Ventilation-perfusion relationships following experimental pulmonary contusion

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[1]*U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas;* [2]*Department of Surgery, Blanchfield Army Community Hospital, Fort Campbell, Kentucky;* [3]*Southwest Foundation for Biomedical Research, San Antonio, Texas;* [4]*Department of Surgery, William Beaumont Army Medical Center, El Paso, Texas*

Batchinsky AI, Weiss WB, Jordan BS, Dick EJ Jr, Cancelada DA, Cancio LC. Ventilation-perfusion relationships following experimental pulmonary contusion. *J Appl Physiol* 103: 895–902, 2007. First published June 14, 2007; doi:10.1152/japplphysiol.00563.2006.—Ventilation-perfusion changes after right-sided pulmonary contusion (PC) in swine were investigated by means of the multiple inert gas elimination technique (MIGET). Anesthetized swine (injury, $n = 8$; control, $n = 6$) sustained a right-chest PC by a captive-bolt apparatus. This was followed by a 12-ml/kg hemorrhage, resuscitation, and reinfusion of shed blood. MIGET and thoracic computed tomography (CT) were performed before and 6 h after injury. Three-dimensional CT scan reconstruction enabled determination of the combined fractional volume of poorly aerated and non-aerated lung tissue (VOL), and the mean gray-scale density (MGSD). Six hours after PC in injured animals, Pa_{O_2} decreased from 234.9 ± 5.1 to 113.9 ± 13.0 mmHg. Shunt (Q_S) increased (2.7 ± 0.4 to $12.3 \pm 2.2\%$) at the expense of blood flow to normal ventilation/perfusion compartments (97.1 ± 0.4 to $87.4 \pm 2.2\%$). Dead space ventilation (V_D/V_T) increased ($58.7 \pm 1.7\%$ to $67.2 \pm 1.2\%$). MGSD increased (-696.7 ± 6.1 to -565.0 ± 24.3 Hounsfield units), as did VOL (4.3 ± 0.5 to $33.5 \pm 3.2\%$). Multivariate linear regression of MGSD, VOL, V_D/V_T, and Q_S vs. Pa_{O_2} retained VOL and Q_S ($r^2 = .835$) as independent covariates of Pa_{O_2}. An increase in Q_S characterizes lung failure 6 h after pulmonary contusion; Q_S and VOL correlate independently with Pa_{O_2}.

ventilation-perfusion mismatch; shunt; multiple inert gas elimination technique; computed tomography

PULMONARY CONTUSION (PC), a frequent complication of thoracic trauma (10, 47), is associated with a high risk of acute respiratory distress syndrome (ARDS) and a mortality of 10–25% (9, 10, 29). The hallmark of PC is hypoxia (1, 40). Previous investigations of hypoxia after PC involved assessment of the ventilation/perfusion (V/Q) relationships in the lower end of the V/Q ratio scale by calculation of the venous admixture (7). Garzon et al. reported sustained elevation (25%) of calculated shunt fraction on day 2 after injury, which remained high (17%) for 8 days in 6 patients with flail chest (21). Diffusion limitation, as measured by carbon monoxide rebreathing, did not contribute significantly to hypoxemia (21). Fulton and Peter, in a model of PC in oxygen-ventilated dogs, reported increased calculated shunt fraction in a group subjected to vigorous (65 ml/kg) resuscitation and reinfusion of shed blood

(18). In spontaneously breathing dogs subjected to PC, Rutherford and Valenta reported elevation of intrapulmonary venous admixture but not of true shunt, measured by ^{99m}Tc-labeled albumin microspheres (44). Oppenheimer et al. found in anesthetized dogs with right-sided PC that ventilation, perfusion, lung volume, and V/Q as measured by xenon^{133} all decreased in the contused lung, and that calculated shunt was not a cause of hypoxemia (40).

These studies have been limited, however, by the fact that calculation of the venous admixture does not permit differentiation between true shunt (Q_S) and low V/Q areas. The multiple inert gas elimination technique (MIGET), on the other hand, allows for more precise quantitative evaluation of V/Q relationships in the lung, as it enables the construction of a virtually continuous distribution of V/Q ratios (49). MIGET has been applied to several lung injury models, but only in a limited way to PC. Bein et al. showed that increased true shunt and dead space ventilation, as well as V/Q mismatch, caused hypoxia in 2 trauma patients with PC (6).

We sought to determine the etiology of decreased oxygenation following PC by means of the MIGET in a porcine model of blunt chest trauma followed by a moderate hemorrhage and resuscitation, hypothesizing that PC leads to an increase in Q_S.

In addition, to evaluate pulmonary lesion volume in this model and to relate that volume to the functional derangements postinjury, we applied a new method for assessment of pulmonary density distributions involving semiautomatic 3-dimensional reconstruction of chest computed tomography (CT) scans.

MATERIALS AND METHODS

This study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee and was carried out in accordance with the guidelines set forth by the Animal Welfare Act and other federal statutes and regulations relating to animals and studies involving animals.

Animal preparation and measurements. Female Yorkshire pigs ($n = 14$) weighing 32.2 ± 0.8 kg SE were fasted, premedicated, and intubated. While each pig was under isoflurane anesthesia, a tracheostomy was performed; the right carotid artery, right external jugular vein, and both femoral arteries and veins were cannulated; and a Foley catheter was placed. At completion of surgery, total intravenous anesthesia was initiated (ketamine, 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and propofol, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and continued throughout the experiment. After surgery, baseline chest CT scans were performed. Next, the animals were taken to the intensive care unit (ICU) and placed on a

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Siemens Servo 300 A ventilator (Siemens-Elema AB, Sweden) in the volume-control mode, at a tidal volume of 12 ml/kg, respiratory rate of 12/min, Fi_{O_2} of 50%, and positive end expiratory pressure (PEEP) of 0. Respiratory rate was adjusted to provide normocapnia (Pa_{CO_2} = 35–45 mmHg). A pulmonary arterial catheter was inserted via the right external jugular vein for determination of core temperature, central venous pressure, and cardiac output by bolus thermodilution. Hourly and during each MIGET sampling, arterial blood gases were analyzed at body temperature (Omni, Roche Diagnostics, Mannheim, Germany).

