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Dependence of shunt on cardiac output in unilobar oleic acid edema

Distribution of ventilation and perfusion

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Abstract. *Objective:* In acute respiratory failure, increased cardiac output ($\dot{Q}_t$) increases shunt ($\dot{Q}_s/\dot{Q}_t$). We have tested if this is caused by: 1) a redistribution of blood flow towards edematous regions, or 2) a decrease of regional ventilation in the edematous region.
Design: Oleic acid edema was induced in the left lower lobe (LLL) of 11 pigs. $\dot{Q}_t$ was varied with bleeding and infusion of blood and dextran. Blood flow to the LLL was measured at low and high $\dot{Q}_t$ with electromagnetic low probes in 6 animals and with a gamma camera in 5. In the gamma camera pigs regional ventilation was also measured.
Measurements and results: $\dot{Q}_t$ was increased by 45% (electromagnetic flow probes) and 73% (gamma camera). $\dot{Q}_s/\dot{Q}_t$ increased from 24.9–31.3% ($p<0.05$) and from 17.6–28.8% ($p<0.001$) respectively.
No change in fractional perfusion of LLL could be seen, neither with flow probes nor with gamma camera. A decrease in ventilation of LLL, 2.6%, was observed when Q_t was increased ($p<0.05$).
Conclusion: Theoretically a small decrease in ventilation can explain the increase in shunt, if regions with low ventilation/perfusion ($\dot{V}A/\dot{Q}$) ratio are transformed to shunt. This is, however, unlikely since earlier studies have shown that blood flow is distributed either to regions with normal $\dot{V}A/\dot{Q}$ ratio or to shunt regions. We conclude that the cardiac output dependent shunt is not caused by redistribution of blood flow between lobes or by decreased ventilation in the edematous region. We cannot exclude that blood flow is redistributed within the edematous lobe.

Key words: Edema – Oleic acid – Pig – Ventilation – Lung blood flow

It has been known for more than ten years that fractional shunt ($\dot{Q}_s/\dot{Q}_t$) increases with an increase in cardiac output ($\dot{Q}_t$) in patients with acute respiratory failure [1, 2]. In a dog model with diffuse oleic acid lung edema, a similar dependence of $\dot{Q}_s/\dot{Q}_t$ on $\dot{Q}_t$ has been seen [3–6]. One possible explanation is that a greater proportion of increased pulmonary blood flow perfuses edematous, non-ventilated lung units to increase $\dot{Q}_s/\dot{Q}_t$. This was tested in a dog study by creating uni-lobar oleic acid edema and then injecting radioactive labelled microspheres at low and high $\dot{Q}_t$, but no redistribution of blood flow was seen on an increase in $\dot{Q}_t$ with this technique [7]. Since redistribution seems to be the most attractive and straight-forward explanation we considered it important to re-evaluate this possibility using a different technique.

Thus we implanted an electromagnetic flow probe around the left lower lobar artery in an animal preparation and compared its share of total lung blood flow, assessed by thermodilution at low and high $\dot{Q}_t$, after the creation of oleic acid edema in the left lower lobe (LLL). This preparation required thoracotomy as did the previous preparations for assessing lobar blood flow [7]. It may be argued that the invasive procedure in itself contributes to edema also in the other lung lobes, and that the model is not clear enough to detect a blood flow redistribution between lobes with increased $\dot{Q}_t$. We therefore proceeded with a less invasive procedure by injecting oleic acid via a pulmonary artery catheter, advanced to the LLL, and measured blood flow distribution with radioactive labelled (99m-Tc) microspheres and a gamma camera. This protocol eliminated the need of a thoracotomy. We also addressed the question whether the $\dot{Q}_t$ dependent $\dot{Q}_s/\dot{Q}_t$ could be explained by an altered ventilation distribution instead of blood flow changes. We therefore studied regional ventilation with a gamma camera during ventilation with radioactive gas (81m-Kr). For practical reasons, we used a pig-model instead of the previously used dog-model. This also required some methodological work before the animal model could be used in the experiments. This study describes the animal preparation and the results on blood flow and ventilation distributions.

