The role of submucosal oedema in increased peripheral airway resistance by intravenous volume loading in dogs

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The role of submucosal oedema in increased peripheral airway resistance by intravenous volume loading in dogs. G-J. Tang, A.N. Freed. ©ERS Journals Ltd 1994.

ABSTRACT: Pulmonary congestion leads to an increase in airway resistance. It is still unknown whether this is due to vascular engorgement or to submucosal oedema. The present study was designed to determine the relative contribution of these two potential mechanisms.

We examined the effect of intravenous volume loading on canine peripheral airway resistance (Rp). Bronchoscopes were wedged in contralateral sublobar segments and used to record Rp during rapid infusion of normal saline.

Volume loading with normal saline increased pulmonary capillary wedge pressure (PCWP) and Rp. Unlike normal saline, dextran 70 did not increase Rp when infused at a rate that produced similar changes in PCWP. During infusion of normal saline, Δ Rp was significantly enhanced in lung segments previously challenged with dry air when compared to contralateral control lungs, unexposed to dry air, and the use of dextran 70 significantly reduced this effect. Vasoconstriction with phenylephrine significantly decreased baseline Rp, but did not completely reverse the effect of fluid infusion. In addition, in lung segments exposed to dry air, Δ Rp was significantly greater after volume loading and treatment with phenylephrine when compared to contralateral control lung. Finally, muscarinic receptor blockade was ineffective in preventing Rp from increasing during infusion of normal saline.

Our results suggest that volume loading-induced increases in Rp are not caused by either vascular engorgement or the stimulation of muscarinic receptors. Our data are consistent with the hypothesis that submucosal oedema formation is the mechanism responsible for normal saline infusion-induced increases in peripheral airway resistance.

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Pulmonary congestion, resulting from either poor left ventricular function [1–3] or rapid volume loading [4], will impair pulmonary function. Increases in airway resistance both in human and animal studies are reported to be more prominent in small rather than large airways [2–6]. The mechanism for this effect remains an issue of debate [7]. The fact that airway obstruction can be abolished by vagotomy or atropine suggests that this response is mediated by a vagal reflex [8–10]. Alternatively, vascular congestion and engorgement may increase peripheral airway resistance (Rp) by altering airway geometry [1, 5]. It is possible that interstitial oedema could increase Rp via airway compression [11], although it is unlikely to compress airways from the serosal side [12]. However, fluid extravasation from the bronchial circulation may produce intra-airway oedema and increase Rp [13–15].

In this study, we characterize the effect of increasing intravascular volume on Rp. To test the hypothesis that oedema formation increases Rp, we volume loaded the vascular system with either normal saline (NS) or dex-

tran 70 (D70), a polysaccharide with a molecular weight of 70,000 which is hyperoncotic to plasma [16]. Hyperpnoea-induced bronchovascular hyperpermeability was recently reported in guinea-pigs [17], ferrets [18] and dogs [19]. Thus, we used dry air hyperpnoea to increase bronchovascular leakage in canine peripheral airways just prior to increasing intravascular volume with either NS or D70. We also used phenylephrine and nitroglycerine to alter vasomotor tone, in an attempt to determine whether vascular engorgement influenced Rp. Finally, we used atropine to test whether a vagal reflex was responsible for volume loading-induced increases in Rp.

Methods

Male mongrel dogs (weight (mean $\pm$ SEM) 18.4 $\pm$ 1.2 kg, range 16–21 kg; n=6) were initially anaesthetized with sodium thiopental (25 mg $\cdot$ kg⁻¹). Anaesthesia was supplemented with a continuous infusion of that drug (1.25 mg $\cdot$ min⁻¹) and a 25 μ g injection of fentanyl every 15 min.

