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Smoke inhalation causes a delayed increase in airway blood flow to primarily uninjured lung areas

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Abstract *Objective:* Single lung inhalation injury causes tissue damage to the contralateral lung. We therefore examined airway blood flow after smoke inhalation in chronic instrumented sheep to get further information about the underlying pathophysiology.
Design/patients: The right lung and lower trachea of 5 animals were smoke-exposed, while their left lung was air-insufflated using a split ventilation technique. Three animals, where both lungs were only air-insufflated, served as controls. Blood flow to the airway was measured using a labeled microsphere technique. All animals were studied for 24 h following smoke inhalation. Then they were sacrificed and their tissues harvested.
Results: The airway blood flow to the smoke-exposed lung was elevated 11-fold immediately after inhalation injury. The bronchial blood flow to the air insufflated lung became significantly elevated 24 h post-smoke, although to a lesser extent. The control animals did not show any changes of bronchial blood flow during the observation time.
Conclusions: Damage to one lung can lead to pathophysiologic changes in the contralateral lung. This response appears to be mediated by hematogenous factors.

Key words Bronchi (blood supply) · Microspheres · Smoke inhalation injury · Splanchnic circulation

Introduction

Smoke inhalation causes lesions of the trachea and airways, which progress with time to include the lung parenchyma. Because the airways are the main areas exposed to smoke, we evaluated the mechanisms responsible for the parenchymal changes noted with inhalation injury. To study this phenomenon, we developed a technique whereby one lung was exposed to smoke while the contralateral lung was insufflated with air [1, 2]. We exposed the trachea and right lung to smoke and found edema and lipid peroxidation products in both lungs [1]. If only the lower area of the lung was exposed to smoke, damage to the contralateral lung could not be demonstrated [1, 2]. The venous drainage from the extrapulmonary airway flows into the right atrium via the vena cava while that of the intrapulmonary airway drains into the pulmonary vasculature at the precapillary level [3, 4]. Damage to the extrapulmonary airway can result in a release of mediators, which in turn enter the pulmonary circulation without being filtered by other organs. This physiological bypass could be partly responsible for the observed indirect lung damage after inhalation injury of the trachea and right lung.

There appears to be a relationship between the elevation in bronchial blood flow noted with inhalation injury and concomitant parenchymal pathophysiology. The bronchial artery supplies most of the blood flow to the sheep lung [3, 5]. Occlusion of this vessel, before inhalation injury, greatly reduced the smoke-induced changes in lung lymph flow and extravascular lung water [6, 7].

We have also reported that blood flow to the splanchnic areas is reduced after inhalation injury [8, 9]. These changes in blood flow are followed by reperfusion. Several studies have reported lung damage following ischemia and reperfusion in the systemic areas [10, 11]. Consequently, smoke-induced injury to the lung could result in the release of mediators that produce a vasoconstriction, resulting in an ischemia/reperfusion injury in systemic areas. Cytotoxins, which enter the venous return and damage the lung further, would be subsequently released.

Our study evaluated changes in airway blood flow in the split lung inhalation injury model. We hypothesized that inhalation injury to the upper airway and right lung releases mediators into the airway venous drainage, ultimately resulting in a hematogenously induced vasodilation in the airway of the contralateral sham-injured lung.

Materials and methods

The present study was approved by the Animal Care and Use Committee of The University of Texas Medical Branch, and adheres to the "Guiding Principles in the Care und Use of Animals" of the American Physiological Society.

Surgical preparation

This study was performed on 8 healthy range ewes of the Merino breed, with a body weight of 43±3 kg. The animals were surgically prepared for the study 5–7 days before the experiment. Under 2–3% halothane anesthesia, a Swan-Ganz thermodilution catheter (model 93A-131-7F, Edwards Laboratories, Palo Alto, CA) was inserted into the pulmonary artery via the common jugular vein. Catheters were placed in the femoral artery and vein for sampling arterial blood, measurement of the arterial pressure, and administration of intravenous solutions.

