where sVA1, sVA2, Q1, and Q2 are the regional sVA and Q of
the two intraregional subcompartments.

Regional gas content fraction (Fgas) for each condition was
estimated from the regional value of the corresponding trans-
mision scan that was proportional to regional tissue density
(\(\varphi_{\text{lung}}\)). By delineating a region of interest over the heart with
assumed density \(\varphi_{\text{heart}} = 1\), Fgas was calculated for each
voxel as

\[
F_{\text{gas}} = 1 - \frac{\varphi_{\text{lung}}}{\varphi_{\text{heart}}}
\]

Calculations. Average regional Q per voxel relative to total
Q of the imaged lung slice per voxel, Qo/imT, was calculated
from the regional Qo/Qt parameter identified by the model as

\[
Q_o/imT = \left[ \frac{Q_s}{Q_T} \right] n_i
\]

where \(i = 1, 2, 3\) for the ND, M, and D ROIs, respectively, and
\(n\) represents the number of voxels in the ith ROI.

The fraction of pulmonary blood flow to shunting regions
relative to the total blood flow to the imaged lung, Qs/imT, was
calculated as

\[
\frac{Q_s}{Q_T} = \frac{\sum (Qs_i - Qs_0)}{\sum (Qs_i - Qs_0)}
\]

where \(Qs_i - Qs_0\) is the regional shunt fraction of each ROI and
\(Qs_i - Qs_0\) is the fraction of regional blood flow relative to cardiac
output.

Regional VA of aerated compartments relative to the total
VA of the imaged lung, VA, for each ROI was

\[
VA_i = \frac{(n \times sVA_i \times F_{\text{gas}})}{\sum (n \times sVA_i \times F_{\text{gas}})}
\]

Finally, the relative VA-Q ratio, VA/Q, for each ROI was
calculated as

\[
\left( \frac{VA}{Q} \right)_i = \left( \frac{VA}{Q} \right)_{imT}
\]

Statistical analysis. Data were analyzed by using repeated-
measures ANOVA techniques. Dunnett’s multiple-compari-
sion procedure was used to compare the difference between
the three time points after smoke inhalation and the baseline
control if there was significant overall difference among the
time points. Mixed-effects regression models were used to
study the relationship between model parameters and
arterial PO2 (PaO2). All statistical analyses were performed by
using SAS (Cary, NC) with significance set at the 0.05 level.

RESULTS

Table 1 shows a summary of physiological variables
measured during the study. Mean carboxyhemoglobin
(COHgb) was 81% immediately after exposure to
smoke. Because inspired gas had FIO2 of 0.50 during
the remainder of the study, COHgb levels consistently
declined, reaching near-normal levels by 4 h. Mean
PaO2 was 63 Torr after smoke exposure. Despite a
relative improvement after 1 h, PaO2 significantly
decreased at 2 and 4 h compared with preexposure. Mean
heart rate declined during the study, reaching signifi-
cance at 4 h. Systolic and diastolic systemic pressures
had significant declines at 1, 2, and 4 h. Qt remained
stable throughout the study. Mean pulmonary artery
pressure increased (reaching significance after 4 h),

<table>
<thead>
<tr>
<th>Table 1. Mean physiological parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANOVA Overall p</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>HR, beats/min</td>
</tr>
<tr>
<td>Qt, l/min</td>
</tr>
<tr>
<td>SBP, mmHg</td>
</tr>
<tr>
<td>DBP, mmHg</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
</tr>
<tr>
<td>Pao, cmH2O</td>
</tr>
<tr>
<td>COHgb, %</td>
</tr>
<tr>
<td>PaO2, Torr</td>
</tr>
<tr>
<td>PVR, dyn·s·cm⁻¹</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; Qt, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; MPAP, mean
pulmonary arterial pressure; Pao, peak airway pressure; COHgb, % carboxyhemoglobin; PaO2, oxygen tension; PVR, pulmonary vascular
resistance. Dunnett adjusted P values: *P < 0.05, †P < 0.005 compared with control values.

J Appl Physiol • VOL 90 • SEPTEMBER 2002 • www.jap.org
whereas pulmonary vascular resistance steadily increased and at 4 h reached levels significantly higher than preexposure levels. Airway opening pressure progressively increased throughout the study.

