Published in final edited form as:

Burns. 2009 September ; 35(6): 802–810. doi:10.1016/j.burns.2008.12.013.

Effect of ablated bronchial blood flow on survival rate and pulmonary function after burn and smoke inhalation in sheep

Atsumori Hamahata¹, Perenlei Enkhbaatar², Sakurai Hiroyuki¹, Motohiro Nozaki¹, and Daniel L. Traber²

¹ Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University, Tokyo, Japan

² Departments of Anesthesiology, University of Texas Medical Branch, Galveston, TX, USA

Abstract

The bronchial circulation plays a significant role in the pathophysiological changes of burn and smoke inhalation injury. There is a marked increase in bronchial blood flow immediately after inhalation injury. In this study we examine the ablation of bronchial artery will attenuate the pathophysiological changes and improve survival rate after burn and smoke inhalation injury in ovine model. Acute lung injury was induced by 40% total body surface area 3rd degree cutaneous burn and cotton smoke (48 breaths of cotton smoke, <40°C) under deep anesthesia. Twelve adult female sheep were divided into two groups: 1) Sham (injured, not ablated bronchial artery, n=6); 2) Ablation (injured, ablated bronchial artery, n=6). Ablation of bronchial artery was performed 72h before-injury. The experiment was continued for 96h. Burn and smoke inhalation injury significantly increased the regional blood flow in Bronchi. Ablation of bronchial artery significantly reduced the acute regional blood flow increase in proximal and distal bronchi. All animals in the ablation group survived until 96h. Four of them were successfully weaned from the ventilator. Three of sham group animals met euthanasia criteria at 60h and one of them met the criteria at 78h. The lung wet/dry weight ratio, the histology score, and myeloperoxidase activity were significantly increased by the insult, but ablation of bronchial artery attenuated these changes. Burn and smoke inhalation injury induced a significant increase in bronchial blood flow and accelerated airway obstruction, pulmonary vascular changes, pulmonary edema and pulmonary dysfunction. The ablated bronchial circulation attenuated these pathophysiological changes.

Keywords

Bronchial artery; smoke inhalation; acute respiratory distress syndrome; neutrophils; survival rate

Burn injury is very traumatic, especially when the thermal injury is associated with smoke inhalation. This combination greatly increases morbidity and mortality [1,2]. After smoke inhalation, there is a rapid appearance of hyperemia in the upper airway of humans and sheep [3–5]. Hyperemia of the airway is the most effective way of diagnosing smoke inhalation [6]. Pulmonary edema has been directly related to smoke inhalation injury as evidenced by an increase in extravascular lung water and lung lymph flow after inhalation injury [7–11]. Smoke

Corresponding author. Address for reprint requests and other correspondence: D. L. Traber, Dept. of Anesthesiology, 301 University Blvd. Galveston TX 77555-0833 (dltraber@utmb.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

inhalation has also been shown to cause an increase in microvascular permeability to protein in the pulmonary and bronchial circulations [8–10,12]. These physiological alterations in pulmonary microvasculature are delayed in onset, and the peak of increased microvascular permeability was observed around 24h after injury [13]. In contrast, there is a marked increase in bronchial blood flow immediately after inhalation injury [3,14]. Because the increased bronchial blood flow largely enters the pulmonary vasculature through pre-capillary anastomoses with the pulmonary microcirculation [15–17], it has been suggested that the bronchial circulation plays a significant role in the spread of injury from the airway of the lung to the parenchyma [11,18]. Reduction of the bronchial artery reduced lung edema formation after inhalation in anesthetized canine model [11] and in a conscious sheep model [10,18]. We performed 96hr survival experiments and analyzed the regional tissue blood flow. The present study was undertaken to provide a detailed analysis of pulmonary function at 96hr after injury and the 96hr survival rate. We hypothesized that ablation of the bronchial artery would not only reduce pulmonary injury following combination burn and inhalation injury but also allow survival to 96hr with weaning from ventilatory support.

MATERIALS AND METHODS

Twelve adult female sheep (30–40 kg) were cared for in the Investigative Intensive Care Unit at our institution. The experimental procedure was approved by the Animal Care and Use Committee of the University of Texas Medical Branch. The National Institutes of Health and American Physiological Society guidelines for animal care were strictly followed. The Investigative Intensive care unit is accredited by The Association for the Assessment and Accreditation of Laboratory Animal Care International.

