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Effects of inspiratory resistance, inhaled beta-agonists and histamine on canine tracheal blood flow

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ABSTRACT: Tracheobronchial blood flow is potentially important in asthma as it could either influence the clearance of mediators from the airways, thus affecting the duration and severity of bronchospasm, or enhance oedema formation with a resultant increase in airflow obstruction.

In anaesthetized dogs, spontaneously breathing *via* a tracheostomy, we investigated the effects of three interventions which are relevant to acute asthma attacks and could potentially influence blood flow and its distribution to the mucosa and remaining tissues of the trachea: 1) increased negative intrathoracic pressure swings (-25±1 cmH_2O) induced by an inspiratory resistance; 2) variable inhaled doses of a beta-adrenoceptor-agonist (terbutaline); and 3) aerosolized histamine sufficient to produce a threefold increase in pulmonary resistance. Microspheres labelled with different radioisotopes were used to measure blood flow.

Resistive breathing did not influence tracheobronchial blood flow. Following a large dose of terbutaline, mucosal blood flow ($\dot{Q}mb$) increased by 50%. After inhaled histamine, $\dot{Q}mb$ reached 265% of the baseline value.

We conclude that, whereas increased negative pressure swings do not influence tracheobronchial blood flow or its distribution, inhalation of aerosolized terbutaline, corresponding to a conventionally nebulized dose, increases mucosal blood flow. Our results also confirm that inhaled histamine, in a dose sufficient to produce moderate bronchoconstriction, increases tracheal mucosal blood flow in the area of deposition.
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The purpose of this study was to examine three interventions which could potentially increase airway blood flow during acute attacks of asthma. A number of factors could affect airway blood flow in asthmatic subjects during acute bronchoconstriction. It has been shown in dogs and humans, that positive airway pressure decreases airway blood flow [1, 2]. During severe attacks of asthma, large negative intrathoracic pressure swings are generated [3] and these could alter airway blood flow by influencing the transmural pressures across bronchial blood vessels. On the other hand, therapeutically administered beta-adrenoceptor agents, commonly used in the treatment of asthma, could vasodilate the bronchial vessels and influence magnitude and duration of airway smooth muscle contraction after the local release of mediators. The bronchial vasculature has been shown to possess beta-adrenoceptors which mediate vasodilation [4]. An increase in blood flow through an inflamed airway mucosa could even contribute to the airflow obstruction by enhancing the degree of mucosal oedema. Whatever the effects, changes in airway blood flow are likely to be important. The aim of this study was to investigate whether negative airway pressure, therapeutic concentrations of a nebulized beta-adrenoceptor agonist, terbutaline, or nebulized histamine alter tracheal blood flow.

Methods

We studied twenty four supine, anaesthetized mongrel dogs (20±4 kg) and measured tracheobronchial blood flow before and after: 1) inspiratory resistive loading (Group 1, n=7); 2) inhalation of terbutaline aerosol (Group 2, n=11); and 3) inhalation of histamine aerosol (Group 3, n=6). Group 1 and 2 dogs were anaesthetized with pentobarbitone sodium (25 $mg \cdot kg^{-1}$) and additional doses of pentobarbitone were administered as necessary to maintain anaesthesia. Group 3 dogs were anaesthetized using a mixture of chloralose (0.1 $g \cdot kg^{-1}$) and urethane (1.0 $g \cdot kg^{-1}$) to minimize interference with vagal reflex mechanisms deemed to be important in effecting histamine-induced increases in pulmonary resistance.

