Mechanisms of airway narrowing in acute pulmonary oedema in dogs: influence of the vagus and lung volume

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Summary
1. In spontaneously breathing dogs (n = 8), maintained in the upright position, bronchial luminal diameter was measured from tantalum bronchograms. Changes in total intrathoracic lung volume were measured from radiographs taken at functional residual capacity (FRCR).
2. With cooling of the cervical vagi to 0-4°C mean bronchial diameter increased to 117 ± 15 (SD)% of baseline diameter and FRCR increased to 113 ± 16 of baseline volumes respectively. There was a significant correlation between changes in FRCR and bronchial diameter.
3. After the vagi were rewarmed, pulmonary oedema was induced by rapid intravenous infusion of Hartmann's solution. Bronchi narrowed to a mean of 86 ± 9% of baseline calibre and FRCR decreased (mean = 95 ± 15%).
4. With vagotomy bronchial diameter increased (mean = 102 ± 12% of baseline diameter) but FRCR did not change significantly.
5. Excluding one dog with gross oedema, changes in bronchial diameter due to oedema correlated positively with changes in FRCR; after vagotomy the relationship between diameter and FRCR was similar to that seen after vagal cooling in the baseline state, though individual values were lower.
6. The shift in the diameter-FRCR relationship with vagotomy demonstrates that the direct bronchoconstrictor effect of the vagus is approximately doubled in the presence of pulmonary oedema.
7. Bronchial and peribronchial oedema does not appear to directly narrow the bronchial lumen.

Key words: bronchoconstriction, bronchomotor tone, functional residual capacity, interdependence of airway calibre, pulmonary oedema, vagal reflex.

Introduction
Patients with pulmonary oedema due to left ventricular failure may present with acute attacks of wheezy dyspnoea, sometimes referred to as 'cardiac asthma' [1]. However, in several studies of patients with left ventricular failure [2-5] peripheral but not central airway narrowing has been demonstrated. We have previously shown that large airway narrowing is a common feature of experimental pulmonary oedema in dogs [6]. The purpose of the present study is to examine the mechanism of this airway narrowing with particular reference to the role of the vagus. In our previous study [6], the reduction of airway luminal diameter with oedema was correlated with a decrease in lower zone lung volume, suggesting that it was a function of volume loss. This relationship is further explored in the presence and absence of vagally mediated bronchomotor tone. The degree to which bronchial and peribronchial oedema may contribute to airway narrowing has also been assessed.

An incidental observation of this study was that in these upright dogs vagal blockade was associated with a prompt increase in functional residual capacity.

Methods

Procedure
Eight mongrel dogs of either sex weighing 10-15 kg were anaesthetized by intravenous administration of thiopentone sodium (20 mg/kg),
followed by gluco-chloralose (Merk, Darmstad) (40 mg/kg). Subsequent doses of 10 mg of chloralose/kg were given every 2–3 h in order to ensure adequate anaesthesia. The dogs were intubated with a cuffed endotracheal tube. Oxygen and sodium bicarbonate were administered to maintain arterial $P_{O_2} > 8$ kPa and arterial $pH > 7.25$.

A catheter was advanced via a femoral vein into the inferior vena cava for administration of drugs and fluids and the femoral artery was catheterized for measurement of arterial blood gases and blood pressure. Under fluoroscopic vision a Cournand catheter was inserted into a pulmonary artery via an external jugular vein for measurement of pulmonary arterial ($Ppa$) and wedge ($Pw$) pressures. Vascular pressures were measured from a zero reference pressure at the level of the left atrium estimated radiographically. All pressures were measured with strain gauges (type SEM 4.86, SE Laboratories, Feltham, Middlesex, U.K.) and recorded continuously.

The cervical vagi were carefully exposed for approximately 1 inch in the neck and they could be cooled reversibly to 0-4°C by positioning the exposed segments of vagi snugly on to copper radiators through which a cold mixture of water and ethylene glycol was circulating. The bronchi of the right lung were then outlined with tantalum powder (nominal particle diameter 1 µm; HC Starke, Berlin, FRG) which had been dried overnight in an oven at 90°C. The powder was insufflated through a catheter directed into the segmental bronchi of the right lung under fluoroscopic vision. The dogs were then placed in a vertical (head-up) position after the abdomen and hind limbs had been firmly bandaged to prevent venous pooling. Pulmonary oedema was induced by extracellular volume expansion with intravenous infusion of Hartman’s solution. A volume equivalent to 20% of the dog’s weight was given over 40–50 min. At the end of the infusion pulmonary arterial and wedge pressures were allowed to return towards baseline level for 20–30 min before other observations were made.