A left thoracotomy was made in the fifth intercostal space. The left pulmonary artery was identified and surrounded with a 12 mm pneumatic occluding cuff (In Vivo Metrics, Heraldsburg, CA) just distal to its origin. The volume for occlusion of the left pulmonary artery was determined intraoperatively by inflating the occluder with saline until no pulsatile changes in the artery were detectable. In previous experiments we found that the same saline vlume was sufficient to occlude the pulmonary artery in the awake sheep by demonstrating that the blood flow (as indicated on a flow meter around a branch of the pulmonary artery) disappeared after inflating the occluder [1]. A silastic catheter was then placed in the left atrium. The thorax was closed and the incision was infiltrated with local anesthetic to minimize post-operative pain. All catheters were filled with heparin solution (1000 U/ml). After surgery the sheep were maintained in metabolic cages with free access to food and water. After a 5–7 day recovery period, blood samples were drawn and a white blood cell count was performed. If the count was between 5000 and 10000×10^6/l and the temperature between 38.6 and 40 °C, the animals in good temperament and eating, they were taken to the laboratory for study.

Procedure for smoke insufflation

At 24 h before the experiment, the heparin was removed from the arterial and venous catheters and the catheters were connected to recording devices. The sheep received an infusion of lactated Ringer's solution (2 ml/kg/h). After obtaining hemodynamic data, the animals were anesthetized with 5 mg/kg ketamine (Ketalar, Parke-Davis, Morris Plains, NJ) and a tracheostomy was performed. A 10 mm tracheostomy tube (Shiley Corp., Irvine, CA) was inserted and connected to a ventilator (Servo Ventilator 900C, Siemens Elena, Sweden). By 2–3 h after this procedure the animals had totally recovered from anesthesia, and were maintained on the Servo ventilator. Baseline data were taken while the sheep were standing. Then halothane was added to the ventilatory system in an inspired concentration of 2–3%. The anesthetic was continued until the sheep were deeply anesthetized; they were ventilated for 2 min with 100% O_2, the tracheostomy tube was removed and a modified left double-lumen Carlen's tube was positioned in the trachea through the tracheostoma in order to ventilate the right and the left lungs separately. In sheep, the right upper bronchus emerges directly from the trachea. This special anatomic feature required an extension of the Carlen's tube between the two cuffs. The proper position of the tube was verified by bronchoscopy (LF1, Olympia Corporation, New York, NY). Additionally, the position was assured by unilateral ventilation and simultaneous flow measurements in the contralateral side using a spirometer (Wright spirometer, Boehringer Laboratories, Wynnewood, PA). After inducing deep anesthesia, the right lung and lower trachea of five animals were insufflated with smoke by a technique described by Kimura et al. [12], a modification of the method of Walker et al. [13]. Briefly, the combustion chamber of a modified bee smoker was filled with segments of smoldering cotton towels (40 g). The bee smoker was attached to the right lumen of the Carlen's tube by a 30 cm segment of 10 mm tubing containing a thermistor. The smoke was delivered by depressing the bellows of the bee smoker. The volume of the bellows was 500 ml. A series fo 12 breaths of smoke were delivered. The animals were then connected to the anesthetic apparatus for 1 min and ventilated with 2% halothane and 98% O_2. Four replicates of this sequence were used for each inhalation challenge so that the animals received a total of 48 breaths of smoke. The temperature of the smoke was monitored at the level of the endotracheal connector and was not allowed to exceed 40 °C. After the smoke procedure, the carboxyhemoglobin level was determined. In 3 animals (sham-smoke = control group) air was insufflated to the trachea and right lung via an Ambu® bag, containing a volume of 500 ml. Following smoke respective air insufflation the separation of the 2 lungs was again verified by ventilating one lung with 100% O_2 and monitoring the gas flow from one lung when the contralateral lung was ventilated. In no cases did the O_2 levels rise and there was no flow indicated in the non-ventilated lung. After smoke insufflation, the double-lumen tube was removed and a 10 mm tracheostomy tube was reinserted into the airway. The tube was reconnected to the Servo ventilator and both lungs of the animals ventilated. The animals were awakened and studied for 24 h. During the investigational period they received maintenance i.v. fluids (3 ml/kg/h lactated Ringer's solution). In addition they had free access to water, but not to food.