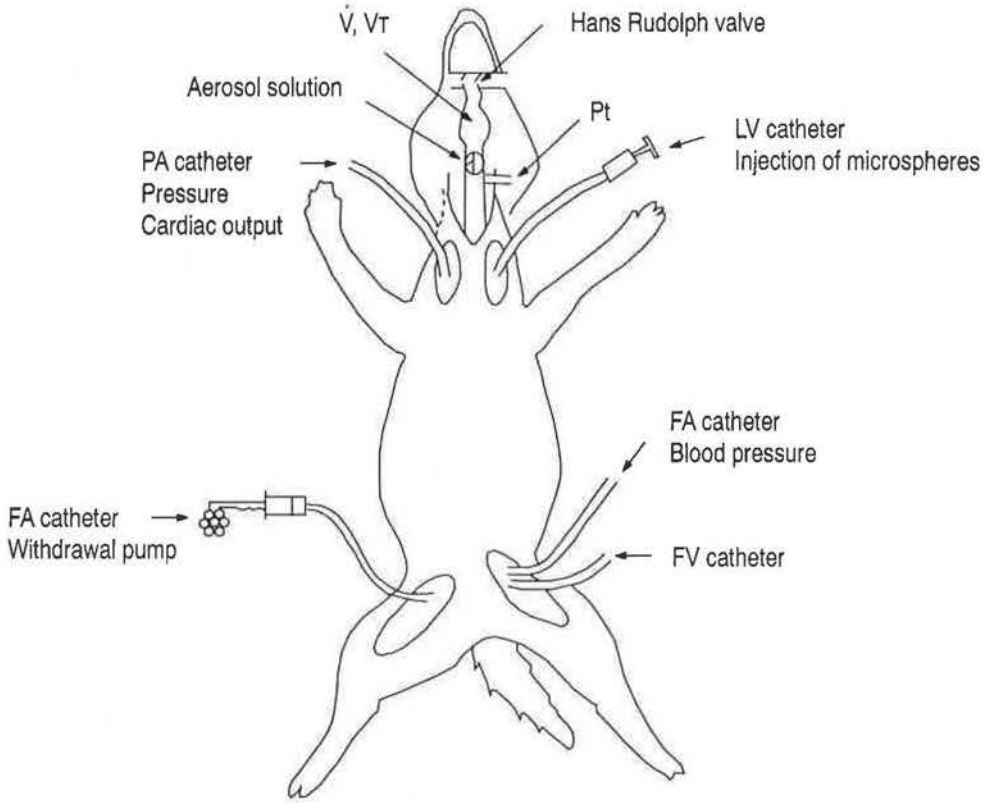

Fig. 1. – Experimental set-up for measurement of blood flow. V̇: airflow; VT: tidal volume; Pt: tracheal pressure; LV: left ventricular; PA: pulmonary arterial; FA: femoral arterial; FV: femoral venous.

After anaesthesia, a short uncuffed tracheostomy tube was inserted between the 10th and 11th tracheal rings and tied securely in place and the dogs breathed warm, humidified air (37°C, 100% relative humidity). A thermistor-tipped triple lumen catheter was inserted into the pulmonary artery for measurement of pulmonary artery pressure (Ppa) and cardiac output (CO) by the thermodilution technique. Catheters were also placed in the femoral arteries for reference blood flow sampling and measurement of mean systemic arterial blood pressure (BP). A size 7 French catheter was inserted *via* the left carotid artery into the left ventricle for later injection of radioactive microspheres (fig. 1).

In all groups, vascular pressures, arterial blood gases and cardiac output were measured before each determination of tracheobronchial blood flow. Blood flow was measured with 15±3 μm diameter microspheres (New England, Nuclear) using the reference flow technique [5]. Microspheres were labelled with one of four different radioisotopes (46 Scandium, 103 Ruthenium, 133 Tin and 95 Strontium) and were injected in random order. Blood flow measurements were made using the following protocol: at time zero, a femoral arterial reference blood flow sample collection was begun, at a constant flow rate of 10 $ml \cdot min^{-1}$, using a Harvard withdrawal pump. Five seconds after starting the pump, between $2.5–12.5 \times 10^6$ microspheres, radiolabelled with 80–100 μCi of one of the four isotopes, uniformly suspended in 5 ml of saline, were injected into the left ventricle, followed by 5 ml of heparinized saline. The duration of the injection extended over 2–3 respiratory cycles. At 2 min the withdrawal pump was stopped.

On completion of each study the dog was killed painlessly by administering an overdose of pentobarbitone sodium (140 $mg \cdot kg^{-1}$) and the trachea was excised. To measure blood flow to the trachea, above and below the tracheostomy site, the tracheal mucosa of each portion was stripped from the remaining tracheal tissue. In addition, in Group 3, the trachealis muscle was isolated and excised. The two tracheal rings immediately above and below the tracheostomy site were not included in the analysis of blood flow, because the placement of endotracheal tubes has been shown to cause an increase in tracheal blood flow [6]. All tissue samples were placed in preweighed plastic vials and reweighed to obtain the wet weight. Tissue and weighed reference blood samples were counted in a gamma scintillation well counter (Searle) and the relative counts of each isotope were determined after correction for background radioactive decay and gamma spectrum overlap. Blood flow to each of the tissue samples ($\dot{Q}$) was calculated by the following equation:

$$\dot{Q} = [Ati/Aref] \times \dot{Q}ref$$

where Ati and Aref are the count rates in the tissue and reference samples, respectively. Blood flow was then calculated either in $ml \cdot min^{-1}$ or in $ml \cdot min^{-1} \cdot 100\ g^{-1}$ tissue wet weight. Total blood flow

was measured above ($\dot{Q}a$) and below ($\dot{Q}b$) the tracheostomy site. Similarly, mucosal blood flow was measured above ($\dot{Q}ma$) and below the tracheostomy site ($\dot{Q}mb$). In Group 3, blood flow to the trachealis muscle above ($\dot{Q}ta$) and below ($\dot{Q}tb$) the tracheostomy was also determined.

Group 1, inspiratory resistive loading

Vascular pressures, arterial blood gases and airway blood flow were measured at baseline (B1) and after application of an inspiratory resistance sufficient to increase the intratracheal inspiratory negative pressure swings, generated with each breath, to approximately -25 cmH_2O (table 1). The second set of measurements was made 15 min after a stable negative intrathoracic pressure had been achieved and while the dogs continued to breathe through the resistance (R1). In five of the seven dogs, the protocol described above was repeated (B2 and R2). Tracheal pressure was measured using a differential pressure transducer (Validyne 45 MP±100 cmH_2O).

