Bronchial edema alters $^{99m}$Tc-DTPA clearance from the airway surface in sheep

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Wagner, Elizabeth M., and W. Michael Foster. Bronchial edema alters $^{99m}$Tc-DTPA clearance from the airway surface in sheep. J Appl Physiol 91: 2567–2573, 2001.—Airway wall edema, present in inflammatory airways disease, may alter barrier properties at the airway air-liquid interface such that normal absorption of soluble substances into the airway circulation is altered. We studied the effects of bradykinin-induced airway wall edema on the clearance of the soluble tracer technetium-99m-labeled diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) from subcarinal airways in sheep ($n = 8$). $^{99m}$Tc-DTPA (6–10 μl) was delivered by a microspray nozzle inserted through a bronchoscope to a fourth-generation bronchus both before and 1 h after bradykinin (20 ml; $10^{-6}$ M) had been infused through a cannulated and perfused bronchial artery. Airway retention (by scintigraphy) and blood levels of radiolabel were monitored for 30 min after the local delivery of $^{99m}$Tc-DTPA. During control conditions, 85–90% of the tracer cleared from the deposition site within 30 min. The maximum blood level during that time was 17% of the total delivered tracer. However, 1 h after bradykinin infusion, there was significant retention of the marker at the deposition site with clearance within 30 min reduced to 63–70% and decreased blood levels of radiolabel (8%; both $P < 0.05$). These results demonstrate that moderate airway wall edema alters blood uptake and removal of soluble substances delivered to the subcarinal airways. We suggest that the interplay between vascular and mucociliary clearance routes will impact the resident time for clearance of soluble air toxins and/or therapeutic agents from the epithelial surface.

bradykinin; bronchial blood flow; mucociliary transport; soluble-particle clearance; technetium-99m-labeled diethylenetriamine pentaacetic acid

A DENSE NETWORK OF BLOOD VESSELS envelopes bronchial smooth muscle in the form of parallel vascular plexuses within the airway wall. The mucosal capillary plexus, located in the subepithelial space, provides systemic access for all soluble substances that are deposited on the airway surface and traverse the epithelium. The bronchial artery supplies the mucosal plexus and provides the major blood supply to the conducting airways from the level of the carina to the terminal bronchioles (6). The participation of the bronchial circulation in the absorption and clearance of soluble particles that deposit onto airway surfaces and penetrate the bronchial epithelium impacts both toxicology and physiological function of the airway. For example, in physiological studies, the passive clearance by the bronchial circulation of bronchospastic and pharmacological agonists can modulate bronchial smooth muscle tone (8, 16, 29).

For substances deposited onto the airway surface, the major routes of clearance are 1) a mucociliary pathway that is dependent on several components, i.e., ciliated epithelium, quality and quantity of mucus protein secretions, and bronchial blood flow (23); and 2) a vascular pathway that is influenced by the degree of perfusion (24). We have recently demonstrated that, for a soluble, hydrophilic substance, i.e., technetium-99m-labeled diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA), these two pathways appear to be independent and that reduced bronchial blood flow inhibits both routes of clearance (24). The rate of diffusion of substances into submucosal tissues depends on their lipid and water solubility and on the size and shape of the particles. Lipophilic molecules pass mainly via transcellular routes, and hydrophilic molecules pass via paracellular pathways (2, 30). $^{99m}$Tc-DTPA has commonly been used for physiological studies of epithelial integrity and is favored because of its small molecular size (492 Da) and radius (0.57 nm) that enable easy penetration into the vascular compartment (12).

