Gas exchange during simulated airway secretion in the anaesthetized rabbit

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ABSTRACT: We wished to study the effect of airways secretion on gas exchange.

Peripheral airway secretion was simulated in 9 rabbits by the continuous inhalation of nebulized isotonic saline, at a droplet size of about 3 μm. Intrapulmonary deposition of saline in the peripheral airways (83% in airways smaller than 0.5 mm) did not alter total inspiratory resistance (mean 5.4 kPa·l^{-1}·s), but led to a decrease in compliance of the total respiratory system from 45.9 to 21.8 ml·kPa^{-1} after one hour of nebulization.

Arterial oxygen tension decreased from 17.8 kPa to 12.1 and 6.9 kPa after 5 and 60 min of nebulization, respectively. PaCO_2 was unaffected after 5 min (4.5 kPa) but increased to 7.0 kPa after 60 min of nebulization. Ventilation-perfusion relationships ($\dot{V}_A/\dot{Q}$) showed a significant increase in perfusion of areas with low $\dot{V}_A/\dot{Q}$ ratios (from 0.7 to 6.3% of cardiac output) and in shunt (from 1.4 to 4.3%) after 5 min of nebulization. At the end of the experiment shunt was increased markedly to 29.7% of cardiac output whereas perfusion of low $\dot{V}_A/\dot{Q}$ regions remained at the same level (7.3%).

The results from this animal model indicate that all gas exchange abnormalities known to occur in asthma can be reproduced without measurably increasing the resistance of the respiratory system.
Eur Respir J., 1992, 5, 1215–1222.

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Since the multiple inert gas elimination technique for the assessment of ventilation-perfusion relationships ($\dot{V}_A/\dot{Q}$) was introduced in 1974 [1], several studies have described and characterized the gas exchange impairment in obstructive airways disease. Abnormally broad and sometimes bimodal distributions of the perfusion have been shown in patients with asymptomatic asthma [2], in patients with moderate clinical signs of asthma [3] as well as in patients with exercise-induced asthma [4] and in patients recovering from acute severe asthma [5]. The bimodal distribution and the poor correlation between the time courses of ventilation-perfusion mismatch and forced expiratory flows may indicate that $\dot{V}_A/\dot{Q}$ abnormalities in patients with bronchial asthma are mainly related to peripheral airways obstruction, presumably by airway secretions and oedema, whereas airflow limitation would rather reflect central bronchoconstriction [2–7].

The aim of the present study was to examine whether the gas exchange abnormalities occurring in asthma can be produced without provoking measurable asthma can be produced without provoking measurable airway constriction. In a previous study we have presented a rabbit model for asthma studies where the multiple inert gas elimination technique was used for the assessment of the $\dot{V}_A/\dot{Q}$ distribution [8]. In this model we have simulated airway hypersecretion by inhalation of small droplets of isotonic saline by means of an ultrasonic nebulizer.

Material and methods

Twelve healthy New Zealand White rabbits weighing 2.3–5.0 kg were studied. Nine rabbits were used for the gas exchange study and the other 3 for analysis of deposition of isotonic saline droplets in the lung. The rabbits were anaesthetized with pentobarbitone sodium and tracheostomy was performed. Ventilation was maintained with a Harvard ventilator (Harvard Apparatus Co., Mass. USA). Breathing frequency was 40 breaths·min^{-1} and ventilation, which was kept constant for each rabbit, varied from 0.90 to 2.27 l·min^{-1}. The inspired oxygen fraction was kept at 0.30.

Gas exchange study

Catheterization: A short catheter (Viggo Venflon 2, 32 mm, diam 1.0 mm) was inserted into an ear artery and a specially designed catheter (15 cm long and J-shaped with the distal 2 cm turned 120°) was inserted into the right jugular vein and advanced *via* the right ventricle into the pulmonary artery [8]. The vascular pressures were measured to verify the catheter position (equipment from Siemens Elema, Stockholm, Sweden).