Group 2, terbutaline aerosol

All measurements of vascular pressures, arterial blood gases and airway blood flow were made while the dogs breathed warmed humidified air. In 7 out of 11 dogs, measurements were made during baseline conditions, after administering saline aerosol and again after administering one or two increasing concentrations of terbutaline. In these dogs, comparisons were made between measurements obtained before and after administration of saline aerosol to test for a nonspecific effect of saline aerosol. Because there was no significant effect of saline aerosol on haemodynamics or tracheobronchial blood flow, values obtained during baseline conditions or after administration of the saline aerosol were used for subsequent comparison with values obtained after administration of terbutaline aerosol. For the remaining four dogs, only one baseline value was obtained, either with or without saline aerosol (table 2). Five dogs received terbutaline solutions of 0.25 $mg \cdot ml^{-1}$, five dogs 0.75 $mg \cdot ml^{-1}$, three dogs 5 $mg \cdot ml^{-1}$, and three dogs 10 $mg \cdot ml^{-1}$.

The dose of terbutaline delivered was calculated as: [nebulizer output ($ml \cdot min^{-1}$) × mean inspiratory duration (min) × breathing frequency ($breaths \cdot min^{-1}$)]. The dogs were grouped according to the calculated dose delivered, as follows: small dose, 0.02±0.005 mg; moderate dose, 0.07±0.02 mg; and large dose, 0.86±0.37 mg. The effects of these doses were assessed by comparing the responses obtained after administration of the aerosol with those obtained during baseline conditions or after saline. Saline or terbutaline aerosol was administered for 2 min using a Hudson jet nebulizer driven with compressed air at 6 $l \cdot min^{-1}$ and connected to the tracheostomy tube *via* a T-tube.

Group 3, inhaled histamine

Transpulmonary pressure (Ptp) was measured using an oesophageal balloon catheter placed in the lower oesophagus and connected to a Validyne differential pressure transducer, which compared oesophageal and tracheal pressure.

All measurements were made while the dogs were breathing warm humidified air. Baseline values were obtained 15 min after inhalation of 0.3 ml of saline aerosol, delivered by the Hudson jet nebulizer (B). Incremental concentrations of nebulized histamine were then administered for periods of 1 min, until intrathoracic pressure swings had doubled when compared with those observed under baseline conditions. The dogs were then switched to breathing warm humidified air and measurements were repeated (H). Intrathoracic pressure swings were allowed to return toward baseline values (20–40 min). Another 0.3 ml of saline was nebulized and, after a recovery period of 45 min, a final set of measurements was made (R).

Table 1. – Group 1: physiological variables and tracheal blood flow in response to inspiratory resistance

	B1	R1	B2	R2
	n=7		n=5	
pH	7.35±0.01	7.30±0.02	7.35±0.01	7.32±0.01
$Paco_2$ kPa	5.3±0.13	5.7±0.13	5.3±0.13	5.9±0.27
mmHg	40±1	43±1	40±1	44±2
Pao_2 kPa	10.3±0.27	8.3±0.40*	10.8±0.13	9.3±0.53
mmHg	77±2	62±3*	81±1	70±4
CO $l \cdot min^{-1}$	3.26±0.22	3.43±0.39	3.42±0.42	3.23±0.34
$\dot{Q}b$ $ml \cdot min^{-1} \cdot 100\ g^{-1}$	29±5	28±5	26±6	22±4
$\dot{Q}mb$ $ml \cdot min^{-1} \cdot 100\ g^{-1}$	150±30	130±19	130±29	104±19

B1 and B2: baseline runs; R1 and R2: inspiratory resistance; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; CO: cardiac output; $\dot{Q}b$: tracheal total blood flow below the tracheostomy; $\dot{Q}mb$: tracheal mucosal blood flow below the tracheostomy; *: $p<0.01$.

Table 2. – Group 2: tracheal mucosal blood flow below the tracheostomy site ($\dot{Q}mb$) - effects of terbutaline

	Baseline		Terbutaline dose		
Dog no.	No saline	Saline	Small	Moderate	Large
1	57	70	109 [0.03]	87 [0.10]	–
2	72	97	91 [0.02]	92 [0.05]	–
3	55	60	71 [0.02]	59 [0.06]	–
4	59	70	83 [0.03]	52 [0.08]	–
5	98	101	101 [0.02]	74 [0.07]	–
6	118	–	–	–	203 [0.41]
7	53	–	–	–	54 [1.02]
8	50	45	–	–	66 [0.9]
9	77	62	–	–	99 [1.10]
10	–	73	–	–	168 [0.39]
11	–	58	–	–	92 [1.3]
n	9	9	5	5	6
Mean±SD	72.6±24.5	70.7±18.2	91.9±14.9 [0.02±0.005]	72.7±17.1 [0.07±0.02]	113±59 [0.86±0.37]

Blood flow is expressed as $ml \cdot min^{-1} \cdot 100$ g tissue. Values in square brackets are the calculated doses of terbutaline delivered to the trachea in mg.