In the present investigation in a large-animal model in which the level of bronchial perfusion to the airways was controlled, we generated airway wall edema with the infusion of bradykinin and altered interstitial barrier function to absorption of soluble substances. Our observations support the hypothesis that airway wall edema that results from bronchial vascular fluid extravasation leads to an increase in airway particle retention and limits the ability of the airway circulation to take up soluble substances.
METHODS

Experimental preparation. The Johns Hopkins Animal Care and Use Committee approved the study protocol. Anesthesia was induced in sheep (25–35 kg) with intramuscular ketamine (30 mg/kg) and subsequently maintained with intravenous pentobarbital sodium (20 mg·kg⁻¹·h⁻¹). The sheep were positioned supine on a surgical table, and, after a tracheotomy was performed, the animals were intubated and paralyzed with pancuronium bromide (2 mg iv). The lungs were mechanically ventilated with a tidal volume of 10–12 ml/kg at a rate (12–15 breaths/min) sufficient to maintain normal blood gases. Then, 5 cmH₂O positive end-expiratory pressure were applied. The left thorax was opened at the fifth intercostal space, and heparin (20,000 U iv) was administered. The esophageal and thoracic tracheal branches of the bronchoesophageal artery were ligated as previously described (25). The bronchial branch of the bronchoesophageal artery was isolated, cannulated, and perfused (0.6 ml·min⁻¹·kg⁻¹) with autologous blood withdrawn from the descending aorta and pumped through a variable-speed roller pump.

Local tracer delivery. The small (492 Da), soluble, hydrophilic tracer ⁹⁹ᵐTc-DTPA was used to assess clearance from the airways and uptake by the bronchial circulation. DTPA was freshly prepared on each experiment day as ⁹⁹ᵐTc-labeled DTPA (Medi-Physics, Arlington Heights, IL). Occasionally, ⁹⁹ᵐTc-DTPA was sampled predelivery and assayed for unbound ⁹⁹ᵐTc with silica gel media and thin-layer chromatography to verify the labeling procedure (2). Local airway delivery was performed to ensure deposition of the tracer exclusively onto surfaces of conducting airways perfused by the bronchial circulation. A fiber-optic bronchoscope (5-mm OD, Olympus, Lake Success, NY) was advanced through the trachea, beyond the carina, and into a fourth-generation bronchus. A polyethylene catheter with a microspray nozzle (11) at the tip was advanced through the working channel of the bronchoscope and visualized beyond the end of the bronchoscope. After ventilation was momentarily stopped, 6–10 μl of ⁹⁹ᵐTc-DTPA that had been loaded into the catheter tip were sprayed radially onto the airway wall. Absolute activity delivered was determined by measuring the catheter tip after it was loaded and again after deposition of label to the airways. The average activity delivered was 66 μCi (84% delivery efficiency). The catheter was then retracted into the channel of the bronchoscope, and the bronchoscope was removed from the animal. Controlled ventilation resumed, and serial dynamic images of clearance of the ⁹⁹ᵐTc-DTPA were acquired every 2 min for 30 min using NuclEar MAC (Scientific Imaging, Littleton, CO) and a gamma camera (Maxi-Camera, General Electric, Waukesha, WI). Animals were imaged from the ventral aspect, and the camera was set with a 15% window around the peak energy of 140 keV and shielded by a parallel-hole collimator. Radioisotope delivery and clearance data were quantitated with techniques modified from Foster and Stetkiewicz (8). The initial bronchial image acquired immediately after delivery of the ⁹⁹ᵐTc-DTPA was stored on a computer screen, and this enabled a region of interest to be selected by cursor manipulation and drawn to cover the site of ⁹⁹ᵐTc-DTPA delivery (150–160 pixels = ~3 cm × 3 cm). For the clearance of ⁹⁹ᵐTc-DTPA, activity-time plots were constructed for the region of interest and the retention of radioactivity during the 30-min washout was corrected for radioactive decay and expressed as a percentage of the ⁹⁹ᵐTc-DTPA delivered to the region at time 0 (immediately after the nozzle catheter and bronchoscope were withdrawn from the bronchial airway). Because remaining activity before the second deposition was always such a small amount (<5% of the original delivered activity), we did not background correct. In this model, this level of clearance has become a selection criterion for normal tracer clearance. Systemic venous blood samples (0.5 ml) were withdrawn from the inferior vena cava via a catheter inserted into a femoral vein every 6 min for the 30-min time period. Activity in blood (counts per min/0.5 ml) was counted in a gamma counter (GammaTrac, TmAnalytic, Tampa, FL) and corrected for the baseline activity measured 1–2 min before airway deposition. Counts per minute per milliliter were converted to microcuries per milliliter after calibration of the gamma counter with a Capintec counter (Capintech, Ramsey, NJ) which allowed measurement of both counts per minute per milliliter and microcuries per milliliter of ⁹⁹ᵐTc-DTPA. Estimates of total blood ⁹⁹ᵐTc-DTPA were made by multiplying blood activity by a nominal blood volume equal to 8.5% body weight (19). Total blood levels of radiolabel were determined as a fraction of delivered radiolabel.