Ventilation-perfusion relationships: Ventilation-perfusion relationships were evaluated by the multiple inert gas elimination technique [1]. Six inert gases: sulphur hexafluoride, ethane, cyclopropane, enflurane, diethylether and acetone dissolved in isotonic saline, were infused into an ear vein at a rate of 1 ml·min^{-1} (Imed volumetric infusion pump, Model 922). After 45 min of infusion, 3 ml samples of arterial and mixed venous blood (from the pulmonary artery) and 20 ml of mixed expired gas were collected in air-tight glass syringes. The expiratory port of the ventilator was connected to a 120 ml metal mixing box from which the mixed expired gas was collected. All parts containing expired gas were heated to 40°C to avoid water vapour condensation.

The inert gas concentrations in the blood and expired gas samples were analyzed by gas chromatography (HP5880, Hewlett Packard, Palo Alto, CA, USA) and the retention and excretion of each gas were calculated. The solubility in blood of each gas was also measured. Retention and excretion data, together with solubilities, were processed to obtain representative distributions of ventilation-perfusion ($\dot{V}A/\dot{Q}$) ratios [1]. Cardiac output was calculated by using the Fick principle on the inert gases. The reproducibility of the inert gas data (gas chromatography peaks, retention and excretion data) were of the same magnitude as in our earlier studies in larger animals and humans, despite the smaller blood samples from the rabbit (see also [8]). From the $\dot{V}A/\dot{Q}$ distributions, data were derived for shunt (perfusion of lung regions with $\dot{V}A/\dot{Q}$ ratios <0.005); "low $\dot{V}A/\dot{Q}$" (perfusion of lung regions with $0.005 < \dot{V}A/\dot{Q}$ ratios < 0.1); "high $\dot{V}A/\dot{Q}$" (ventilation of lung regions with $10 < \dot{V}A/\dot{Q}$ ratios < 100), and dead space (VD: ventilation of lung regions with $\dot{V}A/\dot{Q}$ ratios >100).

Blood gases: Standard techniques were used for measurement of arterial and mixed venous oxygen tensions (Pao$_2$, P$\bar{v}$o$_2$) and carbon dioxide tensions (Paco$_2$, P$\bar{v}$co$_2$), as well as pH (blood gas analyzer: ABL 300, Radiometer, Copenhagen).

Mechanics of the respiratory system: Airflow was measured with a pneumotachograph (Fleish No. 00) and the tidal volume was calculated by electric integration of the flow signal. Pressures were measured at the distal tip of the tracheal tube by pressure transducers (Validyne, Engineering corp. Northridge, CA, USA) and all signals were processed by amplifiers (Validyne) and recorded on an ink jet recorder

(Siemens Elema, Stockholm, Sweden). The inspiratory resistance of the total respiratory system (lung and chest wall) was calculated at a flow rate of 80 ml·s^{-1}. The resistance of the airway tube was subtracted and the resulting value is presented as "inspiratory resistance". The mean values from 3 consecutive breaths were used. Static compliance of the total respiratory system was measured by inflating the lungs of the completely relaxed rabbit (pancuronium bromide, 0.05 ml) with 5 ml air and recording the pressure increase after 5 s of apnoea. For further details [8].

Nebulization of isotonic saline: Inhalation of nebulized isotonic saline was accomplished by using an ultrasonic nebulizer (DeVilbiss, 35B, Somerset, PA, USA) which was connected between the ventilator and the rabbit. The inspiratory tubings between the nebulizer and the rabbit were curved downwards to trap large droplets and drain liquid.

Procedure: After baseline measurement of ventilation-perfusion relationships, inspiratory resistance, and compliance, the ultrasonic nebulization started. The nebulization was maintained continuously, throughout the periods of measurements. All measurements were repeated at 5, 15, 30 and 60 min after the start of nebulization. The slow, large inflation of the lungs was also repeated after 45 min of nebulization, in order to create a similar pressure-volume history 10–15 min before each recording session. Changes in the ventilatory pattern immediately prior to measurements were avoided in order to create an optimal steady state during the gas exchange measurement.