Statistical analysis

Parameters were expressed as means±SEM unless SD indicated. The effect of each resistive load or drug was assessed by one way analysis of variance. A Scheffe's F-test was used to determine which groups differed. Measurements of haemodynamics, blood gases and tracheobronchial blood flow were compared as follows: Group 1, with and without resistive loading; Group 2, before, and after small, moderate, or large doses of terbutaline; Group 3, before, during and after recovery from histamine-induced bronchoconstriction.

Results

To examine the distribution of systemic blood flow to the tracheal tissue and the tracheal mucosa above and below the tracheostomy site we combined the values obtained during baseline conditions for 16 of the dogs studied in Group 1 (n=7) and Group 2 (n=9). Total tracheal blood flow was 4.0±0.01 $ml \cdot min^{-1}$; 68% of this supplied the trachea below the tracheostomy site and 32% the trachea above. When expressed as flow per 100 g tissue, the flow above the tracheostomy was 18±2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ and below the tracheostomy 21±3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. Baseline values for tracheal mucosal blood flow, above ($\dot{Q}ma$) and below ($\dot{Q}mb$) the tracheostomy site, and for total tracheal blood flow above ($\dot{Q}a$) and below ($\dot{Q}b$) the tracheostomy site are shown in figure 2. Absolute $\dot{Q}ma$ was 4% of the corresponding absolute $\dot{Q}a$, whereas $\dot{Q}mb$ was 55±5% of the corresponding $\dot{Q}b$. When normalized for tissue weight, $\dot{Q}ma$ (71±12 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) was almost four times greater than $\dot{Q}a$ (18±2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$; $p<0.01$). Similarly, normalized $\dot{Q}mb$ (106±17 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) was five times greater than $\dot{Q}b$ (21±3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$; $p<0.01$). Normalized $\dot{Q}mb$ was larger than $\dot{Q}ma$ ($p<0.01$); the difference between normalized $\dot{Q}b$ and $\dot{Q}a$ was not significant ($p=0.052$).

Group 1, inspiratory resistive loading

There were no changes in haemodynamics, arterial carbon dioxide tension ($Paco_2$) or pH after inspiratory loading, but arterial oxygen tension (Pao_2) fell from 10.3±0.27 kPa (77±2 mmHg) to 8.3±0.4 kPa (62±3 mmHg) during the first period of resistive loading ($p<0.01$; table 1). In the five dogs that were subjected to a second period of resistive loading, the fall in Pao_2 from the second baseline period was not significant. There were no differences in total tracheal or mucosal blood flows between baseline periods and resistive breathing (table 1).

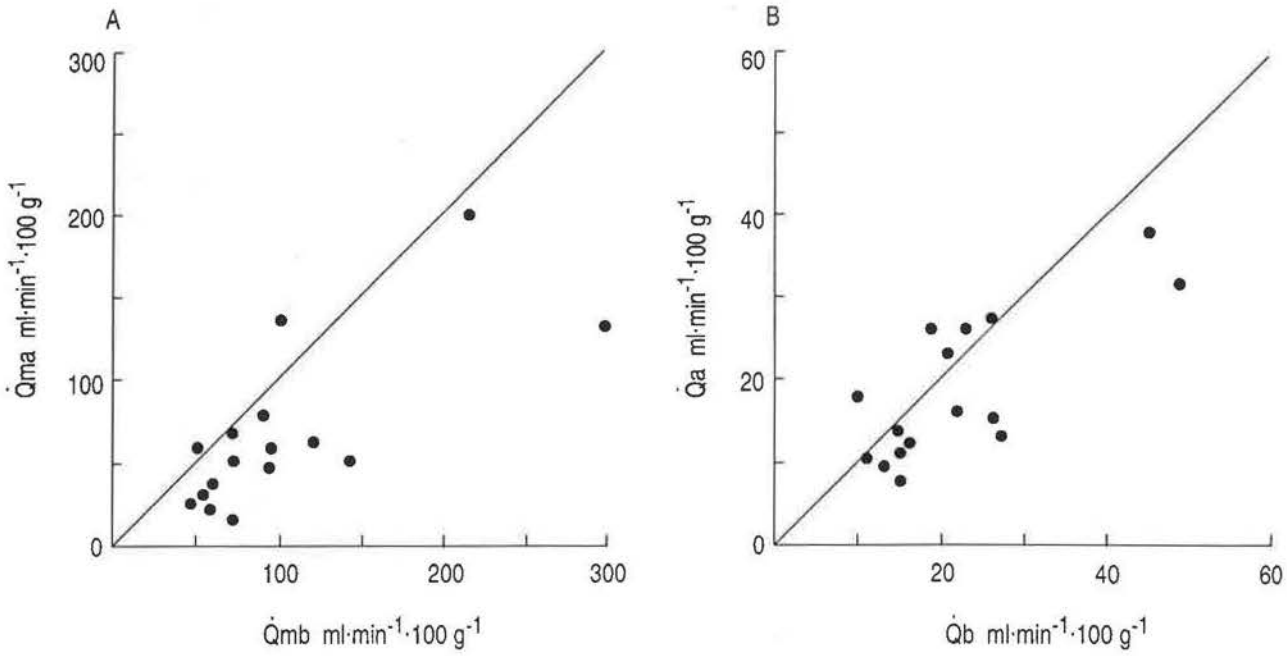

Fig. 2. – A) Tracheal mucosal blood flow above ($\dot{Q}ma$) and below ($\dot{Q}mb$) site of tracheostomy, during control period (n=16 dogs). B) Total tracheal blood flow above ($\dot{Q}a$) and below ($\dot{Q}b$) tracheostomy under control conditions (n=16 dogs).