Experimental procedure

The right lung and lower trachea of 8 animals were exposed to smoke ($n = 5$) or air (sham-smoke, $n = 3$), respectively. Before the smoke procedure and 3 times after smoke insufflation (at 0.5, 12, and 24 h) the bronchial blood flow of the right and left lung was measured using the microsphere technique. At the same time points, cardiac output was measured with the thermodilution technique. In the air insufflated animals the data were obtained in the same fashion before the sham-smoke procedure and three times thereafter (at 0.5, 12 and 24 h). All data, except those at the 0.5 h recording, were collected while the animals were in a standing position (the sheep were not fully recovered from the anesthetic at the 30 min recording). During the study period the animals were ventilated with a tidal volume of 15 ml/kg and a positive end-expiratory airway pressure of 5 cmH_2O. The inspiratory/expiratory ratio was set at 1:2. The fraction of inspired O_2 (FIO_2) was periodically adjusted to maintain the PaO_2 between 70–100 mmHg. End-tidal CO_2 was maintained between 30 and 35 mmHg by adjusting the respiratory rate and the minute volume. The sheep were slightly hyperventilated to reach an acceptable tolerance to the ventilator. Secretions were suctioned from the airway periodically.

After the 24 h study period the animals were sacrificed by an injection of saturated solution of KCl while under ketamine anesthesia (10 mg/kg i.v.); their lungs were harvested and prepared for determination of radioactivity.

Hemodynamic measurements

Body surface area (m^2) was calculated as 0.084×body weight$(kg)^{2/3}$ [14]. Cardiac output was determined by the thermodilution technique using a Cardiac Output Computer (Model 9520, American Edwards Laboratories, Irvine, CA). The indicator was 10 ml of 5% glucose solution, at a temperature of 0 °C. Vascular pressures were measured with transducers (P231D) Statham-Gould Instruments, Oxnard, CA) connected to a physiologic recorder (OM 9 Electronics for Medicine, Pleasantville, NY). Pressures were measured in the sheep with a zero calibration taken at the level of the left atrium.

PaO_2 and $PaCO_2$ were measured with a blood gas analyzer (System 1302, Instrumentation Laboratory, Inc., Cidra, PR), corrected to the animal's temperature.

Cardiac index was calculated by dividing body surface area into the cardiac output. Systemic vascular resistance index was determined by dividing the mean arterial pressure by the cardiac index. Total pulmonary vascular resistance index was determined by dividing the difference between the mean pulmonary arterial and left atrial pressures by the cardiac index. The results were multiplied by 80 to convert them to metric units ($dynes \cdot s \cdot cm^{-5} \cdot m^2$).

Microsphere technique

The intrapulmonary distribution of bronchial blood flow to the airways was measured using a modified microsphere technique previously described [15, 16]. The microspheres were suspended in 10% Dextran with Tween 80 (3M Medical Products, St. Paul, MN) and were tagged with one of four isotopes: ^{141}Ce, ^{85}Sr, ^{95}Nb, or ^{46}Sc. Before injection each vial of microspheres was thoroughly mixed and placed in an ultrasonic bath for 5 min. A different isotope was injected at 4 different time periods in each animal. A Harvard withdrawal pump was connected to the femoral arterial catheter and blood was withdrawn at a rate of 10 ml/min, starting 20 s before injection of the microspheres and continuing for three minutes after injection. The microspheres in this arterial blood sample were used to determine the reference arterial calibration constant. About 5 s after the microsphere injection, the left pulmonary artery was occluded for 3 min to prevent the left lung from trapping microspheres that might have passed through shunts in the systemic circulation. This transient occlusion has been shown to interfere minimally with cardiovascular function and airway blood flow [15, 16]. At least 5×10^6 microspheres were injected with each measurement of blood flow into the left atrium. This number guarantees that more than 400 microspheres/g stayed in most tissue samples under baseline conditions for a 95% confidence level of an error less than 10% [17]. Fewer microspheres were often trapped in the small tissue samples of airways and in tissues that have very low baseline flows (i.e. tracheal cartilage). We therefore accepted greater levels of expected error when measuring low flow. For example, with 96 spheres in a sample the expected error is ± 20%. Expected errors are random and multiple measurements and experiments reduce these.