Experimental protocol. After 1–2 h of stabilization in the ICU, in the injured group ($n = 8$) a right-sided PC was induced at end expiration according to the method of Davis et al. (13), by means of a modified captive-bolt humane stunner (Model MKL, Karl Schermer, Packers Engineering, Omaha, Nebraska). A chest tube was placed immediately on the side of the impact. Ten minutes after PC, hemorrhage and resuscitation were performed (14). The animals underwent a constant-rate 12-ml/kg hemorrhage (corresponding approximately to 20% of total blood volume). After a 30-min shock period, resuscitation with $3\times$ the shed blood volume of lactated Ringers' (LR) solution was carried out. Then the shed blood was reinfused. A maintenance infusion of LR (4 ml/h for first 10 kg, 2 ml/h for next 10 kg, 1 ml/h for additional kg) was then started and adjusted to maintain a urine output of 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$. Animals in the control group ($n = 6$) were treated identically with respect to instrumentation, general timeline, and maintenance fluid administration, but received no injury, hemorrhage, resuscitation, or tube thoracostomy. After completion of the protocol, animals were euthanized by an overdose of sodium pentobarbital (Fatal-Plus, Dearborn, Michigan).

CT scan acquisition and analysis. At baseline and 6 h after injury, chest CT scans were performed with a Philips Tomoscan M/EG (Philips Medical Systems International, Eindhoven, Netherlands). Slices (10 mm) were acquired at full inspiration with settings of 120 kV and 40 mA. The images were examined offline, and semiautomated image analysis was performed with a software package, 3D-Doctor (Able Software, Lexington, MA), as previously reported by our group (4, 5, 41). The pulmonary parenchyma was separated into four regions based on the Hounsfield unit (HU) ranges reported by Gattinoni et al. (23) via a segmentation process executed by the software that involved generation of closed polygons around an image region (52). Air, ($-1,000$ HU), hyperinflated (-998 to -900 HU), normally aerated (-900 to -500 HU), poorly aerated (-500 to -100 HU), and nonaerated areas (-100 to 100 HU) were defined by the software in each of the slices for each of the lungs. CT scan analysis enabled calculation of the mean gray-scale density (MGSD), as well as of the fractional volume of abnormal lung tissue (VOL), i.e., the sum of the volumes of poorly aerated and nonaerated lung divided by the total lung volume. For all calculations the volume of the accessory lobe was added to the volume of the right lung.

Multiple inert gas elimination technique. MIGET was carried out according to the method of Wagner et al. (50) in the modification without mixed venous sampling (3, 5, 20), at baseline and 6 h after injury. Briefly, a 1-l bag of 5% dextrose was saturated with six inert gases: SF_6, ethane, cyclopropane, halothane, ethyl ether, and acetone. This mixture was infused intravenously at a constant rate of half the minute ventilation (V_E) rate expressed in ml/min, yielding a total of 800–1,000 ml of fluid intake for each animal. At each time point, after a period of 45 min of infusion, duplicate 7-ml samples of arterial blood and 30 ml of expired air were collected into airtight glass syringes. Simultaneously, minute ventilation, thermodilution cardiac output (CO), and arterial and mixed venous blood gas sampling occurred. A gas chromatograph (GC; Hewlett Packard Model 6890 with a J&W GS-Gas Pro capillary column) was used to determine the levels of the inert gases in expired air and arterial blood. Previously the GC had been calibrated, and the coefficients of correlation between peak height and sample concentration were 0.999 for SF_6, halothane, and diethyl ether; 1.0 for ethane and cyclopropane; and

0.997 for acetone. For each inert gas, solubility in blood was determined individually for each animal. These data, along with the peak heights for each inert gas, the arterial blood gas values, the V_E, and the CO, were entered into software provided by P. D. Wagner. Mixed venous levels of the six gases were calculated from Fick's equation (20). The retention (ratio of the arterial to mixed venous levels) and excretion (ratio of the expired air to mixed venous levels) for each gas were represented as a function of solubility in blood. V/Q ratios were assessed graphically and numerically. To simplify interpretation of the results, the V/Q ratios initially calculated on the 50-compartment scale were "binned" into 5 compartments: blood flow and ventilation to the true shunt (V/Q = 0); and low (0 < V/Q < 0.1), normal (0.1 < V/Q < 10), high (10 < V/Q < 100), and dead space (V/Q = ∞) compartments. MIGET results showed excellent reproducibility for all gases and a low mean residual sum of squares of 4.2 ± 0.6 SE ($n = 28$) as an indicator of experimental error (42).

Histopathology. Representative tissue samples of the contused area and contralateral site in the left lung were excised and stained (H&E). The slides were scored for the presence of 4 features: hemorrhage, alveolar edema, inflammation, and necrosis, each graded on a scale of 0 through 4 (0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe). A summed score was calculated using all parameters to produce a final score. The data were evaluated based upon location (right or left) and injury status.

Statistical analysis. SPSS version 10.1 (SPSS, Chicago, Illinois) and SAS Version 8.1 for Windows (Cary, NC) were used. When appropriate, multivariate repeated-measures ANOVA was performed with "side", "compartment", and "time" as within-subjects factors, and "injured" as the between-subjects factor. This accounted for the possible interdependency of results across functional (MIGET) or anatomic (CT) lung compartments. Post hoc t-tests were performed to assess for changes over time within the injured group, and after injury between the control and injured groups with adjustment for multiple comparisons. Bivariate and multivariate linear regression was also performed, considering both groups and both time points together. For the pathology scores, a comparison of means was performed by the Cochran-Mantel-Haenszel test for the summed score and for each parameter that was scored. Data are presented as means $\pm$ SE; significance was accepted at $P < .05$.