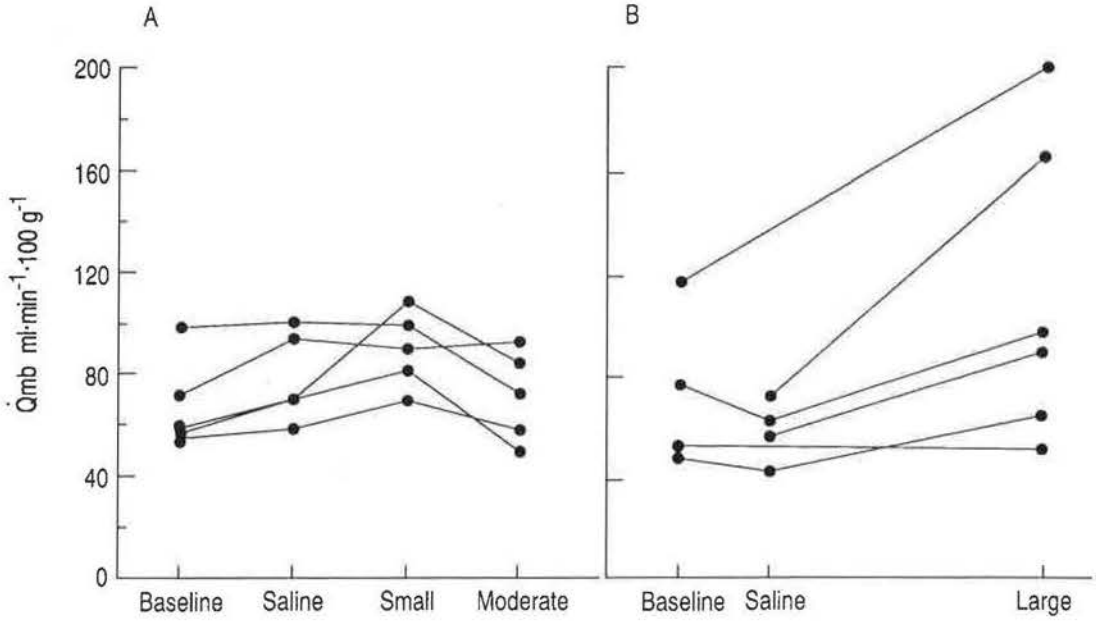

Fig. 3. – Tracheal mucosal blood flow below ($\dot{Q}mb$) the tracheostomy during baseline conditions, after aerosolized saline, and after small (0.02±0.005 mg), moderate (0.07±0.02 mg) and large (0.86±0.37 mg) doses of terbutaline aerosol. A) Dogs received small and moderate doses of terbutaline (n=5). B) Dogs received large dose of terbutaline (n=6).

Group 2, terbutaline aerosol

The values for $\dot{Q}mb$ during baseline conditions and after aerosolized terbutaline, are shown in table 2. There was no difference in any of the variables between baseline measurements and those after aerosolized saline or those obtained after administration of the small or moderate doses of terbutaline (fig. 3). In the six dogs that received the large dose of terbutaline there was an increase in $\dot{Q}mb$ from 71±25.8 ml·min^{-1}·100 g^{-1} to 113±59.0 ml·min^{-1}·100 g^{-1} ($p<0.05$) (fig. 3). In this group there was also an increase in heart rate (from 162±14 to 193±11 beats·min^{-1}; $p<0.05$), cardiac output (from 3.97±0.63 to 5.28±0.80 l·min^{-1}; $p<0.05$) and breathing frequency (from 14±3 to 21±2 breaths·min^{-1}; $p<0.05$), whereas $Paco_2$ decreased (from 5.2±0.13 to 4.4±0.13 kPa (39±1 to 33±1 mmHg); $p<0.02$). $\dot{Q}ma$ did not increase even after the large dose of terbutaline.

Group 3, inhaled histamine

Histamine inhalation resulted in bronchoconstriction in all dogs. Pulmonary resistance, measured by the isovolume method [7], increased from 5.3±1 $cmH_2O \cdot l^{-1} \cdot s$ during the control period to 17±4 $cmH_2O \cdot l^{-1} \cdot s$ after histamine inhalation. During the recovery period, resistance returned towards baseline (11.6±3.1 $cmH_2O \cdot l^{-1} \cdot s$) in all except one dog, which had a higher resistance during recovery than after histamine inhalation (table 3). For the purpose of analysis, this dog's data, obtained during the period of highest resistance, were included in the "histamine period". In another dog, measurements could not be made during the recovery period for technical reasons. During bronchoconstriction there were considerable changes in the respiratory pattern, characterized by rapid shallow breathing.