In order to assess the contribution of the vagus to the airway changes in pulmonary oedema, observations were made during four phases: (a) during baseline period with the vagi intact, (b) after vagal blockade by cooling the vagi to 0-4°C over a period of 10–30 min, (c) during the period of pulmonary oedema, induced after the vagi had been allowed to rewarm for a period of 15–30 min and, finally, (d) after vagal section in the presence of pulmonary oedema. In all dogs these observations included the measurement of radiographic lung volumes and airway diameters, pulmonary vascular pressures, and arterial blood gases.

At the end of the experiment 2 µCi of $^{125}$I-labelled human serum albumin ($^{125}$I-HSA) was administered intravenously for measurement of lung plasma volume. Three minutes were allowed for equilibration of the radioisotope before the dogs were killed with intravenous sodium pentobarbitone. At the time of death a heparinized blood sample was taken for determinations of packed cell volume, haemoglobin and plasma concentration of $^{125}$I-HSA. The dead dog was then frozen whole in the upright position overnight at $-20°C$ in a cold room.

**Chest radiographs**

Chest radiographs in the anteroposterior and right lateral positions were taken with a narrow (0.3 mm) focal-spot tube (Siemens, Sunbury-on-Thames, Middlesex, U.K.), by the method previously reported by Snashall et al. [7]. The same settings of the X-ray tube were used in all four phases of the experiment. Artificial hyperventilation for 20 s with an Ambu bag was used before exposure in order to prevent the dog from breathing at the moment of exposure. All radiographs were taken at FRC.

**Lung volume changes.** Changes in total intrathoracic volume were estimated from the anteroposterior and right lateral radiographs. The vertical dimension through an intrapulmonary marker (e.g. an apical airway) to the diaphragmatic surface and the anteroposterior and lateral dimensions at a level one-third of the distance from the diaphragm to the apex were measured. The product of the three dimensions gives a ‘volume’ which is an indication of the total volume of lung measured, allowing estimation of changes in volume in all phases of the experiment. This method has been previously validated [6].

**Airway diameter changes.** Changes in the luminal calibre of bronchi outlined with tantalum powder were assessed for each phase of the experiment. The bronchi measured were between 0.2 and 1.5 cm in diameter, being main stem, lobar, segmental and subsegmental divisions. The same section of airway was identified in each film. Where possible straight cylindrical segments between bifurcations were chosen and were measured with dividers at right angles to the direction of the bronchus. The diameters of three to eight bronchi from the upper, middle and lower zones in each dog were measured and mean change in airway diameter was calculated.

**Analysis of lungs**

The frozen thorax was cut into horizontal sections approximately 2 cm thick. By using a 15 mm
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Diameter cork borer two or three samples each containing at least one airway were taken from each slice. Bronchi with luminal diameters ranging from 1.0 to 9.0 mm were sampled and their positions were noted on photographs of the lung slices. These lung samples were freeze-dried at -80°C for 48 h and later examined by low power microscopy. In these sections it was not possible to accurately distinguish bronchial wall from surrounding oedema cuff, and therefore our measurements of 'bronchial wall' are an estimate of the total thickness of wall plus cuff. The thickness of the bronchial wall and the luminal diameter were measured with a micrometer in each sampled bronchus. In bronchi which had apparently not been sectioned at right angles the narrowest bronchial luminal diameter and wall width were measured. The values for luminal diameter as a percentage of the external bronchial diameter were compared with those of four control dogs handled identically.

**Lung water measurements**

The rest of the lung slices were used for measurement of extravascular lung water, as previously described [8]. The lung was pooled from each slice and homogenized in a blender and aliquots of homogenate were taken (a) for drying in an oven at 90°C, (b) for radioisotope counting of 125I-HSA in a gamma counter and (c) for estimation of haemoglobin concentration by the cyanmethaemoglobin method. The equations of Selinger et al. [9] were used to calculate extravascular lung water (Qwl).