Deposition of isotonic saline droplets

Nebulised Evans blue (10 mg·ml^{-1}, Merck, Darmstadt) dissolved in isotonic saline was delivered for 5, 10 or 30 min to each of 3 rabbits. Immediately after the aerosol generation the whole animal was perfused with a heparinized saline solution *via* the right jugular vein and bled out until no blood was left in the lung. The lungs were taken out, inflated with air to "total lung capacity" (inflation pressure 3 kPa) and dried under constant pressure in a microwave oven [9]. Lung sections, two mm thick, were cut from apex to base with a meat slicer (Graef E-2000, Arnsberg, Germany). A sagittal section from a middle part of each lung was further evaluated for central and peripheral deposition of Evans blue. Pieces of central airways (diameter > 0.5 mm) and peripheral airways (diameter < 0.5 mm) were separated and Evans blue extracted in acetone and sodium sulphate 7:3 (Kebo Lab AB, Lund, Sweden) for at least 15 hours. All deposited Evans blue was extracted from both lungs and trachea. The absorbance of the supernatant was measured by a spectrophotometer (U-3200, Hitachi Ltd, Tokyo, Japan) at a wave length of 620 nm [10]. The absorbance of Evans blue in the lung was used as a measure of the distribution of the tracer aerosol in the lung. The particle size distribution of saline or Evans blue droplets was measured by a light

scattering device (Master Sizer, Malvern Instruments Ltd., Malvern, UK) at a distance of 1 cm from the tip of the endotracheal cannula.

Statistics

Data are presented as means and standard deviations. Wilcoxon's signed rank test and Bonferroni's adjustment were used for assessing the significance of a difference between group mean values before and at different times after nebulization. A p value <0.0125 was considered significant (comparison of 4 groups, using Bonferroni's correction).

Results

Baseline data, before nebulization

Baseline measurements are shown in tables 1 and 2 and in fig 1. Mean total ventilation of 1.42 $l \cdot min^{-1}$ was large in comparison to the size of the animal. However, total dead space ventilation, including apparatus and physiological dead spaces, amounted to as much as 60% of the total ventilation, resulting in an alveolar ventilation of approximately 0.56 $l \cdot min^{-1}$.

Peak airway pressure averaged 1.1 kPa. Cardiac output averaged 0.36 $l \cdot min^{-1}$ and mean pulmonary artery pressure 15 mmHg. Mean inspiratory resistance and total compliance averaged 5.73 $kPa \cdot l^{-1} \cdot s$ and 45.9 $ml \cdot kPa^{-1}$, respectively. Arterial Po_2 was high (mean 17.8 kPa) due to ventilation with 30% oxygen in nitrogen. Arterial Pco_2 was nearly normal (mean 4.6 kPa) and arterial pH slightly increased (mean 7.48).

During baseline conditions all rabbits displayed a unimodal bloodflow distribution, centered upon a $\dot{V}A/\dot{Q}$ ratio (Qmean) (the mean $\dot{V}A/\dot{Q}$ ratio of the bloodflow distribution) of 1.6. This is similar to the overall $\dot{V}A/\dot{Q}$ ratio that can be calculated from alveolar ventilation ($\dot{V}A$, 0.56 $l \cdot min^{-1}$) divided by cardiac output ($\dot{Q}$, 0.36 $l \cdot min^{-1}$), equal to 1.6. The $\dot{V}A/\dot{Q}$ distributions had a broad base, as evidenced by a high logarithmic standard deviation of the perfusion distribution, log SDQ (the 2nd moment of distribution, a common description of $\dot{V}A/\dot{Q}$ inequality) (mean 0.76). Perfusion of regions with low $\dot{V}A/\dot{Q}$ ratios was absent in all but one rabbit which had about 6% of perfusion to regions with low $\dot{V}A/\dot{Q}$. The shunt was below 3% in all rabbits. Ventilation of regions with high $\dot{V}A/\dot{Q}$ was present in 3 rabbits, with values of 0.4, 5 and 32% of the total ventilation, respectively.

Table 1. – Ventilation, lung mechanical and haemodynamics before and during nebulization

	Before nebulization	During nebulization			
		5 min	15 min	30 min	60 min
Ventilation $l \cdot min^{-1}$	1.42 (0.39)	1.44 (0.39)	1.43 (0.39)	1.40 (0.39)	1.40 (0.45)
Peak airway pressure kPa	1.11 (0.23)	1.23 (0.19)	1.45* (0.25)	1.59* (0.32)	1.89* (0.50)
Insp. resistance $kPa \cdot l^{-1} \cdot s$	5.73 (2.15)	5.76 (1.98)	5.41 (1.44)	4.96 (1.45)	4.89 (1.63)
Compliance $ml \cdot kPa^{-1}$	45.9 (10.8)	37.1* (8.7)	34.2* (7.3)	28.3* (9.7)	21.8* (5.9)
Heart rate $beats \cdot min^{-1}$	279 (24)	322 (46)	310 (33)	294 (44)	296 (41)
Cardiac output $l \cdot min^{-1}$	0.36 (0.41)	0.28 (0.16)	0.30 (0.31)	0.22 (0.15)	0.18 (0.10)
Mean PAP mmHg	14.5 (6.0)	16.6 (2.8)	16.3 (5.6)	16.1 (6.8)	14.2 (4.5)

Results are expressed as means (±sd). PAP: pulmonary artery pressure; *: significantly different from baseline, $p<0.01$.

