SHOCK, Vol. 33, No. 4, pp. 419 425, 2010

DYNAMIC CHANGES IN SHUNT AND VENTILATION-PERFUSION MISMATCH FOLLOWING EXPERIMENTAL PULMONARY CONTUSION

Andriy I. Batchinsky, Bryan S. Jordan, Corina Necsoiu, Michael A. Dubick, and Leopoldo C. Cancio

US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Building 3611, Fort Sam Houston, Texas

Received 12 May 2009; first review completed 1 Jun 2009; accepted in final form 15 Jul 2009

ABSTRACT The objective of this study was to investigate early changes in oxygenation by means of the multiple inert gas elimination technique and in coagulation by means of thromboelastography (TEG) after right-sided pulmonary contusion (PC) in swine. Anesthetized swine (group 1; n 8) sustained a right-chest PC by a captive-bolt stunner. Multiple inert gas elimination technique, TEG, and thoracic computed tomography (CT) scans were performed before and 10, 30, 60, and 120 min after injury. Three-dimensional CT scan reconstruction enabled measurement of volumes of poorly (Vol_{Poor}) and nonaerated (Vol_{Non}) lung. Eight animals (group 0) were used as uninjured controls. Pulmonary contusion led to sustained tachycardia and transient hypotension. Partial pressure of arterial oxygen (PaO_2) decreased from 83.9 ± 4.2 mmHg at baseline to 51.3 ± 2.8 mmHg 10 min after PC ($P < 0.001$). Vol_{Poor} and Vol_{Non} on the right increased significantly after PC, followed by gradual progression in injury marked by decreased Vol_{Poor} and increased Vol_{Non}. By the multiple inert gas elimination technique, blood flow to the true shunt compartment increased from 4.4% ± 1.0% at baseline to 21.2% ± 4.9% 10 min after PC, $P < 0.001$, peaked at 33.2% ± 7.5% 30 min after PC, $P < 0.001$, and remained significantly higher compared with controls. Transient increase in blood flow to low and very low ventilation-perfusion (V/Q) compartments was also seen. Clot reaction time and formation rate by TEG increased at 2 h after PC. True shunt is the major cause of hypoxemia after PC, but V/Q mismatch also contributes significantly early after injury. By CT, PC leads to significant loss of functional lung volume on the side of injury. A mild hypocoagulable state was identified 2 h after injury.

KEYWORDS Pulmonary contusion; true shunt, multiple inert gas elimination technique; computed tomography

INTRODUCTION

Chest trauma resulting in pulmonary contusion (PC) is a common finding in both civilian and military casualties and can lead to pulmonary failure, acute respiratory distress syndrome, and a 10% to 25% mortality rate (1, 2).

It is commonly assumed that an increase in true shunt (Q_{shunt}) is the principal cause of hypoxemia after PC. This assumption is based, in part, on historical studies that used the Berggren calculated venous admixture method (3–5) and on anecdotal clinical reports (6). We recently confirmed those results using the multiple inert gas elimination technique (MIGET) (7), a criterion-standard method of elucidating the intrapulmonary causes of hypoxemia, in a porcine model of PC (8). Specifically, we demonstrated that the predominant cause of impaired oxygenation at 6 h after a combined model of PC, 12-mL kg^{-1} hemorrhage, and fluid resuscitation is an increase in Q_{shunt} (8). Because that model combined PC with hemorrhage and resuscitation, it was not entirely clear whether the observed changes were a function of PC alone or whether hemorrhage and resuscitation also contributed. These methodological considerations led us to perform the study presented here, which focused on investigating the cause of hypoxemia after right-sided PC without concomitant blood loss and resuscitation. We hypothesized that PC would induce hypoxemia primarily by increasing Q_{shunt}.

However, in the previous study, we also observed a transient increase in ventilation-perfusion (V/Q) mismatch (increased blood flow to low V/Q areas, as distinct from Q_{shunt}) in two animals studied at several intermediate time points (8). Because of this increase, we performed more frequent MIGET measurements in the present study to define whether V/Q mismatch contributes to hypoxemia soon after injury. We also quantified pulmonary lesion volume by semiautomatic analysis of pulmonary computed tomography (CT) scans as previously described (8, 9). Finally, because trauma patients often present with coagulation disturbances and no animal model of posttraumatic coagulopathy exists (10), we also investigated coagulation status after PC using thromboelastography (TEG) and standard coagulation tests.

MATERIALS AND METHODS

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee and was performed 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 weighing 35.1 ± 0.7 kg SEM in the contused group (group 1; n = 8) and 38.7 ± 1.2 kg SEM in the control group (group 0; n = 8) were fasted overnight and then premedicated and intubated. Anesthetized with isoflurane, the pigs underwent a tracheostomy. The carotid artery, external jugular vein, and femoral artery on the right side and both femoral veins were cannulated with arterial tubing. A Foley catheter was placed in the bladder. At completion of surgery, total intravenous anesthesia was initiated (ketamine,

Address reprint requests to Andriy I. Batchinsky, MD, Library Branch, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX 78234-6315. E-mail: andriy.batchinsky@amedd.army.mil.

Funded by the Combat Casualty Care Research Program and the Telemedicine and Advanced Technology Research Center, US Army Medical Research and Materiel Command.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

DOI: 10.1097/SHK.0b013e3181b8bcd9

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2010	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Dynamic changes in shunt and ventilation-perfusion mismatch following experimental pulmonary contusion	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Batchinsky A. I., Jordan B. S., Necsoiu C., Dubick M. A., Cancio L. C.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**7**	

200 μg kg ^{1} min ^{1} and propofol, 100 μg kg ^{1} min ^{1}) and was continued throughout the experiment. After surgery, the animals were left in the supine position on the CT scan table, and baseline CT scans were performed. The animals were ventilated with a Siemens Servo 300 A ventilator (Siemens Elema AB, Sweden) in the volume control mode at a tidal volume of 12 mL kg ^{1}, respiratory rate of 12/min, fraction of inspired oxygen (FiO_2) of 21%, and positive end expiratory pressure of 0. The respiratory rate was adjusted to provide normocapnia, defined as partial pressure of carbon dioxide in arterial blood ($PaCO_2$) = 35 to 45 mmHg. A pulmonary arterial catheter was inserted via the right external jugular vein to determine core temperature, central venous pressure, and cardiac output by bolus thermodilution. Correct catheter placement was confirmed via CT scanning in each experiment. Body temperature was monitored via both a rectal probe and the pulmonary artery catheter and was maintained at a steady state throughout the entire experiment. Arterial blood gases were analyzed at body temperature (Omni, Roche Diagnostics, Mannheim, Germany).