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Material and methods

Ten pigs weighing 28–50 kg each underwent thoracotomy for electromagnetic flow probe measurements, 6 of which were successful and comprise the material of this part of the study (2 pigs died before completion of the study, and in the other 2 catheter and flow probe failures invalidated the study).

In the other part of the study, 8 pigs (22–31 kg) were used for the gamma camera measurements. Five of these were successful and were included in the study. Of the other 3, one died at the induction of anaesthesia, one died from bleeding during preparation and one died from hypoxia as a result of the oleic acid spreading over both lungs. The study had been approved by the animal ethics committee of Uppsala University Hospital.

Anaesthesia

The pigs who underwent thoracotomy were sedated with 10 mg diazepam intramuscularly and were anaesthetized with an i.v. dose of pentobarbital (30 mg/kg) and paralyzed by an i.v. injection of suxamethonium, 3–4 mg/kg. Anaesthesia was maintained with intermittent doses of pentobarbital (2–4 mg/kg) as necessary. The pigs studied with the gamma camera were premedicated with 400–600 mg mebumal (15–20 mg/kg) given intra-abdominally. Anaesthesia was induced 30 min later with either i.v. ketamine (500 mg, pigs no. 1 and 2) or i.v. mebumal (300–600 mg, pigs no. 3, 4, and 5). Anaesthesia was then maintained with continuous infusion of chlomethiazole (400–800 mg/h) and pancuronium (2–4 mg/h).

After endotracheal intubation, the pigs were ventilated with a tidal volume of 10–15 ml/kg and 16–20 breaths/min. Minute volume was adjusted to get a baseline $PaCO_2$ at around 5 kPa. At baseline F_iO_2 was 0.4. After induction of oleic acid edema, the pigs were ventilated with F_iO_2 1.0 and PEEP of 5 cmH_2O was applied.

Catheterization and blood analysis

A triple lumen balloon-tipped thermistor catheter was advanced via an external jugular vein to the left lower lobar pulmonary artery. In the thoracotomy pigs, the catheter was manually guided, and fluoroscopy was used in the gamma camera pigs. The postition of the catheter was confirmed when the lungs were taken out at the end of the experiment.

The right carotid artery was cannulated for recordings of systemic arterial pressure and sampling of blood. An additional large bore catheter was inserted in the opposite jugular vein and advanced to the superior vena cava. This catheter was used for bleeding the pig and for fast infusion of blood and dextran. Systemic and pulmonary artery pressures were measured with Gould transducers and recorded on a Hewlett Packard recorder.

$\dot{Q}_t$ was measured by thermodilution: 10 ml ice cold glucose, 5%, being injected in the right atrium, and the thermodilution curve being recorded in the pulmonary artery (cardiac output computer: Edwards 9520) For each $\dot{Q}_t$ measurement three injections were given, evenly distributed over the respiratory cycle. Before the first injection, the catheter was flushed with ice cold solution. Mixed venous and systemic arterial blood samples were collected for analysis of blood gas tensions, oxygen saturation and hemoglobin concentration (ABL 2 and 3, OSM 2 and 3, Radiometer, Copenhagen).

$\dot{Q}_s/\dot{Q}_t$ was calculated from the Berggren shunt formula: $\dot{Q}_s/\dot{Q}_t = (CcO_2\text{-}CaO_2)/(CcO_2\text{-}CvO_2)$. CaO_2 is the oxygen content of systemic arterial blood, CvO_2 is the oxygen content of mixed venous blood, and CcO_2 is the oxygen content of pulmonary capillary blood. It was assumed that pulmonary end capillary oxygen tension equalled alveolar PO_2. The latter was calculated as $P_IO_2\text{-}PaCO_2/0.8$, where P_IO_2 is inspired pressure of oxygen. During oxygen breathing, the Berggren shunt equals "true" shunt as determined by inert gas technique, and is uninfluenced by lung regions with low $\dot{V}_A/\dot{Q}$ ratios [8].