Protocols. Airway clearance and blood uptake of ⁹⁹ᵐTc-DTPA were measured in sheep during control conditions and immediately after and 1 h after the completion of an infusion of bradykinin (20 ml; 1 ml/min; 10⁻⁶ M) directly into the bronchial artery. Our laboratory has previously shown this bradykinin dose causes peribronchial edema (21) and a sustained increase in lung lymph flow (22). Because bradykinin dilates the bronchial vasculature (21), during the 20-min infusion we increased pump flow to maintain bronchial artery pressure approximately equal to the pressure before drug infusion. In eight sheep, we deposited ⁹⁹ᵐTc-DTPA in an attempt to study clearance after two control depositions (randomizing the order of left lung, right lung, and control depositions) and then immediately after bradykinin and 1 h after bradykinin in all animals. The lung was imaged for 30 min after each deposition. Thus, for example, we made the first control deposition in the right lung and measured blood and obtained images for 30 min. There was a 15–30-min interval of time before the next control deposition. Just before the second control deposition, we took a baseline blood sample. This baseline provided the background to correct the subsequent blood samples for the second deposition. Then, the second control deposition was made in the contralateral lung. Bronchoscopy was performed by mapping into a specific fourth-generation bronchus for each control deposition. The subsequent deposition after bradykinin infusion took place in the same location. Thus one control lobe (either left or right) was used for comparison to the measurement immediately after bradykinin, whereas the other lobe (the contralateral control) was used for comparison to the 1-h postbradykinin measurement. This experimental design was implemented so that paired comparisons could be made within a specific airway so as to 1) eliminate issues of attenuation of radioactivity due to regional differences in airway geometry and the subsequent two-dimensional image acquisition and 2) eliminate error due to left-right lung differences in clearance (9). In preliminary studies, we have confirmed the reproducibility of retention-time data during control conditions. Additionally, we have demonstrated previously the stability of the preparation over the time period of the measurements (23).

Statistics. All data are presented as means ± SE. Wilcoxon signed-ranks test was used to evaluate differences between responses observed during control conditions and after bradykinin-induced airway wall edema. For paired depositions in the same lung, we evaluated the percentage of retained activity at 30 min and the average retention time of ⁹⁹ᵐTc-DTPA at the delivery site (Δactivity × time/Δactivity for 0–30 min) (24) and the area under the blood activity-time
curves. A two-tailed $P$ value of 0.05 was accepted as significant.

RESULTS

Baseline bronchial artery pressure was $87 \pm 8$ mmHg for the group of sheep ($n = 8$) studied. This pressure was obtained during perfusion at the control flow ($14 \pm 1$ ml/min), which had been based on sheep body weight ($24 \pm 2$ kg). Mean systemic arterial pressure for the group of sheep studied was $100 \pm 4$ mmHg, and peak inspiratory pressure was $17 \pm 1$ cmH$_2$O. Because of the vasodilator properties of bradykinin, bronchial blood flow was increased to $34 \pm 2$ ml/min during bradykinin delivery to maintain bronchial artery pressure close to the preinfusion level. After termination of the bradykinin infusion, bronchial artery pressure reversed spontaneously during control perfusion and returned to baseline level. The average time course of $^{99m}$Tc-DTPA airway clearance for 13 depositions (3 of 16 control depositions did not meet all inclusion criteria) during control conditions is presented in Fig. 1 and demonstrates the rapid removal of the radiolabeled DTPA. At 30 min postdeposition, the average retention of $^{99m}$Tc-DTPA at the delivery site was $11.6 \pm 2.5\%$ of the initial activity delivered. The average retention time, based on analysis of the area under individual retention-time curves, was $9.2 \pm 0.6$ min. Figure 2 shows retention-time data for the region of interest drawn in over the airway delivery site before and after the induction of airway wall edema with bradykinin infusion. Figure 2A compares the time course of bronchial $^{99m}$Tc-DTPA clearance at baseline (control) with that immediately after the 20-min administration of bradykinin ($n = 5$). Bradykinin had a small, immediate effect on tracer retention to slow the overall clearance process. The increase in retention compared with paired controls (Table 1) was significantly increased ($P = 0.043$). However, by 1 h after bradykinin infusion (Fig. 2B), the bronchial clearance of $^{99m}$Tc-DTPA was markedly delayed. At this later time, retention of $^{99m}$Tc-DTPA at the delivery site 30 min after deposition averaged $36.9 \pm 9.6\%$ of the initial amount delivered compared with $9.8 \pm 2.5\%$ for paired control conditions ($P = 0.017$). It should be noted that the retention curves during control conditions (presented in Fig. 2, A and B) are not completely superim-