In order to derive the blood-free dry lung weight free of tantalum, tantalum was recovered in an aliquot of dried homogenate after digestion in concentrated hydrochloric acid, followed by repeated washings with distilled water and centrifugation. Extravascular lung water (Qwl) was expressed as per unit blood-free dry lung weight free of tantalum (dQl), i.e. Qwl/dQl.

**Results**

**Effects of vagal cooling**

This resulted in bronchodilatation and in an increase in radiographic lung volume (FRCR). Airway luminal calibre increased by 17 ± 15% (n = 8), and FRCR increased by 13 ± 16% (n = 8). Heart rate increased and respiratory rate decreased but these changes were not significant (paired t-test, P > 0.2). There were no significant changes in mean Ppa and Pw (Fig. 1).

**Effect of pulmonary oedema**

With vagal rewarming and pulmonary oedema the bronchi narrowed and FRCR fell generally below baseline values. Airway diameter decreased to 86 ± 9% of control value. FRCR fell in seven dogs and increased in one dog (Fig. 2). In five dogs,
**FIG. 2.** Changes in FRC<sub>R</sub> measured by standard chest radiographs (△) and airway diameter (○) for the eight individual dogs (D1 to D8) during the four phases of the experiment, as described for Fig. 1. Lung water (Qwl/dQI) for each dog is indicated in parentheses.

FRC<sub>R</sub> fell below baseline values and in two dogs, FRC<sub>R</sub> had increased compared with the baseline period. Mean FRC<sub>R</sub> fell to 95 ± 15%.

Mean respiratory rate increased above the baseline value (P < 0.05). Heart rate was not significantly changed. Both P<sub>Pa</sub> and P<sub>W</sub> showed a non-significant increase (P > 0.2). Mean arterial P<sub>CO</sub><sub>2</sub> was not significantly changed from its baseline value of 5.52 ± 0.49 kPa to 5.03 ± 1.16 (P > 0.20).

**Effect of vagal section**

In all dogs bronchi dilated after vagal section but not to the calibre seen after vagal cooling, except for dog D3 in which lung water (Qwl/dQI = 4.0) was within our range for control dogs (4.3 ± 0.3). Interestingly this dog had no bronchoconstrictor vagal tone during the baseline period, but after expansion of extracellular fluid volume the observed bronchial narrowing was entirely
vagally mediated. In five dogs final airway calibre was above baseline values, and in the other three dogs it remained below baseline values. Mean final airway calibre was 102 ± 12%. Major increases in FRCR were seen in two dogs (D3, D4), but these did not reach the FRCR values seen after vagal cooling. In the remaining six dogs FRCR showed little change, ranging from −3.7% to +2.6%. Final FRCR was 98 ± 14% of baseline FRCR.

Mean respiratory rate fell from 17.5 ± 8.7 min⁻¹ to 6.7 ± 3.4 min⁻¹, and was not significantly different from that of the vagal cooled state (P > 0.20). Heart rate increased. Mean Ppa and Pw were not significantly changed after vagal section (for Ppa, P > 0.20; for Pw, P > 0.50).

Relationship between FRCR and airway diameter changes (Fig. 3)

After vagal cooling there was a significant linear relationship between the change in FRCR and the change in airway diameter (y = 0.74x + 6.4, r = 0.82, P < 0.05). This relationship was not significant after pulmonary oedema (r = 0.54, P > 0.2) and after vagotomy (r = 0.56, P > 0.2).

However, the lack of correlation was entirely due to one dog (D2) with gross oedema, where lung water was more than twice that of the next most oedematous dog (Qwl/dQl = 22.0). When this animal was excluded from the analysis, changes in FRCR were significantly related to changes in airway diameter (after pulmonary oedema: y = 0.60x - 7.3, r = 0.96, P < 0.01; after vagotomy: y = 0.71x + 4.7, r = 0.85, P < 0.05). There was no significant difference between the linear regression equation obtained during the two vagotomized states (for slope, P > 0.20; for elevation, P > 0.25).

