Pathophysiological analysis of combined burn and smoke inhalation injuries in sheep

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In this study, we investigated the pathophysiological alterations seen with combined burn and smoke inhalation injuries by focusing on pulmonary vascular permeability and cardiopulmonary function compared with those seen with either burn or smoke inhalation injury alone.

To estimate the effect of factors other than injury, the experiments were also performed with no injury in the same experimental setting. Lung edema was most severe in the combined injury group. Our study revealed that burn injury does not affect protein leakage from the pulmonary microvasculature, even when burn is associated with smoke inhalation injury. The severity of lung edema seen with the combined injury is mainly due to augmentation of pulmonary microvascular permeability to fluid, not to protein. Cardiac dysfunction after the combined injury consisted of at least two phases. An initial depression was mostly related to hypovolemia due to burn injury. It was improved by a large amount of fluid resuscitation. The later phase, which was indicated to be a myocardial contractile dysfunction independent of the Starling equation, seemed to be correlated with smoke inhalation injury.

Pulmonary vascular permeability; lung edema formation; myocardial depression

More than 30% of burn patients admitted to burn centers have a concomitant smoke inhalation injury (5, 11, 18). Although the survival from burn injury has increased in recent years with the development of effective fluid resuscitation management or early surgical excision of burned tissue, the mortality rate in this combination injury is still high (5, 28, 36). In these fire victims, progressive pulmonary failure associated with lung edema (acute respiratory distress syndrome) and cardiac dysfunction are important determinants of morbidity and mortality (5, 36).

In patients with extensive cutaneous burns in which the burned area exceeds 30% of the total body surface area (TBSA), capillary hyperpermeability occurs not only at the injured site but also in regions distant from the injury (4, 10, 34). This vascular hyperpermeability leads to a large amount of fluid flux from the circulating plasma to the interstitial spaces. The lung is especially affected by this phenomenon in the large-burn cases. The pulmonary microvascular permeability to water and small molecules increases after major cutaneous burns alone (7, 10). This lung edema formation is even more severe when the thermal damage is combined with inhalation injury (6, 20). Isago et al (13) and Traber et al. (33) have previously reported that smoke inhalation causes pulmonary microvascular hyperpermeability to both fluid and protein. Although Sakurai and colleagues (24, 25) have reported some of the cardiopulmonary changes that occur with combined burn and smoke inhalation, the pulmonary vascular permeability changes observed in combined burn and smoke inhalation injury in sheep have not been compared with those in sheep that had received either burn or smoke inhalation injury alone.

Patients with massive cutaneous burns also suffer myocardial contractile depression, which can be a serious complication, especially in the early postburn period (8, 12). On the other hand, our laboratory has demonstrated that smoke inhalation causes a delayed onset of myocardial depression. Sugi et al. (30) reported that left ventricular contractility was significantly decreased 24 h after smoke inhalation. However, the time course and mechanism responsible for the cardiopulmonary hemodynamic alterations are still unclear when cutaneous burn injury is associated with smoke inhalation injury.

In this study, we investigated the pathophysiological alterations seen with burn and smoke inhalation combined injury by focusing on pulmonary microvascular permeability and cardiopulmonary function compared with those seen with either burn or smoke inhalation injury alone. To estimate the effect of the factors other than injury, the experiments were also performed with no injury in the same experimental setting.

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MATERIALS AND METHODS

This study was approved by the Animal Care and Use Committee of the University of Texas Medical Branch (Galveston, TX) and conducted in compliance with the guidelines of the National Institutes of Health and the American Physiological Society for the care and use of laboratory animals.

Surgical preparation. Twenty-four female sheep were surgically prepared for chronic study under halothane anesthesia. The right femoral artery and vein were cannulated with Silastic catheters (Intracath; 16 gauge, 24 in.; Becton Dickinson Vascular Access, Sandy, UT). A thermomililation catheter (Swan-Ganz model 131F7, Baxter, Edwards Critical-Care Division, Irvine, CA) was introduced through the right external jugular vein into the pulmonary artery. Through the left fifth intercostal space, a catheter (Durastic silicone tubing DT08, 0.062-in. ID, 0.125-in. OD; Allied Biomedical, Paso Robles, CA) was positioned in the left atrium. Through the right fifth intercostal space, an efferent lymphatic vessel from the caudal mediastinal lymph node was cannulated with a silicone catheter (Alliedsil silicone tubing 1264/T056, 0.025-in. ID, 0.047-in. OD; Allied Biomedical) with a modified method based on the technique of Staub et al. (29). Ligation of the tail of the caudal mediastinal node and catherization of the systemic diaphragmatic lymph vessels removed the systemic lymph contribution. The animals were given 5–7 days to recover from the surgical procedure, with free access to food and water.