![Fig. 1. Bronchial retention of soluble radiotracer vs. time curves. Values are average retentions (± SE) for a bronchial region observed in 13 depositions in 8 sheep at indicated times during control conditions. Retention is expressed as percentage of technetium-99m-labeled diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) activity initially delivered to the airway surface; time = 0 min immediately follows delivery of radioactivity.](image1)

![Fig. 2. A: bronchial retention-time data comparing control bronchial flow with retention-time data immediately after a 20-min infusion of bradykinin (bradykinin-i). Values are average retentions (± SE) for a bronchial region observed in 5 sheep. See Fig. 1 legend for details. Radiolabeled tracer retention is significantly greater after bradykinin treatment than during control conditions ($P < 0.05$). B: bronchial retention-time data comparing control bronchial flow with retention-time data 1 h after a 20-min infusion of bradykinin (bradykinin-L). Values are average retentions (± SE) for a bronchial region observed in 8 sheep.](image2)

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<th>Group</th>
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<th>Average Retention Time, min</th>
<th>$P$ Value</th>
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Values are means ± SE. $^{99m}$Tc-DTPA, technetium-99m-labeled diethylenetriamine pentaacetic acid.
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posable, because the samples used for these analyses were not identical and demonstrate slight intergroup variations in clearance efficiency during control conditions. In Table 1, the respective 30-min retention values for $^{99m}$Tc-DTPA are presented as well as the average retention times.

Figure 3 shows the average systemic blood levels of $^{99m}$Tc-DTPA at respective sample times after delivery of the radiotracer to the bronchial surface. Figure 3 compares the blood levels in paired experiments at baseline (control) and 1 h after the completion of the bradykinin infusion in six sheep. Analysis of the area under the activity-time curves showed that, during the clearance of $^{99m}$Tc-DTPA, blood activity levels were higher during control conditions than 1 h after bradykinin administration ($P = 0.028$). The average maximum blood level was 17% of the delivered total during control conditions. However, after bradykinin treatment, at the same time points that resulted in control maximum levels, the blood activity was 8% ($P = 0.043$). Although the time course of additional blood level data is not shown, the blood levels in paired measurements at baseline and during the period immediately after infusion of bradykinin ($n = 5$) were similar to each other ($P = 0.893$).

DISCUSSION

Airway wall edema, prominent in inflammatory airway disease, may alter barrier properties at the airway air-liquid interface such that normal absorption of soluble substances into the airway circulation is altered. In this study, we have utilized our established in vivo model of airway wall edema to demonstrate interaction between the primary clearance pathways for soluble, hydrophilic substances that have been deposited directly on the bronchial airway surface. We assured ourselves of the uniform diffusivity of our marker by using a radiotracer that was discrete with respect to molecular size and radius. In addition, we guaranteed the routes available for clearance by limiting the delivery of the tracer directly to a small region of the bronchial airway surface. We found that, during control conditions, clearance of the tracer was rapid and, within 30 min, most of the tracer was removed from the deposition site (>85%), and maximum blood uptake was 17% of the deposited tracer. These observations are consistent with those previously reported in this model (24). Clearance pathways were significantly altered by airway edema that was induced by bronchial artery infusion of bradykinin. The time course of clearance was such that substantial changes were not present immediately postinfusion but developed to a more significant level within 1 h of the bradykinin delivery. Clearance of the isotope from the initial delivery site was substantially impaired by bradykinin treatment, resulting in an increased retention at the deposition site (~35%) and decreased blood uptake (8%).