Tissue sampling for determination of bronchial blood flows

After euthanasia the trachea and the lung were removed en bloc. The trachea was resected and the distal segments dissected into samples of whole tracheal wall and its individual components including mucosa/submucosa, cartilate, and muscularis. Samples of the mainstream bronchi and intrapulmonary airways were taken from the left and right lungs and stripped of all attached lung parenchyma. The airways were separated into 5 samples, with diameters ranging from 0.5 to 12 mm. Samples of central airways of diameter greater than 5 mm normally weighed 0.5–1.5 g, whereas for smaller airways multiple samples were collected to increase the sample size. The tissue samples were placed in preweighed polypropylene tubes. Tubes containing arterial blood and tissue samples were then placed in a gamma scintillation counter (model A5550, Packard, Laguna Hills, CA). Individual isotope activities were determined by gamma spectroscopy. Blood flow is reported in ml/min/100 g as determined by the following formula:

$$Q_t = M_t \cdot Q_{ref} / M_{ref} \cdot 100 / W_t$$

where

Q_t = tissue blood flow
M_t = microsphere radioactivity in tissues
Q_{ref} = withdrawal rate of aortic reference sample
M_{ref} = microsphere radioactivity in reference blood samples
W_t = sample weight (g).

Statistical evaluation

The data are presented as means ± the standard error of the means (SEM). The time effect of each variable was determined by ANOVA. Dunnett's test was used to compare the time points following inhalation injury to baseline. The analysis of the bronchial blood flow data was performed by a two-factor variance analysis for repeated measures. Fisher's least-significant difference test was used to determine whether significance was present between the bronchial blood flow of the airway sections in the right and left lung at different time points. $p < 0.05$ was considered significant.

Results

Bronchial blood flow

After smoke inhalation of the right lung and upper airways the animals showed an arterial carboxyhemoglobin level of 55±5%. Figure 1 presents the blood flow of the smoke exposed distal trachea and its components. with the highest absolute values in the mucosa/submucosa tissues. The airway blood flow of the mucosa/submucosa tissues declined over time but remained significantly higher, when compared with baseline. While the blood flow of the muscularis did not vary between 0.5 and 24 h, blood flow to the cartilage increased during the study period and reached a significantly elevated level at 24 h after insult.

The baseline bronchial blood flow of the airways of the right lung approximated baseline values determined in airways of the left lung (Figs. 2 and 3). When the trachea and right lung were exposed to smoke, blood flow was markedly elevated 30 min after the smoke procedure in all airway sections. The blood flow remained increased during the remainder of the study period, although the absolute values reached a lower level when compared to the 30 min recording. The magnitude of the blood flow changes for the different size airways were 11 times the respective baseline values and were of virtually the same magnitude for all airways.

In contrast to the right lung, the bronchial blood flow of the airways of the left (air-insufflated) lung did not rise until the end of the study period (Fig. 2). This increase reached statistical significance 24 h after the smoke exposure in all airway sections, except in the large 8–12 mm axial airways. The elevation in bronchial blood flow extended with the distance of the airway sections from the trachea. This is illustrated in Fig. 3, which shows the changes in blood flow noted at 24 h after the right lung was insufflated with smoke. In the 0.5–1 mm airways of the air-insufflated lung the bronchial blood flow showed more than a 5 fold increase with the blood flow to the larger airways showed increases of 2–3 fold. The 24 h blood flow changes of these small airways of the air-insufflated lung could not be shown to be different from the contralateral smoke damaged lung. There was a transient increase in bronchial blood flow of the 8–12 mm axial airways of the left lung immediately after the smoke procedure.