Dogs were intubated and ventilated with a Harvard constant volume respirator (Harvard Apparatus Co., Millis, MA, USA). End-expiratory CO_2 was constantly monitored with a CO_2 analyser (Beckman LB-2; Beckman Instruments, Fullerton, CA, USA) and maintained between 4–5% by adjusting respirator frequency. Body temperature was maintained with a warming pad throughout the experiment. Heart rate (HR) and systemic blood pressure (BP) were monitored using a noninvasive blood pressure and heart rate monitor (Datascope Accutorr 1A; Datascope Corp., Paramus, NJ, USA). A Swan Ganz catheter was inserted through the femoral vein and pulmonary arterial pressure (PAP) and central venous pressure (CVP) were continuously monitored on a polygraph (Model 7E polygraph, Grass Instrument Co., Quincy, MA, USA). Pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were measured every 4 min using thermodilution in conjunction with a cardiac output computer (Model 9520A; American Edward Laboratories, Irvine, CA, USA).

Measurements of peripheral airway resistance

A fibreoptic bronchoscope (Olympus BF-4B2, 5.5 mm OD; Olympus Corp. of America, New Hyde Park, NY, USA) was visually guided into either a right or left sublobar segment until the tip obstructed the bronchus. Ventilation through this blocked segment could then occur only through collateral channels [20]. A constant flow ($200 \text{ ml}\cdot\text{min}^{-1}$) of room temperature (23°C) 5% CO_2 in air was delivered to the wedged segment through one lumen of a dual lumen catheter inserted through the suction port of the bronchoscope. Sublobar segment airway pressure (Paw) distal to the tip of the bronchoscope was recorded *via* the other lumen. Peripheral airway resistance (Rp) under quasi-static conditions was calculated from measurements made at functional residual capacity. With the ventilator stopped, Paw plateaus at a pressure (Palv) above alveolar pressure in the surrounding unobstructed lung. At this time, $\text{Rp} = (\text{Paw} - \text{Palv}) \cdot 200 \text{ ml}^{-1}\cdot\text{min}$. Rp data are presented in $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$. Approximately 90% of the Rp measured with our wedged bronchoscope technique occurs in respiratory bronchioles and alveolar ducts [20].

Challenge with dry airflow

Airflow was increased from 200 to $1,500 \text{ ml}\cdot\text{min}^{-1}$ for a 2 min period. After 2 min, airflow was returned to the prechallenge flow rate and Rp was monitored until a stable baseline was re-established.

Experimental Protocols

Rp during volume loading with either normal saline (NS) or dextran 70 (D70). After establishing stable baselines for Rp, PAP, PCWP, CO and haematocrit, NS was infused at a rate of $\sim 50 \text{ ml}\cdot\text{min}^{-1}$ over a 15–20 min period until PCWP increased to 15 mmHg. Rp, CO, PAP, BP and

HR were recorded every 4 min. Immediately after the infusion was completed, blood was obtained for measurement of haematocrit. At least two weeks later, the same dogs were used in a similar protocol in which D70 (Pharmacia, UK) was used in place of NS. D70 was infused at a rate of $\sim 25 \text{ ml}\cdot\text{min}^{-1}$ over a 15–20 min period until PCWP increased to 15 mmHg.

Rp during volume loading with either NS or D70 after dry air challenge. Two bronchoscopes were simultaneously wedged, one in each lung. One randomly selected lung was used for control, and the contralateral lung was exposed for 2 min to dry airflow ($1,500 \text{ ml}\cdot\text{min}^{-1}$) 30 min post-challenge. When Rp on the dry air challenged side had returned to control levels, NS was infused at a rate of $50 \text{ ml}\cdot\text{min}^{-1}$ over a 15–20 min period until PCWP increased to 15 mmHg. At least two weeks later, the same dogs were used in a similar protocol with D70 substituted for NS. Rp, CO, PAP, BP and HR were recorded every 4 min.

Rp after vasoconstriction with phenylephrine. Phenylephrine (Sigma, MO, USA) ($10 \mu\text{g}\cdot\text{kg}^{-1} \text{ i.v.}$) was injected *via* the femoral vein after recording baseline values for Rp, CO, PAP, PCWP, BP and HR. Changes in Rp and haemodynamic data were recorded at 30 s, 2 and 6 min after administration of the drug.

Rp after vasodilation with nitroglycerine. Nitroglycerine (American Hospital Supply, UK) ($10 \mu\text{g}\cdot\text{kg}^{-1} \text{ i.v.}$) was injected into the femoral vein after recording baseline values for Rp, CO, PAP, PCWP, BP and HR. Changes in Rp and haemodynamic data were recorded at 30 s, and at 2 and 6 min after treatment with the drug.