RESULTS

Sixty minutes after PC with hemorrhage and resuscitation, Pa_{O_2} decreased from 234.9 ± 5.1 to 113.9 ± 13.0 mmHg ($P < .05$) in the injured group (Fig. 1). It remained lower than
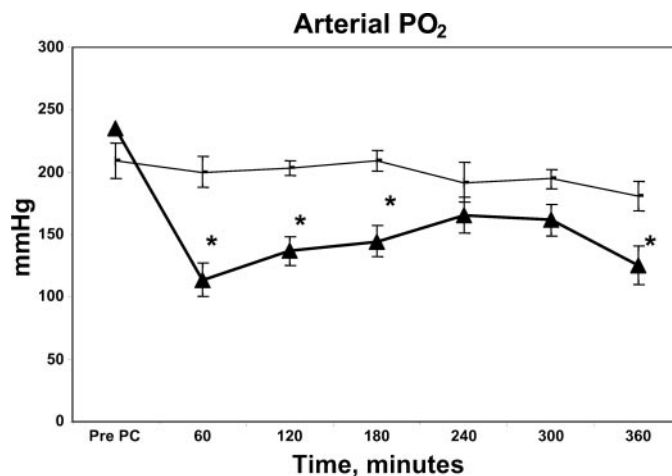
Fig. 1. Arterial oxygenation over time. Solid line, control group; ▲, injured group. *$P < .05$ between groups.

in controls at hours 1, 2, 3, and 6 (Fig. 1). Pa_{CO_2} increased in injured animals from 46.0 ± 2.1 mmHg at baseline to 54.8 ± 3.1 mmHg at hour 6 ($P < .05$). Peak airway pressure increased in injured animals from 12.5 ± 0.9 at baseline, peaking at 21.0 ± 1.2 at hour 2, and remaining elevated at hour 6 at 17.3 ± 1.1 ($P < .01$; data not shown).

Systolic arterial pressure decreased from 121.13 ± 3.1 mmHg at baseline to 63.75 ± 2.2 mmHg ($P < .05$) and reached a nadir after completion of the 12-ml/kg bleed at 20 min after PC. It remained decreased compared with controls thereafter, except at hour 5 (Fig. 2). Sixty minutes after PC, at the peak of resuscitation, central venous pressure was higher in the injured group ($P < .05$), but it did not differ between groups at any other time point (Fig. 3).

The injury group received a total of $2,339.3 \pm 38.4$ ml, and the control group received $1,287.3 \pm 11.6$ ml of fluids ($P < .05$), including MIGET infusate, over the 6-h experiment. The two groups also differed in the volume of fluid infused per kilogram of weight over the whole course of the experiment (37.3 ± 1.15 vs. 77.7 ± 0.8 ml/kg, $P < .05$, control and injured, respectively).

MIGET results. Gas exchange at baseline was unimpaired, as levels of log SD_Q, an index of V/Q heterogeneity, were similar to those reported by others in healthy, supine, spontaneously breathing pigs (28). We believe that the clinically insignificant Q_S observed at baseline was a function of general anesthesia and/or of ventilation with 50% O_2 (27, 43).

Total blood flow (Q_{TOTAL}) to the lungs did not change in either of the groups or time points (Table 1). Q_S was low in the control group and, despite doubling at the end of study, stayed below 5% of CO. Total blood flow to low V/Q areas did not change in either control or injured groups 6 h after PC. Injury caused a 5-fold increase in Q_S from 2.7 ± 0.4 to $12.3 \pm 2.1\%$ of CO, at the expense of perfusion to normal V/Q compartments (Q_{NORMAL}), which decreased from 97.1 ± 0.4 to $87.4 \pm 2.2\%$ in the injured group (Table 1). The degree of Q_S correlated well with the Pa_{O_2} ($r^2 = .79$, $P < .001$). For Q_{NORMAL}, differences were noted between the control and injured groups after injury. Redistribution of blood flow to shunt accounted for a shift in the mean of the blood flow distribution, which was significantly different between injured ($0.54 \pm 3\%$) and unin-
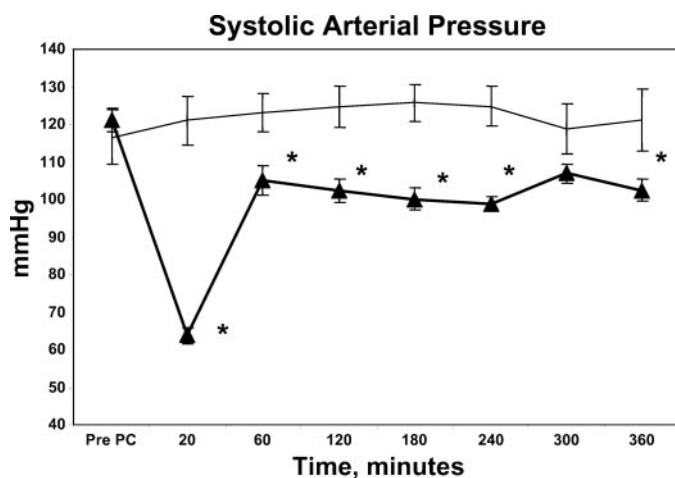
jured ($0.70 \pm 3\%$) animals at the end of the study (Table 1). Log SD_Q, the standard deviation of blood flow distribution and an index of overall mismatch (dispersion) (20) did not change 6 h after injury. Figure 4 illustrates our MIGET findings in the injury group.