Respiratory frequency increased ($p<0.05$) and the dogs also developed hypoxaemia ($p<0.05$; table 3). Values for regional tracheal blood flows are shown in table 4. Above the tracheostomy site there were no changes in $\dot{Q}ma$, $\dot{Q}ta$, or $\dot{Q}a$ during histamine inhalation or on recovery. Below the tracheostomy $\dot{Q}mb$ increased from 100±24 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ to 265±42 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ and $\dot{Q}b$ increased from 24±5

Table 3. – Group 3: physiological variables - histamine challenge

	Baseline n=6	Histamine n=6	Recovery n=4
R_L $cmH_2O \cdot l^{-1} \cdot s$	5.3±1.0	17.0±4.1$^+$	11.6±3.1
$\dot{V}_E$ $l \cdot min^{-1}$	5.4±0.6	7.8±1.4	5.8±1.3
f $breaths \cdot min^{-1}$	16±2	31±8$^+$	20±3*
Pao_2 kPa	12.4±0.40	8.8±0.53^{++}	11.2±0.40*
mmHg	93±3	66±4^{++}	84±3*

R_L: pulmonary resistance; $\dot{V}_E$: minute ventilation; f: breathing frequency; Pao_2: arterial oxygen tension. $^+$: $p<0.05$; $^{++}$: $p<0.01$ compared with control values; *: $p<0.01$ compared with values after histamine.

Table 4. – Group 3: regional tracheal blood flow in response to histamine

	Above tracheostomy			Below tracheostomy		
	Baseline	Histamine	Recovery	Baseline	Histamine	Recovery
$\dot{Q}m$	62±24	55±19	57±18	100±24	265±42$^+$	177±19
$\dot{Q}t$	26±5	15±2	17±2	29±6	35±8	26±8
$\dot{Q}$	21±7	13±2	15±2	24±5	51±7$^+$	35±3

Regional tracheal blood flows ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) measured before (Baseline), immediately after inhalation of histamine aerosol (Histamine) and during the recovery period (Recovery). $\dot{Q}m$: mucosal blood flow; $\dot{Q}t$: trachealis muscle blood flow; $\dot{Q}$: total tracheal blood flow. $^+$: $p<0.01$.

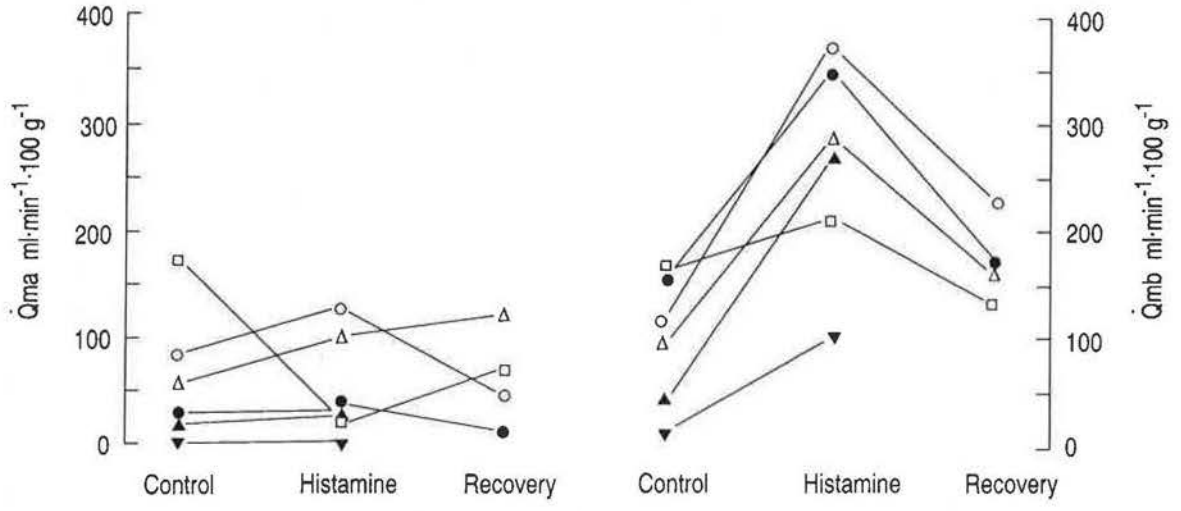

Fig. 4. – Blood flow to tracheal mucosa above ($\dot{Q}ma$) and below ($\dot{Q}mb$) the tracheostomy following aerosolized saline (baseline, recovery) or aerosolized histamine.