Examination of lungs and airways

Mean Qwl/dQl was 7.9 ± 5.6. In six dogs it ranged from 4.0 to 6.2 and in the other two it was grossly elevated at 10.2 and 22.0 respectively.
In these latter dogs the lower lobes were solid and unaerated. Perivascular cuffs of oedema were seen in all dogs and in five dogs these extended to form peribronchial cuffs. We studied 42 airways sampled from all eight dogs. Mean luminal diameter was $3.6 \pm 1.9$ mm, $76.8 \pm 12.5\%$ of external bronchial diameter. In four control dogs mean luminal diameter of ten airways was $3.2 \pm 1.7$ mm, $89.3 \pm 2.1\%$ of external diameter.

If we assume that external bronchial diameter remained constant, the percentage increase in wall thickness due to peribronchial cuffs of oedema for the 42 airways studied was $111 \pm 45\%$ of the mean thickness during the control phase. This increase in wall thickness would narrow the lumen by an average of $12\%$. In fact the observed narrowing at the end of the experiment, compared with the vagal-cool baseline state, was $13 \pm 7\%$. However, in individual dogs there was no correlation between wall thickening and luminal narrowing ($r = 0.38$, $P > 0.2$) or between $\frac{Q_{wl}}{dQ_l}$ and narrowing ($r = 0.60$, $P > 0.1$).

Discussion

This study has confirmed our previous finding [6] that there is narrowing of the central bronchi in pulmonary oedema, and that this narrowing is linked to a reduction of lung volume. Oedema was induced by rapid extracellular fluid volume (ECFV) expansion in these experiments, whereas our previous study used both ECFV expansion and alloxan (to increase microvascular permeability), but the relationships between lung volume and airway calibre in both studies are remarkably similar (Fig. 4).

![Fig. 4. Relationship between change in radiographic FRC (FRCR) and airway diameter during the phase of pulmonary oedema with the vagi intact (\(
\)). These data points are the same as those shown on Fig. 3. In addition, values from a previous series, studied under similar circumstances [6], are included (\(
\)). In these nine dogs pulmonary oedema was induced by both extracellular fluid volume expansion and alloxan. Excluding dog D2 of the present series, whose value has been circled, there is a similarity between FRCR and airway diameter changes in these two groups. Regression equations for the present series: $y = 0.60x - 7.30$ ($P < 0.01$) and for the previous series: $y = 0.61x - 7.01$ ($P < 0.025$).

We have considered three factors which may act together to narrow bronchi in oedematous lungs. In order of importance these are: (1) loss of lung volume, (2) vagally mediated bronchoconstriction, (3) peribronchial ‘cuffing’ with oedema fluid. Factors (1) and (2) influence most dogs irrespective of the severity of oedema. Factor (3) appeared to play little part in most dogs, but perhaps was a cause of narrowing in one grossly oedematous dog.

Loss of lung volume

We have found that a 10% decrease in FRCR in oedema is associated with 6% decrease in bronchial luminal diameter (Fig. 3). Airway size is known to be a function of lung volume, and when isolated lungs were studied over a wide range of volumes it was found that bronchial diameter varied approximately with the cube root of lung volume [13]. Changes in calibre that we have observed occurred over a relatively restricted range of lung volumes around FRC, in which region airway dimensions clearly change more rapidly than lung dimensions. Similar relationships between volume and calibre were also seen after vagal cooling and after vagotomy (Fig. 3). Thus, bronchodilatation with vagal cooling was most marked in those dogs with the largest increases in lung volume; with oedema, vagotomy caused bronchodilatation without significant lung volume changes and the relationship between volume and calibre was preserved but shifted upwards.

The mechanisms of the loss of lung volume in oedema are not fully understood. Alveolar flooding is associated with a decrease in alveolar volume [14, 15] but in this series and also in our previous studies [6, 7] volume loss was frequently seen in minimally oedematous lungs in which alveolar flooding would not be expected, and the correla-
tion between oedema and loss of volume was poor. One probable cause is the accumulation of fluid in the abdomen after ECFV expansion with consequent elevation of diaphragms [6, 16]. This study has demonstrated that the vagus has little influence on lung volume in oedema. Although lung volume increased with vagotomy in two dogs there was no significant increase in lung volume after vagotomy in the group as a whole.