Animal Preparation

All animals were endotracheally intubated and ventilated during the operative procedure while under isoflourane anesthesia. Arterial catheters (16 gauge, 24 in., Intracath, Becton Dickinson, Sandy, UT) were placed in the descending aorta via the femoral artery. A Swan-Ganz thermal dilution catheter (model 93A-131-7F, Edwards Critical-Care Division, Irvine, CA) was positioned in the right pulmonary artery via the right external jugular vein. A silastic catheter was positioned in the left atrium through a left thoracotomy. A 10-mm pneumatic occluding cuff (In Vico Metrics, Healdsburg, CA) was implanted around the left pulmonary artery just distal to its origin. Sheep have a single bronchial artery, which was called “carinal artery” [19]. In the ablation group (n=6), the bronchial artery “carinal artery” was exposed near its origin on the aorta through a left 4th thoracotomy, and 1mL of 70% ethanol were injected into the artery after the ligation of the bronchial artery with 5-0 silk suture. In sham group (n=6), the bronchial artery was exposed but left intact.

Experimental Procedures

After a recovery period, the sheep were deeply anesthetized with isoflourane and were given a flame burn [40% total body surface area (TBSA), third degree] and inhalation injury (48 breaths of cotton smoke, <40°C). After burn and inhalation injury, all sheep were placed on a ventilator with positive end-expiratory pressure set to 5 cm H₂O and tidal volume maintained at 15 mL/kg in an awake condition. The latter tidal volume is equal to about 10 mL/kg in humans due to the large ventilatory dead space of sheep [20]. All animals were given fluid resuscitation with Ringer’s lactate solution strictly according to the Parkland formula (4 mL/kg/% TBSA burned/24 hr) [21]. The experiment was continued for 96 h. The ventilation weaning was begun if the animal was clinically stable and her PaO₂/FIO₂ was higher than 250 at 48h after initial insult. In ventilation weaning, the ventilation setting was changed to pressure support ventilation (PSV) in combination with synchronized intermittent mandatory ventilation (SIMV) and tried SIMV with a low rate and low-level PSV, then transitioned to

continuous positive airway pressure (CPAP). If the animals' condition remained steady, the animal was taken from ventilatory support and transferred to blow-by. Escharectomy of cutaneous wound was not performed but the wound was disinfected with Betadine Solution (Purdue Pharma, Stamford, CT) every day. Euthanasia criteria were determined when systolic blood pressure was below 60 mmHg, heart rate continued below 40/min for 1 hour, PaCO₂ was above 100 Torr, PaO₂ was below 45 Torr (FIO₂ at 100%). If the animal met one of these criteria, the measurement was repeated after another 1 hour. If the animal met the criteria again, it was anesthetized with ketamine and euthanized by high dose of i.v. KCl (60ml).

Measurements

To substantiate the changes in bronchial blood flow, flow was measured with the fluorescent microsphere technique (Interactive Medical Technologies, West Los Angeles, CA) which we had previously developed [22]. After operation, before injury and 3, 6, 24, 72, 96 h after injury, $\sim 12 \times 10^6$ fluorescent colored microspheres ($15.0 \pm 0.1 \mu\text{m}$) were injected into the left atrium. Since some of the microspheres may pass through some of the larger vessels in the non bronchial pulmonary circulation, the pneumatic occluder on the left pulmonary artery was inflated immediately after microsphere injection to prevent any pulmonary artifact to the bronchial blood flow measurement [22]. To calibrate microsphere numbers per blood flow, blood was withdrawn from the aorta with a Harvard pump (Harvard Apparatus model 55-1143, South Natick, MA) at a rate of 10 mL/min; the withdrawal was started before microsphere injection and continued for 2 min. Trachea, left proximal bronchi (6–8 mm bronchi near carina) and left distal bronchi (2–4 mm bronchi in distal lower lobe) were obtained postmortem and used to quantify the bronchial blood flow to the bronchi. The parenchymal tissues were removed from the latter by careful dissection.

Arterial and mixed venous blood samples were taken at different time points for measurement of blood gases (IL GEM Premier 3000 Blood Gas Analyzer; GMI, Minnesota) and white blood cells, neutrophil counts were also counted at different time points (HEMAVET® HV950FS; Drew Scientific, Inc, Texas). PaO₂/FIO₂ ratio was measured to help assess pulmonary gas exchange. Pulmonary shunt fraction (Qs/Qt) was calculated using standard equations. Sheep were sacrificed under deep ketamine anesthesia 96 h after injury or at the time sheep met euthanasia criteria.

For histological assessment of the lung tissue, the right lung was then removed, and a 1-cm-thick section was taken from the middle of the lower lobe, gently injected with 10% formalin in various areas to facilitate fixation and immersed in formalin and fixed for 2 to 3 days. The slice of tissue was then sampled per protocol by a technician unaware of the study conditions into four samples representing approximately 60% of the initially collected lung slice. Fixed samples were then embedded in paraffin, sectioned at $4\mu\text{m}$, and stained with hematoxylin and eosin. A pathologist without knowledge of the group assignments evaluated the lung histology. Levels of airway obstruction were obtained with a standardized protocol by estimating the degree of obstructive material (0 to 100%) localized within the airway lumen. Typically between 10 and 20 bronchi and 100 to 200 bronchioles are scored per animal. Mean bronchial and bronchiolar obstruction were obtained from these estimated [23,24]. The parenchyma from each of the four sections from each animal were also examined and semiquantitatively scored for the degree of alveolar edema and the presence of neutrophils localized in the alveolar space. A score of 0 was used to represent the absence or normal appearance of the parenchyma, with scores of 1–4 representing increasing areas of the histological section exhibiting the pathological parameter. A mean score for each parameter was calculated from the four individual scores. The remaining lower one-half of the right lower lobe was used for the determination of bloodless wet-to-dry weight ratio [25].