This study tested the hypothesis that the presence of wall edema within the large airways delays the normal removal of soluble agents from the epithelial surface. This question is relevant to the fate of xenobiotic agents that, when inhaled into the lung, deposit onto the airway surface and become engaged with a number of host defense mechanisms. Previously, in the anesthetized and instrumented sheep model, we found that clearance of $^{99m}$Tc-DTPA from the epithelial surface was delayed (as in the present study, delivery of the radiotracer was limited to a defined area of the bronchial airway) when bronchial blood flow was increased threefold above control perfusion (24). Simultaneously with retention of $^{99m}$Tc-DTPA at the airway surface, there was a decrease of radiotracer uptake into blood. A similar observation was made by Hanafi and colleagues (10) examining tracer uptake in the tracheal vasculature. To explain this paradox, i.e., a higher local concentration of a soluble marker in the presence of greater tissue perfusion, we proposed a mechanism that was related to an earlier observation of our laboratory in which increased bronchial perfusion led to accumulation of airway edema fluid (3). Soluble tracers placed onto the airway surface may follow several routes of clearance, including for hydrophilic substances a paracellular pathway through the epithelial surface and diffusion into the airway interstitium and entrance into the bronchial vasculature (26). We proposed that, whenever the tissue-fluid barrier became enhanced (evidenced morphometrically by a significant increase in airway wall area), this would delay paracellular clearance of the tracer.

Building on these initial observations, in the present study we induced a state of airway edema with an exogenous infusion of bradykinin. Bradykinin is thought to cause endothelial gap formation and thus permits fluid and protein to leak from the airway circulation (13, 14). Previously, we have successfully used bronchial artery infusions of bradykinin in the sheep model to induce and control the magnitude of airway wall edema (21). In this model, when using morphometric and computed tomographic imaging methodology, our laboratory found that 30 min of bradykinin infusion leads to ~50% increase in airway wall area of the bronchial airway (4). Consistent with the

Fig. 3. Normalized $^{99m}$Tc-DTPA activity in blood as a percentage of the delivered dose over the course of 30 min. Late, activity 1 h after bradykinin infusion. Values are average blood activities (± SE) for 6 sheep.
development of bradykinin-induced airway wall edema, we found that, within 10 min of bradykinin infusion, there was a substantial increase in lung lymph flow that was sustained for over 60 min (22). Thus, in the present study, we found that there was increased retention of the soluble tracer at the delivery site and overall lower blood levels. These data add further support to our hypothesis that an enhanced tissue-interstitial fluid barrier delays clearance and diffusion of soluble substances into the vasculature.

However, the reason for a considerably greater airway retention 1 h after bradykinin administration compared with the immediate, postinfusion assessment of tracer kinetics is not clear. Because the effects of bradykinin on vascular permeability are rapid (18, 22), we fully expected to see a large immediate effect. However, the more pronounced effect on tracer retention was observed at the later time point (Fig. 2A vs. 2B). Blood uptake was not significantly altered until 1 h after bradykinin administration. We can only speculate that, with time after the initial stimulus, there is a translocation of interstitial fluid, an enhanced endothelial barrier, or an altered airway wall matrix that leads to decreased vascular uptake. It is possible that fluid flux into the airway lumen occurred at the later time point and served to exert a dilutional effect on the deposited tracer. Accordingly, the uptake of tracer into the blood might have been related to a decreased concentration gradient. Additionally, solvent drag might also have contributed to decreased uptake. Overall, these findings are somewhat inconsistent with the concept put forward by Persson and colleagues (17) that proposed that plasma exudation provides the first line of respiratory defense. These authors suggested that increased fluid extravasation might prove beneficial to the removal of airborne substances. However, the results of the present study suggest that changes in wall and/or surface liquid properties retard soluble-particle removal.