The increase in FRCR after oedema in two dogs (D1 and D2, Fig. 1) is more difficult to explain. It is possible that an increase in closing volume occurred, as has been shown in isolated oedematous lung lobes [17], and in dog D2 part of the increase in radiographic volume could have been accounted for by the massive increase in its lung water content.

**Vagal bronchoconstriction**

Where the vagi were cut in these oedematous dogs central bronchi dilated by 17%, which was almost identical with the dilatation that occurred with vagal cooling in the non-oedematous state (16%). Despite this we believe we have evidence of augmented vagal reflex bronchoconstriction in oedema.

The two vagotomized states are not strictly comparable since in the baseline state vagal cooling resulted in an increase in lung volume, which was not seen after vagal section in oedematous dogs. Thus, with vagal cooling, bronchi dilated owing to a relaxation of muscle tone and also increased lung elastic recoil, but in oedema only the former mechanism was operating. In Fig. 3 the intercepts of the regression lines at zero volume change demonstrate that in the absence of a volume change vagal cooling would have caused a 6.4% increase in airway calibre; with oedema calibre would have fallen 7.3% below baseline level; with vagotomy it would have risen to 4.7% above baseline. Thus tonic vagal bronchoconstriction in the baseline period was narrowing the bronchi by approximately 6.4%, whereas with oedema they were narrowed by 12%. Although in the final state bronchi did not dilate to the same extent as after vagal cooling, the regression lines of airway calibre on lung volume for these two states were very similar, suggesting that the sole cause of narrowing after vagotomy was lung volume loss. In dog D2, excluded from the linear regression analysis, there is also evidence of an increased vagal bronchoconstrictor tone after oedema.

**Bronchial wall and peribronchial oedema**

We have found little evidence of bronchial luminal narrowing due to peribronchial and bronchial wall oedema, despite the fact that bronchial wall thickness was increased in all dogs (mean increase = 111%), and in five out of eight dogs macroscopic peribronchial cuffs were observed. However, the degree of bronchial narrowing did not correlate with either the calculated increase in wall thickness or measured extravascular lung water. In fact, in seven out of eight dogs the observed narrowing is largely explicable by consideration of lung volume changes and increased vagal bronchoconstrictor tone. We therefore assume that the increase in bronchial wall thickness is accommodated by stretching of the surrounding bronchovascular connective tissue sheath, rather than by encroachment on the bronchial luminal diameter. In all but one of these dogs FRCR was reduced after oedema and, therefore, tension on the bronchovascular sheath due to lung elastic recoil is likely to have been reduced. This would facilitate peribronchial accumulation of oedema. In the grossly oedematous dog (D2), in which bronchial narrowing occurred despite an increase in FRCR, bronchial wall thickness was increased by 181% and this is adequate to explain the observed bronchial narrowing (17%). If, in this case, the bronchovascular sheath was near its elastic limit then peribronchial oedema would narrow the bronchial lumen.

Of course, as a bronchus narrows from any cause it is inevitable that its wall becomes thicker if wall volume remains constant. This, however, is a relatively minor factor. Thus if the observed mean bronchial luminal narrowing of 13% had occurred without any change in wall volume we calculate that wall thickness would increase by approximately 13%.

**Effect of the vagus on lung volume**

The increase in FRCR that was observed after vagal cooling was an unexpected finding. We were surprised that a change of this magnitude (13% increase in FRCR) and consistency (seen in seven out of eight dogs) had not been previously reported in dogs. A similar phenomenon has been described in rabbits [18]. In a subsequent study of this phenomenon [19] the increase in FRC was found to be a feature of the upright, but not of the supine dog. Expiratory muscle firing was demonstrated at FRC and was abolished by vagotomy. In placing the animal in an upright (head-up) position from the supine position there is an increase in FRC [20], the magnitude of which is limited by this vagally mediated homoeostatic reflex [19].

In summary, pulmonary oedema due to ECFV expansion in the upright, anaesthetized dog induces vagally mediated bronchoconstriction. We specu-
late that stimulation of pulmonary C-fibres (J receptors) after an increase in interstitial volume or pressure in interstitial oedema [21] resulted in reflex airway narrowing [22]. The relevance of our findings in the clinical context of ‘cardiac asthma’ deserves further study.

References