Measured variables. Lung lymph flow (QLymph) was measured with a graduated test tube and stopwatch. Lymph and blood samples were collected in tubes containing EDTA. The total lymph protein concentration (Clymph) was measured with a graduated test tube and stopwatch. Lymph and blood samples were collected in tubes containing EDTA. The total lymph protein concentration (Clymph) was measured with a refractometer (National Instrument, Baltimore, MD). For estimation of pulmonary microvascular permeability to protein, net protein transvascular flux in the lung (QLymph × Clymph, in g/ml) was calculated.

Mean arterial (in mmHg), pulmonary arterial (in mmHg), left atrial (LAP, in mmHg), and central venous (CVP, in mmHg) pressures were measured with pressure transducers (model PX-1800, Baxter, Edwards Critical-Care Division) that were adapted with a continuous flushing device. The transducers were connected to a hemodynamic monitor (model 78304A, Hewlett-Packard, Santa Clara, CA). The pressures were measured with the animals in the standing position. Zero calibrations were taken at the level of the olecranon joints on the front leg of the animals. Cardiac output was measured with the thermodilution technique with a cardiac output computer (COM-1, Baxter, Edwards Critical-Care Division). A 5% dextrose solution was used as the indicator. For evaluation of cardiac function, cardiac index (CI; in 1 min−1 m−2), left and right ventricular stroke work indexes (LVSWI and RVSWI, respectively; in g m−2 m−2), and systemic and pulmonary vascular resistance indexes (SVRI and PVRI, respectively; in dynes cm−5m−2) were calculated with standard equations. Blood gases were measured with a blood gas analyzer (model IL 1600, Instrumentation Laboratory, Lexington, MA). The blood gas results were corrected for the body temperature of the sheep. Oxyhemoglobin saturation and carboxyhemoglobin concentration were analyzed with a CO-Oximeter (model IL 482, Instrumentation Laboratory). Hematocrit (Hct) was measured in heparinized microhematocrit capillary tubes (Fisherbrand, Pittsburgh, PA). The arterial blood flow was serially determined with colored microspheres (15 ± 0.1 μm; Interactive Medical Technologies, Los Angeles, CA). Reference blood for the calibration of microsphere activity was withdrawn from the femoral arterial catheter at a constant rate of 10 ml/min for 2 min while the microspheres were injected. The color of the microspheres was changed with each injection.

Experimental protocol. Twenty-four hours before the experiment, the vascular catheters were connected to the monitoring devices, and maintenance fluid administration (Ringer lactate, 2 ml/kg) via the femoral vein was started. After baseline measurements and sample collections were completed, the animals were randomized into four groups: a burn group that received a 40% TBSA third-degree burn alone as described in Burn and smoke inhalation injury (n = 6), a burn/smoke group that received both a 40% TBSA third-degree burn and 48 breaths of smoke from burning cotton as described in Burn and smoke inhalation injury (n = 6), a smoke group that received 48 breaths of smoke from burning cotton alone as described in Burn and smoke inhalation injury (n = 6), and a control group that received no injury (n = 6). Immediately after injury, anesthesia was discontinued, and the animals were allowed to awaken but were maintained on mechanical ventilation (Servo Ventilator 900C, Siemens-Elema) throughout the 48-h experimental period. Ventilation was performed with a positive end-expiratory pressure of 5 cmH2O and a tidal volume of 15 mg/kg. During the first 3 h after injury, the inspiratory O2 concentration was maintained at 100% and respiratory rate was kept at 30 breaths/min to induce rapid clearance of carboxyhemoglobin after smoke inhalation. Then the ventilation was adjusted according to blood gas analysis to maintain arterial O2 saturation > 90% and PCO2 between 25 and 30 mmHg. The burn and the burn/smoke groups received fluid resuscitation during the experiment with Ringer lactate solution following the Parkland formula (4 ml%burned surface area−1 kg body wt−1 for the first 24 h and 2 ml%burned surface area−1 kg body wt−1 for the next 24 h). One-half of the volume for the first day was infused in the initial 8 h, and the remainder was infused in the next 16 h. Because the mechanical ventilation and/or fluid resuscitation itself might affect the physiological parameters, even the control group received the identical amount of fluid resuscitation following the Parkland formula and underwent the same ventilatory support as the injured animals during the whole experimental period. The smoke group was mechanically ventilated with the same setting as the other groups but was not resuscitated following the Parkland formula. The animals in the smoke group received maintenance fluid resuscitation (Ringer lactate solution, 3 ml kg−1 h−1) to mimic the clinical situation. Previously, Shenarts et al. (26) have demonstrated that the fluid requirement to maintain LAP at ±2 mmHg and mean arterial pressure at ±5 mmHg of the baseline values after smoke inhalation injury alone is an average of 3 ml kg−1 h−1 of Ringer lactate. During this experiment, the animals were allowed free access to food but not to water to accurately measure fluid intake.