V_E did not change (control: 6.40 ± 0.4 baseline vs. 7.06 ± 0.2 l/min at 6 h, not significant; injured: 5.26 ± 0.12 baseline vs. 6.57 ± 0.3 l/min at 6 h, not significant). Figure 4A shows a variant of normal baseline appearance of V, featuring matched V and Q, centering of both V and Q around 1 (mean V_E for controls 99 ± 5 and 98 ± 8, not significant for injured at end experiment). Bimodal (double-peaked) distribution of V was seen in some animals at baseline ($n = 4$ of 14) as well as at end of study ($n = 7$ of 14). Log SD_V, the standard deviation of ventilation distribution and an index of dispersion, did not change (data not shown). Injury was associated with an increase in dead space ventilation (V_D/V_T) from $58.7 \pm 1.6\%$ to $67.2 \pm 1.2\%$ in the injured group (Table 1, Fig. 4).

Fig. 3. Changes in central venous pressure over time. Solid line, control group; ▲, injured group. *$P < .05$ between groups.

Table 1. *MIGET results*

	Baseline		6 h	
	Control	Injured	Control	Injured
Q_{TOTAL}, l/min	3.8 ± 0.4	3.4 ± 0.3	3.8 ± 0.2	3.7 ± 0.2
Q_S, %	2.6 ± 0.9	2.7 ± 0.4	4.4 ± 0.6	$12.3 \pm 2.2*\dagger$
Q_{LOW}, %	1.4 ± 1.0	0.0 ± 0.0	0.6 ± 0.6	0.1 ± 0.1
Q_{NORMAL}, %	96.0 ± 0.8	97.1 ± 0.4	95.0 ± 0.5	$87.4 \pm 2.2*\dagger$
Q_{HIGH}, %	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1
V_D/V_T, %	61.1 ± 1.5	58.7 ± 1.7	58.8 ± 2.0	$67.2 \pm 1.2*\ddagger$
Mean Q_T	0.6 ± 0.0	0.6 ± 0.1	0.7 ± 0.0	$0.5 \pm 0.0\ddagger$
Log SD_Q	0.7 ± 0.1	0.5 ± 0.0	0.6 ± 0.1	0.6 ± 0.0

Values are means $\pm$ SE. Significance levels determined by post hoc *t*-test. MIGET, multiple inert gas elimination technique; Q_{TOTAL}, cardiac output; Q_S, percentage of cardiac output to true shunt compartment [ventilation/perfusion (V/Q) = 0], measured by MIGET; Q_{LOW}, percentage of cardiac output to the low V/Q compartment (0 < V/Q < 0.1); Q_{NORMAL}, percentage of cardiac output to normal V/Q compartment (0.1 < V/Q < 10); Q_{HIGH}, percentage of cardiac output to the high V/Q compartment (10 < V/Q < 100); V_D/V_T, percentage of ventilation to dead space, measured by MIGET; mean Q_T, mean of blood flow distribution; log SD_Q, SD of blood flow distribution. *$P < .01$ between baseline and 6 h in the injured group. †$P < .05$. ‡$P < .01$ between control and injured groups at 6 h.

Fig. 2. Changes in systolic arterial pressure over time. Solid line, control group; ▲, injured group. *$P < .05$ between groups.

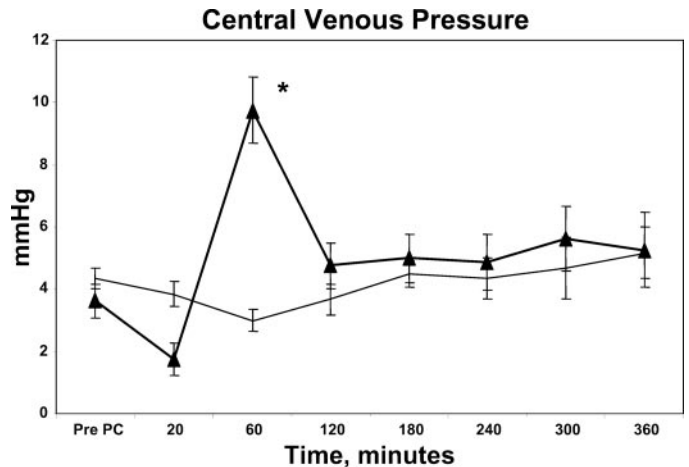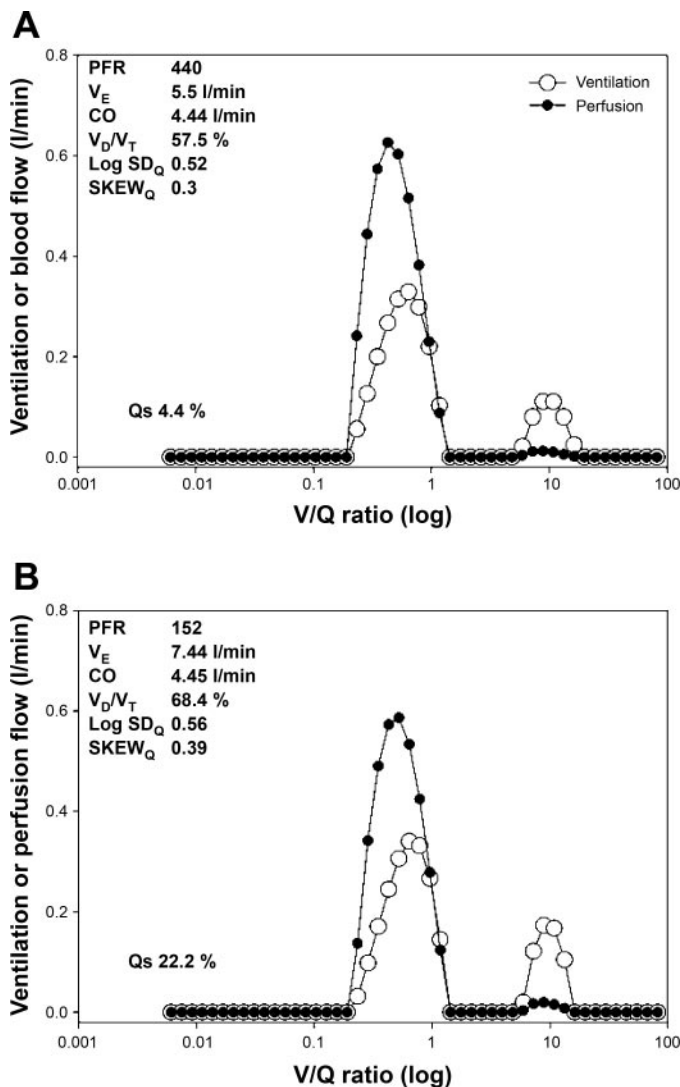Fig. 4. Distributions of ventilation (V) and perfusion (Q) as a function of V/Q ratio, by multiple inert gas elimination technique (MIGET). *A*: One of the variants of V/Q distributions at baseline. Note a bimodal distribution of V (function of relatively high tidal volume ventilation). True shunt (Q_S) is low. Standard deviation of blood flow distribution (Log SD_Q) and skewness of blood flow distribution ($SKEW_Q$) values are within normal limits. Blood flow to low-V/Q areas (0 < V/Q < 0.1) is absent. *B*: Six hours postinjury. Graphically the V/Q distribution is similar to the one at baseline. Note distribution of 22.2% of CO to Q_S, increase in dead space ventilation (V_D/V_T), severe hypoxia, consistent with acute respiratory distress syndrome Pa_{O_2}-to-FI_{O_2} ratio (PFR) was 152. V_E, minute ventilation; CO, cardiac output.