Thoracotomy

Thoracotomy was done by an incision in the 5th intercostal space on the left side. The left lower lobar artery was carefully freed from surrounding tissue, and an electromagnetic flow probe was fitted onto the artery (blood flow meter: Nycotron model 376, Copenhagen, Denmark). To obtain a zero flow for calibration purposes, a thread was positioned around the artery proximal to the flow probe to permit intermittent occlusions of the artery. During surgery the lungs were prevented from collapsing with PEEP of 5 cmH_2O, as mentioned above. At the end of surgery a few deep breaths were given, or the PEEP level was increased during a few breaths, to expand any collapsed lung tissue.

Radionuclide Methods

All animals were studied in the supine position. A digital gamma camera was used, equipped with a low energy, high resolution, hexagonal-parallel hole collimator (Picker SX-300 Digital Dyna Camera, Cleveland, OH).

In 2 pigs planar studies were acquired with images in the frontal view. In another 3 pigs, single photon emission computed tomography (SPECT) was acquired with the gamma camera rotating stepwise around the animal while detecting the activity of the perfusion and ventilation isotopes. The results of the SPECT-studies, which potentially could be more sensitive to regional changes in ventilation/perfusion in deeper parts of the lungs, were however similar to the results of the planar images and did not contribute additional information. The planar studies and the SPECT data have therefore been pooled.

Data were acquired using 20% symmetric energy windows peaked at 140 kev (99m-Tc) and 191 kev (81m-Kr). Data were collected in a 64×64 matrix on a computer system (PDP 11/73), and analyzed with standard software (Gamma 11 - MSE version 1.3A/TSX). The spatial resolution for this technique and equipment was approximately 11 mm. The obtained images had very high signal-to-noise ratios in as much as the tracers used were either trapped in the lungs (Tc-Macro Aggregated Albumin (MAA)) or were non-penetrating with short half-life (81-mKr) – thus resulting in no real background activity, defined as activity (noise) not related to the object (signal). The signal to noise ratios were in the order of 35:1 for perfusion and 6:1 for ventilation (see also below).

Pulmonary perfusion: Evaluation of pulmonary perfusion at low $\dot{Q}_t$ was done by means of 25 Bq 99m-Tc-MAA injected as a bolus. At high $\dot{Q}_t$, 100 MBq as a bolus was used. The time between the two measurements of perfusion was 30–40 min.

Regional perfusion was calculated by dividing the lung fields into 6 regions, and computing the regional fraction of total perfusion. When estimating regional perfusion at high $\dot{Q}_t$, the low $\dot{Q}_t$ image was subtracted from the high $\dot{Q}_t$ image, and regional perfusion computed as described above for low $\dot{Q}_t$. Because of the short time between the recordings (30–40 min) and since only relative rates were calculated, no correction of the decay of the isotope was made. The errors introduced in calculating regional fractional perfusion will be less than 2–3%.

Regional ventilation: Evaluation of regional ventilation was done by means of a commercially available continuous 81m-Krypton (Kr) delivery system (Mallinckrodt). The animals were mechanically ventilated and the Kr delivery system connected to the ventilator. After 30 s run-in, the studies were performed with constant Kr-inflow (9). The inflow of Kr was kept constant with a flow meter on the Kr delivering system that was set at 3 l/min.

Regional ventilation was computed according to the same model used for regional perfusion.

Procedure

After catheterization and surgery (thoracotomy pigs) approximately 20 min were allowed before baseline measurements of central hemodynamics, LLL blood flow (thoracotomy pigs) and arterial and mixed venous blood gases and saturations. Oleic acid was then administered to the LLL via the Swan Ganz catheter, with the balloon of the catheter inflated. The balloon was kept inflated for 1 min after the injection to prevent the oleic acid from distributing to other parts of the lungs. The dose of oleic acid was 0.1–0.15 ml/kg. When the pigs were in a stable hypoxic state (approximately 1.5–2 h after the injection), 0.3–0.5 l blood was drawn from the pig to get a low $\dot{Q}_t$. During this

stable state, the same measurements recorded at baseline were again recorded, and perfusion and ventilation scans were obtained on the gamma camera pigs. Pulmonary capillary wedge pressure (PCWP) was recorded in the gamma camera pigs at low and high $\dot{Q}_t$. $\dot{Q}_t$ was checked intermittently during the gamma camera investigation to ensure maintenance at a low value.