For airway blood flow determination, 5 million colored microspheres were injected into the left atrium before and 3, 6, 12, 24, and 48 h after injury. The lymph and blood samples for determination of total protein concentration were collected 3, 6, 12, 18, 24, 36, and 48 h after injury in all groups. Hemodynamic variables and blood gases were obtained at 3, 6, 12, 18, 24, 30, 36, 42, and 48 h postinjury in all groups. Forty-eight hours after injury, animals were killed after an injection of ketamine followed by saturated KCl. Immediately after death, the entire right lung was harvested for measurement of blood-free wet weight-to-dry weight ratios (an index of pulmonary edema) as described by Pearce et al. (21). The lower part of the trachea just above the carina (to
which blood is supplied only by the bronchial artery) was harvested to determine airway blood flow (23, 26).

**Burn and smoke inhalation injury.** Before the injury, a tracheostomy was performed under ketamine anesthesia (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) and auffed tracheostomy tube (10-mm diameter; Shiley, Irvine, CA) was inserted. Then anesthesia was continued with halothane. Thereafter, the animals in the burn group were subjected to a 40% TBSA third-degree burn. After the wool was shaved, a 20% TBSA flame burn was made on one side of the flank with a Bunsen burner until the skin was thoroughly contracted. After this procedure, another 20% TBSA third-degree burn was made on the remainder of the flank. The burn/smoke group received both a 40% TBSA third-degree burn and smoke inhalation from burning cotton. The smoking procedure was performed between the series of 20% thermal injury (17). Smoke inhalation was induced with a modified bee smoker. The bee smoker was filled with 40 g of burning cotton toweling and then attached to the tracheostomy tube via a modified endotracheal tube containing an indwelling thermistor from a Swan-Ganz catheter. Four sets of twelve breaths of smoke (total 48 breaths) were delivered, and the carboxyhemoglobin level was determined immediately after each set. The temperature of the smoke was not allowed to exceed 40°C during the smoking procedure (14). The smoke group received only smoke inhalation with the same procedure as the burn/smoke group. In the control group, the tracheostomy was performed under ketamine anesthesia, and then the animal was connected to the mechanical ventilator.

**Statistical methods.** Summary statistics of data are expressed as means ± SE. In the burn and burn/smoke groups, data were analyzed with analysis of variance (ANOVA) for a two-factor experiment, with repeated measures on time. The two factors were experimental group (burn and burn/smoke) and time. Another two-way ANOVA was also performed in the smoke and burn/smoke groups. In the control group, data were analyzed with ANOVA for a one-factor experiment, with repeated measures on time. Fisher’s least significant difference procedure was used for multiple comparisons (or post hoc analysis). The differences in the wet weight-to-dry weight ratios of the right lung among groups were evaluated by means of Student’s unpaired t-test. A P value < 0.05 was considered to be significant.

**RESULTS**

All animals in all groups survived the 48-h experimental period. The arterial carboxyhemoglobin levels immediately after the smoke exposure were 69.6 ± 4.1% in the burn/smoke group and 72.1 ± 9.2% in the smoke group. There was no significant difference between these values.