The baseline bronchial blood flow of the control animals approximated the respective values of smoke ex-

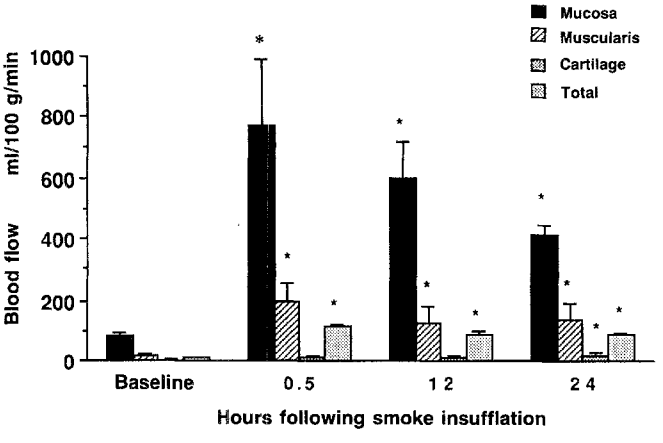

Fig. 1 Blood flow of the components of the lower trachea after inhalation injury of the right lung and upper airways. The bronchial blood flow increased significantly in the mucosa/submucosa and the muscularis immediately after smoke insufflation, while the blood flow of the cartilage was not significantly elevated until the 24 h recording and to a lesser extent than that observed in the other tissue components. Data are presented as means and standard error of the means. * = $p<0.05$ versus the baseline value

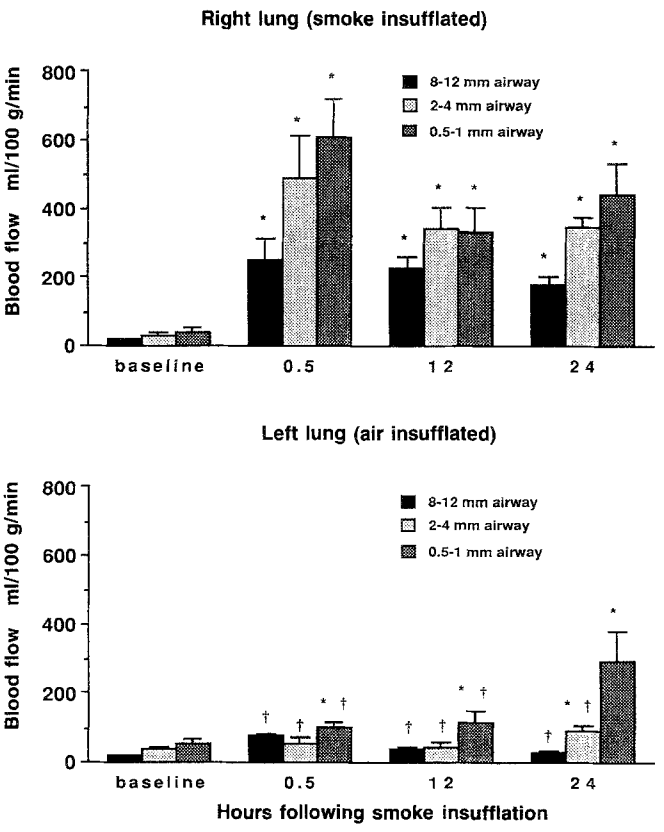

Fig. 2 Bronchial blood flow of the airways of the right and left lung after inhalation injury of the right lung and upper airways. The bronchial blood flow of the smoke-exposed lung areas increased immediately after smoke inhalation and remained elevated during the remainder of the study period. The bronchial blood flow of the air-insufflated left lung rose over time and reached significantly elevated levels at the 24 h recording with a more pronounced response in the smaller airway sections. Data are presented as means and standard error of the means. * = $p<0.05$ versus the baseline value. † = $p<0.05$ right (smoke insufflated) versus left (air insufflated) lungs