Rp during volume loading and vasoconstriction in lung segments previously challenged with dry airflow. Two bronchoscopes were simultaneously wedged, one in each lung. One sublobar segment served as control, while a contralateral segment was exposed for 2 min to dry airflow ($1,500 \text{ ml}\cdot\text{min}^{-1}$). After recording baseline values for Rp, CO, PAP, PCWP, BP and HR, phenylephrine ($10 \mu\text{g}\cdot\text{kg}^{-1} \text{ i.v.}$) was injected into the femoral vein and Rp and haemodynamic data were recorded at 30 s, 2 min and 6 min after drug delivery. The effect of phenylephrine was transient and disappeared within 2 min. When all physiological variables had returned to baseline, NS was infused at a rate of $50 \text{ ml}\cdot\text{min}^{-1}$ over a 15–20 min period until PCWP increased to 15 mmHg. Rp, CO, PAP, BP and HR were recorded every 4 min. At the end of infusion, phenylephrine ($20 \mu\text{g}\cdot\text{kg}^{-1}$) was injected intravenously, and Rp and haemodynamic data were recorded at 30 s and 2 min after administration of the drug.

Rp during volume loading in the presence of muscarinic blockade. Dogs were pretreated with atropine (Sigma, MO, USA) ($0.1 \text{ mg}\cdot\text{kg}^{-1} \text{ i.v.}$). When a stable baseline Rp had been established, NS was infused at a rate of $50 \text{ ml}\cdot\text{min}^{-1}$ over a 15–20 min period until PCWP increased to 15 mmHg, and Rp, CO, PAP, BP and HR were recorded every 4 min.

Statistical analyses

Repeated measures analysis of variance (ANOVA) and Duncan's multiple range tests were used to analyse all time course data. Mean data compared before and after treatment were analysed using paired t-tests. Pearson's product-moment correlation coefficient (r) was used to analyse haemodynamic data. Spearman's rank correlation (R_s) analysis was used to examine the relationship between dry air- and NS infusion-induced responses in the canine lung periphery. All values represent mean $\pm$ SEM. Statistical significance was judged at $p < 0.05$ in all cases.

Results

R_p during volume loading with either NS or D70

Infusion of NS produced a stepwise increase in R_p from 0.69 ± 0.11 to 0.93 ± 0.14 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ (fig. 1) and was correlated with increasing PCWP ($r = 0.78$, $p < 0.01$) and infusion volume ($r = 0.67$, $p < 0.01$). In contrast, R_p was not significantly (1.27 ± 0.22 to 1.29 ± 0.24 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$; $p > 0.05$) affected by infusion of D70, despite increases in PCWP similar to that seen with NS (fig. 2). During volume loading with NS, R_p was significantly greater than that recorded with D70 at 8 ($p < 0.05$), 12 ($p < 0.01$) and 16 min ($p < 0.01$) during the infusion period (fig. 1). On average, 397 ± 13 ml of D70 ($n = 6$) was needed to increase PCWP to 15 mmHg, which was significantly ($p < 0.01$) less than the 808 ± 39 ml of NS used for the same purpose (fig. 2). CO significantly increased ($p < 0.01$) after infusion of either NS or D70, and the magnitude of the increase was similar regardless of infusate (fig. 2).

PAP and mean systemic blood pressure (MBP) significantly increased ($p < 0.01$) after NS and D70 infusion, but the increases were similar regardless of infusate (table

Fig. 1. — Change in peripheral airway resistance (ΔR_p) during continuous infusion of either normal saline or dextran 70. *: 0.05; and **: 0.01 level of significance comparing normal saline to dextran 70. Values represent mean $\pm$ SE ($n = 6$). —●—: normal saline; —○—: dextran 70.

Fig. 2. — Pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and volume of infusate during continuous infusion of either normal saline or dextran 70. *: 0.05; and **: 0.01 level of significance comparing normal saline to dextran 70 ($n = 6$). —●—: normal saline; —○—: dextran 70.