Experimental protocol

After 1 to 2 h of stabilization in the CT room, a right sided PC was induced at end inspiration in group 1 according to the method of Davis et al. (11) and, as we previously reported (8), using a modified captive bolt humane stunner (model MKL, Karl Schermer, Packers Engineering, Omaha, NE). A flat, round, 7.5 cm diameter steel plate was attached to the tip of the captive bolt. When the cartridge fires, the bolt moves forward, and the plate strikes the right chest at the intersection of the midaxillary line and a line perpendicular to the base of the xiphoid process of the sternum. The injury was performed at full inspiration. A chest tube was placed immediately after injury on the side of the impact because pneumothoraces were frequently observed during model development. No maintenance fluid therapy was provided. Animals in the control group (n = 8) were treated identically with respect to instrumentation, general timeline, and MIGET procedure but received no injury or tube thoracostomy. After completion of the 2 h experimental period, all animals were euthanized with an overdose of sodium pentobarbital (Fatal Plus, Dearborn, Mich).

CT scan acquisition and analysis

At baseline and at 10, 30, 60, and 120 min after injury, chest CT scans were performed with a Toshiba Aquilion CT scanner (Toshiba America Medical Systems Inc., Tustin, Calif). Slices (0.5 mm) were acquired at full inspiration with settings of 120 kV and 40 mA. The images were reconstructed with a 20 mm step to reduce the number of images for analysis. Images were examined off line, and semiautomated image analysis was performed with a software package (3D Doctor; Able Software Corp., Lexington, Mass), as previously reported by our group (8, 9, 12). The pulmonary parenchyma was separated into four regions based on the Hounsfield unit (HU) ranges reported by Gattinoni et al. (13). A segmentation process was executed by the software that involved generation of closed polygons around an image region (14). Normally aerated lung (Vol_{Normal}) denotes lung regions within the window of 500 to 900 HU; poorly aerated lung (Vol_{Poor}), those within 100 to 500 HU; and nonaerated lung (Vol_{Non}), those within 100 to 100 HU. Volumes of lung occupying each such region were calculated by the software and are reported in milliliters. 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 performed according to the method of Wagner et al. (7) using the modification without mixed venous sampling as previously described (8, 9, 15). Measurements were performed at baseline; between 5 to 10 min after injury (hereinafter referred to as the 10 min time point); and 30, 60, and 120 min after injury. Briefly, a 1 L bag of 5% dextrose was saturated with six inert gases: SF6, ethane, cyclopropane, halothane, ethyl ether, and acetone. The mixture was infused intravenously at a constant rate of one half the minute ventilation rate expressed in mL/min, yielding a total of approximately 500 to 700 mL of total fluid intake for each animal over a 3 to 4 h period (including baseline stabilization). At baseline (after a period of 60 to 90 min of infusion), duplicate 7 mL samples of arterial blood and 30 mL samples of expired air were collected into airtight glass syringes. Simultaneously, minute ventilation (VE), thermodilution cardiac output (CO), and core temperature were recorded; and arterial blood gas sampling was performed. The same procedure was repeated at 10, 30, 60, and 120 min after PC. Hemodynamic stability was observed for several minutes before each sampling.

A gas chromatograph (Hewlett Packard Model 6890 with a J&W GS GasPro capillary column) was used to determine the levels of the inert gases in expired air and arterial blood. For each inert gas, its solubility in swine blood was determined. These data, along with the peak heights for each inert gas, the arterial blood gas values, the VE, and the CO, were entered into custom MIGET software. Mixed venous levels of the six gases were calculated from the Fick equation (15). 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 six compartments: blood flow (Q) and ventilation (V) to the Q_{shunt} (V/Q = 0); very low ($Q_{very\ low}$; 0 < V/Q < 0.001); low (Q_{low}; 0.001 < V/Q < 0.1); normal (Q_{normal}; 0.1 < V/Q < 10); high (Q_{high}; 10 < V/Q < 100); and dead space (V/Q = ∞) compartments. In addition, percentage of ventilation distributed to dead space (Vd/Vt), mean of blood flow distribution (mean Qt), and SD of blood flow distribution (logSDQ, an index of V/Q heterogeneity) are also reported.

MIGET results showed excellent reproducibility for all gases and a low mean residual sum of squares of 1.97 ± 0.2 SEM (n = 80) as an indicator of experimental error (16). In addition to V/Q relationship estimation, the MIGET allows for assessment of diffusion limitation (DL). The technique assumes that the partial pressure of each inert gas in an alveolus shows a linear relationship to its concentration in the blood passing by the alveolus (Henry's law). For each of the gases used for the MIGET, it is expected that diffusion equilibrium will be achieved between alveolar gas and capillary blood in all cases because the inert gases are invulnerable to DL. This principle lays the groundwork for calculations of DL by the MIGET because the arterial PaO_2 predicted by the traffic of the inert gases can be compared with the measured PaO_2. If DL is present, the PaO_2 predicted by the MIGET techniques from Va/Q inequality and shunt will systematically exceed the measured PaO_2.

TEG and coagulation analyses

TEG tests were completed at baseline, that is, after line placement but before injury and at each time point thereafter. For the TEG tests, the 10 min time point was omitted. At the other time points, 2.7 mL of arterial blood was collected in a 3 mL syringe preloaded with 300 μL of 0.105 M of sodium citrate. Samples were incubated at 39°C (normal pig body temperature) for 15 min before experimentation. Next, 10 μL tissue factor (Innovin; diluted 1:200), 20 μL of 0.2 M $CaCl_2$, and 4.45 μL of 1.6 mg mL ^{1} corn trypsin inhibitor were added to each cup and allowed to equilibrate. Then, 340 μL of citrated blood was added to each cup, and the assays were started immediately. The measurements were performed with TEG machines (Model 5000; Haemoscope, Skokie, Ill) set to the animals' temperatures and continued at least 30 min after maximum clot strength was reached. Variables measured included clot reaction time (TEG R, min), clot formation time (TEG K, min,), clot formation rate (TEG α, degrees), and maximum clot strength (TEG MA, mm). Similarly, at each time point, standard coagulation assays were performed. Activated clotting time (ACT), in seconds, was calculated by using the Hemochron Jr. whole blood microcoagulation system (ITC Europe, Rodano, Italy). Fibrinogen; prothrombin time (PT), in seconds; and activated partial thromboplastin time (aPTT), in seconds, were calculated by using the BCS XP System (Dade Behring Marburg GmbH, Marburg, Germany).

