Hypoxic Pulmonary Vasoconstriction in the Human Lung: Effect of Repeated Hypoxic Challenges during Anesthesia

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Six patients, ages 29–58 yr, were investigated during barbiturate and fentanyl anesthesia. After intubation with a double-lumen bronchial catheter, one lung was ventilated continuously with 100% O_2, and the other was rendered hypoxic during three 15-min periods by ventilation with 95% N_2 + 5% O_2, with intervening 15-min periods of oxygen ventilation. Cardiac output was determined by thermodilution, and the distribution of blood flow between the lungs was assessed from the excretion of a continuously infused poorly soluble gas (SF6). The first hypoxic challenge resulted in a 10% increase in cardiac output (QT) and a reduction in the fractional perfusion of the test lung from 57% to 31% of QT. The pulmonary artery mean pressure increased by 54%, and the vascular resistance of the test lung increased threefold. The venous admixture increased from 19% to 40% of QT, whereas the inert gas shunt remained unaltered at 15% (inert gases also being eliminated by nitrogen-ventilated areas). The arterial oxygen tension decreased from 353 mmHg to 79 mmHg. On resumption of the control state, central hemodynamics and gas exchange returned to the initial values. The second and third hypoxic challenges resulted in reductions in the fractional perfusion of the test lung to 35% and 37% of QT. All other variables were altered to the same degree as during the first challenge. The authors conclude that hypoxic challenge of one lung in an intravenously anesthetized human subject elicits a maximum vasoconstrictor response within the first 15 min, and this response cannot be potentiated by repeated challenges. (Key words: Lung. Hypoxic pulmonary vasoconstriction. Shunt: hypoxia.)

THE HYPOXIC PULMONARY VASOCONSTRICTOR (HPV) response, first described by von Euler and Liljestrand[1] in 1946, is a mechanism for diverting the blood flow away from poorly ventilated to better ventilated lung areas. In this way hypoxic pulmonary vasoconstriction is believed to adjust perfusion to ventilation.[2]

Preservation of the HPV response, or even an augmentation, in the anesthetized subject would be desirable. Benumof et al.[3,4] have shown that repeated hypoxic challenges[5–8] to the left lower lobe of canine lungs

potentiate the HPV response. Consequently, they have recommended that "in the initiation of one-lung ventilation [we] employ several cycles of deflation–inflation to the lung which is to be deflated in order to maximize hypoxic vasoconstriction in that lung."[3]

The purpose of the present study was to investigate the hypothesis put forward by Benumof et al.,[4] i.e., to determine whether repeated hypoxic challenges potentiate the HPV response in anesthetized humans during unilateral whole-lung hypoxia.

Patients and Methods

Six subjects—two women and four men, ranging in age from 29 to 58 yr, weight from 58 to 90 kg and height from 172 to 190 cm—were investigated during intravenous anesthesia immediately before elective surgery. No subject had a history of chest disease. Four were moderate smokers (10–20 cig/day). The clinical examination, chest x-ray, and ECG were all normal. The study was described in detail to the subject before his or her consent was obtained. The Ethical Committee of the Karolinska Institute had approved the study. There were no complications attributable to the investigation.

ANESTHESIA

Premedication consisted of morphine (0.14 mg/kg) and scopolamine (0.06 mg/kg) administered intramuscularly approximately 1 h before anesthesia. Anesthesia was induced with a "sleep dose" (250–300 mg) of thiopental. Muscular relaxation was obtained by means of pancuronium bromide (0.1–0.2 mg/kg), endobronchial intubation being performed with a double-lumen bronchial catheter (French gauge 37–39). The position of the endobronchial tube was checked by inflating each lung separately while auscultating the breath sounds. The absence of leaks between the lungs was confirmed by ventilating one lung at a PEEP of 10 cmH₂O; any leak to the opposite lung was detected by a balloon attached to the proximal end of its tube connection. Low and similar peak airway pressures in both lungs (range 10–15 cmH₂O as read on the manometer of the ventilator) were considered a sign of nonobstructed gas flow through the endobronchial tube.

Anesthesia was maintained with repeated doses of thiopental (50 mg/20 min) and fentanyl (0.05 mg/20 min) and, when required, pancuronium bromide.