$ml \cdot min^{-1} \cdot 100\ g^{-1}$ to 51±7 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ ($p<0.01$). After histamine inhalation the proportion of blood flow to the mucosa increased from 55±4 to 69±3% ($p<0.01$). During the recovery period $\dot{Q}mb$ remained elevated relative to the baseline values. Although 5 out of 6 dogs showed an increase in $\dot{Q}tb$ histamine inhalation, this change was not significant due to a large fall in $\dot{Q}tb$ in one dog (fig. 4). This dog (identified by open squares) had a large $\dot{Q}tb$ and cardiac output during baseline measurements. Other effects of histamine in this animal were also considerable: there was a 625% increase in pulmonary resistance and a 36% fall in cardiac output.

Discussion

Our results indicate that inspiratory resistive loading, as well as small and moderate concentrations of inhaled terbutaline, do not change tracheal blood flow. However, concentrations of terbutaline sufficient to increase heart rate and cardiac output significantly increased $\dot{Q}mb$. In addition, we found that aerosolized histamine, in a concentration sufficient to increase pulmonary resistance 200%, resulted in a substantial increase in $\dot{Q}mb$, as well as a modest increase in $\dot{Q}tb$ (fig. 4). Our results also confirm those of other investigators, showing that the proportion of blood flow supplying the tracheal mucosa is considerably greater than that supplying the remainder of the tracheal tissue [8].

Blood flow partitioning

Our technique for measuring tracheobronchial blood flow is a modification of that developed by BAILE *et al.* [9]. Whereas, those authors studied open chested dogs mechanically-ventilated by positive pressure ventilation, our measurements were made in spontaneously breathing dogs with the chest intact. In studies of anaesthetized and awake sheep it has been shown that during baseline conditions the tracheal mucosal blood flow is about 10 times greater than that of the entire trachea [8] and about 20 times that of the muscularis [10].

The values for $\dot{Q}tb$ measured in this study are intermediate between those of the tracheal mucosa and the entire tracheal wall. The muscularis blood flow below the tracheostomy site is 17% of the blood flow to the entire tracheal wall, which agrees with that described by KRAMER *et al.* [10].

Because we intended to examine the influence of mechanical factors as well as aerosolized agents administered *via* the tracheostomy, we distinguished between the segments of the trachea above and below the tracheostomy. Under control conditions, there was no significant difference in overall tracheal blood flow between the two segments, whereas the mucosal blood flow $\dot{Q}mb$ was significantly greater than $\dot{Q}ma$. This could have been due to a greater handling of the lower trachea. NORDIN *et al.* [6] found a greater than tenfold increase in the mucosal blood flow to rabbit trachea when an uninflated endotracheal tube was inserted. Although our dogs were not intubated, the tracheostomy tube may have modified mucosal blood flow distal to the insertion site. The pattern of our results is consistent with an increased fraction of tracheal flow below the tracheostomy being diverted to the mucosa, rather than a significant increase in total flow.

Resistive loading

Airway blood flow is responsive to alterations in intrathoracic pressures. Several investigators have shown that positive end-expiratory pressure causes a decrease in tracheobronchial blood flow [1, 11]. This decrease in blood flow is partly due to an increase in the vascular resistance of the bronchial vessels.

We examined the influence of increased negative intrathoracic pressure swings on tracheal blood flow. Increases in negative pleural pressure swings (equivalent to those induced by external resistive loading in this study) can occur during acute severe asthmatic attacks [3]. Negative intrathoracic pressures could potentially influence airway blood flow, by changing the peribronchial pressure in the interstitial space of the airway walls. Although the external resistive loads, used in this study, were sufficient to increase negative intrathoracic pressure swings to -25 cmH_2O, this had no significant effect on tracheobronchial blood flow or on the distribution of flow between mucosa and the remainder of the tracheal tissue.

Inhaled terbutaline

Inhaled beta-adrenoceptor-agonists are the most commonly used therapeutic agents in both stable and acute severe asthma. Tracheal vascular resistance decreases in a dose-dependent manner during administration of salbutamol in dogs [12]. Using a bronchial arterial perfusion preparation, LUNG *et al.* [13] found that isoproterenol infusion produced bronchial artery vasodilatation. A similar conclusion was reached by HIMORI and TAIRA [14]. Recently, BARKER *et al.* [15] estimated the effect of a beta-agonist on tracheal mucosal blood flow in lightly anaesthetized sheep by measuring the steady-state uptake of dimethyl ether. They found a 40% increase in flow after inhalation of an aerosol of isoproterenol (total dose 0.8 mg). On the basis of studies with selective antagonists, they concluded that the adrenoceptor agonist acted on the bronchial vasculature *via* the $beta_2$-receptor subtype.

Changes in airway blood flow caused by beta-adrenoceptor agonists may have considerable clinical and physiological significance. KELLY *et al.* [16] have recently shown that pulmonary and bronchial blood flow influence the rate of recovery from pharmacologically-induced bronchoconstriction in the dog. An increase in airway blood flow could potentially accelerate recovery from spontaneous acute asthmatic

attacks by removing locally released mediators from the bronchial wall before the excessive contraction of smooth muscle, stimulation of mucous glands or formation of oedema occurs. Alternatively, vasodilatation of bronchial vessels could have a detrimental effect on the outcome of asthma by increasing the capillary hydrostatic pressure in the microvessels. It is known that in asthmatic patients inflammatory mediators increase bronchial microvascular permeability [17]. Therefore, any increase in capillary pressure might exaggerate oedema formation.