Statistical analysis

SPSS version 16 (SPSS Inc., Chicago, Ill) and SAS Version 9.1 for Windows (Cary, NC) were used for statistical analysis. When appropriate, multivariate repeated measures analysis of variance (ANOVA) was performed with "time" as within subjects factors and "injured" as the between subjects factor. Post hoc *t* tests were performed to assess changes over time within the injured group and after injury between the control and the injured groups with adjustment for multiple comparisons. Data are presented as mean ± SEM; significance was accepted at $P < 0.05$.

RESULTS

All the pigs survived the experimental period. PC led to tachycardia, which began immediately after PC and persisted until the end of the experiment (Fig. 1). A short period of hypotension was observed approximately 1 min after PC, after which blood pressure returned to near-baseline values (Fig. 2). Peak airway pressure increased in group 1 from 21.4 ± 0.6 mmHg at baseline to 28.6 ± 0.8 mmHg at 10 min ($P <$ 0.0001) and remained elevated compared with group 0 at all time points of the experiment (data not shown; value at end study, 27.0 ± 0.9 mmHg; $P < 0.0003$). PaO_2 decreased after injury and remained significantly depressed until the end of the experiment (Fig. 3). Lactate was higher at all time

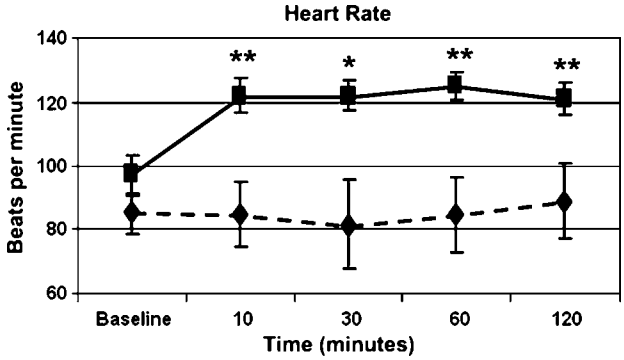

FIG. 1. **Changes in heart rate over time**. Solid line indicates control group; dashed line, injured group. Asterisks denote significant differences between the groups by repeated measures ANOVA; $*P < 0.05$; $**P < 0.01$. X Axis is not to scale.

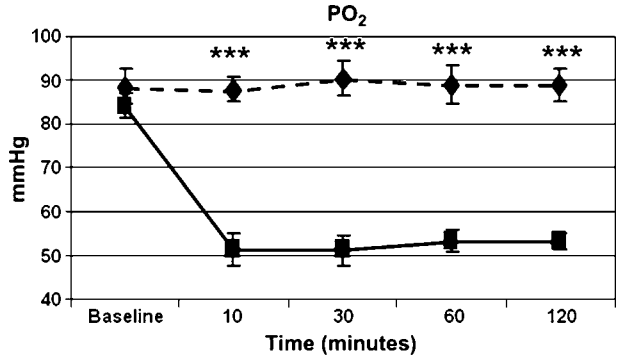

FIG. 3. **Changes in arterial oxygen tension**. Solid line indicates control group; dashed line, injured group. Asterisks denote significant differences between the groups by repeated measures ANOVA, $***P < 0.001$. X Axis is not to scale.

points after injury compared to controls (Table 1). Minute ventilation, cardiac output, central venous pressure, and core temperature were not different between groups. All corresponding values in the controls remained at baseline levels throughout the experiment.

MIGET results

Throughout the entire study in group 0, Q_{shunt} was low; there was no blood flow to the $Q_{very\ low}$ and Q_{low} V/Q compartments, and Q_{normal} stayed above 97%. Vd/Vt remained low and constant, as did logSDQ (Table 1). In contrast, group 1 showed marked increases in Q_{shunt} at all time points after PC (Fig. 4, Table 1). Both $Q_{very\ low}$ and Q_{low} increased after injury, then gradually declined. These changes occurred at the expense of Q_{normal}, which decreased at all time points after PC in group 1 (Table 1). Mean Qt was decreased at 10 and 30 min after PC compared with controls. LogSDQ increased at all time points after injury (Table 1). Diffusion limitation to oxygen was not observed in any of the animals. Figure 5 provides details of MIGET analysis in one of the animals that developed the highest changes in Q_{shunt}.

CT scan results

Vol_{Normal} remained unchanged in group 0 throughout the duration of the experiment (Table 2). In group 1, there was a profound decrease in Vol_{Normal} and an increase in Vol_{Poor} and Vol_{Non} on the side of the contusion. During the 2-h experiment, Vol_{Poor} then gradually decreased, whereas Vol_{Non} increased (Table 2, Fig. 6). Changes in the left lungs of the injured animals consisted of lesser increases in Vol_{Poor} at 30 and 60 min and in Vol_{Non} at 10 and 30 min compared with controls (Table 2). Figure 6 shows CT scan changes in group 1 over time in a representative animal.

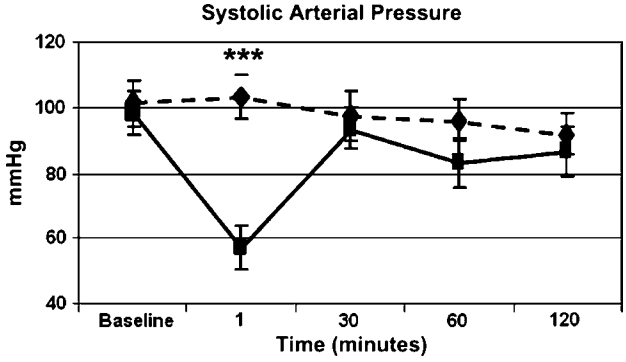

FIG. 2. **Changes in systolic arterial pressure over time**. Solid line indicates control group; dashed line, injured group. The first time point for systolic arterial pressure was recorded at 1 min after PC. Asterisks denote significant differences between the groups by repeated measures ANOVA, $***P < 0.001$. X axis is not to scale.