Average results of regional PET-derived parameters are presented in Fig. 3 and Table 2. There was a vertical gradient in $Q_{R/imT}$ favoring the D regions at all time points in the study. After smoke inhalation, $Q_{R/imT}$ of the ND region was relatively unchanged. In D regions, $Q_{R/imT}$ slightly declined in the hours after injury, whereas $Q_{R/imT}$ gradually increased in the M region. These changes did not reach significance by ANOVA. Thus there was only a minor redistribution of $Q$ from D regions to M regions over the course of the study.

$V_A$ of D regions decreased throughout the study, reaching statistically significant levels after 2 h. $V_A/Q_R$ gradually increased in ND regions, whereas it steadily decreased in D regions reaching significance after 4 h.

Shunt, represented by a gradual drop in regional activity during the breath-hold period, was not detected in ND regions throughout the study. $Q_S/Q_R$ progressively increased in D regions after smoke exposure and reached statistical significance by 2 h ($P < 0.05$) and 4 h ($P < 0.005$). Because of the large $Q_{R/imT}$ of the D regions and the progressive increase in $Q_S/Q_R$ of those regions, the fraction of shunting imaged

Table 2. Regional PET-derived data at control and 1, 2, and 4 h after smoke inhalation exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ROI</th>
<th>Control SE</th>
<th>1 Hour</th>
<th>2 Hours</th>
<th>4 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{R/imT}$</td>
<td>ND</td>
<td>0.33 ± 0.01</td>
<td>0.34 ± 0.05</td>
<td>0.36 ± 0.04</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.86 ± 0.02</td>
<td>0.93 ± 0.05</td>
<td>0.94 ± 0.07</td>
<td>1.06 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.71 ± 0.02</td>
<td>1.58 ± 0.06</td>
<td>1.54 ± 0.08</td>
<td>1.45 ± 0.08</td>
</tr>
<tr>
<td>$Q_S/Q_R$</td>
<td>ND</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.06 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>0.05 ± 0.02</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.10 ± 0.01</td>
<td>0.16 ± 0.02</td>
<td>0.35 ± 0.06</td>
<td>0.47 ± 0.06</td>
</tr>
<tr>
<td>$V_A$</td>
<td>ND</td>
<td>0.51 ± 0.03</td>
<td>0.46 ± 0.03</td>
<td>0.67 ± 0.07</td>
<td>0.98 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>1.10 ± 0.04</td>
<td>1.23 ± 0.05</td>
<td>1.37 ± 0.09</td>
<td>1.32 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.38 ± 0.05</td>
<td>1.24 ± 0.06</td>
<td>0.97 ± 0.11</td>
<td>0.76 ± 0.12</td>
</tr>
<tr>
<td>$V_A/Q_S$</td>
<td>ND</td>
<td>1.59 ± 0.10</td>
<td>1.56 ± 0.14</td>
<td>1.95 ± 0.18</td>
<td>2.30 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>1.27 ± 0.03</td>
<td>1.36 ± 0.05</td>
<td>1.50 ± 0.10</td>
<td>1.29 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.80 ± 0.03</td>
<td>0.79 ± 0.04</td>
<td>0.62 ± 0.05</td>
<td>0.49 ± 0.07</td>
</tr>
<tr>
<td>$F_{gas}$</td>
<td>ND</td>
<td>0.65 ± 0.01</td>
<td>0.70 ± 0.01</td>
<td>0.62 ± 0.02</td>
<td>0.67 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.58 ± 0.02</td>
<td>0.64 ± 0.01</td>
<td>0.55 ± 0.03</td>
<td>0.52 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.45 ± 0.02</td>
<td>0.45 ± 0.02</td>
<td>0.37 ± 0.03</td>
<td>0.26 ± 0.03</td>
</tr>
<tr>
<td>$Q_{S/imT}$</td>
<td>ND</td>
<td>0.08 ± 0.01</td>
<td>0.11 ± 0.01</td>
<td>0.22 ± 0.04</td>
<td>0.28 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE. $Q_{R/imT}$, relative regional perfusion; $Q_S/Q_R$, regional shunt fraction; $V_A$, relative effective ventilation; $V_A/Q_S$, relative regional $V_A/Q$ ratio; $F_{gas}$, regional fraction of gas content; $Q_{S/imT}$, fraction of shunt flow relative to total flow measured in imaged lung. Pairwise comparisons with Dunnett adjustments: *$P < 0.05$, †$P < 0.005$ for change vs. control.
blood flow, $Q_{S/imT}$, increased after each time interval reaching significance by 4 h. There was also a vertical dependence of $F_{gas}$ favoring ND regions and decreasing toward D regions. Such a gradient increased with time after smoke exposure as $F_{gas}$ significantly decreased in D regions from 0.45 in control to 0.26 after 4 h of exposure to smoke. A plot between regional shunt fraction and $F_{gas}$, including all animals at all data points in the study for M and D regions (Fig. 4), showed a negative correlation ($R = -0.86$) between these PET-derived parameters.