Table 2. – Arterial blood gases and ventilation-perfusion relationships before and during nebulization

		Before nebulization	During nebulization			
			5 min	15 min	30 min	60 min
Pao_2	kPa	17.8 (1.8)	12.1* (3.4)	8.4* (1.8)	6.7* (1.8)	6.9* (1.1)
$Paco_2$	kPa	4.6 (1.2)	4.5 (1.3)	5.3 (1.7)	6.1* (1.8)	7.0* (1.9)
pH		7.48 (0.10)	7.47 (0.10)	7.42* (0.10)	7.33* (0.10)	7.23* (0.08)
Qmean		1.59 (1.05)	1.29 (0.92)	0.99 (0.70)	1.00* (0.86)	0.91 (0.49)
log SDQ		0.76 (0.23)	1.08 (0.44)	1.24 (0.55)	1.56* (0.55)	1.44 (0.61)
Vmean		2.97 (1.99)	2.28* (1.36)	2.52 (1.53)	3.75 (3.23)	3.44 (3.01)
log SDV		0.76 (0.25)	0.57 (0.13)	0.82 (0.66)	0.70 (0.28)	0.68 (0.16)
Shunt[†]	%QT	1.4 (0.7)	4.3* (2.9)	16.2* (13.2)	31.2* (21.5)	29.7* (16.3)
Low $\dot{V}A/\dot{Q}$[†]	%QT	0.7 (2.1)	6.3* (7.1)	8.5* (10.6)	9.0* (9.9)	7.3* (6.5)
High $\dot{V}A/\dot{Q}$[†]	%VE	4.2 (10.6)	1.1* (3.2)	0.5 (0.9)	2.5* (5.0)	2.1 (3.9)
Dead space[†*]	%VE	60.3 (22.3)	71.0 (11.9)	80.6 (6.9)	81.5* (9.0)	84.2* (4.3)