1). Volume loading with either solution did not significantly alter HR (table 1). After infusion of NS and D70, haematocrit decreased ($p < 0.01$) from 39 ± 0.6 to $28 \pm 0.4\%$ and from 39 ± 0.9 to $29 \pm 1.0\%$, respectively. There was no significant difference ($p = 0.68$) in the effect of NS and D70 on haematocrit.

R_p during volume loading with either NS or D70 after dry air challenge.

On average, R_p increased from 1.08 ± 0.18 to 1.88 ± 0.31 $\text{cmH}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{s}$ 2 min after dry air challenge; representing an $84 \pm 34\%$ increase above the original baseline ($n = 6$; $p < 0.01$).

The increase in R_p during infusion of NS was significantly greater ($p < 0.01$) in sublobar segments previously challenged with dry airflow than contralateral control

Table 1. — Haemodynamic changes before and after infusion of either normal saline or dextran 70

		Normal saline		Dextran 70	
		Before	After	Before	After
PCWP	mmHg	4.8±0.3	14.5±0.5**	5.3±0.6	14.7±0.3**
PAP	mmHg	14.9±0.86	21.4±0.93**	12.8±0.84	21.6±0.63**
CO	l·min ⁻¹	2.67±0.15	5.23±0.13**	2.47±0.41	5.27±0.36**
MBP	mmHg	83.6±9.05	112±7.27*	78.0±4.26	105±10.1*
HR	beats·min ⁻¹	90.4±6.15	104.5±9.05	90.2±8.00	98.5±8.00
CVP	mmHg	5.67±0.49	13.8±0.48**	5.33±0.42	12.8±0.60**

Data are presented as mean±SEM. PCWP: pulmonary artery wedge pressure; PAP: pulmonary artery pressure; CO: cardiac output; MBP: mean systemic blood pressure; HR: heart rate; CVP: central venous pressure. *: 0.05; and **: 0.01 level of significance comparing before and after fluid infusion.

Fig. 3. — Changes in peripheral airway resistance (Rp) during infusion of either normal saline (NS) or dextran 70 (D70) in unexposed control and contralateral sublobar segments previously exposed to dry air (1,500 ml·min⁻¹). Data for NS and D70 are reproduced from figure 1. *: 0.05; and **: level of significance comparing dry air + NS to NS. †, ††: 0.05 and 0.01. level of significance comparing dry air + NS to dry air + D70 (n=6). —■—: dry air + NS; —□—: dry air + D70; —●—: NS; —○—: D70.

Fig. 4. — Baseline peripheral airway resistance (Rp) before and after phenylephrine (10 μg·kg⁻¹ i.v.). Mean±SEM and individual values are depicted (n=6). **: p<0.01.

segments that were not exposed to dry air (fig. 3). After dry air challenge, ΔRp during infusion of NS (1.33±0.2 to 1.86±0.29 cmH₂O·ml⁻¹·s) was significantly greater (p<0.01) than the ΔRp during infusion of D70 (1.38±0.48

to 1.54±0.53 cmH₂O·ml⁻¹·s) in the same animals (fig. 3). In the D70 experimental series, Rp increased from 1.07±0.26 to 1.89±0.63 cmH₂O·ml⁻¹·s 2 min after the dry air challenge (n=6; p<0.01). An average of 26±1.8 min (n=12) separated the end of the dry air challenge from the beginning of volume infusion. Spearman's rank analysis revealed a significant correlation (r_s=0.77, p=0.038; n=6) between the peak response to dry air challenge (ΔRp=0.90±0.25 cmH₂O·ml⁻¹·s) before volume loading with NS and the maximum change in Rp at the end of infusion with NS (ΔRp=0.53±0.15 cmH₂O·ml⁻¹·s).

Rp after vasoconstriction with phenylephrine.

Phenylephrine (10 μg·kg⁻¹) significantly decreased (p<0.01) baseline Rp (fig. 4), HR (p<0.01), CO (p<0.05), and increased PCWP (p<0.01), CVP (p<0.01), PAP (p<0.01) and MAP (p<0.01) (table 2).

Rp after vasodilation with nitroglycerine.