$\dot{Q}_t$ was then increased by reinfusing the blood together with 0.3–0.5 l dextran (thoracotomy pigs) or with dextran only (gamma camera pigs). All measurements were then repeated and new perfusion and ventilation scans were obtained.

At the end of the experiment the pigs were killed with an intravenous injection of potassium chloride and the lungs were taken out for inspection and weighing of the separate lobes.

Statistical analysis

Data in the text, tables and figures are presented as mean±SE. The significance of a difference in a variable between 1) baseline and lung injury (after oleic acid injection) and 2) low and high $\dot{Q}_t$ was tested with paired *t*-test.

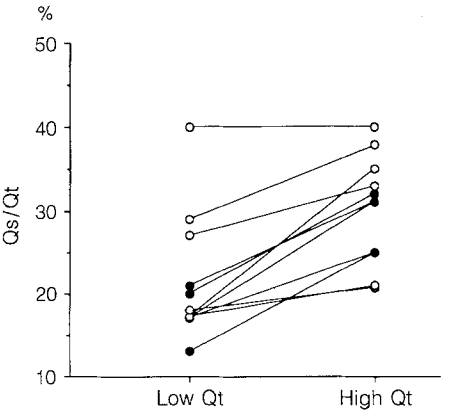

Fig. 1. Dependence of shunt ($\dot{Q}_s/\dot{Q}_t$) on cardiac output ($\dot{Q}_t$) in gamma camera pigs (●) and thoracotomy pigs (○). Note the similar increase in shunt on an increase in cardiac output in both groups of animals

Results

Thoracotomy study

Results are given in Table 1 and Fig. 1. During baseline recordings before oleic acid injection, LLL blood flow averaged 33% of $\dot{Q}_t$, and the calculated venous admixture (F_IO_2: 0.4) was on average 7%. After oleic acid administration and bleeding. Q_t was reduced from 2.2–1.3 l/min, corresponding to a 40% reduction. LLL blood flow was reduced even more, so that the fractional blood flow was a mean of 24% of $\dot{Q}_t$, but the change was not clearly significant because of large inter-individual variation. Venous admixture (F_IO_2 1.0) was markedly increased to a mean 25%. PaO_2 averaged 37 kPa which should be compared to a calculated alveolar PO_2 of 89 kPa. $PaCO_2$ was not significantly altered, although its mean value was increased by 0.8 kPa. Systemic artery mean pressure (MAP) was reduced on an average, and mean pulmonary artery pressure (MPAP) tended to increase. Peak airway pressure (P_{aw}) was increased.

After reinfusion of blood and additional plasma expander, $\dot{Q}_t$ was increased by 44% compared to the previous recording, from 1.3–1.9 l/min, but it was still lower than during baseline measurements. LLL blood flow increased approximately in proportion to $\dot{Q}_t$ so that its fractional perfusion remained much the same. $\dot{Q}_s/\dot{Q}_t$, on the other hand, was further increased, although the significance of this change was borderline ($p = 0.05$). A mean reduction in arterial oxygen tension (PaO_2) was noted, and a significant increase in mixed venous oxygen tension (PvO_2). $PaCO_2$ remained unaltered. MAP was increased compared to the previous recording at lower $\dot{Q}_t$, whereas MPAP was essentially unaltered. P_{aw} remained unaltered compared to the recordings at low $\dot{Q}_t$.

Table 1. Cardiac output ($\dot{Q}_t$), left lower lobar blood flow ($\dot{Q}_{LLL}$), total venous admixture ($\dot{Q}_s/\dot{Q}_t$), arterial and mixed venous tensions (PaO_2, PvO_2), arterial carbon dioxide tension ($PaCO_2$), pulmonary and systemic mean artery pressure (MPAP, MAP), peak airway pressure (P_{aw}) and pulmonary capillary wedge pressure (PCWP) during baseline recordings and 2 h after oleic acid administration to the left lower lobe (post oleic acid) at low and high $\dot{Q}_t$