*: significantly different from baseline, $p<0.01$; [†]: For definition see methods section, [*]: including apparatus dead space ventilation 0.60 $l \cdot min^{-1}$. QT: cardiac output; VE: total ventilation; log SDQ/V: logarithmic standard deviations of the perfusion/ventilation distribution.
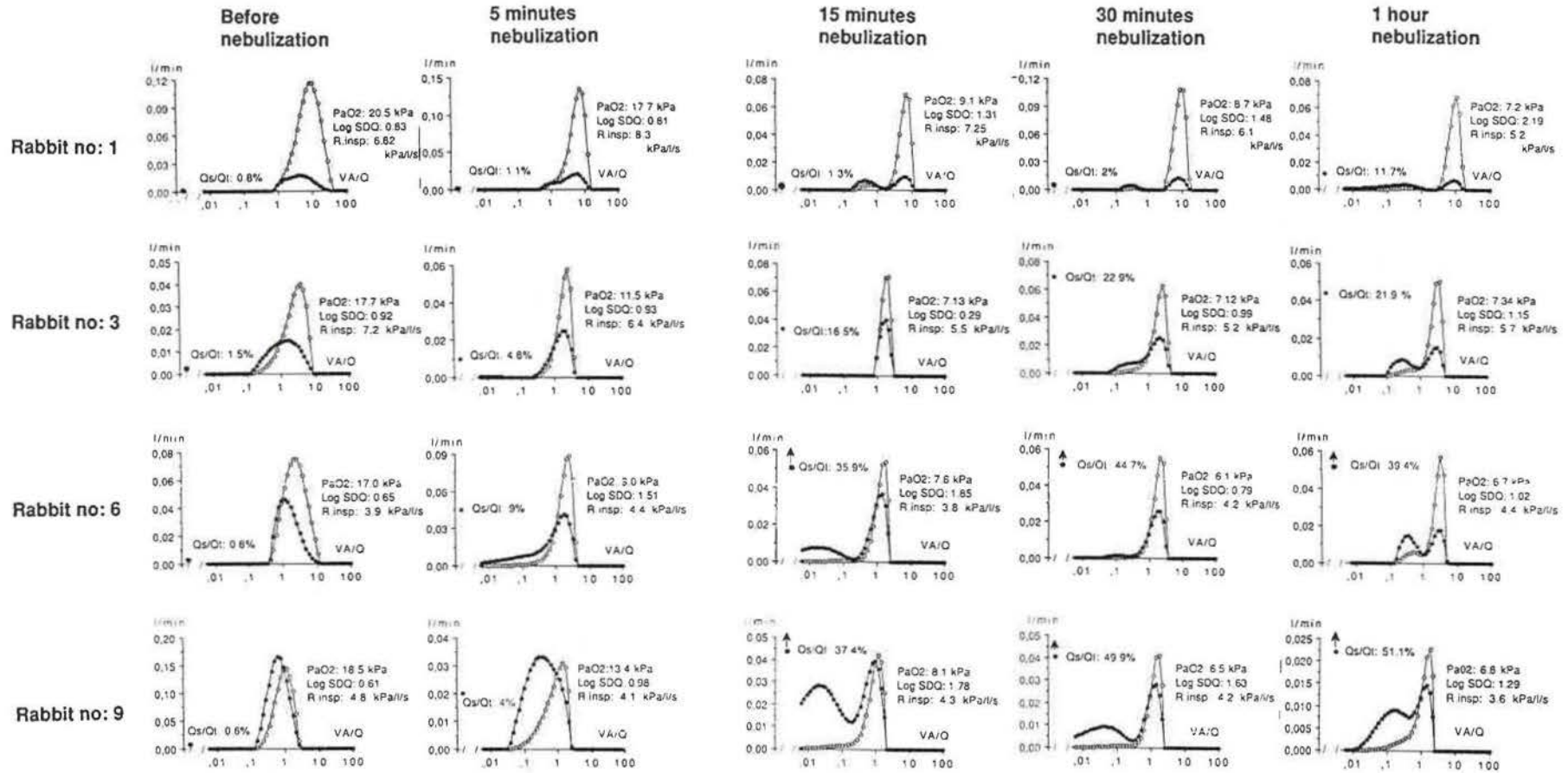
Fig. 1. – Ventilation-perfusion distributions in 4 rabbits during 1 h nebulization of isotonic saline showing the development of gas exchange impairment with shunt, low $\dot{V}_A/\dot{Q}$ and a broad distribution of the perfusion on different $\dot{V}_A/\dot{Q}$ ratios. O: ventilation; ●: perfusion; R.insp: inspiratory resistance.

Effect of nebulization

During the whole 60 min nebulization period total minute ventilation was kept constant around 1.4 l·min^{-1} (table 1). Peak airway pressure rose significantly (p<0.01) during the nebulization and was 70% higher at the end of the experiment, compared to baseline. The nebulization resulted in a decreasing compliance which was reduced by nearly 20% (37.1 ml·kPa^{-1}; p<0.01) after 5 min. After 60 min challenge, compliance was reduced by about half the baseline value. Inspiratory resistance was, however, unchanged during the whole experiment.

Cardiac output tended to fall during the nebulization period and was half the baseline value after 60 min (0.18 l·min^{-1}). Heart rate and pulmonary artery pressures did not vary to any significant extent during the experiment (table 1).

Arterial Po$_2$ was markedly reduced during the nebulization to 12.1 kPa after 5 min (p<0.01) of nebulization, and 6.9 kPa after 60 min (p<0.01) (table 2). Arterial Pco$_2$ was significantly increased after 30 min (mean 6.1 kPa; p<0.01) with a further increase to 7.0 kPa after 60 min. Arterial pH fell significantly (p<0.01) after 15 min with a further reduction to 7.23 after 60 min (table 2).