**Airway blood flow.** The tracheal blood flow in the smoke and burn/smoke groups dramatically increased immediately after injury (1,666 ± 168 and 1,671 ± 360% of the baseline values in the smoke and burn/smoke groups, respectively, 48 h after injury; P > 0.05). The burn-alone group showed a mild but significant increase in tracheal blood flow at 48 h (545 ± 151% of baseline value at 48 h; P < 0.05; Fig. 1). The airway blood flow consists of two blood supplies, the systemic and pulmonary circulations (23, 28, 33). The lower trachea harvested in the present study is supplied by the bronchial arteries from the systemic circulation.

These vessels of the airway circulation anastomose with each other and empty into the pulmonary circulation (bronchopulmonary shunt). Previous studies conducted in our laboratories (23, 24) have demonstrated that major burn alone can increase pulmonary microvascular permeability to water (7). The burn/smoke group and smoke-alone group showed significant increases in Q_\text{lymph} at 12 h after injury (Fig. 2). It has been demonstrated that major burn alone can increase pulmonary microvascular permeability to water (7). The burn/smoke group and smoke-alone group showed significant changes in Q_\text{lymph} after injury. In the smoke-alone group, the Q_\text{lymph} increased more slowly than in the combined injury group and reached significance 24 h after injury (9.8 ± 2.0 ml/h at baseline; 35.4 ± 8.0 ml/h at 24 h; P < 0.05; Fig. 2). This delayed onset of pulmonary microvascular hyperpermeability seen with smoke inhalation injury has been demonstrated to be due to the progress of inflammation from the injured airway to the lung tissue subsequent to a marked increase in airway blood flow (1, 23). The Q_\text{lymph} tended to be higher in the burn/smoke group than in the smoke group throughout the experiment (by 69.3% at 30 h), although there was no significant difference between the groups. This result suggests that burn injury contributes to the augmentation of transvascular-
lar fluid flux in the pulmonary microvasculature when
smoke inhalation injury is associated with burn injury. Net protein transvascular flux in the lung ($Q_{\text{lymph}} \times C_{\text{lymph}}$) increased significantly in both the burn/smoke and smoke groups; however, there was no significant difference between the groups (Fig. 3). In the burn-alone group, the net protein flux in the lung was relatively constant but tended to be lower than the control group (Fig. 3). These data suggest that burn injury does not affect protein leakage from the pulmonary microvasculature. The blood-free wet weight-to-dry weight ratios of the right lung were burn/smoke > smoke > burn > control. The burn/smoke group showed significantly higher wet weight-to-dry weight ratios compared with either smoke-alone or burn-alone injury group. *Significant difference from the burn group, $P < 0.05$. †Significant difference from the control group, $P < 0.05$. ‡Significant difference from the smoke group, $P < 0.05$.

Cardiac functions. Hemodynamic variables are summarized in Tables 1 and 2. Although a large amount of fluid was administered rapidly, both the burn and burn/smoke groups showed hemoconcentration as evident from the significant increase in Hct immediately after injury (Fig. 5) due to fluid loss from the circulating plasma to the systemic interstitial space. In the burn group, it peaked 3 h after injury and recovered to the baseline value within 12 h, whereas in the burn/smoke group, hemoconcentration was significantly worse than in the burn group. However, the Hct in the burn/smoke group peaked 24 h after injury and then improved, which suggests that hemoconcentration was not sustained after 24 h even when the burn injury was associated with the smoke inhalation injury. The control group did not show significant changes in the Hct throughout the study.

The burn and burn/smoke groups showed a significant decrease in CI immediately after injury (71.1 ± 3.9 and 69.0 ± 3.7% of the baseline values in the burn and burn/smoke groups, respectively, 3 h after injury; $P < 0.05$; Fig. 6A). In the burn-alone group, a trough in CI was observed 3 h after injury. Thereafter, it recovered smoothly and returned to near baseline level within 6 h, whereas hemoconcentration was restored by fluid resuscitation. In the burn/smoke group, the CI improved slightly 6 h after injury but remained depressed for >36 h and then gradually returned toward baseline. There was a significant difference between the burn and burn/smoke groups during the 24–30 h after injury. The CI in the smoke-alone group decreased slowly and reached significance 12 h after injury (82.4 ± 6.1% of the baseline value; $P < 0.05$; Fig. 6B). The control group did not show significant changes in CI throughout the experimental period (Fig. 6). This
result indicates that the depressed CI seen in the later phase after burn and smoke combined injury correlates with the smoke inhalation injury.