The activity of myeloperoxidase (MPO), an indicator of neutrophil accumulation, was determined spectrophotometrically in whole lung homogenates. MPO concentrations were evaluated on homogenized right lung with a commercially available assay. Myeloperoxidase activity was reported as U/g tissue (CytoStore, Calgary, AB, Canada)

Statistical Analyses

Summary statistics of data are expressed as means $\pm$ standard error of the mean. Statistical significance was determined using an analysis of variance, and for the differences between each value, Tukey-Kramer honestly significant difference was used (post-hoc analysis). Effects and interactions were assessed at $p < 0.05$ level of significance. Chi-square analysis of survival differences was calculated between ablation and sham groups.

RESULTS

Figure 1 shows the regional blood flow changes measured with fluorescent colored microspheres. In the trachea, burn and smoke inhalation injury significantly increased in both injection and sham groups (Ablation group; Base Line: 0.18 ± 0.04 vs. 6h: 1.25 ± 0.22 , Sham; Base Line: 0.15 ± 0.02 vs. 6h: 1.67 ± 0.16 mL/g tissue). The regional blood flow at 6h in trachea had 6.9 and 11 times higher than base line and the ablation of the bronchial artery didn't reduce the acute regional blood flow increase in trachea (Figure 1A). In the proximal and distal bronchi, burn and smoke inhalation injury significantly increased the regional blood flow at 6h, 10 times and 9.6 times higher than base line in sham group (Proximal bronchi; Base Line: 0.24 ± 0.01 vs. 6h: 2.47 ± 0.18 , Distal Bronchi; Base Line: 0.30 ± 0.04 vs. 6h: 2.89 ± 0.42). Ligation and ethanol injection in the bronchial artery significantly reduced the acute regional blood flow increase in proximal and distal bronchi (Proximal bronchi; Base Line: 0.13 ± 0.02 vs. 6h: 0.51 ± 0.25 , Distal Bronchi; Base Line: 0.20 ± 0.04 vs. 6h: 0.44 ± 0.25). Notably, smoke inhalation did not induce hyperemic changes in proximal and distal bronchi in the ablation group. However, the regional blood flow in ablation group was slightly increased between after injection and base line (after 72h) (Proximal bronchi; After Injection: 0.08 ± 0.02 vs. Base Line: 0.13 ± 0.02 , Distal Bronchi; After Injection: 0.15 ± 0.05 vs. Base Line: 0.20 ± 0.04) (Figure 1B,C).

Figure 2 shows the animal survival proportions. All animals in ablation group survived until 96h. Four of them were successfully weaned from the ventilator but two of them didn't meet the ventilation weaning criteria ($\text{PaO}_2/\text{FIO}_2 > 200$ at 48h). None of the animals in sham group met criteria for the removal from the ventilator. Three of these sheep in the sham group met euthanasia criteria at 60h and one of them met the criteria at 78h. There is a significant difference between ablation group and sham group ($p=0.02$).

Figure 3 shows the effect of ablated bronchial artery blood flow on pulmonary gas exchange. In $\text{PaO}_2/\text{FIO}_2$ ratio graph, four of injection animals did not fall below 200 within 48h but two of them dropped below 200. All sham animals dropped below 200 within 48h. After 48h, four of injection animals were started on ventilation weaning because they met the ventilation weaning criteria. Two of them didn't meet criteria, so they were not started ventilation weaning. None of the animals in the sham group met the criteria. The graph lines were separated after 48h in the ablation group because the ventilation settings were different. There was no significant difference but overall the ablation group had higher $\text{PaO}_2/\text{FIO}_2$ ratios than the sham group. In the pulmonary shunt fraction graph, there was no significant difference but overall, the ablation group had a lower pulmonary shunt fraction than sham group.

Figure 4 shows the effect of ablated bronchial artery blood flow on pulmonary circulation. Overall, the sham group had higher pulmonary artery pressure than the ablation group and remained higher until 72h. Significant differences at 12h, 36h and 48h were found between the ablation group and sham group (Figure 4A). Figure 4B shows the pulmonary vascular

resistance index. The value was remarkably increased at 12h and remained high until 36h and then decreased in the sham group. On the other hand, the values were lower in the ablation group. Significant differences were found at 12h, 18h, 24h, 30h and 36h.