TEG and coagulation results

Clot reaction time was shorter at 30 min after PC, and both R and K times were longer and TEG α lower in group 1 at 120 min, indicating that clot initiation and formation rate took longer compared with controls. Maximum clot strength was not significantly different between groups; this result suggests that overall clot strength was not affected by PC. ACT was also higher in group 1, indicating a slower clot formation. No significant differences in PT, aPTT, or fibrinogen levels were observed between groups (Table 3).

DISCUSSION

This study in anesthetized, mechanically ventilated swine shows that right-sided PC caused acute lung injury, manifested by hypoxemia and radiological evidence of ground-glass opacification and confluent consolidation. The study's main finding is that a persistent increase in Q_{shunt} is the primary mechanism of hypoxemia, with an additional contribution by V/Q mismatch during the early postinjury period. In addition, CT scan measurements revealed loss of normally aerated lung volume and an increase in poorly and nonaerated lung volumes on the side of injury, with lesser changes in the contralateral lung. Over time, the volume of poorly aerated lung decreased on the right side, and the volume of nonaerated lung increased, denoting a transition of poorly aerated lung to fully consolidated lung. TEG and ACT measurements pointed to development of a mild hypocoagulable state 120 min after PC.

We investigated the effect of PC on oxygenation by means of MIGET. MIGET is a well-established method for identifying and quantifying the intrapulmonary causes of hypoxemia. We confirmed our previous MIGET findings, historical data using less accurate methods, and the long-standing clinical impression that increased Q_{shunt} is the predominant cause of

TABLE 1. **MIGET data before and 10, 30, 60, and 120 min after PC**

		Time point				
Variable	Group	Baseline	10 min	30 min	60 min	120 min
Lactate, mM	0	2.88 ± 0.57	2.91 ± 0.77	2.60 ± 0.58	2.26 ± 0.35	2.75 ± 0.56
	1	4.65 ± 1.12	4.84 ± 0.54*	6.65 ± 0.49‡	6.19 ± 0.68‡	5.88 ± 1.11*
Q_{total}, L min ^{1}	0	4.30 ± 0.34	3.71 ± 0.35	3.39 ± 0.34	3.25 ± 0.41	3.60 ± 0.42
	1	4.81 ± 0.51	4.18 ± 0.47	4.42 ± 0.70	4.07 ± 0.46	4.12 ± 0.44
Q_{shunt}, %	0	2.63 ± 0.53	2.03 ± 0.37	1.98 ± 0.44	2.04 ± 0.62	1.98 ± 0.50
	1	4.36 ± 1.02	21.20 ± 4.94‡	33.15 ± 7.49‡	28.94 ± 7.26‡	26.48 ± 6.81‡
$Q_{very\ low}$, %	0	0.00 ± 0	0.00 ± 0	0.00 ± 0	0.00 ± 0	0.00 ± 0
	1	0.00 ± 0	4.14 ± 0.56†	2.13 ± 0.76*	2.05 ± 0.79*	0.14 ± 0.14
Q_{low}, %	0	0.00 ± 0	0.00 ± 0	0.00 ± 0	0.20 ± 0.20	0.00 ± 0
	1	1.65 ± 0.75	12.93 ± 2.72‡	2.89 ± 0.78‡	3.01 ± 1.39*	1.65 ± 0.88*
Q_{normal}, %	0	97.25 ± 0.55	97.64 ± 0.49	97.45 ± 0.61	97.29 ± 0.78	97.89 ± 0.52
	1	93.76 ± 1.37	60.76 ± 5.57‡	61.03 ± 7.67‡	65.16 ± 8.07‡	70.23 ± 6.86‡
Q_{high}, %	0	0.13 ± 0.09	0.34 ± 0.16	0.58 ± 0.32	0.47 ± 0.24	0.44 ± 0.12
	1	0.36 ± 0.12	0.58 ± 0.15	0.76 ± 0.24	0.85 ± 0.19	1.23 ± 0.34
Vd/Vt, %	0	32.00 ± 3.50	36.04 ± 2.31	35.54 ± 2.93	34.00 ± 4.55	33.39 ± 1.84
	1	32.97 ± 1.68	43.53 ± 2.76*	40.08 ± 2.13	39.26 ± 1.71	38.8 ± 1.94
Mean Qt	0	0.55 ± 0.04	0.63 ± 0.04	0.72 ± 0.07	0.79 ± 0.14	0.69 ± 0.06
	1	0.47 ± 0.05	0.33 ± 0.05‡	0.53 ± 0.04*	0.55 ± 0.06	0.69 ± 0.07
LogSDQ	0	0.85 ± 0.03	0.77 ± 0.03	0.81 ± 0.02	0.82 ± 0.04	0.81 ± 0.01
	1	0.88 ± 0.05	1.67 ± 0.12‡	1.38 ± 0.15†	1.33 ± 0.18*	1.08 ± 0.08†

Group 0, controls; group 1 injured.
Values are mean ± SE. Significance levels by repeated measures ANOVA. Asterisks denote *P* values for group 0 vs. group 1.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$ (see text for details).
Lactate, lactate level in arterial blood, mM; Q_{shunt}, percentage of cardiac output to Q_{shunt} compartment (V/Q = 0), measured by MIGET; $Q_{very\ low}$, percentage of cardiac output to the low V/Q compartment ($0 < V/Q < 0.01$); Q_{low}, percentage of cardiac output to the low V/Q compartment ($0.01 < V/Q < 0.1$); 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 ($10 < V/Q < 100$); Vd/Vt, percentage of ventilation to dead space, measured by MIGET, %. Mean Qt, mean of blood flow distribution; Log SDQ, SD of blood flow distribution; Q_{total}, cardiac output (L/min).

hypoxemia after PC. Specifically, in the present study, we demonstrated that PC caused a sustained increase in Q_{shunt} that peaked at 30 min after injury and that remained significantly elevated throughout the duration of the study. However, we also demonstrated that V/Q mismatch contributed to hypoxemia, particularly at the 10-min time point. Vd/Vt increased significantly only at 10 min after PC and remained not different from controls thereafter. Diffusion limitation was not present in this model.