In the burn/smoke group, the LVSWI significantly decreased immediately after injury (45.8 ± 3.8% of the baseline value at 3 h; \( P < 0.05 \)). It showed slight improvement transiently and then deteriorated again, and it remained depressed throughout the remainder of the experimental period (Table 2). The burn-alone group also showed a rapid fall in LVSWI (52.7 ± 11.3%...
of the baseline value at 3 h; \( P < 0.05 \), but it recovered smoothly toward the baseline value in a later phase (Table 2). There was a significant difference in the LVSWI between the burn and burn/smoke groups during the 18–42 h after injury. The smoke group showed a significant decrease in LVSWI in only the later phase, during the 18- to 48-h period (72.1 ± 9.2% of the baseline value at 18 h; \( P < 0.05 \); Table 2). The LAP and CVP (preload) increased rather than decreased in all groups after injury, with a large amount of fluid resuscitation and mechanical ventilation with positive end-expiratory pressure (Table 1). The relationships between preload and stroke work (LAP and LVSWI; CVP and RVSWI) are shown in Fig. 7 as indexes of myocardial contractility. The values for the burn/smoke group are clearly shifted downward and to the right. This result indicates that this cardiac dysfunction seen in the burn/smoke group was due to myocardial contractile depression independent of the Starling mechanism.

Vasoconstriction after injury. Both the burn and burn/smoke groups showed a rapid increase in PVRI and SVRI (Table 2). In contrast, in the smoke-alone group, the increase in the PVRI and SVRI was delayed in onset. Each reached significance 18 h after injury (Table 2). In the burn-alone group, these vascular constrictions improved smoothly with fluid resuscitation. However, in the burn and smoke inhalation combined group, recovery from the initial vasoconstriction was
DISCUSSION

It is well known that morbidity and mortality risk increases when thermal injury is associated with inhalation injury (5, 28, 36). The present study reproduced the typical response to this combination injury. In the burn and smoke combined injury group, a pulmonary failure associated with more severe lung edema formation, increase in fluid requirement, and prolonged cardiac depression were noted compared with those in the burn-alone group.

The results confirmed that lung edema formation and secondary pulmonary failure are much more severe when thermal injury accompanies smoke inhalation injury. However, the results revealed that burn injury does not contribute to the increase in protein leakage from the pulmonary microvasculature. Demling et al. (7) and Harms et al. (10) reported that major thermal injury alone caused a selective increase in pulmonary microvascular permeability only to water and small solutes but not to protein. Our results are in agreement with their work. In our study, the smoke group showed a significant increase in Q$_{\text{lymph}}$, the ratio of lymph to plasma protein content, and net protein flux from the pulmonary vasculature in the lung. In contrast, in the burn/smoke group, the Q$_{\text{lymph}}$ was significantly increased and to a somewhat greater degree. On the other hand, the increase in protein flux was no greater than that observed in the group with smoke inhalation alone. The edema formed in the combined injury group, which was over and above what was seen with smoke injury alone, is probably due to changes in permeability to small molecules. More exacting techniques such as measurement of the reflection coefficient and filtration coefficient need to be utilized in these models to make a final confirmation of this hypothesis. Isago et al. (13) from our laboratory previously showed that the reflection coefficient decreased and the filtration coefficient increased in the pulmonary microvasculature after smoke inhalation injury. These findings suggested that pulmonary vascular permeability to both water and protein increased after smoke inhalation through both transcellular and paracellular pathways. The present study suggests that burn injury does not affect the paracellular pathway even when the burn is associated with smoke inhalation injury. Again, this will have to be confirmed by further investigation. Interestingly, our findings are not in agreement with results reported in rats by Till and Ward (32). They have shown that there is an increase in pulmonary microvascular permeability to protein after burn injury. The difference in experimental model and the degree of resuscitation of the animals may relate to the results. The burn wound in their rat model was second degree (partial thickness) as opposed to the third-degree burns in our studies and those of Demling et al. (7) and Harms et al. (10). We are unable to study second-degree burns in our ovine model because the injury is painful. In third-degree burns, animals feel no pain because the nerve endings are destroyed. Inadequate resuscitation may result in lung damage secondary to reperfusion injury (31).