Figure 5 shows the effect of ablated bronchial artery blood flow on white blood cells (WBC) counts and neutrophil counts. Burn and smoke inhalation injury increased WBC and neutrophil counts in the sham group animals. However, ablation of the bronchial artery attenuated the changes. Significant differences occurred at 24h in neutrophil counts.

We separated the pathological data, wet to dry ratio data and myeloperoxidase data in each survival time hour because these results are different in each time course [23]. In the bronchial artery ablation and no injury animals (control group, n=2), the average airway obstruction score in bronchi and bronchiole were 2.6 and 2.3 respectively. The airway obstruction scores revealed an increase in the mean degree of obstruction in both bronchi and bronchioles in the 60h and 78h sham group. The obstruction score was much lower in the sheep with ablated bronchial blood flow (4.4 ± 1.6). There was a significant difference between the 60h sham group and ablation group (Figure 6A,B). The average scores representing the degree of PMNs and edema seen in the alveolar areas of the lung were 0.6 ± 0.3 and 0.79 ± 0.48 , respectively. In the bronchial artery ablation and no injury animals (control group, n=2), the scores representing the presence of PMNs and edema in the alveoli were 0.0 and 0.0 respectively. The PMN cells score and edema formation scores were remarkably increased in sham group. The obstruction score was much lower in the sheep with ablated bronchial blood flow. There was a significant difference between the 60h sham group and ablation group (Figure 6C,D).

In the bronchial artery ablation and no injury animals (control group, n=2), the average lung bloodless wet to dry ratio was 2.9 and 4.4 respectively. Lung bloodless wet to dry weight ratio, a measure of lung water content, was remarkably increased in the sham group. However, the lung wet to dry ratio was much lower in the in the group with ablated bronchial blood flow (4.6 ± 0.5). The activity of myeloperoxidase (MPO), an indicator of neutrophil accumulation, was also remarkably increased in the sham group. However, the MPO activity was much lower in the in the group with ablated bronchial blood flow (Figure 7).

DISCUSSION

The systemic circulation of the lung supplies nutrient materials to airways, blood vessels, and supporting structures. The bronchial circulatory system has been thought to play a significant role in certain physiological functions such as warming and humidification of inspired air [26]. Normally the bronchial circulation comprises ~1–3% of cardiac output [19,22]. In several disease states, including pulmonary artery obstruction, congenital pulmonary atresia, chronic bronchiectasis, and chronic lung abscess, its proportion of the cardiac output may be much larger [27–29]. Acute elevations of bronchial blood flow have also been noted after infusion of bradykinin, histamine, and endotoxin in dogs and sheep [30–32]. These increases in bronchial blood flow may contribute to airway edema, bronchiectasis, and airway occlusion.

After smoke inhalation, there is a rapid appearance of hyperemia in the upper airway of humans and sheep [3–5]. There is a more than 10 fold increases in bronchial blood flow immediately after inhalation injury [3,14,33]. In the present experiment, there is an approximate 10-fold increase at 6h in trachea, proximal and distal bronchi. On the other hand, ligation and sclerosis of the bronchial artery significantly reduced the regional blood flow changes in proximal and distal bronchi. Trachea receives systemic blood supplied from the tracheal bronchial and thoracic tracheal branch of the aorta in sheep [34]. These branches were not ablated in present study because the bronchial artery is the major source of the circulation to the airway, at the level of the carina and below it [19,34]. Considering the fact, it is easy to understand that the

regional blood flow in trachea wasn't reduced in ablation group and our results also show that these tracheal branches contributed less to lung parenchyma than the bronchial artery itself. The regional blood flow in proximal and distal bronchi slightly increased at base line compared to after ablation. The ablation of bronchial artery was performed 72h before injury. Baile et al. [35] used radioactive microspheres and reported that ethanol injection (total 4ml) into the bronchoesophageal artery reduced systemic arterial blood flow into the sheep lung by ~75%, whereas ligation of the bronchoesophageal artery reduced by ~50%. We also previously reported that the reduction of airway blood flow in the ligation and 70% 4ml ethanol ablation groups was 32.1 ± 12.0 and $86.3 \pm 7.2\%$, respectively (35). Trachea and bronchi blood circulation have longitudinal anastomosis [36,37] and only mechanical obstruction of bronchial artery easily leads to opening of the collateral blood flow. In order to ablate the bronchial artery, we ligated with 5-0 silk and injected 1ml ethanol into the bronchial artery but the regional blood flow slightly increased 72h after injection. It was suspected that this increase was because of the collateral blood flow opening and 1ml ethanol was not enough to ablate all anastomoses, some blood flow come back via collateral vessels.