There are several important differences between the current study and our previous work with PC in this species. The previous study used a combined model of PC, hemorrhage, and fluid resuscitation with lactated Ringer solution and blood. In the current study, no hemorrhage was performed, and fluid administration was minimized. This approach allowed us to focus on the pathophysiology of PC alone without the potentially confounding effects of hemorrhagic shock and resuscitation-induced pulmonary edema. In the previous study, animals were ventilated with an FiO_2 of 0.5. In the current study, an FiO_2 of 0.21 was used, which enabled measurement of DL to oxygen. Finally, multiple postinjury MIGET measurements were performed in the current study that permitted identification of increases in Q_{low} and $Q_{very\ low}$ at intermediate time points. Despite these methodological differences, the two studies, taken together, confirm the central role of Q_{shunt} in PC.

Several clinically relevant conclusions can be drawn from these studies. First, the current study builds on previous observations in animals (8, 9, 17) and humans (18, 19) that after lung injury, blood flow is transiently redistributed not only to Q_{shunt} but also to low V/Q areas (Fig. 5) (4, 12). The low V/Q areas may subsequently be "lost" to Q_{shunt} by progressive alveolar flooding or collapse or may be "rescued" back to Q_{normal}. This loss or rescue suggests the clinical importance of careful fluid titration in the first 2 h after PC to avoid exacerbation of acute lung injury during the period in which

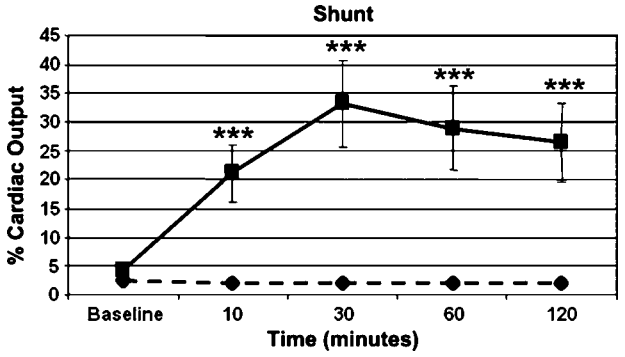

FIG. 4. **Changes in true shunt**. Solid line indicates control group; dashed line, injured group. Asterisks denote significant differences between the groups by repeated measures ANOVA, ***$P < 0.001$. X Axis is not to scale.