Table 2 and fig. 1 show ventilation-perfusion data during nebulization. A broadening of the perfusion distribution with an increasing log SDQ (1.56; p<0.01 after 30 min) was seen during the whole nebulization period. At the same time lower $\dot{V}_A/\dot{Q}$ ratios developed resulting in a decreased $\dot{Q}$mean. After 5 min of nebulization the magnitude of low $\dot{V}_A/\dot{Q}$ was significantly increased compared to baseline, (mean 6.3%; p<0.01) with only a moderate further rise over the succeeding 55 min. The mean $\dot{V}_A/\dot{Q}$ ratio of the ventilation distribution ($\dot{V}$mean) decreased 5 min after nebulization (p<0.01), whereas the dispersion of the ventilation (log SDV) remained unaltered throughout the whole period of study.

After 15 min a clearly bimodal $\dot{V}_A/\dot{Q}$ distribution of the perfusion developed in 6 rabbits. Thus, an additional low $\dot{V}_A/\dot{Q}$ mode was observed alongside the normal mode. During the total experiment all 9 rabbits showed bimodal $\dot{V}_A/\dot{Q}$ distributions, the low $\dot{V}_A/\dot{Q}$ mode varying from 1% of cardiac output to about 31%.

Increased shunt during nebulization was seen in all rabbits with significant changes after only 5 min (mean 4.3%; p<0.01), averaging 29.7% of cardiac output after 60 min. The magnitude of shunt showed a negative correlation with compliance of the respiratory system (shunt = -0.0704 × compliance +0.382; r=0.48, p<0.01). Ventilation of areas with high $\dot{V}_A/\dot{Q}$ did not increase, whereas dead space ventilation increased continuously during the nebulization period, and averaged 84% after 1 hour (p<0.01) (table 2).

Table 3. – Deposition of nebulized Evans Blue in three rabbit lungs

Rabbit	1	2	3
Nebulization time min	5	10	30
Nebulized volume ml	1.45	2.58	6.96
Dye Deposition			
Trachea µg	82	60	219
Left lung µg	175	218	582
Right lung µg	264	267	777
Total deposition µg	521	545	1578
Total water deposition ml	0.052	0.055	0.158
Sagittal slice of each lung:			
Peripheral deposition µg	121	147	402
Central deposition µg	26	34	70

A

B

Fig. 2. – The deposition of nebulized saline with Evans blue in a rabbit lung, inflated to total lung capacity and dried, showing an even distribution mainly in peripheral airways. A. Whole lung. B. Sagittal section in the middle of the right lung.

Deposition of isotonic saline

The proportional distribution of nebulized saline or Evans blue dissolved in saline showed the same mass median diameter of 3.1 μm with a geometric standard deviation of 1.6. Only a small fraction of the nebulized volume was deposited in the lung, the major part being trapped in the tubings or exhaled (table 3). The deposition of Evans blue is shown in fig. 2 and table 3. The mean percentage distribution was 50% in the right lung, 37% in the left lung and 13% in the trachea. The major part, or 83% of the pulmonary deposition, was in small airways (diameter <0.5 mm) and 17% was found in central airways. An even distribution was found except for the most peripheral parts of the apex and base (fig. 2).

Discussion

The main findings in the present study were the development of broad bimodal bloodflow distribution and shunt, without the simultaneous increase in inspiratory resistance. This functional disturbance was achieved by the pulmonary deposition of isotonic saline, mainly in small airways. Thus $\dot{V}_A/Q$ patterns observed in asthmatic patients may be reproduced in this rabbit model without a change in inspiratory resistance. However, there are several methodological aspects that deserve consideration and also results that differ from that normally found in the asthmatic subject.

Inspiratory resistance, as recorded here, not only includes the resistance to gas flow in the airways but also lung tissue resistance and the resistance in the chest wall. Hence, the presently used technique may have been less sensitive to subtle changes in airway resistance. Moreover, any technique for recording airway resistance fails to detect accurately constriction or occlusion of small peripheral airways. The peripheral deposition of the isotonic saline and the $\dot{V}_A/Q$ findings suggest that occlusion or narrowing of small airways has been induced in the present study. However, it should also be stated that asthmatics do not seem to bronchoconstrict after inhalation of isotonic saline, nor do normal subjects show signs of bronchoconstriction following inhalation of distilled water or saline in any measured concentration [11–14].