In this study, only the large dose of inhaled terbutaline produced a significant increase in airway mucosal blood flow. The fact that the blood flow to the mucosa above the tracheostomy site did not change following inhaled terbutaline, suggests that this is due to a local effect of terbutaline rather than to an effect on systemic circulatory haemodynamics. To examine the possible clinical relevance of these findings, we must compare the concentrations of terbutaline used in these tracheostomized dogs to the concentrations used during therapeutic administration of beta-adrenoceptor-agonists in humans. If we make the assumption that the fractional tracheobronchial deposition of an inhaled substance administered endotracheally is similar to that which occurs during mouth breathing, then approximately 40% of a delivered dose is deposited when inhaling 3 μ diameter particles [18]. This would mean that in the dogs that received the large dose of terbutaline, approximately 340 μg of terbutaline was deposited in the lower tracheobronchial tree. This would correspond to the dose delivered to the lower airways of humans after inhaling 13–14 puffs from a terbutaline metered dose inhaler (250 μg per puff), assuming 10% deposition, or to approximately 2/3 of a conventional dose (5.0 mg) from a jet nebulizer [19].

Based on the above estimates, it seems likely that conventional doses of terbutaline delivered from metered dose inhalers have no effect on bronchial blood flow. However, large doses, such as those delivered after repeated nebulized terbutaline, may increase mucosal blood flow in the area of deposition in the tracheobronchial tree. This may have clinical significance, as changes in the bronchial blood flow have been shown to modify the rate of recovery from bronchial constriction induced by histamine [16]. It is possible that the duration of responses caused by endogenously released mediators is also modified by variations in bronchial blood flow. Thus, removal of asthma mediators by terbutaline-induced increase in mucosal blood flow may accelerate recovery from spontaneous attacks of asthma. More importantly, if airway capillary permeability were abnormally high during attacks of asthma, increases in mucosal blood flow could potentially aggravate mucosal oedema and contribute to the degree of airflow obstruction.

Recently, SEARS *et al.* [20] reported that regular *vs* on-demand inhalation of a $beta_2$-sympathomimetic agent was associated with deterioration of asthma control in the majority of 89 asthmatics studied prospectively. Other studies, indicating a fall in forced expiratory volume in on second (FEV_1) [21] and a rise in airway responsiveness to methacholine [22] in subjects regularly inhaling $beta_2$-agonists, have also suggested that the latter may have some adverse effect. The mechanism of such an effect is unknown, although tachyphylaxis has been excluded [20]. The results of our study offer a plausible, though highly speculative, explanation for the potential adverse effects of high doses of $beta_2$-sympathomimetic agents in asthma.

Inhaled histamine

Our results are in agreement with those of other investigators, who reported that histamine inhalation [23], or infusion [10, 24], increases tracheobronchial blood flow. However, whereas in previous studies the changes in blood flow could potentially have been due to haemodynamic changes produced by hypoxaemia or the systemic absorption of histamine, our findings of blood flow changes limited to the trachea below the tracheostomy demonstrate that histamine has a local effect on the resistance vessels of the trachea.

In this study, most of the observed increase in blood flow was to the tracheal mucosa, and in four of the five dogs there was also a consistent increase in blood flow to the trachealis muscle. However, the protocol used did not allow us to determine whether the increase in blood flow to the trachealis muscle was due to a direct effect of histamine on vessels or was secondary to trachealis muscle contraction. LONG *et al.* [23] measured bronchial artery blood flow after inhalation of aerosolized histamine in anaesthetized sheep and reported increases in airway resistance and bronchial blood flow which were similar to those in this study. They were able to block the bronchoconstriction by pretreatment with an H_1 receptor antagonist, whereas the increase in bronchial artery blood flow was blocked by an H_2 antagonist. To the degree that these findings are applicable to dogs, it seems that histamine-induced increases in bronchial blood flow are independent of the changes in bronchomotor tone. However, species differences may be important. YANAURA *et al.* [25] examined the effect of arterial infusion of histamine on the bronchial vasculature of dogs and showed that the histamine-induced bronchial vasodilatation was mediated through both H_1 and H_2 receptors. WEBBER *et al.* [26] investigated the effects of arterial injection of histamine on tracheal vascular resistance in anaesthetized sheep. The response was variable, producing either a triphasic response or just a constriction. The vasodilation appeared to be mediated by H_1 receptors but not by H_2 receptors.

In summary, our results demonstrate a significant increase in tracheal mucosal blood flow in dogs following inhalation of aerosolized terbutaline, at a dose corresponding to nebulized doses used in the treatment of severe asthma. In contrast, moderate negative intrathoracic pressure and more modest doses

of inhaled terbutaline did not influence airway blood flow. Aerosolized histamine, sufficient to increase pulmonary resistance by 200% more than doubled mucosal blood flow to the trachea.

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