Although nitroglycerine (10 μg·kg⁻¹) significantly decreased PCWP (p<0.01), CVP (p<0.05), PAP (p<0.01) and MAP (p<0.05), and significantly increased HR (p<0.01) and CO (p<0.05), it did not affect Rp (p=0.50)(fig. 5, table 2).

Fig. 5. — Baseline peripheral airway resistance (Rp) before and after nitroglycerine (10 μg·kg⁻¹ i.v.). Mean±SEM and individual values are depicted (n=6). NTG: nitroglycerine.

Table 2. — Haemodynamic changes before and after either nitroglycerine ($10 \mu\text{g}\cdot\text{kg}^{-1}$ i.v.) or phenylephrine ($10 \mu\text{g}\cdot\text{kg}^{-1}$ i.v.)

		Nitroglycerine		Phenylephrine	
		Before	After	Before	After
PCWP	mmHg	6.67±0.21	4.43±0.21**	6.17±0.31	13.8±0.79**
PAP	mmHg	17.0±0.58	14.0±0.71**	17.0±1.41	34.3±0.48**
CO	$\text{l}\cdot\text{min}^{-1}$	3.12±0.03	4.53±0.32*	3.15±0.1	1.80±0.14**
MBP	mmHg	102±8.3	90.5±7.38*	83.0±4.52	115±3.61**
HR	$\text{beats}\cdot\text{min}^{-1}$	69.3±3.3	96.9±6.72**	63.5±6.13	38.8±3.22**
CVP	mmHg	5.25±0.97	4.23±0.68*	5.10±0.77	12.7±0.82**

Data are presented as mean±SEM. *: 0.05; and **: 0.01 level of significance comparing before and after drug intervention. For abbreviations see legend to table 1.

Rp during volume loading and vasoconstriction in lung segments previously challenged with dry airflow

Phenylephrine significantly decreased Rp in control segments before (fig. 6: points 1–2, 1.25 ± 0.31 to 0.99 ± 0.23 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.01$) and after (fig. 6: points 3–4, 1.43 ± 0.37 to 1.24 ± 0.32 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.05$) volume loading with normal saline. Volume loading significantly increased Rp (fig 6: points 2–3, 0.99 ± 0.23 to 1.43 ± 0.37 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.05$). After volume loading, although treatment with phenylephrine decreased Rp (1.43 ± 0.37 to 1.24 ± 0.31 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.05$), Rp remained significantly elevated when compared to the preinfusion value (fig. 6: 4 vs 2; $p<0.01$).

In the contralateral lung, dry air challenge increased Rp on average from 0.69 ± 0.23 to 1.20 ± 0.38 $\text{cm H}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$ 2 min after dry air challenge; representing an $83\pm20\%$ increase above the original baseline ($n=6$, $p<0.01$). Treatment with phenylephrine tended to decrease Rp in contralateral lung segments that were previously chal-

Fig. 6. — Change in peripheral airway resistance (ΔR_p) during volume loading and vasoconstriction in control lung segments and contralateral lung segments previously challenged with dry airflow. Open symbols represent Rp before and after phenylephrine ($10 \mu\text{g}\cdot\text{kg}^{-1}$; points 1 vs 2; $p<0.01$), after infusion of normal saline (points 2 vs 3; $p<0.01$), and after a second treatment with phenylephrine ($20 \mu\text{g}\cdot\text{kg}^{-1}$; points 3 vs 4; $p<0.01$) in control sublobar segments ($n=5$). Closed symbols represent Rp before and after phenylephrine ($10 \mu\text{g}\cdot\text{kg}^{-1}$; points 5 vs 6; $p>0.05$), after infusion of normal saline (points 6 vs 7; $p<0.01$), and after a second treatment with phenylephrine ($20 \mu\text{g}\cdot\text{kg}^{-1}$; points 7 vs 8; $p>0.05$) in sublobar segments previously challenged with dry air ($1,500 \text{ ml}\cdot\text{min}^{-1}$; $n=5$). In addition, points 2 vs 4; $p<0.01$; points 6 vs 8; $p<0.01$; points 4 vs 8; $p<0.01$ ($n=5$). —●—: dry air; —○—: control.