A negative correlation was detected between $P_{aO_2}$ and $V_{A}/Q_{R}$ for ND regions and a positive correlation between the same parameters for D regions (Table 3). In D regions, changes in $V_{A}$, $Q_{R/imT}$, $Q_{S}/Q_{R}$, and $F_{gas}$ correlated most strongly with the decline in $P_{aO_2}$ seen in the hours after inhalation exposure (Table 3). A substantial negative correlation was found between $P_{aO_2}$ and $Q_{S}/Q_{R}$ in D regions and overall shunt fraction $Q_{S/imT}$.

**DISCUSSION**

More than two million Americans suffer from thermal injury each year. Of the nearly 8,000 associated fatalities, more than 80% are attributed to smoke inhalation (25). It is presently believed that there are three mechanisms through which injury is induced: thermal injury to the airways, asphyxiation secondary to the gaseous products of pyrolysis, and injury induced by the inhalation of particulate matter in the smoke (1, 5a, 9, 18, 21, 23, 25). In our study, intubation of the animal and cooling of the smoke in an anesthesia bellows before delivery to the animal (Fig. 1) minimized local thermal injury to the airway as a factor leading to pulmonary dysfunction. Alterations in the gaseous environment during a fire predispose the victim to asphyxiation secondary to the low ambient oxygen tension and high concentrations of noxious gases created through the process of pyrolysis. Carbon monoxide exerts its detrimental effects by shifting the oxygen hemoglobin saturation curve to the left. Thus there is interference with oxygen binding to hemoglobin; therefore, delivery of oxygen to the tissues and cellular respiration is hampered. In an effort to assure an adequate level of smoke exposure in our study, all animals received 100 breaths of cotton smoke, which resulted in mean COHgb levels of 81% immediately postexposure. By all standards, this level of COHgb indicates a very severe level of exposure. In an effort to minimize generalized and particularly cardiac ischemia and/or dysfunction due to the leftward shift of the oxygen hemoglobin saturation curve and thus the resultant hypoxemia, animals were placed on $F_{IO_2}$ of 0.50 immediately after induction of injury. As indicated in Table 1, this resulted in relatively rapid reduction of COHbg levels to nearly normal after 4 h. There was a significant decrease in $P_{aO_2}$ values seen within the first hour after induction of the injury. However, no significant changes in relative $V_{A}$, $Q$, and shunt were seen at that time (Table 2). It is likely that the changes in $P_{aO_2}$ at this early time interval are due to carbon monoxide replacement of oxygen bound to the hemoglobin, but we cannot rule out early changes in $V_{A}/Q$ distributions occurring at length scales smaller than the size of the ROIs analyzed in this study. As the hours after injury progressed, carbon monoxide levels gradually decline and hemoglobin molecules are more available to bind with oxygen. The progressive declines in $P_{aO_2}$ at 2 and 4 h are more likely to be attributable to changes in lung function (6, 13) than those seen at 1 h.

By analyzing the tracer kinetics data derived from the PET scans with the methodology described in the accompanying paper (3), we were able to quantify regional alterations in $V_{A}$, $Q_{R}$, and $Q_{S}/Q_{R}$ during smoke inhalation injury for the first time. Before we discuss the imaging results, it is important to acknowledge the technical limitations of our technique. First, because we used a single-slice PET camera, the data obtained come only from a 1-cm slice of the lung. Although we positioned the animal in the camera so as to maximize