The quality of the $\dot{V}_A/Q$ data can be assessed by calculating the remaining sum of squares (RSS) [15]. It describes the fit of the derived $\dot{V}_A/Q$ distributions to the measured retention and excretion data. The low mean RSS value of 2.0 before nebulization indicates that the multiple inert gas elimination technique in rabbits is technically feasible. It was anticipated that the most soluble gases would, in part, be lost by dissolving in the nebulized saline. To reduce the effect of these losses, the infusion rate of the inert gases was increased to 1.0 ml·min⁻¹ compared to 0.67 ml·min⁻¹ in an earlier study [8]. RSS was also <6.0 in most (31/44) measurements, in good accordance with the requirements of the inert gas technique [15]. However, low acetone concentration in expired gas was still

a cause of high values of RSS. This will have negligible effect on the calculation of shunt and perfusion of low $\dot{V}_A/Q$ regions but will cause an overestimation of the dead space. Its magnitude is difficult to assess, but the exclusion of acetone had only a minor effect on the calculated dead space, which decreased by <1% during baseline (before nebulization) and by 5–6% after 1 hour of nebulization. Moreover, a substantial increase in dead space, with subsequent marked decrease in alveolar ventilation, has to be expected to explain the considerable increase in arterial P_{CO_2} during the study.

Postmortem analysis of three rabbits showed that the nebulized saline had been deposited to a major extent in small, peripheral small airways. Only small amounts were deposited in the trachea and in the larger airways, which may be consistent with the recording of an unaltered inspiratory resistance. The marked decrease in static compliance is surprising in view of the small amount of saline that was retained in the lung, 0.16 ml after 30 min of nebulization. Closure of small airways by saline droplets may offer an explanation for both the reduced compliance and the increase in shunt (see below). It is also possible that the nebulized saline had affected surface tension of small airways and alveoli, causing them to collapse. The correlation between decrease in compliance and increase in shunt in the present study, lends support to such explanations. Finally, extravasation of fluid in the lung, producing oedema cannot be ruled out. However, it has been shown that moderate increases of interstitial lung fluid do not reduce compliance to any great extent [16, 17].

Four main patterns of ventilation-perfusion impairment developed during nebulization of isotonic saline in the rabbit airways. These were development of: a broad distribution of the perfusion (increased log SDQ), areas with low $\dot{V}_A/Q$ ratios, a bimodal distribution of the perfusion, and areas with shunt. The first three are typical of obstructive lung diseases. Fig. 3 shows the similarity of the $\dot{V}_A/Q$ distributions between a patient with chronic asthma (previously unpublished figure from data in [3]), a patient with allergic asthma after allergen challenge (from [18]), a rabbit after methacholine challenge [8] and a rabbit after nebulization of isotonic saline (present study). An interesting observation was that the asthma-like perfusion distributions with low $\dot{V}_A/Q$ developed early, *i.e.* before shunt (table 2). This finding suggests that low $\dot{V}_A/Q$, but not necessarily shunt, is related to the primary deposition of isotonic saline droplets in peripheral airways as detected by the distribution of Evans blue.