	Thoracotomy protocol			Gamma camera protocol	
	Baseline	Low $\dot{Q}_t$	High $\dot{Q}_t$	Low $\dot{Q}_t$	High $\dot{Q}_t$
$\dot{Q}_t$ (l/min)	2.22±0.27	1.32±0.25*	1.93±0.27**	2.60±0.48	4.50±0.48***
$\dot{Q}_{LLL}$ (%$\dot{Q}_t$	33.0±2.2	23.6±6.2	20.7±5.6	19.0±8.0	20.2±8.0
$\dot{Q}_s/\dot{Q}_t$ (%)	7.1±1.2[a]	24.9±3.7**	31.3±3.4*	17.6±3.1	28.8±3.5***
PaO_2 (kPa)	23.3±1.0	36.9±6.1	27.3±6.1	27.9±12.5	29.3±10.8
PvO_2 (kPa)	5.5±0.3	5.1±0.6	5.9±0.7*	5.6±0.8	6.9±1.2*
$PaCO_2$ (kPa)	5.2±0.7	6.0±0.5	5.8±0.6	6.1±0.4	6.7±1.0
MPAP (mmHg)	18.0±1.5	21.3±1.7	23.2±2.6	29.2±6.8	41.0±4.8***
MAP (mmHg)	83.6±3.4	65.2±7.1	86.8±14.2	89.0±31.0	107.0±37.0
P_{aw} (mmHg)	11.5±1.9	14.8±1.5*	14.7±1.4		
PCWP (mmHg)				7.8±1.6	8.0±1.6

Statistical analysis two-sided paired *t*-test between baseline and low $\dot{Q}_t$, and between low and high $\dot{Q}_t$. *p*-Values imply difference between baseline and low $\dot{Q}_t$ and between low and high $\dot{Q}_t$

FIO_2 is 0.4 at baseline and 1.0 at low and high $\dot{Q}_t$

[a] Since $\dot{Q}_s/\dot{Q}_t$ at baseline was measured at F_IO_2 0.4, it should be denoted venous admixture

*$p<0.05$, **$p<0.01$, ***$p<0.001$

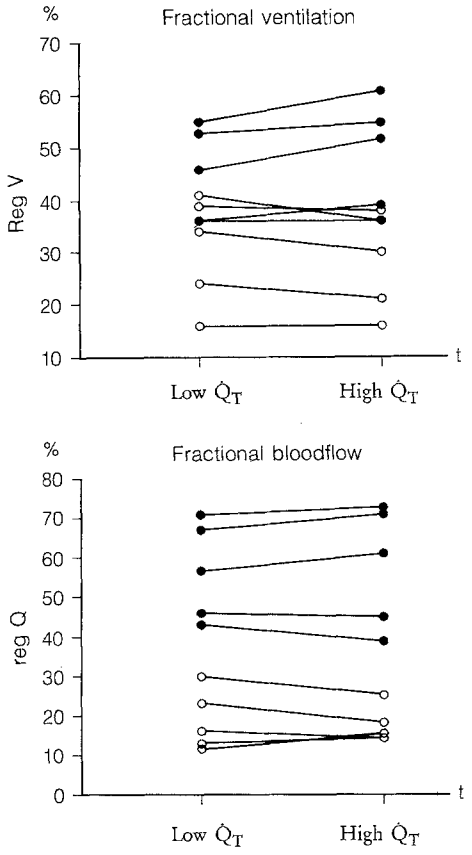

Fig. 2. Gamma camera study. Fractional ventilation ($\dot{V}$) and bloodflow ($\dot{Q}$) in left (○) and right (●) lower lobes at low and high cardiac output. Note the small but significant changes in ventilation and the absence of a consistant change in blood flow when cardiac output was altered.

Gamma camera study

Results are given in Tables 1 and 2 and Figs. 1 and 2.

At low $\dot{Q}_t$, 2 h after the injection of oleic acid, $\dot{Q}_t$ was 2.6 l/min and PaO_2 was 27.9 kPa. $\dot{Q}_s/\dot{Q}_t$ was at this point mean 18%. MPAP averaged 29.2 mmHg and mean PCWP was 7.8 mmHg.