The changes of pulmonary vascular pressure and pulmonary vascular resistance were much greater in our present study of combined burn and smoke injury in comparison to our previous report in which sheep had bronchial artery ablation and the animals had smoke inhalation injury alone (37, 40). Burn and smoke inhalation injury increases reactive oxygen and nitrogen species than smoke inhalation injury alone and these differences might affect the results (32, 42). If only smoke inhalation injury were given, the mortality rate is lower and the changes in WBC, neutrophils, MPO are not as great.

All animals in ablation group survived until 96h and the four of them were succeeded ventilation weaning. Two of them didn't meet the ventilation weaning criteria at 48h. Whereas, four of sham animals died within 96h and none of these animals met the ventilation weaning criteria at 48h. To our knowledge there is no previous report on the effect of ablation of the bronchial artery on survival, and the success of ventilation weaning in sheep after burn and smoke inhalation injury. The ablated bronchial arterial flow resulted in improved pulmonary gas exchange and pulmonary vascular resistance changes after burn and smoke inhalation injury (Figure 3,4). The mechanism by which the bronchial circulation contributes to the pathogenesis in lung parenchyma has not been clearly defined. With inhalation of smoke, there is a reduction in reflection coefficient (permeability to protein), an increase in filtration coefficient (permeability to small particles), and an increase in pulmonary microvascular pressure [13,38]. These changes could be virtually eliminated by ablation of bronchial circulation to the lung [10,11]. The increased bronchovascular permeability accelerates airway exudation and causes airway obstruction. Certainly airway obstruction must also play a role in gas exchange. We have reported a good correlation between airway obstruction and reduced $\text{PaO}_2/\text{FIO}_2$ [23]. However, ablated bronchial circulation attenuated the formation of airway obstruction and improved pulmonary gas exchange.

In the present study, the edema formation score in parenchyma and lung wet to dry ratio were remarkably increased after burn and smoke inhalation injury in sham group but the ablated bronchial artery significantly attenuated the edema formation score in parenchyma and lung wet to dry ratio (Figure 6D, 7A). Bronchial circulation supplies 88% of the intrapulmonary airway blood flow except the right apical lobe [19, 39] and most of intrapulmonary airway blood flow drained into the pulmonary microcirculation at the pre-capillary level [16, 40], only 13% of bronchial circulation drain into the bronchial venous system into the right heart [41]. Increased bronchial blood flow elevates pulmonary transvascular fluid flux and causes pulmonary edema [38, 42]. Perhaps the answer to the key role of the bronchial circulation is that the venous drainage of the bronchial circulation to the airways that lie within the lung drains into the pulmonary microvasculature while the systemic venous drainage from airways

outside the lung drain into the azygos [16, 43]. We confirmed these studies in experiments in which we isolated the bronchial venous drainage to the pulmonary microvasculature [44].

Neutrophils also play a critical role in burn and smoke inhalation injury induced adult respiratory distress syndrome (ARDS) [45,46]. In present study, PMN cells score in parenchyma and myeloperoxidase in lung tissue were remarkably increased after burn and smoke inhalation injury in sham group but ablated bronchial artery significantly attenuated PMN cells score in parenchyma and myeloperoxidase in lung tissue (Figure 6C,7B). Thus with smoke inhalation injury the airway could release mediators into the bronchial venous drainage that could in turn deliver them to the pulmonary parenchyma where they could elicit lung damage. Under many circumstances one would consider the venous drainage to be somewhat insignificant since it is only 1 % of the total pulmonary blood flow. However in the situations when the blood flow in the bronchial vessel is increased 10 fold it assumes 10% of the total pulmonary blood flow. Neutrophils activated in the bronchial circulation flow out into the pulmonary microcirculation [42]. Treatment of the cells with an antibody to L-selectin prevents the changes in transvascular fluid flux and other aspects of parenchymal damage [46]. Burn and smoke inhalation injury increases bronchial circulation flow and drain out inflammatory mediators and cells into pulmonary parenchyma, whereas ablated bronchial artery reduces a rapid increase of bronchial circulation and suppresses the inflammation. The parenchymal damage which causes pulmonary failure and mortality would be ameliorated by the reduction of rapid bronchial blood flow increase.

In the limitations of this experiment, it is impossible for us to have a true sham group with intact bronchial artery, weaned from the ventilator by 96h. If we compare our survivor animals to the two animals still on the ventilator at 96h and to other injured animals that expired at earlier time periods, there were certainly fewer markers of lung injury in the bronchial artery ligation group. While some might attribute some of this injury to barotraumas from the ventilator, comparison to animals that did not have burn/smoke insult but the same ventilators settings, showed little or no pathological changes.