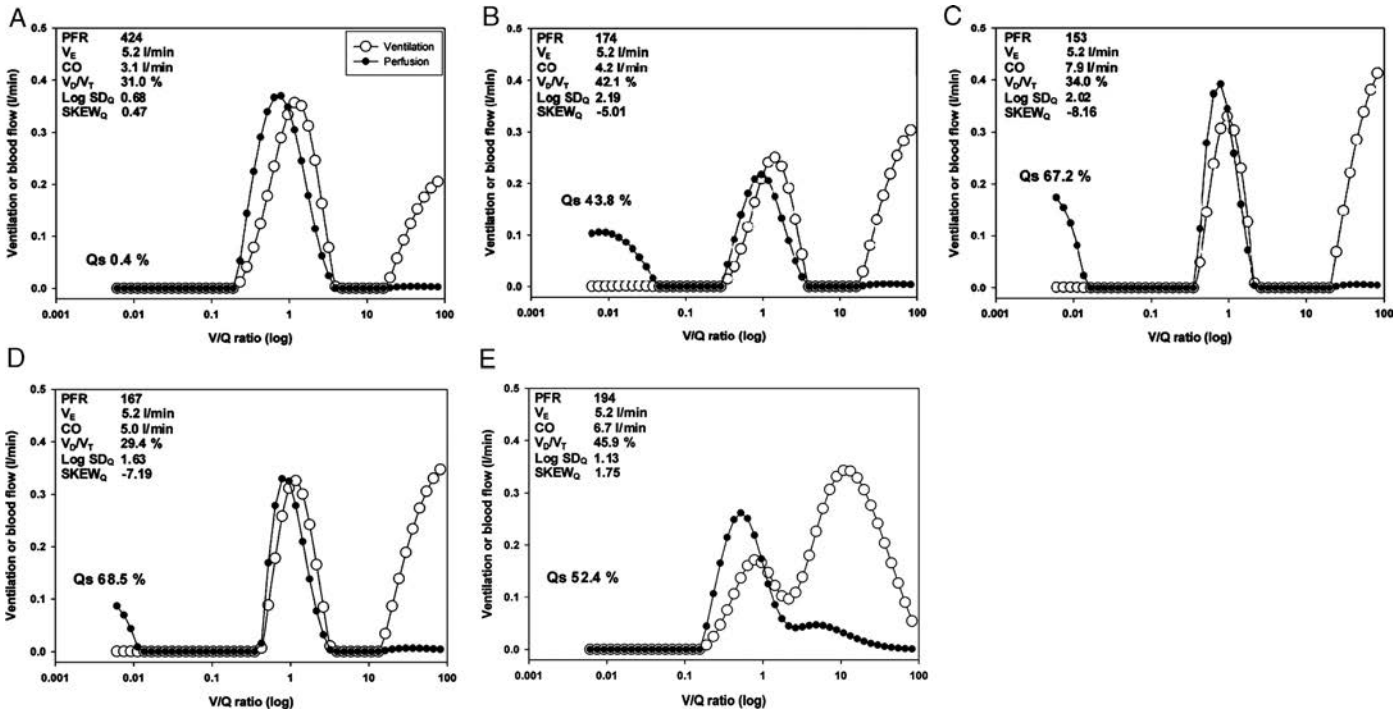

FIG. 5. **Distributions of ventilation (V) and perfusion (Q) as a function of V/Q ratio in a single animal before (A) and 10 (B), 30 (C), 60 (D), and 120 (E) min after PC**. FiO_2 = 21%. PFR, PaO_2 to FiO_2 ratio; V_E, minute ventilation; CO, cardiac output; Vd/Vt, dead space ventilation, %; log SDQ, SD of the blood flow distribution; SkewQ, skewness of the blood flow distribution; Q_{shunt}, true shunt. A, At baseline, Q_{shunt} is low, and no blood flow is distributed to low but other than shunt V/Q areas. Q_{normal} is 98.9%. B, Q_{shunt} increased to 43.8%, and Q_{normal} decreased to 36.9% 5 min after PC. The elevated black circles at the lower end of the V/Q spectrum represent distribution of 18.5% of cardiac output to low V/Q areas ($0 < V/Q < 0.1$). V/Q mismatch, severe hypoxia PFR = 174, acute respiratory distress syndrome; increase in dead space ventilation. C, At 30 min after PC, Q_{shunt} increased to 67.2%, blood flow to low V/Q areas decreased to 7%, and blood flow to normal V/Q areas decreased to 25%. V/Q mismatch, severe hypoxia PFR reaches nadir at 153. D, At 60 min, Q_{shunt} increased to 68.5%. V/Q mismatch persists as 3.1% of blood flow is distributed to low V/Q areas. Blood flow to Q_{normal} is 27.7%. Some improvement in PFR = 167. E, 120 min postinjury Q_{shunt} decreased to 52.4%. Blood flow from low V/Q areas is redistributed to Q_{normal}, which now receives 45.1% blood flow, V/Q mismatch, severe hypoxia, PFR = 194.

the Q_{shunt} fraction is not definitively established. It also suggests that recruitment maneuvers, positive end-expiratory pressure (20), and/or high-frequency percussive ventilation (21) may be particularly useful early after PC. These therapeutic interventions may open up the partially flooded but still ventilated alveoli represented by the low V/Q compartments,

TABLE 2. **Absolute volumes of normally aerated, poorly aerated, and nonaerated lung in milliliters as calculated by 3D doctor before and 5 10, 30, 60, and 120 min after PC**

		Time point				
Compartment	Group	BL	5 10 min	30 min	60 min	120 min
Right lung Vol_{Normal}	0	579 ± 0.59	594 ± 51	595 ± 54	597 ± 59	622 ± 46
	1	598 ± 34	324 ± 40*	340 ± 29*	308 ± 28†	303 ± 23*
Left lung Vol_{Normal}	0	402 ± 30	381 ± 26	380 ± 25	391 ± 25	405 ± 26
	1	390 ± 56	417 ± 50	413 ± 53	402 ± 50	403 ± 58
Right lung Vol_{Poor}	0	86 ± 8	78 ± 8	77 ± 8	77 ± 12	66 ± 7†
	1	70 ± 7	281 ± 22‡	253 ± 18‡	222 ± 16‡	187 ± 20‡
Left lung Vol_{Poor}	0	72 ± 7	61 ± 7	60 ± 5	58 ± 9	56 ± 5
	1	64 ± 14	80 ± 11	95 ± 9*	93 ± 9*	87 ± 13
Right lung Vol_{Non}	0	24 ± 2	37 ± 5†	38 ± 5	38 ± 4	37 ± 4
	1	21 ± 3	117 ± 14‡	166 ± 24‡	179 ± 30‡	194 ± 28‡
Left lung Vol_{Non}	0	16 ± 1	23 ± 5	19 ± 4	25 ± 6	24 ± 3*
	1	11 ± 2	29 ± 7†	29 ± 8*	28 ± 7	33 ± 9

Group 0 indicates controls; group 1, injured. Vol_{Normal}, normally aerated lung regions within HU window 500 to 900 HU; Vol_{Poor}, poorly aerated lung regions within window 100 to 500 HU; Vol_{Non}, lung regions within 100 to 100 HU. Significance levels by repeated-measures ANOVA. Asterisks denote *P* values for group 0 vs. group 1.
*$P < 0.05$.
†$P < 0.01$, $P < 0.01$.
‡$P < 0.001$ (see text for details).

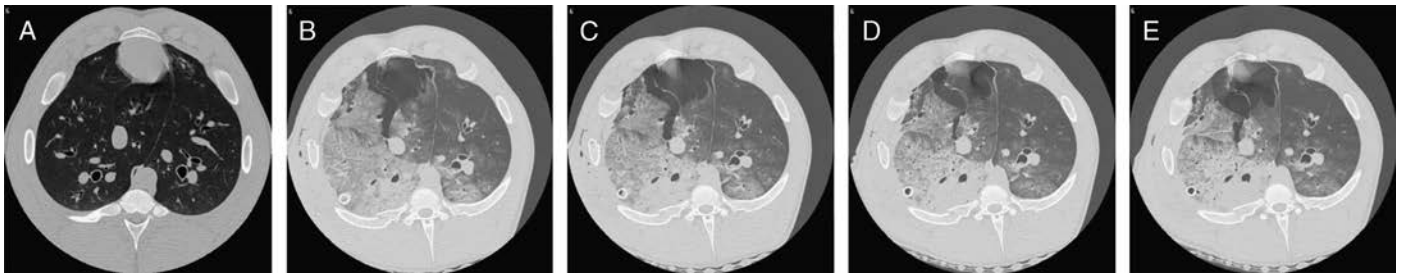

FIG. 6. **Porcine chest CT scan before and after PC**. Massive lung consolidation on the injured right side, right sided pneumothorax, pneumomediastinum. Note the increase in density in the dependent areas of the contralateral left lung. A, Baseline right Vol_{Normal}, 583 mL; right Vol_{Poor}/Vol_{Non}, 46 mL; B, 10 min after PC. Right Vol_{Normal}, 169 mL; right Vol_{Poor}/Vol_{Non}, 400 mL; C, 30 min after PC. Right Vol_{Normal}, 143 mL; right Vol_{Poor}/Vol_{Non} increased to 472 mL; D, 60 min after PC. Right Vol_{Normal}, 216 mL, right Vol_{Poor}/Vol_{Non}, 368 mL; E, 120 min after PC. Right Vol_{Normal}, 242 mL; right Vol_{Poor}/Vol_{Non}, 404 mL.

thus preventing further increases in Q_{shunt}. Further studies would be required to establish these hypotheses.