The proposed theory for developing a bimodal perfusion distribution in asthma is that bronchial wall oedema and/or mucus close peripheral airways but that some collateral ventilation prevents development of shunt [2, 6, 7]. Animals without collateral ventilation, *e.g.* pigs, develop shunt instead of low $\dot{V}_A/Q$ upon airway provocation with methacholine [19].
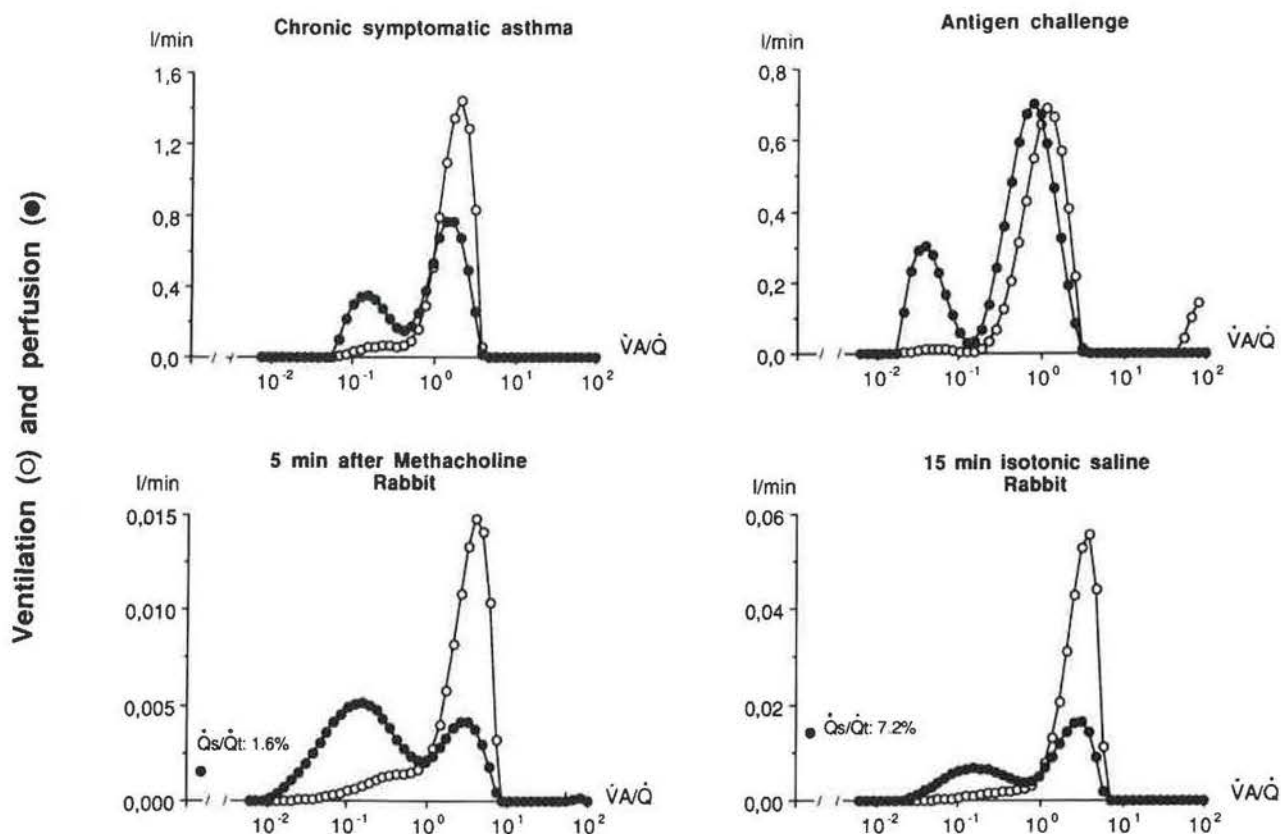
Fig. 3. – Ventilation-perfusion distribution in a patient with chronic asthma (previously unpublished figure from, material of WAGNER *et al.* [3]) a patient with allergic asthma after antigen challenge (with permission from Eur Respir J [18]), a rabbit after methacholine challenge (with permission from Clinical Physiology [8]), and a rabbit after nebulization of isotonic saline (this study). Note the similar bimodal perfusion-distributions. O: ventilation; ●: perfusion.

Our findings of a bimodal $\dot{V}A/\dot{Q}$ distribution may also be explained by this theory in view of the peripheral deposition of the nebulized saline. Another method for producing small airway occlusions was used by LEE and coworkers who occluded airways of anaesthetized dogs with beads of 1.6–4.8 mm in diameter [20]. They found an increased dispersion of $\dot{V}A/\dot{Q}$ ratios in experiments with the smallest beads, whereas the large beads (4.8 mm) produced a bimodal $\dot{V}A/\dot{Q}$ distribution, similar to the present findings. They interpreted their results as evidence of collateral ventilation, postulating that bimodal distributions developed when large but peripheral airways were occluded. With occlusion of smaller airways collateral ventilation was efficient enough and only a broadening of the $\dot{V}A/\dot{Q}$ distribution occurred. Interestingly, the authors also found an increased shunt, averaging 12%, similar to our findings during the first 15 min of nebulization.

In summary, the present study shows that all gas exchange abnormalities characterizing asthma can be demonstrated when small droplets of isotonic saline are nebulised in rabbit airways without any increase in airway resistance. The results support the hypothesis that gas exchange impairment in asthma is related to small airways narrowing and probably mucus secretion and/or mucosal oedema. Even if bronchoconstriction contributes to gas exchange impairment, it is not a *sine qua non* condition for the ventilation-perfusion mismatch shown in patients with asthma.

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