We succeeded in cannulating a catheter to the bronchial artery while maintaining bronchial artery flow, and injected ethanol 1 hr after injury into the catheter. The ablation of bronchial artery after inhalation injury also attenuated the pulmonary dysfunction induced by burn and smoke inhalation injury. Nonetheless, interventional therapy has progressed rapidly and multiple cannulation techniques have been developed. In the future, we will be able to infuse pharmacological agents into human bronchial arteries. Consequently, it will be possible to suppress the bronchial artery flow in situations of pulmonary hyperemia in humans via the interventional technique.

In conclusion, burn and smoke inhalation injury induced a rapid increase of bronchial blood flow and accelerated airway obstruction, pulmonary vascular changes, pulmonary edema and pulmonary dysfunction. Ablation of the bronchial circulation suppressed the inflammation, attenuated these pathophysiological changes of smoke/burn injury and improved animal survivability. Interventional therapy to modulate the bronchial circulation using pharmacological agents may be an effective strategy in the management of ARDS induced by burn and smoke inhalation injury.

Acknowledgments

We thank Jeffrey D. Meserve for his editorial assistance and Nettie Biondo and John R. Salsbury for their technical assistance.

This work was supported by National Institute for General Medical Sciences Grant GM66312, GM060688 and Grants 8954, 8450 and 8460 from the Shriners of North America.

References

1. Saffle JR, Davis B, Williams P. Recent outcomes in the treatment of burn injury in the United States: a report from the American Burn Association Patient Registry. *J Burn Care Rehabil* 1995;16(3 Pt 1): 219–32. [PubMed: 7673300]discussion 288–9
2. Barrow RE, Spies M, Barrow LN, Herndon DN. Influence of demographics and inhalation injury on burn mortality in children. *Burns* 2004;30(1):72–7. [PubMed: 14693089]
3. Stothert JC Jr, Ashley KD, Kramer GC, et al. Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol* 1990;69(5):1734–9. [PubMed: 2272966]
4. Linares HA. A report of 115 consecutive autopsies in burned children: 1966–80. *Burns Incl Therm Inj* 1982;8(4):263–70. [PubMed: 7066724]
5. Linares HA, Herndon DN, Traber DL. Sequence of morphologic events in experimental smoke inhalation. *J Burn Care Rehabil* 1989;10(1):27–37. [PubMed: 2921256]
6. Pruitt BA Jr, Cioffi WG, Shimazu T, Ikeuchi H, Mason AD Jr. Evaluation and management of patients with inhalation injury. *J Trauma* 1990;30(12 Suppl):S63–8. [PubMed: 2254994]
7. Herndon DN, Barrow RE, Traber DL, Rutan TC, Rutan RL, Abston S. Extravascular lung water changes following smoke inhalation and massive burn injury. *Surgery* 1987;102(2):341–9. [PubMed: 3303400]
8. Kimura R, Traber LD, Herndon DN, Linares HA, Lubbesmeyer HJ, Traber DL. Increasing duration of smoke exposure induces more severe lung injury in sheep. *J Appl Physiol* 1988;64(3):1107–13. [PubMed: 3366733]
9. Traber DL, Schlag G, Redl H, Traber LD. Pulmonary edema and compliance changes following smoke inhalation. *J Burn Care Rehabil* 1985;6(6):490–4. [PubMed: 3855227]
10. Sakurai H, Johnigan R, Kikuchi Y, Harada M, Traber LD, Traber DL. Effect of reduced bronchial circulation on lung fluid flux after smoke inhalation in sheep. *J Appl Physiol* 1998;84(3):980–6. [PubMed: 9480960]
11. Hales CA, Barkin P, Jung W, Quinn D, Lamborghini D, Burke J. Bronchial artery ligation modifies pulmonary edema after exposure to smoke with acrolein. *J Appl Physiol* 1989;67(3):1001–6. [PubMed: 2793693]
12. Herndon DN, Traber LD, Linares H, et al. Etiology of the pulmonary pathophysiology associated with inhalation injury. *Resuscitation* 1986;14(1–2):43–59. [PubMed: 3024279]
13. Isago T, Noshima S, Traber LD, Herndon DN, Traber DL. Analysis of pulmonary microvascular permeability after smoke inhalation. *J Appl Physiol* 1991;71(4):1403–8. [PubMed: 1757363]
14. Abdi S, Herndon D, McGuire J, Traber L, Traber DL. Time course of alterations in lung lymph and bronchial blood flows after inhalation injury. *J Burn Care Rehabil* 1990;11(6):510–5. [PubMed: 2286604]
15. Sakurai H, Kikuchi Y, Traber LD, Traber DL. Altered bronchial venous drainage after smoke insufflation (Abstract). *Am J Crit Care* 1996;153:A820.
16. Charan NB, Turk GM, Dhand R. Gross and subgross anatomy of bronchial circulation in sheep. *J Appl Physiol* 1984;57(3):658–64. [PubMed: 6490455]
17. Hinder F, Booke M, Traber LD, et al. Nitric oxide synthase inhibition during experimental sepsis improves renal excretory function in the presence of chronically increased atrial natriuretic peptide. *Crit Care Med* 1996;24(1):131–6. [PubMed: 8565518]
18. Abdi S, Herndon DN, Traber LD, et al. Lung edema formation following inhalation injury: role of the bronchial blood flow. *J Appl Physiol* 1991;71(2):727–34. [PubMed: 1938747]
19. Magno MG, Fishman AP. Origin, distribution, and blood flow of bronchial circulation in anesthetized sheep. *J Appl Physiol* 1982;53(1):272–9. [PubMed: 7118641]
20. Vidal Melo MF, Harris RS, Layfield D, Musch G, Venegas JG. Changes in regional ventilation after autologous blood clot pulmonary embolism. *Anesthesiology* 2002;97(3):671–81. [PubMed: 12218535]
21. Baxter CR. Problems and complications of burn shock resuscitation. *Surg Clin North Am* 1978;58(6):1313–22. [PubMed: 734611]