Because, at any time point, the activity in the blood and the amount retained at the site of deposition did not account for all the delivered tracer, another clearance route in addition to the assumed renal excretion appeared to be operative. As previously reported, a significant portion of deposited soluble tracer can be cleared by mucociliary activity (24). This observation was made again from scintigraphic images in which radioactivity could be visualized moving up the conducting airways. To estimate the contribution of this clearance pathway, we assumed that systemic distribution of tracer to other organs would be minimal and that the major compartments for tracer would be the airway, blood, and kidneys (5). Our calculations were based on the following equation: total delivered tracer (100%) = percent in blood + percent cleared by kidneys + percent retained at airway site + percent cleared by mucociliary activity. We estimated renal clearance as 4.5% of the blood volume/min (10, 20) and used the mean blood activity values in microcuries that were used to calculate the results presented in Fig. 3. The percent retained values are the averages from the sheep with blood measurements used to generate the 30-min results presented in Fig. 2B. Figure 4 shows the distribution of 99mTc-DTPA activity in blood, excreted by the kidneys (calculated estimate), retained in the airway, and attributed to mucociliary clearance. Although the estimate for the amount of label excreted by the kidney over 30 min demonstrated a significant decline after bradykinin treatment, as might be predicted because it is based on blood tracer level, the component attributed to mucociliary clearance was not significantly altered after treatment. Although we cannot state with certainty whether bradykinin delivered to the bronchial vasculature affected the kidney or any other organ, our laboratory has shown previously this dose does not affect the pulmonary vasculature (22). Overall, this analysis is an attempt at estimating distribution based on mass balance. Precise information on the effects of bradykinin on mucociliary clearance in this model remain to be determined. The calculation of the mucociliary component falls short only if there is a large amount of tracer penetrating into the blood while in mucociliary transit in the trachea where tracheal vessels will be involved in blood uptake or if there is systemic distribution to other organs.

We designed our experiments to assess clearance mechanisms both immediately after and 1 h after bradykinin administration because several cellular functions have been shown to be acutely affected by bradykinin. For example, in a study in human subjects, large-airway mucociliary clearance was enhanced after inhalation of bradykinin (18). This response may reflect a combination of responses, i.e., ciliary beat rate, mucus secretion, or local axon reflexes. Wong and associates (27) have demonstrated in an in vivo canine model that an aerosol administration of bradykinin caused an immediate and maximal stimulation in the ciliary beat frequency of tracheal airway epithelium that lasted ~30 min. This stimulatory effect on ciliary beat frequency was modulated by both neural and cyclooxygenase pathways and thus could be inhibited by hexamethonium bromide and indomethacin, respectively. In an in vitro model, Leikauf and colleagues (13) demonstrated that serosal or mucosal additions of bradykinin to canine tracheal epithelium stimulated Cl

![Fig. 4. Distribution of 99mTc-DTPA activity in blood, excreted by the kidneys (calculated estimate), retained in the airway, and attributed to mucociliary clearance (calculated estimate) at 30 min during paired control conditions and 1 h after bradykinin administration. Values are average retentions (± SE) for 6 sheep.](http://jap.physiology.org/DownloadedFrom/10.22033.1)
faces diffuse into the bronchial vasculature. In a prior study, we clearly demonstrated an interdependence between the mucociliary and vascular absorption pathways for clearance of soluble substances such that, at low perfusion pressure or when perfusion was halted, clearance of DTPA by both pathways was impeded (24). In the present investigation, the presence of airway wall edema limited the access of DTPA to the vascular clearance pathway. Thus airway wall edema that may result from bronchial vascular fluid extravasation and that is a prominent pathological feature of inflammatory airway disease may increase the diffusion distance, widen the interstitial barrier and limit the ability of the airway circulation to absorb soluble substances. If the mucociliary clearance apparatus is also compromised by the presence of inflammatory airway disease (7), unlike our healthy sheep in which normal mucociliary clearance of secretions and soluble substances could still take place, xenobiotic substances of a injurious nature would have prolonged retention times at epithelial surfaces and within interstitial spaces of the bronchi.

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REFERENCES