Fig. 7. — Change in peripheral airway resistance (ΔR_p) during continuous infusion of normal saline before and after atropine ($0.1 \text{ mg}\cdot\text{kg}^{-1}$ i.v.) treatment ($n=5$). —●—: atropine; —○—: control.

lenged with dry air (fig. 6: 5–6, 1.38 ± 0.35 to 1.26 ± 0.29 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.05$), and volume loading significantly increased Rp in these segments (fig. 6: 6–7, 1.26 ± 0.29 to 1.68 ± 0.42 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.01$). After volume loading, although treatment with phenylephrine tended to decrease Rp (fig. 6: 7–8, 1.68 ± 0.42 to 1.62 ± 0.38 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p>0.05$), Rp was still significantly elevated when compared to the preinfusion level (fig. 6: 6 vs 8, $p<0.01$). Furthermore, when compared to control segments, Rp in lung segments previously challenged with dry air was significantly elevated after volume loading and treatment with phenylephrine (fig. 6: 4 vs 8; $p<0.01$).

Rp during volume loading in the presence of muscarinic blockade. Rp increased significantly (1.05 ± 0.32 to 1.28 ± 0.36 $\text{cmH}_2\text{O}\cdot\text{ml}^{-1}\cdot\text{s}$; $p<0.01$) after NS infusion, even in the presence of muscarinic blockade (fig. 7). The increase in Rp before and after administration of i.v. atropine did not differ significantly ($p=0.90$) at any point in time.

Discussion

In our model, Rp reflects the resistance of peripheral airways that connect at the level of the respiratory bronchiole or alveolar duct, and provide collateral ventilation between adjacent sublobar regions of the canine lung [20]. Volume loading with NS increases PCWP (*i.e.*

produces pulmonary congestion) and increases peripheral airway resistance in canine lungs (figs 1 and 2). These results are similar to those reported previously by other investigators using different techniques to study canine peripheral airways. HOGG *et al.* [5] demonstrated that increased left atrial pressure (LAP) reversibly increased Rp in dogs, and suggested that this increase was due to a vascular effect. ISHII *et al.* [6] reported a biphasic increase in canine Rp after increasing LAP, and suggested that the initial phase resulted from a vagal reflex. They speculated that the second phase was due to either peribronchial or airway oedema formation. Finally, ROLLA *et al.* [4] rapidly infused NS into human volunteers and found that small airway resistance increased. They suggested that pulmonary interstitial oedema developed during volume loading.

Fluid movement between intravascular and interstitial spaces of the lung should follow Starling's equation [21], and infusion of NS should facilitate vascular leakage. In contrast, infusion of 6% dextran 70 to produce a similar degree of pulmonary congestion (*i.e.* the same level of PCWP as that seen with NS) should reduce vascular leakage. We have demonstrated that in contrast to NS, infusion of D70 does not increase Rp even though the PCWP, CVP and CO is similar to that recorded during NS infusion (figs 1 and 2 and table 1). Thus, D70 and NS infusions should produce a similar degree of vascular engorgement. The fact that these two infusates differentially alter Rp indicates that vascular engorgement does not affect Rp, and suggests that formation of oedema increases Rp after NS infusion.

The volume needed to increase PCWP during infusion with NS was significantly greater than that needed with D70 (fig. 2). Several studies [22, 23] have demonstrated that fluid resuscitation during shock requires less D70 when compared to NS to produce the same LAP. Furthermore, pulmonary function was better and the accumulation of lung water was less when D70 was compared to crystalloid infusate [22]. These results are consistent with the present study, and suggest that deterioration of pulmonary function during crystalloid resuscitation is associated with oedema formation.