Infusion of blood and/or dextran increased $\dot{Q}_t$ to 4.5 l/min, i.e. by 73%. At the same time a significant increase in $\dot{Q}_s/\dot{Q}_t$ to 28.8% was seen. There were no significant changes of PaO_2 or $PaCO_2$. PvO_2 and venous saturation both increased significantly when $\dot{Q}_t$ was increased, there was also a significant increase in MPAP, to 41 mmHg, whereas PCWP remained unaltered at 8 mmHg.

When analyzing regional perfusion and ventilation, assessed by the gamma camera, the edematous LLL was compared with the unaffected (or less affected) RLL. At both low and high $\dot{Q}_t$, perfusion and ventilation of the edematous LLL was significantly lower than of RLL. No significant change in the fractional perfusion of LLL and RLL was seen on a change of $\dot{Q}_t$. However, a small but significant change in the fractional ventilation of both the LLL and RLL was seen, with a 2.6% decrease of ventilation in LLL and a 3.4% increase of ventilation in RLL on an increase in $\dot{Q}_t$. Minute ventilation averaged 5.5 l/min so a 2.6% reduciton in the LLL represents 0.14 l/min.. There was no correlation between the increase in shunt and the decrease in ventilation of LLL ($r = 0.14$, $p = 0.60$).

Table 2. Gamma camera study. Fractional ventilation and perfusion of RLL and LLL at low and high $\dot{Q}_t$. Change of ventilation and perfusion from low to high $\dot{Q}_t$. Mean % ± SD. $*p<0.05$

	Reg V		Reg Q	
	LLL	RLL	LLL	RLL
Low $\dot{Q}_t$ (%)	31±6	45±6	19±8	57±9
High $\dot{Q}_t$ (%)	28±6	48±7	20±8	56±9
% change from low to high $\dot{Q}_t$	−2.6±2.0*	+3.4±2.6*	−1.6±3.5	+1.2±3.7

Table 3. Left and right lung and individual lobar weights (g) after oleic acid administration to the left lower lobe. RUL, RML, RCL and RLL are right upper, middle, cardiac and lower lobe. LUL, LML and LLL are left upper, middle and lower lobe. Pooled data from both the thoracotomy and gamma camera studies ($n = 11$). (There was no significant difference in lobar weights between the two studies)

Right lung		Left lung	
RUL	28± 7	LUL	33±13
RML	26± 4	LML	36±12
RCL	19± 5		
RLL	142±36	LLL	287±40
Total	215±32		375±61

Lung morphology

Post-mortem macroscopic analysis of thoracotomy pigs and gamma camera pigs showed that the LLL was much heavier than any other lobe and bluish in colour. However, the left middle lobe (LML) and right lower lobe (RLL) also appeared edematous in some pigs, although not as marked as the LLL. Thus, the mean weight of the LLL was on average two times heavier than that of the RLL, indicating that the edema was confined mainly to the LLL (Table 3).

Discussion

$\dot{Q}_s/\dot{Q}_t$ was found to increase when $\dot{Q}_t$ was increased during oleic acid edema both in the thoracotomy pigs and in the intact gamma camera pigs. This is similar to previous observations both in patients with acute respiratory failure [1, 2] and in animal models with oleic acid edema [3–6]. The cardiac output-dependent shunt has been demonstrated both by measurements of oxygen content in blood (i.e., venous admixture) as in the present study, and by using multiple inert gas elimination technique [1, 4, 7]. This study was designed to evaluate the contributions of changes in 1) perfusion and 2) ventilation to the cardiac output dependent shunt.

The study was performed in a pig model, a species that is known to develop a strong vascular response to hypoxia [10]. The pigs reacted to oleic acid injection, and to changes in $\dot{Q}_t$ in the same way previously observed in

dog experiments [3–7], although the oleic acid dose had to be higher in the pig than in the dog to produce a similar degree of hypoxemia. In our study, $\dot{Q}_t$ was increased by infusion of blood and/or dextran. It might be argued that such an infusion can produce a hydrostatic edema. However, PCWP remained constant whether $\dot{Q}_t$ was high or low, giving no support for the formation of high pressure, hydrostatic edema. Another objection may be that the sequence of low and high $\dot{Q}_t$ was not randomized so that increased shunt at the latter recording could have been an effect of progression of the lung injury rather than the increase in $\dot{Q}_t$. However, using arterio-venous fistulae $\dot{Q}_t$ has been varied in both directions with concomitant changes in shunt (see for example [7]).