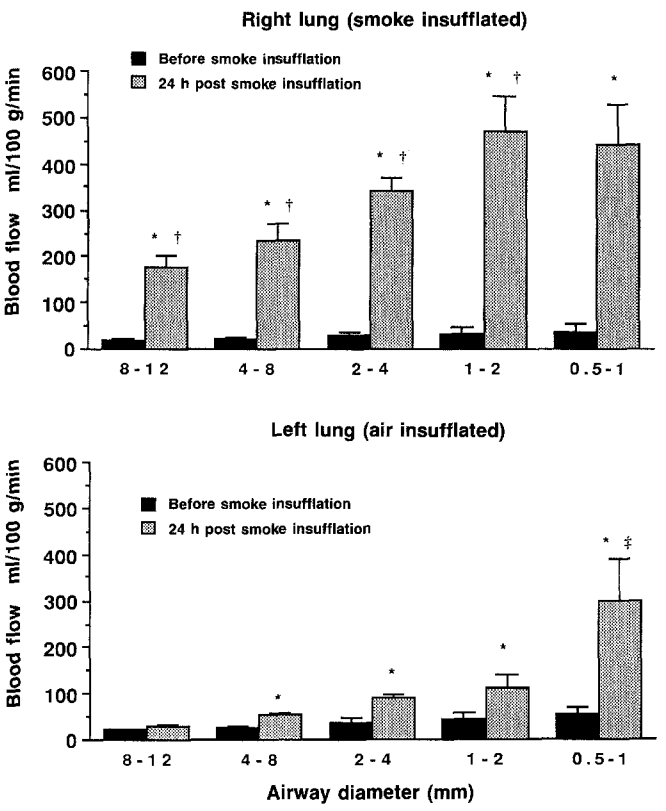

Fig. 3 Changes in the blood flow to the airways at 24 h after inhalation injury. The right lung was insufflated with smoke while the left lung was insufflated with air. The figures show the blood flow at baseline and 24 h after smoke inhalation. Data are means ± standard error of the means. * = $p<0.05$ versus baseline value. † = $p<0.05$ right (smoke insufflated) versus left (air insufflated) lungs. ‡ = $p<0.05$ 0.5–1 versus 1–2 mm airways

posed animals. There was no change in bronchial blood flows 0.5, 12 and 24 h following the sham-smoke procedure, compared to baseline (Table 1).

Hemodynamic variables

Hemodynamic variables are summarized in Table 2. Smoke inhalation of the right lung and upper airways caused an increase in the mean pulmonary pressure and total pulmonary vascular resistance index. While mean aortic and left atrial pressures remained virtually unchanged during the study period, cardiac index fell, with a significantly decreased value, at the 18 h recording as compared to baseline. The systemic vascular resistance index increased continously over time. These latter changes were not of statistical significance.

In the control animals the hemodynamic variables did not change over the time.

Discussion

When we began the present study, we intended to measure bronchial blood flow only in the air-insufflated left lung according to a modified method of Baile et al. [15] and Wu et al. [16], since the left lung was the focus of our interest. We placed an occluder around the left pulmonary artery using the occlusion technique in the left lung to avoid lung trapping of microspheres that might have recirculated from the systemic circuit [15, 16]. After analyzing the data we found no difference in baseline values for bronchial blood flow in all measured airway sections between the right and the left lung. A dysfunction of the pneumatic occluder seemed unlikely, since none of the implanted pneumatic occluders showed any damage or dysfunction at the end of the study period, when the occluders were removed from the harvested lungs. The pre-

Table 1 Blood flow to the airways after sham-smoke inhalation

Time (hours after sham-smoke)		ml min pro 100 g			
		Baseline	0.5	12	24
Trachea		30 ± 1	36 ± 2	33 ± 1	33 ± 2
8–12 mm airway	right lung	25 ± 6	33 ± 4	27 ± 11	27 ± 9
	left lung	25 ± 2	28 ± 2	30 ± 1	20 ± 1
2–4 mm airway	right lung	39 ± 12	50 ± 16	49 ± 11	38 ± 18
	left lung	38 ± 15	42 ± 11	42 ± 10	24 ± 8
0.5–1 mm airway	right lung	54 ± 17	92 ± 12	65 ± 22	33 ± 8
	left lung	63 ± 21	80 ± 27	53 ± 29	25 ± 2