MICHEL *et al.* [12] demonstrated morphometrically that interstitial pulmonary oedema *via* the pulmonary circulation did not compress small airways. However, pulmonary congestion could increase capillary hydrostatic pressure *via* the bronchial circulation [24], increase fluid exudation, and cause airway submucosal oedema [25, 26]. Fluid extravasation from the bronchial circulation could then increase Rp in our canine model [13, 14]. Thus, if the increase in Rp after volume loading was due to submucosal oedema, Rp should increase more after exposure to an agent known to increase bronchovascular permeability. Many agents, such as histamine, bradykinin, substance P [27], platelet-activating factor [28] and dry air [17–19], can increase bronchovascular permeability. Twenty five min after exposing the peripheral airways to dry air, we found that Rp was significantly greater after a 20 min NS infusion than when compared to unexposed control segments (fig. 3). We also found that the magnitude of dry airflow-induced bronchoconstriction

(AIB) was significantly correlated with NS infusion-induced increases in Rp. These observations are consistent with the hypothesis that submucosal oedema formation is responsible for infusion-induced increases in Rp. However, we cannot rule out the possibility that oedema formation at the level of the alveolar duct, in addition to submucosal oedema, contributes to volume loading-induced increases in Rp.

Pulmonary congestion and its associated vascular engorgement may increase airway wall thickness and airway resistance. OHCHIMI *et al.* [29] found a good correlation between submucosal bronchial vessel dilation and PCWP in patients with chronic pulmonary venous hypertension, and CABANES *et al.* [1] demonstrated that inhalation of an α -agonist (methoxamine) reversed bronchial hyperresponsiveness in patients with poor left ventricular function. CSETE *et al.* [30] showed that vasodilation with nitroglycerine increased Rp in ewes and was partially reversed by vasoconstriction with vasopressin. LAITINEN *et al.* [31] reported that a wide variety of drugs decreased canine vascular resistance and increased tracheal mucosal thickness. They also showed that phenylephrine increased vascular resistance and decreased mucosal thickness. In our experimental model, a single intravenous injection of phenylephrine significantly decreased baseline Rp by 25% (fig. 4). In contrast, despite significant haemodynamic effects reflecting vasodilation (table 2), intravenous nitroglycerine did not significantly increase baseline Rp (fig. 5). The fact that vasodilation did not alter Rp is consistent with our hypothesis that vascular engorgement is not a major factor in this model.

If the increase in Rp after NS infusion was purely due to vascular engorgement, then phenylephrine should reverse the infusion-induced increase in Rp. Our results demonstrate that after fluid infusion, even after administering a double dose of phenylephrine to compensate for the added volume of distribution of the drug, Rp remained significantly higher than the preinfusion level after phenylephrine (fig. 6: points 2 *vs* 4). We hypothesize that this phenylephrine-resistant elevation in Rp is due to submucosal oedema formation in the peripheral airways. Consistent with this hypothesis is the fact that Rp remained significantly higher in the dry air challenged segments (with presumably increased bronchovascular permeability), when compared to contralateral control segments, after reversing the vascular distention with phenylephrine (fig 6: 4 *vs* 8).

Several studies have suggested that airway narrowing during pulmonary congestion was vagally-mediated, because airway obstruction during pulmonary congestion was abolished with either atropine or vagotomy [8–10]. However, pretreatment with a dose of atropine that totally blocks muscarinic receptor activity [32] does not affect the increase in canine Rp associated with volume loading in our model. This difference may be due to either: 1) differences between canine trachea and peripheral airway [10]; 2) differences in the time of treatment (we pretreated with atropine whereas the other investigators used this drug to reverse pulmonary congestion [8, 9]); or 3) differences in protocols, *e.g.* ISHII *et al.* [6] abruptly increased left atrial pressure by inflating a

balloon to 30 mmHg, whereas we gradually increased PCWP to 15 mmHg with a 20 min infusion of normal saline.

In summary, NS infusion causes pulmonary vascular congestion and a concomitant increase in peripheral airway resistance. In contrast to NS, infusion of D70 produces similar degrees of pulmonary congestion but does not increase R_p . When sublobar segments are challenged with dry air in an attempt to alter bronchovascular permeability, ΔR_p is increased during NS infusion when compared to control segments. Phenylephrine decreases R_p after fluid infusion, but does not completely reverse the effect of volume loading on R_p . In addition, ΔR_p during fluid infusion is not altered by muscarinic receptor blockade.

We conclude that vascular engorgement does not increase R_p during NS infusion; and that submucosal oedema is the most likely mechanism responsible for normal saline infusion-induced increases in R_p .

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