---

**Table 3. Correlation between $P_{aO_2}$ and lumped-parameter model indexes of $V_{A}$, $Q_{R/imT}$, $Q_{S}/Q_{R}$, and $F_{gas}$ using a mixed-effect regression model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ROI</th>
<th>$r$</th>
<th>Prob $F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{R/imT}$</td>
<td>ND</td>
<td>-0.49</td>
<td>0.2292</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>-0.50</td>
<td>0.0307</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.63</td>
<td>0.0100</td>
</tr>
<tr>
<td>$Q_{S}/Q_{R}$</td>
<td>ND</td>
<td>-0.01</td>
<td>0.9666</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>-0.66</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.60</td>
<td>0.0009</td>
</tr>
<tr>
<td>$V_{A}$</td>
<td>ND</td>
<td>-0.37</td>
<td>0.1522</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>-0.62</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.60</td>
<td>0.0009</td>
</tr>
<tr>
<td>$V_{A}/Q_{R}$</td>
<td>ND</td>
<td>-0.11</td>
<td>0.0269</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>-0.01</td>
<td>0.1690</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.34</td>
<td>0.0160</td>
</tr>
<tr>
<td>$F_{gas}$</td>
<td>ND</td>
<td>0.17</td>
<td>0.4690</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.35</td>
<td>0.1800</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.67</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

$r$, Pearson correlation coefficient.

---

**Fig. 4. Scattergram of $F_{gas}$ vs. $Q_{S}/Q_{R}$ for D (○) and M regions (□). Data include all animals and all time points in the study.**
Because of this limitation, parameters such as $V_a$ or $Q_R$ were normalized by the average $V_a$ or flow per voxel within the imaged lung and the parameters $Q_{S/imT}$ and $Q_{S/imT}$ are normalized by the total blood flow to the imaged lung slice. The parameters $Q_s/Q_R$ and $F_{gas}$ do reflect absolute regional values within the ROI. A second limitation of our technique relates to the spatial resolution of the PET images and the large size of the ROIs used. As discussed in detail elsewhere (10, 22), our reconstruction algorithm yields images with a spatial resolution of 1 cm limiting information about tracer location to volumetric elements of 1 ml. In this study, we averaged the imaging data into three large ROIs each of approximately the same volume. This averaging had two main advantages: 1) it reduced the amount of computation time required by the nonlinear parameter identification algorithm to a manageable time, and 2) it greatly reduced the magnitude of imaging noise in the data yielding model predictions with excellent fit to the experimental data (3). The disadvantage of averaging the data is the loss of detailed spatial information. Thus the identified parameters $V_a$, $Q_{S/imT}$, and $F_{gas}$ need to be taken as average values within the ROIs, and it is impossible to determine the precise location of shunting units within a resolution element or the ROI. Fortunately, assessment of regional shunt does not depend on spatial resolution but rather on the fraction of the tracer reabsorbed during the apneic period. Thus the parameter $Q_s/Q_R$ should still accurately reflect the fraction of shunting blood flow within the given ROI, and it does not require individual identification of shunting units.

The ND regions showed no evidence of local shunt. In cases showing large intrapulmonary shunt in the D and M regions, a small increase in regional activity was evident in the ND regions toward the end of the apneic period, suggesting the effect of $^{13}$NN tracer recirculation. Maintenance of local $Q_{R/imT}$ along with steadily increasing $V_a$ in ND regions caused the progressive increase in $V_a/Q_R$ during the 4 h of the study. Both $Q_{R/imT}$ and $V_a$ to M regions displayed minor increases resulting in little change in their average $V_a/Q_R$ over the 4 h. There was also little change in $Q_s/Q_R$ with time in M regions. In D regions, however, $V_a$ markedly declined over the course of the study, whereas $Q_{S/imT}$ showed a small decrease, resulting in a monotonic drop in $V_a/Q_R$.

$Q_{S/imT}$ was highest in the D regions at all points of the study. In the control conditions, this distribution would be expected in a normal supine sheep on the basis of previous studies of sheep and dogs in the supine position (5) and consistent with the West et al. model of pulmonary $Q$ (24). As injury progressed, regional $V_a$ and fractional gas content in D regions progressively decreased. In an effort to preserve oxygenation and $V_a/Q$ matching, one would have expected a significant shift of $Q$ away from D regions. This occurred but not to the extent that would have matched the change in $V_a$. As a result, $V_a/Q_R$ progressively decreased in D regions in the hours after smoke inhalation injury. The result of a limited redistribution of $Q_R$ away from D regions is different from results in the model of acute lung injury by intravenously injected oleic acid, which shows a major redistribution of blood flow away from dependent regions and a preservation of oxygenation (4). Instead, our results are similar to those obtained by the same group of investigators when oleic acid was injected together with endotoxin. This suggests that smoke inhalation injury may be accompanied by a local disturbance in hypoxic vasconstriction possibly caused by increased endogenous nitric oxide production.