All values are in ml/100 g/min; data are means ± standard error of the means

Table 2 Pulmonary and systemic hemodynamics after right lung inhalation injury

Time (hours after smoke)	Baseline	6	12	18	24
Pulmonary arterial pressure (mmHg)	21.2 ± 0.9	21.2 ± 1.5	25.4 ± 2.4	26.0 ± 2.2*	25.6 ± 1.2*
Pulmonary vascular resistance index (dynes·cm^{-5}·s·m^2)	184 ± 22	218 ± 69	274 ± 72	325 ± 78*	280 ± 51
Cardiac index (l·min^{-1}·m^{-2})	5.02 ± 0.22	4.18 ± 0.21	4.36 ± 0.05	4.02 ± 0.37*	4.12 ± 0.4
Aortic pressure (mmHg)	95 ± 4	96 ± 7	98 ± 7	97 ± 6	97 ± 6
Left atrial pressure (mmHg)	9.8 ± 1.7	10.4 ± 1.9	10.8 ± 2.0	9.8 ± 2.4	11.4 ± 1.86
Systemic vascular resistance index (10^3 dynes·cm^{-5}·s·m^2)	1.51 ± 0.04	1.85 ± 0.15	1.86 ± 0.17	1.95 ± 0.14	1.94 ± 0.16

Data are means ± standard error of the means
*$p<0.05$ versus baseline

sented data are confirmed by a recent study in our laboratory [18], where no difference in bronchial blood flow was found between the right and left lung airway sections during different levels of positive end-expiratory pressure, although the left pulmonary artery was occluded during the microsphere injection. These findings support the hypothesis that the venous admixture of microspheres to the pulmonary arterial circulation does not affect airway blood flow measurement. We have therefore presented the bronchial blood flows of the airways in the smoke-exposed right lung and compared them with the respective values of the contralateral lung.

Immediately after smoke inhalation injury there was a dramatic rise in blood flow to the smoke-exposed airways. The hyperemic response of the airways increased as the airway diameter decreased to 0.5 mm. All blood flow measurements were normalized to weight of the tissue. The relative component of cartilage decreases. As demonstrated in Fig. 1 the cartilage has a very low blood flow compared with the mucosa/submucosa. Therefore, the content of cartilage in the airways caused different blood flow levels in the collected airway sections. In support of this hypothesis baseline blood flow of the 0.5 – 1 mm airway was 2 – 3 times higher than in the 8 – 12 mm bronchi or the trachea. These findings are in close agreement with our previous reports [6, 19, 20]. With inhalation injury these changes become even more dramatic since flow to the cartilage remains relatively constant, while that to the mucosa increases by 12 fold.

In spite of the fact that the left lung was insufflated only with air, there was still an increase in bronchial blood flow in this lung after smoke insufflation into the right lung and lower trachea (Figs. 2 and 3). Unlike the contralateral smoke-insufflated lung, these changes in blood flow required a considerable amount of time to develop and involved the smaller airways more than the large. Figure 3 illustrates this point in a graphic pattern. The blood flow elevations in the right smoke-insufflated lung are consistently near 11 times their baseline values in all of the bronchi. In the left air-insufflated lung, the blood flow elevation was not statistically changed in the 8 – 12 mm bronchi, elevated 2 fold in the bronchi between 1 and 8 mm in diameter, but elevated by 5 fold in the small 0.05 – 1 mm airways. One might argue that this increase in the lower airway was artifactual, representing the recirculation of microspheres into the pulmonary circuit and is more apparent in the small airways because it is more difficult to separate the parenchyma from them. However, these airways are in the left lung, the structure which had its pulmonary artery occluded before recirculation could take place. In addition, if recirculation of microspheres from the systemic circulation were a problem there should have been recirculation at all times after inhalation injury, not just at 24 h after insult. If these blood flow changes are not artifactual what mechanism could be responsible for them? The size of the blood flow changes and the fact that they are in the very small airway, where there is a close proximity to the alveoli, suggests that vasodilators are delivered to the left bronchi by the pulmonary blood. What could be the source of these putative mediators of increased blood flow?