Diffusion limitation to oxygen was not observed. This is not surprising, since the animals in the main group were ventilated with 50% O_2, which precludes detection of diffusion limitation by MIGET. We completed an additional experiment in one animal that followed the same study protocol, with the exception that the animal was ventilated with room air. In that study diffusion limitation was present at baseline (3 ml/mmHg), 25 min (5.91 ml/mmHg), and 45 min (1.95 ml/mmHg) after PC, but resolved thereafter.

MIGET results: immediate postcontusion changes. We performed another experiment in one animal not included in the main study group that followed the same study protocol, in which immediate postcontusion MIGET sampling was per-

formed. Figure 5 explains the results in this animal ventilated with 50% O_2. In brief, blood flow not only to Q_S, but also to low compartments, was present at 4 and 8 min after PC. By 30 min, blood flow to low-V/Q but other-than-shunt compartments resolved and became redistributed to Q_S and Q_{NORMAL} (Fig. 5).

CT scan results. In controls, 6 h of mechanical ventilation led to a mild increase in density distributions within the dependent areas of both lungs. In injured animals at end study, CT scans typically featured areas of confluent consolidation spanning the mid-to-posterior sections of the right lung and adjacent dependent areas, featuring ground-glass opacification and consolidation (Fig. 6). The changes in the left lungs of the injured animals were mild and consisted of patchy ground-glass opacification (Fig. 6).

Semiautomatic CT scan analysis revealed that at baseline, MGSD was not different between groups. MGSD increased in injured animals (-696.7 ± 6.1 to -565.0 ± 24.3 HU; Table 2). CT VOL likewise increased (4.3 ± 0.5 to $33.5 \pm 3.2\%$). For both of these variables, differences were significant after injury and over time within the injured group ($P < .01$). At baseline the fractional volume of normally aerated lung (FracNorm) was not different between groups. Six hours of mechanical ventilation led to a decrease of the FracNorm in controls ($P < .001$) and an insignificant change in fractional volume of poorly aerated lung (FracPoor). No side-specific changes were seen in control animals at 6 h. Six hours after injury, the FracNorm decreased ($P < .001$) and the FracPoor ($P < .01$) and fractional volume of nonaerated lung (FracNon) ($P < .01$) lung compartments significantly increased (Table 2). At 6 h in injured animals, the FracNon was higher ($P < .01$) in the right lung compared with left (Table 2). Changes in the left lungs of the injured animals were not significant when baseline was compared with end of study.

Covariates of reduced oxygenation. Multivariate linear regression with MGSD, VOL, V_D/V_T, and Q_S was performed, and retained VOL and Q_S ($r^2 = .835$, $P < .001$, $n = 28$) as independent covariates of Pa_{O_2}. VOL was linearly related to Q_S ($r^2 = .702$, $P < .001$, $n = 28$).

Histopathology. Qualitatively, PC led to extensive edema within the alveolar and bronchiolar spaces of the right lung, and alveolar hemorrhage and flooding. Necrosis and subacute and acute inflammation were also present on the right side. The summed pathology score demonstrated a significant difference in the injured vs. uninjured animals for the right lung ($P = .008$); specifically, differences were observed for hemorrhage ($P = .008$) and alveolar edema ($P = .021$). Likewise, when comparing the scores for the right and left lung within the injured group, the summed ($P = .02$), hemorrhage ($P = .001$), and edema ($P = .01$) scores differed significantly, and no difference was observed for inflammation and necrosis. Injury scores were not different when scores for left lungs of injured vs. uninjured animals were considered.