22. Wu CH, Lindsey DC, Traber DL, Cross CE, Herndon DN, Kramer GC. Measurement of bronchial blood flow with radioactive microspheres in awake sheep. *J Appl Physiol* 1988;65(3):1131–9. [PubMed: 3182482]
23. Cox RA, Burke AS, Soejima K, et al. Airway obstruction in sheep with burn and smoke inhalation injuries. *Am J Respir Cell Mol Biol* 2003;29(3 Pt 1):295–302. [PubMed: 12936906]
24. Cox RA, Burke AS, Oliveras G, et al. Acute bronchial obstruction in sheep: histopathology and gland cytokine expression. *Exp Lung Res* 2005;31(9–10):819–37. [PubMed: 16684715]
25. Pearce ML, Yamashita J, Beazell J. Measurement of Pulmonary Edema. *Circ Res* 1965;16:482–8. [PubMed: 14289157]
26. Baile EM, Dahlby RW, Wiggs BR, Pare PD. Role of tracheal and bronchial circulation in respiratory heat exchange. *J Appl Physiol* 1985;58(1):217–22. [PubMed: 3917992]
27. Fishman AP. The clinical significance of the pulmonary collateral circulation. *Circulation* 1961;24:677–90. [PubMed: 13700013]
28. Fishman AP. Pulmonary circulation. *Handbook of Physiology. The Respiratory System* 1985:93–165.
29. Charan NB, Turk GM, Dhand R. The role of bronchial circulation in lung abscess. *Am Rev Respir Dis* 1985;131(1):121–4. [PubMed: 3966698]
30. Laitinen LA, Laitinen A, Widdicombe J. Effects of inflammatory and other mediators on airway vascular beds. *Am Rev Respir Dis* 1987;135(6 Pt 2):S67–70. [PubMed: 3592420]
31. Kramer GC, Lindsey DC, Wu CH, Mertens S, Russell LA, Cross CE. Airway blood flow distribution and lung edema after histamine infusion in awake sheep. *J Appl Physiol* 1988;65(4):1847–54. [PubMed: 3182544]
32. Pietra GG, Szidon JP, Leventhal MM, Fishman AP. Histamine and interstitial pulmonary edema in the dog. *Circ Res* 1971;29(4):323–37. [PubMed: 5110918]
33. Sakurai H, Soejima K, Nozaki M, Traber LD, Traber DL. Effect of ablated airway blood flow on systemic and pulmonary microvascular permeability after smoke inhalation in sheep. *BURNS* 2007;33(7):885–91. [PubMed: 17493760]
34. Charan NB, Turk GM, Czartolomny J, Andreazuk T. Systemic arterial blood supply to the trachea and lung in sheep. *J Appl Physiol* 1987;62(6):2283–7. [PubMed: 3610924]
35. Baile EM, Minshall D, Harrison PB, Dodek PM, Pare PD. Systemic blood flow to the lung after bronchial artery occlusion in anesthetized sheep. *J Appl Physiol* 1992;72(5):1701–7. [PubMed: 1601775]
36. Salassa JR, Pearson BW, Payne WS. Gross and microscopical blood supply of the trachea. *Ann Thorac Surg* 1977;24(2):100–7. [PubMed: 327958]
37. Deffebach ME, Charan NB, Lakshminarayan S, Butler J. The bronchial circulation. Small, but a vital attribute of the lung. *Am Rev Respir Dis* 1987;135(2):463–81. [PubMed: 3544986]
38. Isago T, Fujioka K, Traber LD, Herndon DN, Traber DL. Derived pulmonary capillary pressure changes after smoke inhalation in sheep. *Crit Care Med* 1991;19(11):1407–13. [PubMed: 1935162]
39. McLaughlin RF Jr. Bronchial artery distribution in various mammals and in humans. *Am Rev Respir Dis* 1983;128(2 Pt 2):S57–8. [PubMed: 6881710]
40. Baile EM, Pare PD, Ernest D, Dodek PM. Distribution of blood flow and neutrophil kinetics in bronchial vasculature of sheep. *J Appl Physiol* 1997;82(5):1466–71. [PubMed: 9134894]
41. Charan NB, Thompson WH, Carvalho P. Functional anatomy of bronchial veins. *Pulm Pharmacol Ther* 2007;20(2):100–3. [PubMed: 16807022]
42. Traber D, Herndon D, Enkhbaatar P, Maybauer MO, Maybauer DM. The pathophysiology of inhalation injury. *Total Burn Care* 2007:248–261.
43. Lakshminarayan S, Kowalski TF, Kirk W, Graham MM, Butler J. The drainage routes of the bronchial blood flow in anesthetized dogs. *Respir Physiol* 1990;82(1):65–73. [PubMed: 2270362]
44. Hinder F, Matsumoto N, Booke M, et al. Inhalation injury increases the anastomotic bronchial blood flow in the pouch model of the left ovine lung. *Shock* 1997;8(2):131–5. [PubMed: 9261904]
45. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1334–49. [PubMed: 10793167]