Second, the PaO_2-to-FiO_2 ratios in the current study were higher than those in the previous work (8). We attribute this difference to the deleterious effects of both hemorrhage and rapid resuscitation on pulmonary edema. Specifically, animals in the previous study were resuscitated with three times the shed volume of lactated Ringer over 10 min, followed by infusion of shed blood. This aggressive strategy, which is similar to what might be performed under conventional trauma-patient resuscitation guidelines, increased both the rate of onset and the severity of postcontusion hypoxemia. This result argues in favor of carefully titrated and timed ("just right") fluid resuscitation in patients with PC.

Third, CT findings in this study demonstrated a significant increase in poorly aerated and nonaerated regions in the right lungs of the injured animals (Fig. 6). Albeit less pronounced, poorly and nonaerated lung volumes also increased in the left lungs of the injured animals. These results reiterate the importance of using lung-protective ventilation in patients with PC. Markedly inhomogeneous parenchymal consolidation decreases preinjury lung capacity into a smaller "baby" lung (22). To prevent ventilator-induced lung injury to the remaining uninjured lung regions, tidal volume should be matched to this new effective volume. Contemporary lung-protective guidelines are one way to accomplish this matching (23). Future studies investigating the spatial distribution of gas exchange by using fluorescent microspheres could define the location of favorable V/Q areas in the lung (24) and perhaps lead to the development of improved ventilatory approaches. The clinically insignificant changes observed in controls can be attributed to gravity-based density distributions in the dependent portions of the lung and relative hypoventilation of those areas during positive-pressure mechanical ventilation. In addition, we identified a gradual transition from Vol_{Poor} to Vol_{Non} on the injured side. This worsening of CT density distributions may be the radiographic equivalent of the changes we also observed by MIGET in ventilation-perfusion matching,

TABLE 3. **Thromboelastography (TEG) and coagulation data before and 30, 60, and 120 min after PC**

		Time point			
Variable	Group	Baseline	30 min	60 min	120 min
TEG R, min	0	4.9 ± 0.2	4.9 ± 0.3	4.8 ± 02	4.3 ± 0.2
	1	4.9 ± 0.6	4.0 ± 0.1*	5.0 ± 0.9	6.8 ± 3.1*
TEG K, min	0	2.2 ± 0.1	2.2 ± 0.2	2.2 ± 0.2	1.8 ± 0.1
	1	2.1 ± 0.3	1.8 ± 0.1	2.1 ± 0.4	3.6 ± 0.8*
TEG α, degrees	0	62.0 ± 1.3	62.8 ± 1.0	61.3 ± 2.3	64.9 ± 1.2
	1	64.3 ± 3.3	64.3 ± 1.3	57.7 ± 6.9	51.9 ± 5.6*
TEG MA, mm	0	68.9 ± 0.9	68.7 ± 1.2	69.0 ± 1.3	69.1 ± 3.1
	1	69.2 ± 1.4	68.0 ± 1.4	66.8 ± 1.8	65.7 ± 1.9
ACT, s	0	109.9 ± 3.7	103.4 ± 3.4	103.8 ± 2.5	101.3 ± 3.0
	1	109.1 ± 3.1	104.3 ± 2.4	105.0 ± 2.8	115.6 ± 3.4*
PT, s	0	10.5 ± 0.1	10.5 ± 0.1	10.5 ± 0.1	10.7 ± 0.2
	1	8.8 ± 1.0	8.6 ± 1.0	8.7 ± 1.0	9.1 ± 1.1
aPTT, s	0	17.9 ± 0.5	17.5 ± 0.4	18.3 ± 0.4	20.3 ± 2.3
	1	14.7 ± 2.0	14.1 ± 1.8	14.3 ± 1.9	15.1 ± 2.2
Fibrinogen, mg dL ^{1}	0	138.7 ± 9.8	144.9 ± 9.8	140.6 ± 8.5	136.9 ± 7.1
	1	124.6 ± 22.7	122.0 ± 24.9	119.6 ± 30.8	120.7 ± 25.0

Group 0 controls, Group 1 injured. TEG R, clot reaction time, TEG K clot formation time, TEG α, clot formation rate, TEG MA, maximum clot strength, ACT, activated clotting time, PT, prothrombin time, aPTT, activated partial thromboplastin. Significance levels by repeated measures ANOVA. Asterisks denote *P* values for Group 0 vs. Group 1: *, $P < 0.05$.

manifested by a transition from early V/Q mismatch to later Q_{shunt}.

Coagulopathy is common in severely injured combat casualties upon arrival at combat support hospitals (25) and in civilian trauma patients, but an animal model of postinjury coagulopathy does not exist (10). Although coagulopathy is traditionally diagnosed when an increase 1.5 times or greater from normal of the international normalized ratio takes place (26, 27), measures derived by TEG may be more sensitive (28, 29). TEG measures the complete coagulation profile, whereas PT and aPTT do not measure coagulation beyond the R time of the TEG. The current study revealed that at 2 h after PC, there were mild increases in clot initiation time (TEG R) and a slower rate of clotting (α-angle) that is affected by thrombin generation, vital for the conversion of fibrinogen to thrombin. These results are consistent with the prolonged ACT observed. Because MA was not affected by PC in this study, it would seem that platelet function was not impaired, but the other TEG data suggest a functional fibrinogen deficiency or clotting factors shunting away from the coagulation process. Because normal blood clotting is a balance among procoagulative, anticoagulative, and fibrinolytic processes, the mechanism of this abnormality in the present study requires further investigation. It does suggest that massive soft-tissue trauma of the sort seen in this model may be one component of postinjury coagulopathy (10, 26, 30). The mechanism of postinjury coagulopathy is likely multifactorial and may include systemic hypoperfusion, acidemia, hemodilution, hypothermia, and trauma-induced release of tissue factor and inflammatory mediators (26, 31).

CONCLUSION

In conclusion, our results implicate not only Q_{shunt} but also transient increases in blood flow to very low and low V/Q compartments in the pathophysiology of hypoxemia after PC. CT scan analysis, meanwhile, demonstrated a gradual shift from poorly to nonaerated lung tissue over the course of the experiment. Finally, PC led to a mild hypocoagulable state 2 h after injury, manifested on TEG by longer clotting initiation times and decreased rate when compared with controls.