DISCUSSION

Six hours after right-sided PC, hemorrhage, and resuscitation in swine, the following were found: *1*) clinically, acute lung injury, associated with an increase in Q_S; *2*) radiologically, parenchymal ground-glass opacification, confluent consolidation, loss of normally aerated lung volume, and an
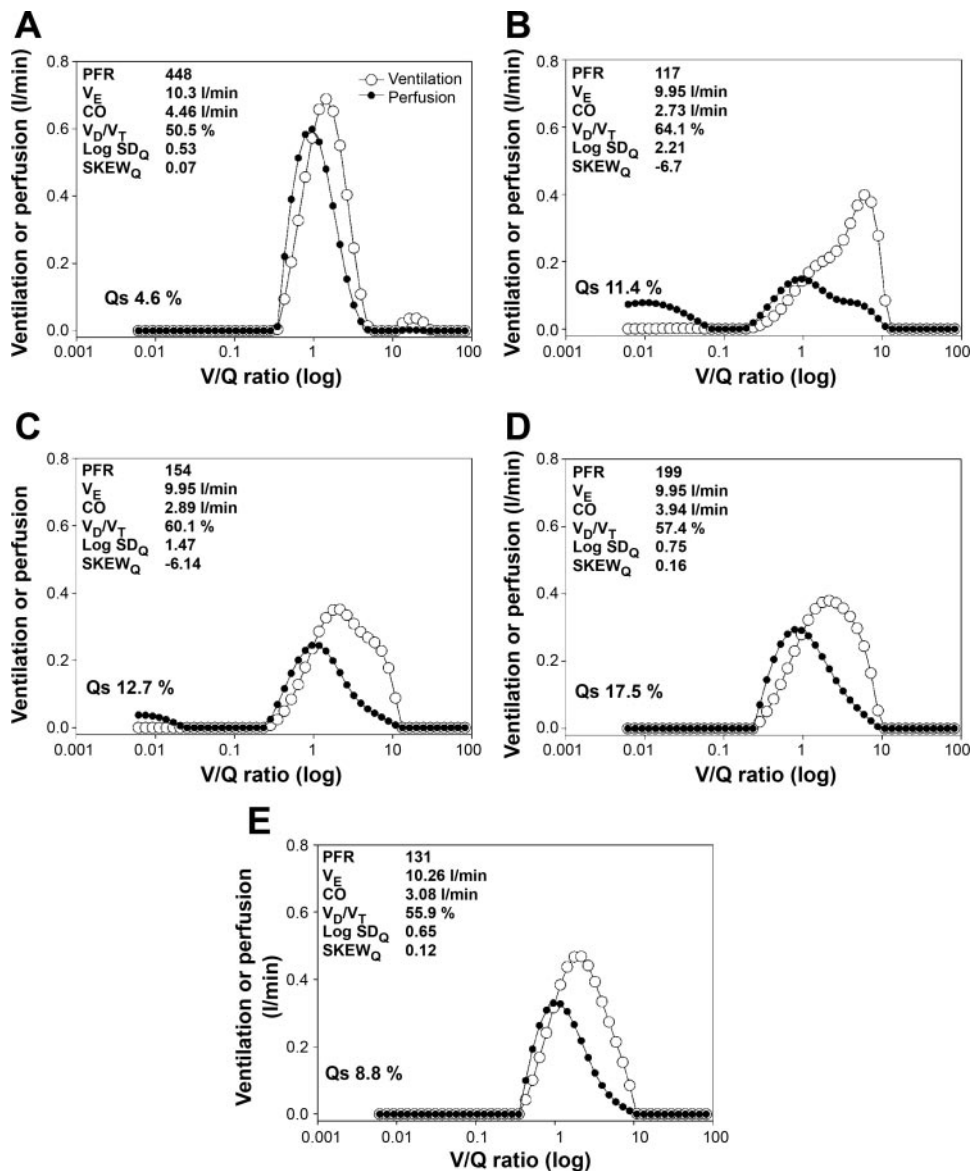
Fig. 5. Distributions of V and Q as a function of V/Q ratio in a single animal before (*A*) and 4 (*B*), 8 (*C*), 30 (*D*) and 360 (*E*) min after pulmonary contusion. FI_{O_2} = 50%. Note the normal V/Q matching at baseline and the low Q_S (*A*). Q_S increased to 11.4% 4 min after pulmonary contusion. Note elevated ● at the lower end of the V/Q spectrum in *B*, representing distribution of 25.3% of CO to low-V/Q areas (0 < V/Q < 0.1) at the expense of Q to normal V/Q compartments (Q_{NORMAL}), which decreased to 63%. The nadir in the index of oxygenation, PFR (117), occurred at 4 m (*B*). Gradually (*C* and *D*), blood from low-V/Q but other-than-shunt areas disappeared, becoming lost to Q_S (increased over baseline to 8.8%) or recruited to Q_{NORMAL} (increased to 91.2%) (*E*). Redistribution of blood flow from low-V/Q areas manifested in transient improvements in PFR (*C*, *D*).

increase in poorly- and nonaerated lung volume on the side of injury; and *3*) histologically, alveolar-capillary membrane injury, edema, and hemorrhage. Both Q_S and VOL correlated independently with Pa_{O_2}.

Other than case reports, our study is the first in the literature to evaluate the pathophysiology of postcontusion oxygenation failure by means of MIGET. We identified an increase in Q_S 6 h after injury. Q_S correlated well with the level of oxygenation.

Bein et al. found shunt and V/Q mismatch to be associated with PC in 2 humans (6). Dantzker et al. reported that in patients with ARDS secondary to pneumonia, aspiration, and sepsis, hypoxia developed primarily due to shunting, with some blood flow to low V/Q areas in select cases. Diffusion limitation was not a factor (12). Neumann and Hedenstierna established that development of true shunt was the major determinant of hypoxia in porcine models of acute lung injury caused by endotoxin infusion, repeated lung lavage, and oleic acid injury. In addition, V/Q mismatch played some role in the

latter 2 models (37). Our results by MIGET also confirm previous reports using simpler techniques. Fulton and Peter in a model of pulmonary contusion in dogs reported increased calculated shunt fraction in a group subjected to vigorous (65 ml/kg) resuscitation and reinfusion of shed blood (18). Garzon et al. reported sustained shunt elevation in patients with flail chest (21). Diffusion limitation, as measured by carbon monoxide rebreathing, did not contribute significantly to hypoxemia (21).