The cardiac dysfunction seen in the burn/smoke group seemed to consist of two phases. An initial depression characterized by a significant decrease in CI and stroke work index was observed within 3 h after injury in both the burn and burn/smoke groups. The depression correlated with the hemoconcentration evident from the significant increase in Hct and the increase in SVRI. These phenomena may be explained by a hypovolemia resulting from a large amount of fluid loss from the circulation due to vascular hyper-permeability because the burn-alone group showed a smooth recovery of cardiac function with fluid resuscitation. The increased peripheral resistance could be the result of sympathetic stimulation. Although there is still controversy over what is the main cause of cardiac depression after thermal injury, hypovolemia or the circulating cardiac depressant factor (2, 8, 19, 27), our results are consistent with hypovolemia as the primary contributor. However, analysis of the relationship between preload and stroke work index revealed that the depressed myocardial contractility in both the burn and burn/smoke groups occurred independent of the Starling mechanism, which may support the existence of a myocardial depressant factor released from the burn wound. We speculate that burn wounds release vasoactive mediators that contribute to the alteration of vascular permeability and vasoconstriction immediately after thermal injury. However, the mediator might be inactivated by the administration of large amounts of fluid. The duration of release and the amount of mediator released from the burn wound may also depend on the depth of the thermal injury.

On the other hand, the left side-dominant myocardial depression seen in the later phase in the burn/smoke and smoke groups cannot be explained by hypovolemia. It was observed beginning 18–24 h after injury. In this regard, the Hct in the burn/smoke group peaked 24 h after injury and then improved, which suggests that hemoconcentration was not sustained beyond 24 h. The delayed-onset cardiac depression seen in the burn and smoke combined injury group is likely related to the smoke inhalation and subsequent progressive lung tissue inflammation. Recent investigations (3, 9, 22) have demonstrated that proinflammatory cytokines are circulating myocardial depressant substances during inflammatory conditions such as septic shock, ischemia-reperfusion injury, or burn. In addition, induction of inducible nitric oxide (NO) synthase (iNOS) and the subsequent overproduction of NO has been suggested as a myocardial depressant factor as well as the inflammatory cytokines (3, 15, 22, 35). Recently, we (Traber, unpublished data) have found a significant increase in plasma concentrations of nitrite/nitrate (metabolites of NO) beginning 24 h after burn and smoke combined injury in a sheep experimental model. It is unlikely that iNOS-NO af-
fects the initial cardiac depression seen with burn injury because iNOS is not expressed before cell activation by inflammatory cytokines and expression takes several hours to occur (16). However, it is possible that NO plays some role in the cardiac dysfunction seen in the later phase with burn and smoke inhalation combined injury.

In the present study, the airway blood flow was determined in each group. The smoke and burn/smoke groups showed a significant increase in blood flow immediately after injury. This augmented airway blood flow, associated with inflammation in the airway, contributes to development of the lung tissue damage seen with smoke inhalation injury by transporting inflammatory mediators from the injured airway to the pulmonary tissue through the bronchopulmonary shunt, which is a communication between the systemic circulation supplying the airway and the pulmonary microcirculation (1, 23). On the other hand, the burn-alone group showed a significant increase in tracheal blood flow 48 h after injury, which indicates that inflammatory events occurred in the airway to which blood is supplied via the bronchial artery from the systemic circulation. This result may support the hypothesis that burn wounds release cytokotic mediators, which play a role in the pulmonary failure seen in the later phase of extensive cutaneous burn injury.

In summary, the acute pathophysiological alterations observed after combination injury with burn and smoke inhalation may be mostly related to burn injury. The effect of the additional smoke inhalation was observed later than 18–24 h after injury as progressive pulmonary failure, with more severe edema formation and sustained left side-dominant myocardial dysfunction. The lung edema formation was most severe when the burn injury was associated with smoke inhalation injury. The severity of lung edema seen with the combined injury is mainly due to augmentation of pulmonary microvascular permeability to fluid, not to protein.

REFERENCES