ACKNOWLEDGMENTS

The authors thank John Jones, Jennifer Beck, Irasema Terrazas, Michael Scherer, David Martini, Belinda Meyers, Michael Lucas, Sarita Shah, and Zachary Bevis for their assistance in conducting the studies.

REFERENCES

1. Clark GC, Schecter WP, Trunkey DD: Variables affecting outcome in blunt chest trauma: flail chest vs. pulmonary contusion. *J Trauma* 28:298 304, 1988.
2. Cohn SM: Pulmonary contusion: review of the clinical entity. *J Trauma* 42: 973 979, 1997.
3. Berggren S: The oxygen deficit of arterial blood caused by nonventilating parts of the lung. *Acta Physiol Scand Suppl* 2:1 92, 1942.
4. Fulton RL, Peter ET: The progressive nature of pulmonary contusion. *Surgery* 67:499 506, 1970.
5. Garzon AA, Seltzer B, Karlson KE: Physiopathology of crushed chest injuries. *Ann Surg* 168:128 136, 1968.
6. Bein T, Reber A, Stjernstrom H, Metz C, Taeger K, Hedenstierna G: Ventilation-perfusion ratio in patients with acute respiratory insufficiency. *Anaesthesist* 45:337 342, 1996.
7. Wagner PD, Naumann PF, Laravuso RB: Simultaneous measurements of eight foreign gases in blood by gas chromatography. *J Appl Physiol* 36: 600 605, 1974.
8. 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.
9. Batchinsky AI, Martini DK, Jordan BS, Dick EJ, Fudge J, Baird CA, Hardin DE, Cancio LC: Acute respiratory distress syndrome secondary to inhalation of chlorine gas. *J Trauma* 60:944 957, 2006.
10. Parr MJ, Bouillon B, Brohi K, Dutton RP, Hauser CJ, Hess JR, Holcomb JB, Kluger Y, Mackway-Jones K, Rizoli SB, et al.: Traumatic coagulopathy: where are the good experimental models? *J Trauma* 65:766 771, 2008.
11. Davis KA, Fabian TC, Croce MA, Proctor KG: Prostanoids: early mediators in the secondary injury that develops after unilateral pulmonary contusion. *J Trauma* 46:824 831, 1999.
12. Park MS, Cancio LC, Batchinsky AI, McCarthy MJ, Jordan BS, Brinkley WW, Dubick MA, Goodwin CW: Assessment of severity of ovine smoke inhalation injury by analysis of computed tomographic scans. *J Trauma* 55:417 427, 2003.
13. Gattinoni L, Caironi P, Pelosi P, Goodman LR: What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 164:1701 1711, 2001.
14. Wu T: Image segmentation: The first step in 3-d imaging. Available at: http://www.Ablesw.Com/3d-doctor/3dseg.Html. Accessed 5 May 2009.
15. Gale GE, Torre-Bueno JR, Moon RE, Saltzman HA, Wagner PD: Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol* 58:978 988, 1985.
16. Powell FL, Wagner PD: Measurement of continuous distributions of ventilation-perfusion in non-alveolar lungs. *Respir Physiol* 48:219 232, 1982.
17. Wagner PD, Laravuso RB, Goldzimmer E, Naumann PF, West JB: Distribution of ventilation-perfusion ratios in dogs with normal and abnormal lungs. *J Appl Physiol* 38:1099 1109, 1975.
18. Dantzker DR, Brook CJ, Dehart P, Lynch JP, Weg JG: Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis* 120:1039 1052, 1979.
19. Markello R, Winter P, Olszowka A: Assessment of ventilation-perfusion inequalities by arterial-alveolar nitrogen differences in intensive-care patients. *Anesthesiology* 37:4 15, 1972.
20. Dueck R, Wagner PD, West JB: Effects of positive end-expiratory pressure on gas exchange in dogs with normal and edematous lungs. *Anesthesiology* 47:359 366, 1977.
21. Cancio LC, Batchinsky AI, Dubick MA, Park MS, Black IH, Gomez R, Faulkner JA, Pfannenstiel TJ, Wolf SE: Inhalation injury: pathophysiology and clinical care proceedings of a symposium conducted at the Trauma Institute of San Antonio, San Antonio, TX, USA, on 28 March 2006. *Burns* 33: 681 692, 2007.
22. Gattinoni L, Pesenti A: The concept of "baby lung." *Intensive Care Med* 31: 776 784, 2005.
23. The acute respiratory distress syndrome. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342:1301 1308, 2000.
24. Altemeier WA, Robertson HT, Glenny RW: Pulmonary gas-exchange analysis by using simultaneous deposition of aerosolized and injected microspheres. *J Appl Physiol* 85:2344 2351, 1998.
25. Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB: Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma* 64:1459 1463; discussion 1463 1465, 2008.
26. Brohi K, Singh J, Heron M, Coats T: Acute traumatic coagulopathy. *J Trauma* 54:1127 1130, 2003.
27. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B: Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. *J Trauma* 42:857 861; discussion 861 862, 1997.
28. Kheirabadi BS, Crissey JM, Deguzman R, Holcomb JB, Flint LM, Moore FA, Brohl K: In vivo bleeding time and in vitro thrombelastography measurements are better indicators of dilutional hypothermic coagulopathy than prothrombin time. *J Trauma* 62:1352 1359; discussion 1359 1361, 2007.
29. Martini WZ, Cortez DS, Dubick MA, Park MS, Holcomb JB: Thrombelastography is better than PT, aPTT, and activated clotting time in detecting clinically relevant clotting abnormalities after hypothermia, hemorrhagic shock and resuscitation in pigs. *J Trauma* 65:535 543, 2008.
30. Shuja F, Shults C, Duggan M, Tabbara M, Butt MU, Fischer TH, Schreiber MA, Tieu B, Holcomb JB, Sondeen JL, et al.: Development and testing of freeze-dried plasma for the treatment of trauma-associated coagulopathy. *J Trauma* 65:975 985, 2008.
31. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, Mackway-Jones K, Parr MJ, Rizoli SB, Yukioka T, et al.: The coagulopathy of trauma: a review of mechanisms. *J Trauma* 65:748 754, 2008.