Similarly, we did not detect diffusion limitation in the main portion of this study. The MIGET technique was not designed to evaluate diffusion limitation during ventilation with oxygen concentrations above 21%. However, the reasonable agreement revealed between the blood gas and MIGET-predicted Pa_{O_2} values in the main study group (r^2 = .71) makes the presence of a clinically significant impairment of diffusion after PC unlikely. The results of an additional experiment with 21% oxygen used for ventilation were inconclusive, as diffusion limitation was present early after PC but resolved thereafter.
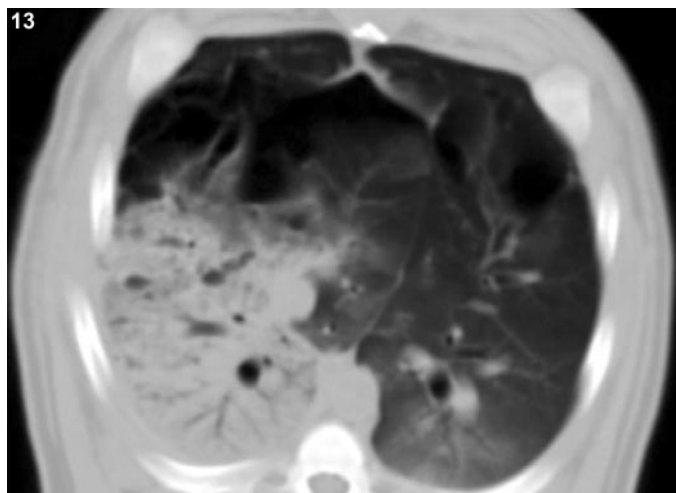
Fig. 6. Porcine chest computed tomography scan 6 h after PC. Massive lung consolidation on the injured right side, right-sided pneumothorax, pneumomediastinum. Note the slight increase in density in the dependent area of the left lung, illustrating the observation that consolidation is largely confined to the injured side in this model.

Thus, our results are consistent with the work of others that suggested that diffusion limitation did not contribute significantly to hypoxia after PC (6, 21).

The large absolute V_D/V_T values in our experiment were most likely caused by dilution of the most soluble gases in the large compressible gas volumes of the ventilator circuits and the MIGET gas sampling box (5 l total volume), and are not unusual in studies involving MIGET (39, 46). In addition, a significant increase in V_D/V_T relative to baseline values was detected in injured animals. Increased V_D/V_T has been reported following chest trauma in humans (6, 36), and as an early feature of ARDS predictive of mortality (38). Indeed, in the setting of pulmonary contusion, large- or small-vessel occlusion may contribute to increased V_D/V_T. Multiple other factors may also increase measured dead space, particularly under conditions of increasing peak airway pressure. These include gas compression in the airways, gas compression in the circuits and mixing box, overdistension of normal alveoli causing compression of capillaries, and expansion of the conducting airways from radial traction. Methods to account for these effects have been described (11, 16, 17, 31) but were not used

in this experiment. Thus, our observation of increased V_D/V_T should be interpreted with caution.

In an additional experiment that was not part of the main study, we examined the dynamics of V/Q changes minutes-to-hours after PC in an animal ventilated at a F_{IO_2} of 50%. We identified that minutes after PC, 25.3% of blood flow was shifted to low but other-than-shunt V/Q areas at the expense of Q_{NORMAL}. Subsequently, these areas disappeared, becoming lost to Q_S or recruited to Q_{NORMAL}. The latter was clinically manifested as an improvement in oxygenation (see Fig. 6, C and D) and may reflect the compensatory role of hypoxic pulmonary vasoconstriction (33). Furthermore, blood flow shifts between true shunt and low V/Q ratio compartments, such as presented in this study (Fig. 6), have been implicated in both animal (5, 48) and human (12, 32) lung injury studies. Dueck et al. suggested that recruitment of partially flooded but ventilating alveoli with moderate PEEP (15) may prevent shunt buildup. We did not use PEEP in this study. However, since we identified a transient pool of low V/Q areas (possibly representing partially flooded alveoli) in the case report, we speculate that PEEP may have a role as an early therapeutic measure in pulmonary contusion.

Histopathologically, PC led to alveolar-capillary membrane injury. This has been shown before, as PC leads to compressive-decompressive application of force to the lung parenchyma, with lesions ranging from localized edema (44) to concussive loss of alveolar-capillary membrane integrity, intraparenchymal and alveolar hemorrhage (45), and atelectasis (1, 19). Clinically, this results in hypoxia (1, 21, 40), ultimately leading to progressive acute lung injury (19).

The summed and side-specific pathology scores for hemorrhage and alveolar edema assessed in this model indicated a localized injury to the right lung. We found no changes in inflammation and necrosis scores, which may reflect the short duration of our experiment, or the relative insensitivity of our scoring system to early changes in these characteristics.

Our study did not involve methods of investigation of the spatial distribution of blood flow and ventilation such as those developed by Altemeier et al. (2). However, we believe that such techniques could localize the greatest increase in Q_S to areas of greatest consolidation on CT scans.

In controls, the mild gain in densities along the dependent areas at 6 h was likely a function of gravity and positive-

Table 2. *CT scan results*

	Baseline		6 h	
	Control	Injured	Control	Injured
MGSD, HU	-687.7 ± 12.6	-696.7 ± 6.1	-643.5 ± 8.5	-565.0 ± 24.3*
FracAir, %	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.2
FracHyper, %	0.0 ± 0.0	0.0 ± 0.0	14.4 ± 14.4	7.5 ± 2.0
FracNorm, %	95.7 ± 1.3	95.7 ± 0.5	71.9 ± 13.4†	58.4 ± 2.3†
FracPoor, %	4.3 ± 0.0	4.2 ± 0.4	9.6 ± 2.6	20.6 ± 0.0*
FracNon, %	0.0 ± 0.0	0.1 ± 0.1	4.1 ± 1.2	13.0 ± 2.2*‡
CT VOL, %	4.3 ± 1.3	4.3 ± 0.5	13.7 ± 1.7	33.5 ± 3.2*