We found blood flow to shunting regions to be the single most predictive factor for the decline in $P_{aO_2}$. Because of the small change in $Q_{S/imT}$ and the regional increase in $Q_s/Q_R$ to D zones, the total fraction of shunting blood flow progressively increased over the experiment from 8 to 27%. The etiology of the increase in shunt may be found in the analysis of $F_{gas}$ that steadily declined in D regions and the inverse relationship between $F_{gas}$ and $Q_s/Q_R$ (Fig. 4). The finding that regional shunt fraction increased as $F_{gas}$ became <0.5 suggests that progressive alveolar derecruitment and/or alveolar flooding by edema and endothelial leak could have been the causes of the increase in $Q_s/Q_R$ after smoke inhalation.

Previously, the most extensive studies of $V_a/Q$ changes by smoke inhalation were carried out by using MIGET. Robinson et al. (17) proposed that in the first 24 h after smoke inhalation exposure, alterations in $V_a/Q$ matching were caused by shifting $V_a$ away from poorly perfused areas causing regions of low $V_a/Q$. Shunt development was found to be minimal (17). However, close analysis of their data reveals consistently higher predicted $V_a/Q$ values in the first 72 h after smoke inhalation. The differences between predicted and actual values were greatest 24 h after exposure. This suggests the presence of shunt that may have not been adequately estimated by their calculations. In fact, Shimazu et al. (19) demonstrated that in moderate and severe inhalation injury both shunt and low $V_a/Q$ regions developed in the first 24 h. Our study clearly indicates that, within the first hours after smoke inhalation, $V_a/Q$ mismatch and hypoxemia result from the development of shunt and low $V_a/Q$ predominantly in the dependent portions of the lung. Blood flow and shunt in nondependent and middle regions are maintained at nearly preinjury levels. MIGET relies on the injection of six inert gases dissolved in saline and then simultaneous sampling of pulmonary gas and systemic blood and determination of the corresponding gas concentrations by chromatography. Such a method yields a global index of $V_a/Q$ heterogeneity but does not allow assessment of the independent contributions of $V_a$ and $Q$ to such heterogeneity. Anal-

J Appl Physiol • VOL 90 • SEPTEMBER 2002 • www.jap.org
ysis of tracer kinetics data from PET assumes each lung region to be composed of two compartments: one of pure shunt and another aerated and ventilated compartment. Because of the low solubility of $^{13}$NN in blood and tissues compared with air, tracer delivered to aerated compartments, in proportion to regional Q, remained constant during apnea. In contrast, tracer delivered to nonaerated regions was carried away by pulmonary Q, providing the basis for estimating an index of regional shunt fraction. Once $Q_R$ and $V_{A}/Q_R$ were identified, regional $V_A$ could be estimated by fitting the model to the tracer kinetics data obtained during the washout. Relative values of regional $V_A/Q$ and $Q_s/Q_R$ can therefore be obtained. It is possible that our method of delivering the smoke may have caused a more rapid progression of the injury, resulting in shunt and low $V_A/Q$ regions that were visible in dependent regions as early as 2 h.

In summary, a nonlinear model for analysis of regional $^{13}$NN kinetics measured by PET yielded information about regional changes in $V_A$, $Q_R$, and $Q_s/Q_R$ after an exposure to smoke inhalation. In contrast to prior studies, we found that in the early hours immediately after smoke inhalation substantial shunt developed that was localized in dependent regions of the lung where Q was highest. The development of hypoxemia correlated with the development of decreasing $F_{gas}$ in dependent regions and increased blood flow to regions of shunt. This study has demonstrated that PET is a useful tool for evaluation of regional alterations in lung function in response to injury. Analysis can be made of the relative contributions of altered airway function ($V_A$), pulmonary Q and shunt, and parenchymal dysfunction ($F_{gas}$) to the alteration in gas exchange. Radiometry estimates for imaging $V_A$ and Q of a whole human lung with this technique using a multiring PET camera yield a total radiation exposure to the patient no greater than that from two high-resolution computed tomography slices. We therefore conclude that this technique may have clinical applicability.

This study was funded by National Heart, Lung, and Blood Institute Grant HL-38267 and by Massachusetts General Hospital Center for Engineering in Medicine, The Shriners Burn Institute, and The Cystic Fibrosis Foundation.

REFERENCES


J Appl Physiol • VOL 93 • SEPTEMBER 2002 • www.jap.org