Results obtained in the open chest preparation must be interpreted with caution. Thus, the thoracotomy will affect regional lung volume expansion and may interfere with distributions of ventilation and blood flow. Moreover, the manipulation of the lung tissue and the insertion of the electromagnetic flow probe may compromise cardiopulmonary function. We also noticed lower $\dot{Q}_t$ in the thoracotomy pigs than in the gamma camera pigs. Finally the placement of the flow probes may cause a denervation of the pulmonary vascular bed so that neural vasomotor responses are attenuated or abolished.

Therefore we experienced another model that eliminated the need of a thoracotomy. We measured the blood flow with radioactively labelled (99mTc) microspheres and a gamma camera. This study, performed on intact animals, documented similar results: the fractional LLL blood flow ($\dot{Q}_{LLL}/\dot{Q}_t$) remained stable when the $\dot{Q}_t$ was changed. The $\dot{Q}_{LLL}/\dot{Q}_t$ reached approximately 20% in both experiments. On the gamma camera the perfusion of the LLL was much lower than that of the RLL. It has been recently reported that the perfusion of a lung lobe decreases rapidly after the injection of oleic acid in its artery, and that vascular obstruction with fat embolism and thrombosis might be responsible for this early drop in perfusion [11]. Our measurements started 2 h after the injection of oleic acid, at a period when other mechanisms such as edema and vasoactive response might have become more important [11]. Ali and Wood estimated that 1.5 h after the oleic acid injection 50% of the decrease in perfusion was due to mechanical effects of the edema and 30% to the vasoconstriction in a dog preparation [12].

Among numerous mechanisms documented to blunt the hypoxic vasoconstriction (HPV), two have been mostly investigated. The increase in PvO_2 with an increase in $\dot{Q}_t$ can modify the pulmonary vascular tone and favour perfusion of previously constricted vessels. Bishop [13] found independent effects of PvO_2 and $\dot{Q}_t$ on $\dot{Q}_s/\dot{Q}_t$ whereas Sandoval [14] proposed PvO_2 as the mediator of the $\dot{Q}_t$ dependent $\dot{Q}_s/\dot{Q}_t$. We found a mean increase in PvO_2 with a mean increase in $\dot{Q}_t$ and an increase in $\dot{Q}_s/\dot{Q}_t$ with an increasing PvO_2. However we can not conclude that the increased PvO_2 initiated a vasodilation in shunted areas as no redistribution of bloodflow between different lobes occurred.

Increasing the MPAP might as well mechanically open constricted vessels and thereby aggravate the shunt [15]. Here again, no change in fractional lobar perfusion was seen when MPAP increased. We conclude that no redistribution of blood flow between different lobes occurred on an increase in $\dot{Q}_t$ and that this finding is independent of the surgical procedure.