Morris et al. discovered that with smoke insufflation into the lung there was a transient decrease in blood flow to the splanchnic areas [8]. These changes were associated with the appearance of bacteria in the circulation of these sheep, a phenomenon referred to as bacterial translocation. We hypothesized that this transient fall in mesenteric blood flow following lung injury induced an ischemia/reperfusion injury to the splanchnic microvasculature. In a recently performed study we have demonstrated a reduction in blood flow to several splanchnic organs, using the microsphere technique [9]. Especially blood flow to the pancreas has dropped after inhalation injury (down to 50% of baseline) and was not restored to normal during the study period. We therefore cannot be assured that a reperfusion injury took place in this organ. Similar changes could have occured in the ileum, where the blood flow was decreased to less than 30% of the baseline value. The fall in blood flow to the splanchnic organs paralleled the drop in cardiac output and an increase in systemic vascular resistance [8]. Decreased cardiac output and increased systemic vascular resistance was likewise observed in the present study. The fall in cardiac output is associated to myocardial depression following inhalation injury [21] and may be partly responsible for the increase in vascular resistance by vascular autoregulative mechanisms.

We have demonstrated an elevation of lipid peroxidation products in the plasma after inhalation injury [22]. Demling et al. have likewise reported that lipid peroxidation products were higher in the venous than in the arterial blood in sheep after inhalation injury [23]. Release of lipid peroxidation products supports the possibility of a reperfusion injury in the splanchnic organs in our model. Released bacteria and endotoxins from the gut can cause the liberation of cytokines (TNF and interleukin 1), which have been shown to induce the formation of a non-constitutive nitric oxide synthase [24, 25]. Nitric oxide (NO) is considered to be the endothelial derived relaxant factor and a potent vasodilator [26]. The production of NO leads to an increase of bronchial blood flow [27]. The non-constitutive NO synthase can be formed by smooth muscle and phagocytic cells; however, the induction of formation of the enzyme requires several hours [25, 28]. Since the vasodilation in the small bronchi requires several hours to become manifest, a cytokine-nitric oxide mediated phenomenon is a good candidate for the bronchial blood flow dilation seen in our model.

Although we have demonstrated that smoke insufflation to the right lung will induce damage to the contralateral air-insufflated lung, the converse may not be true. When we induce damage to the left lung, we are un-

able to show that the contralateral air insufflated lung is injured [1, 2, 29]. There are, however, two major differences between acute damage in these situations. To accommodate the bronchi to the right upper lobe, the branch of the Carlen's tube, which ventilates the right lung, also exposes a large proportion of the trachea and the extrapulmonary bronchi to the gas, while the segment of the tube, that ventilates the left lung, ventilates intrapulmonary airway exclusively. In addition, the right lung of the sheep is considerable larger than the left. Thus, with right lung injury, a much larger mass of tissue is injured and consequently, a larger number of mediators could be expected to be released into the circulation to affect the splanchnic vasoconstriction. In the former situation the venous drainage of the extrapulmonary airway enters the right atrium and thus mediators would be exposed to the microcirculation of both lungs [3, 4]. The venous drainage of intrapulmonary circulation, on the other hand, enters the pulmonary circulation at the precapillary level, and thus, mediators released by the damaged intrapulmonary tissue are exposed first of all to the pulmonary microcirculation of only the damaged lung [3, 4]. This bronchial venous drainage and the mediators it contains may also play a role in damage to the air-insufflated lung in the present study. Hales et al. [7] and our own group [6] have reported that occlusion of the bronchial artery reduces the parenchymal injury noted with inhalation injury. A number of mediators have been identified in the arterial blood after inhalation injury, which may have been released from the airway. Both, Quinn et al. [30] and our own group have found both LTB_4 and the peptidoleukotrienes in the pulmonary lymph after smoke insufflation in sheep. The peptidoleukotrienes are normally associated with vasoconstriction but they have been reported to affect endothelial-mediated vasodilation [31].

In conclusion, we have demonstrated that injury to the distal trachea and right lung of sheep with the chemicals in smoke, not only produces an increase in airway blood flow in the right lung, but also in the contralateral lung, which was not insufflated with air only. The changes in bronchial blood flow to the air-insufflated left lung occur many hours after primary insult and occur predominantly in the small airway, suggesting an association of the bronchial vascular dilation with the blood in the pulmonary microvasculature. These changes in the systemic blood flow to the airway may be mediated by materials released from the airway or possibly the splanchnic viscera.

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