46. Sakurai H, Schmalstieg FC, Traber LD, Hawkins HK, Traber DL. Role of L-selectin in physiological manifestations after burn and smoke inhalation injury in sheep. *J Appl Physiol* 1999;86(4):1151–9. [PubMed: 10194196]

Figure 1.

Changes in airway blood flow after burn and smoke inhalation injury. Burn and smoke inhalation injury significantly increased the airway blood flow. Bronchial ablation didn't reduce the changes in trachea (A). However, bronchial ablation significantly prevented the airway blood flow increases in proximal and distal bronchi (B,C). Data are expressed as mean $\pm$ SE. * Significant difference vs. sham animals ($p < 0.05$), † Significant difference vs. Base line value ($p < 0.05$).

Figure 2.

All ablation group animals survived until 96h. Four of them were succeeded of ventilation weaning. Three animals in sham group died at 60h and one of them died at 78h. Ablation group has significance difference vs. sham group in survival proportions ($p=0.02$).

Figure 3.
 Effect of ablated bronchial blood flow on PaO₂/FIO₂ (A) and pulmonary shunt fraction (B).
 After 48h, four of ablation group's animals was separated to ventilation weaning group (VW)
 and none ventilation weaning group (NVW). Data are expressed as mean±SE.

Figure 4.

Effect of ablated bronchial artery blood flow on pulmonary arterial pressure (PAP) (A) and pulmonary vascular resistance index (PVRI) (B). After 48h, ablation group was separated to ventilation weaning group (VW) and none ventilation weaning group (NVW). Burn and smoke inhalation injury significantly increased PAP and PVRI in sham group. Ablation of bronchial artery significantly attenuated the increases of PAP at 12h, 36h and 48h and PVRI at 12h, 18h, 24h, 30h and 36h. Data are expressed as mean±SE. * Significant difference vs. sham animals ($p < 0.05$), † Significant difference vs. Base line value ($p < 0.05$).

Figure 5.

Effect of ablated bronchial artery blood flow on white blood cells counts (WBC) (A) and neutrophil counts (B). Burn and smoke inhalation injury increased WBC and neutrophil counts in sham group animals. However, ablation of bronchial artery attenuated the changes. Data are expressed as mean $\pm$ SE. * Significant difference vs. sham animals ($p < 0.05$).

Figure 6.

Pathological results. Each graph shows Airway obstruction score in bronchi (A), Airway obstruction score in bronchiole (B), polymorphonuclear (PMN) cells score (C) and edema formation score (D). Sham groups were separated to 60h (n=3), 78h (n=1) and 96h (n=2) following their survival time. Burn and smoke inhalation injury remarkably increased airway obstruction score in bronchia and bronchiole and PMN cells score and edema formation score. Ablated bronchial artery significantly attenuated the increase of airway abstraction score in bronchia and bronchiole and PMN cells score and edema formation score compare to sham groups at 60h. Data are expressed as mean±SE. * Significant difference vs. 60h sham animals ($p < 0.05$).

Figure 7.

Effect of ablated bronchial artery blood flow on Bloodless lung wet to dry ratio (A), Myeloperoxidase in lung tissue (B). Sham groups were separated to 60h (n=3), 78h (n=1) and 96h (n=2) following their survival time. Burn and smoke inhalation injury remarkably increased lung bloodless wet to dry ratio and myeloperoxidase in lung tissue. Ablated bronchial artery significantly attenuated the increase of lung bloodless wet to dry ratio and myeloperoxidase in lung tissue compare to sham groups at 60h. Data are expressed as mean $\pm$ SE. * Significant difference vs. 60h sham animals ($p < 0.05$).