As the vascular hypothesis has failed to explain the link between $\dot{Q}_t$ and $\dot{Q}_s/\dot{Q}_t$, one may argue that the $\dot{Q}_t$ dependent shunt is not the effect of circulatory changes but rather due to altered gas distribution, with cessation of ventilation in certain lung regions. We therefore hypothetized that compression of the small airways may occur when $\dot{Q}_A$ is increased. Hughes [16] suggested that the edema increases the size of the interstitial space, decreases transmural pressure of the airways, and eventually closes them. We observed an increase in the airway pressure during oleic acid edema, and recent studies have shown that not only compliance is reduced but inspiratory tissue and airway resistances are both increased [17]. We noticed no change in peak airway pressure when changing from low to high $\dot{Q}_t$, but our recording technique allows no detailed analysis of any effect on airway resistance. Indeed, we found a decrease in regional ventilation in the edematous lobe by a mean of 2.6% when $\dot{Q}_t$ increased. Theoretically this reduction in ventilation could take place in edematous regions with a low ventilation/perfusion ($\dot{V}_A/\dot{Q}$) ratio. If the ventilation of these regions was inhibited at high $\dot{Q}_t$, they would be transformed into shunt. Is it then possible that this small reduction in ventilation can explain the rise in shunt? LLL ventilation averaged 1.6 l/min, corresponding to 30% of total ventilation. A 2.6% reduced of LLL ventilation is then equal to 0.14 l/min. This should be compared with the increase in shunted blood flow in the same animals (Gamma camera pigs), from 17.6% of 2.6 l/min to 28.8% of 4.5 l/min, corresponding to a rise in shunted blood flow by 0.84 l/min. If cessation of ventilation by 0.14 l/min explains the increased shunt by 0.84 l/min, a change in the $\dot{V}_A/\dot{Q}$ ratio from 0.17 to zero must have occurred in some lung regions when $\dot{Q}_t$ increased.

Although this is a possibility, at least in theory, it has to be noted that the decrease in ventilation may have been more uniform all over the lobe without decreasing ventilation to zero in any particular region. Moreover, there was no correlation between the decrease in ventilation and the increase in shunt when $\dot{Q}_t$ was elevated. Finally, in studies using the multiple inert gas elimination technique for assessing the $\dot{V}_A/\dot{Q}$ distribution in patients with ARDS at low and high $\dot{Q}_t$, the common finding has been that pulmonary blood flow is either distributed to regions with well preserved $\dot{V}_A/\dot{Q}$ ratios or to shunt units [1, 7]. There is no report on low $\dot{V}_A/\dot{Q}$ regions at low $\dot{Q}_t$ that have been reduced or eliminated by increasing $\dot{Q}_t$. Consequently, the decreased regional ventilation is unlikely to explain the cardiac output dependent shunt.

Even if the vascular hypothesis (redistribution of blood flow between lobes) has failed to explain the cardiac output dependent shunt, the possibility remains that the blood flow is redistributed within the edematous lobe. It may seem unlikely that a redistribution can occur within the lobe without affecting distributions between lobes, but knowing that the major vascular resistance is at the

level of the arterioli [18, 19] i.e., within the lobe, flow changes may occur below the macroscopic level studied in the present investigation. Such changes may be due to blunted HPV caused by an increase in PvO_2 or due to mechanical effects of increased MPAP. Furthermore, mediators from the edematous hypoxic areas may attenuate HPV in other parts of the lungs. Further study is required to solve this matter.

It should also be mentioned that other mechanisms for cardiac output dependent shunt have been discussed. Thus, incomplete diffusion equilibrium of O_2 between alveolar gas and pulmonary capillary blood when alveoli are flooded with edema has been suggested [20]. The shortened pulmonary capillary transit time at high $\dot{Q}_t$ would aggravate the diffusion defect, thereby increasing the calculated $\dot{Q}_s/\dot{Q}_t$. However, calculations of $\dot{Q}_s/\dot{Q}_t$ at different inspired oxygen fractions and on multliple inert gas elimination data do not support any diffusion limitation at either high or low $\dot{Q}_t$ [4]. Still another possibility is that the increased $\dot{Q}_t$ increases the edema and thus the $\dot{Q}_s/\dot{Q}_t$. However, there was no correlation between $\dot{Q}_s/\dot{Q}_t$ and degree of edema, expressed as extravascular lung water by double indicator dilution technique [21]. Uneven distribution of hematocrit within the lungs has also been proposed as a mechanism behind the varying $\dot{Q}_s/\dot{Q}_t$, but since $\dot{Q}_s/\dot{Q}_t$ varies when measured by inert gas elimination technique [7] such an explanation also has to be rejected.

We thus conclude that the cardiac output dependent shunt that was seen during oleic acid pulmonary edema, both in thoracotomized and in intact pigs, is not caused by redistribution of blood flow between lobes. Nor is it caused by a decreased ventilation in edematous regions. We can not exclude that blood flow is redistributed within the edematous lobe.

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