Values are means ± SE. Significance levels determined by repeated measures ANOVA. CT, computed tomography; MGSD, mean gray-scale density of the entire lung by CT scan; HU, Hounsfield units; FracAir, fractional volume of air (HU= -1000); FracHyper, fractional volume of hyperinflated lung (-900 HU < FracHyper < -1000 HU); FracNorm, fractional volume of normally aerated lung (-500 < FracNorm < -900); FracPoor, fractional volume of poorly aerated lung (-100 < FracPoor < -500); FracNon, fractional volume of nonaerated lung (100 < FracNon < -100); CT VOL, fractional volume of pathological (poorly and nonaerated) lung tissue by CT. *$P < .01$ over time (see *CT scan results*). †$P < .001$ over time (see *CT scan results*). ‡$P < .01$ between higher FracNon in the right lung of the injured compared to left lung.

pressure ventilation. In injured animals, the complete consolidation of the mid-to-posterior areas of the contused lungs made the densities stemming from the injury indistinguishable from the gravity-dependent changes. Thus if one sought to estimate the relative gain in densities resulting from resuscitation in this model, it could be inferred by inspecting the left lung of the injured animals (Fig. 6). Our results show that despite a significant difference in fluid input between injured animals and controls, there was no significant gain in density on the left side of the injured animals. This suggests that the effects of resuscitation were confined to the injured right lung.

VOL (the sum of poorly and nonaerated lung fractions) and the amount of true shunt were independent covariates of Pa_{O_2}. VOL also correlated well with Q_S. Our data are in agreement with the work of Goodman et al., who found a significant correlation between the amount of consolidation and the Pa_{O_2}-to-Fi_{O_2} ratio, as well as between the amount of consolidation and shunt in humans with ARDS secondary to pulmonary and systemic causes (26). Also, Miller et al. found that contusion size predicted the risk of ARDS in humans with PC (35).

Perspective

There are several clinical implications of our study. First, the CT scan findings clearly document the inhomogeneous manner in which contusion alters the pulmonary parenchyma. Such inhomogeneity exposes the remaining smaller-in-volume normal lung to a risk of overinflation, and thus to volume- and pressure-induced secondary lung injury (25). This underscores the importance of lung-protective ventilation in patients with PC and other types of acute lung injury (22, 24, 34).

Second, the combined injury explored in this study was selected to mimic a civilian trauma or battlefield scenario in which blunt chest trauma would likely be accompanied by blood loss and subsequent fluid resuscitation. We found that a relatively modest hemorrhage (12 ml/kg) in concert with a resuscitation procedure with $3\times$ the shed volume of lactated Ringer's solution and then shed blood greatly worsened the pulmonary injury and hastened the development of lung failure. This may have occurred due to ischemia-reperfusion injury and/or the increased pulmonary vascular pressures that occurred during rapid resuscitation. The latter has been shown to augment ventilator-induced lung injury in isolated rabbit lungs (30). Although it is well known that withholding fluid resuscitation following PC does not improve outcome, it is perhaps as important to avoid overzealous fluid resuscitation. Wiedemann et al. found no difference in mortality between 1,000 patients with acute lung injury managed with a liberal vs. conservative approach to fluid administration. However, they identified important deleterious effects, such as worsening of oxygenation, increase in days on the ventilator, and increased length of stay in the ICU in the liberal group (51). Thus, we would recommend judicious fluid resuscitation in patients with PC, possibly to include attention to variables such as central venous or pulmonary arterial pressures. Future studies should compare the results of aggressive crystalloid-based resuscitation, as employed in this study, and more judicious resuscitation.

Third, this study, together with the other lung injury studies employing MIGET, suggests that ARDS is not a uniform disease with respect to the etiology of hypoxia. For example,

Shimazu et al. using MIGET determined that the principal abnormality following inhalation of wood smoke in sheep was V/Q mismatch, rather than shunt. This is consistent with our understanding of smoke inhalation injury as a process affecting primarily the small airways more than the alveolar-capillary membrane (46). On the other hand, we found that inhalation of chlorine gas in sheep caused a redistribution of blood flow to both shunt and low V/Q compartments, and histologic evidence of both small airway and alveolar-capillary membrane injury (5). Clinically, we would expect those forms of ARDS that feature shunt and alveolar-capillary membrane disruption to be particularly vulnerable to the method of fluid resuscitation. On the other hand, we would expect those forms of ARDS which feature V/Q mismatch and small airways injury to be amenable to efforts to maintain airway patency, such as high-frequency percussive ventilation and nebulized anticoagulants (8).

Our results should be interpreted in light of the following limitations. PEEP has been reported to decrease blood flow to low V/Q areas, increase dead-space ventilation, and decrease cardiac output (12). We chose to avoid PEEP in order to exclude its influence as a confounding variable in this model. We did not control for V/Q effects due separately to hemorrhage, resuscitation, or tube thoracostomy, nor for combinations of each of the above with pulmonary contusion. The blood reinfused in the injured group contained an anticoagulant citrate phosphate dextrose. Thus the V/Q changes that we investigated here represented the cumulative effects of pulmonary contusion, moderate hemorrhage, resuscitation, blood re-infusion, and chest tube placement all under the influence of intravenous anesthesia. The frequent MIGET sampling conducted by us in the additional studies is subject to interpretation with caution, since we did not confirm presence of steady-state conditions by measurements of O_2 consumption and/or CO_2 production.

In conclusion, our results implicate shunt in the development of decreased Pa_{O_2} 6 h after PC. CT scan analysis enabled the quantification of changes in levels of aeration, with lesion volume as an independent predictor of decreased Pa_{O_2}. We speculate that an improved understanding of the differences among various types of ARDS, as revealed by MIGET, may better our clinical management of these patients.

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