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VENTILATION

After induction of anesthesia, relaxation, and double-lumen intubation, the subject was connected to a specially designed Engström ventilator with two separate bag-in-box circuits and pressure-operated nonrebreathing valves. Compressed air was delivered to both bag-in-box chambers by the same piston. In this way the respiratory frequency remained equal and synchronous in both circuits with an inspiration:expiration ratio of 1:2 and a frequency of 12 breaths/min. Each circuit was fed from independent flow meters dispensing 100% oxygen or a gas mixture of 95% nitrogen and 5% oxygen to the right (test) lung.

The expired tidal volume from each lung was separated from the gas compressed in the ventilator tubings by a special nonrebreathing valve and sampled in a bag. The volume was measured by a spirometer (LS75 ventilator monitor, Bourns) and was used for calculation of the individual lung blood flow (see below). All subjects were investigated in the supine position and ventilated with equally large tidal volumes to both lungs to obtain an arterial P_{CO_2} of about 35–38 mmHg.

HEMODYNAMICS

A triple-lumen, thermistor-tipped balloon catheter (Swan-Ganz® No. 7F) was introduced percutaneously by a sleeve technique into a medial cubital vein and was advanced to the pulmonary artery with continuous monitoring of ECG and pressure. Cardiac output was determined by thermodilution. The thermal indicator was 10 ml 5.5% glucose at 0–2° C, injected into the right atrium. Cardiac output was derived from the mean of at least three consecutive measurements (Cardiac Output Computer 9510,® Edwards Laboratories). The radial artery was cannulated for pressure recordings and blood sampling, and, finally, a central venous catheter was introduced percutaneously for inert gas infusion. (In addition to the catheters used for the experiment, one or two venous cannulas were inserted for the maintenance of anesthesia and care of the patient.) All pressures were recorded with pressure transducers (No 840, Microelectronics), the signal being fed into an amplifier (Type XV, 1505 Philips Medical System). The transducers were calibrated against a saline manometer.

REGIONAL PERFUSION AND SHUNT

In order to assess the distribution of blood flow to the two lungs and to calculate the shunt, a mixture of three poorly soluble gases (ST 6, ethane, and cyclopropane) in saline was infused at a slow rate (3 ml/min). Mixed expired gas was collected from each lung under steady state conditions, and the ST 6 concentration was measured in a gas chromatograph (Sigma 3®, Perkin

Elmer).[5] The ST 6 concentration ratio between the two lungs was assumed to reflect the perfusion ratio. The method is dealt with in further detail in the "Discussion."

The magnitude of the shunt, *i.e.*, the amount of mixed venous blood that bypasses the lungs without coming into contact with ventilated lung tissue, was calculated by measuring the retention of all three infused gases. Using an extrapolation method,[6] the shunt was calculated as perfusion of lung regions with a ventilation–perfusion ratio of less than 0.005.

Venous admixture, *i.e.*, the amount of blood that bypasses the lungs or perfuses the lung without being completely oxygenated, was calculated from Berggren's equation[7]:

$$\frac{C\bar{c}_{O_2} - Ca_{O_2}}{C\bar{c}_{O_2} - C\bar{v}_{O_2}}$$

where C denotes content and $\bar{c}$, a, and $\bar{v}$ stand for pulmonary end-capillary, arterial, and mixed venous blood, respectively.

The content was calculated as $S_{O_2} \times Hb \times 1.39 + P_{O_2} \times 0.03$, with S_{O_2} representing the oxygen saturation of hemoglobin, Hb the hemoglobin concentration in g/1, and P_{O_2} the oxygen tension in mmHg. Pulmonary end-capillary oxygen tension ($P\bar{c}_{O_2}$) was assumed to equal alveolar oxygen tension (PA_{O_2}), which was calculated as $PI_{O_2} - Pa_{CO_2}/0.8$ with PI_{O_2} denoting the inspired oxygen tension and Pa_{CO_2} the arterial carbon dioxide tension. Arterial and mixed venous oxygen and CO_2 tensions and pH were measured by standard technique (equipment: BMS-3) and oxygen saturation of the blood (S_{O_2}) by spectrophotometry (OSM-2, Radiometer).

Shunt and the venous admixture were calculated for both lungs together; separate values for the two lungs would have required sampling from the pulmonary veins, which was not possible in this study.

STATISTICS

Data in the text, tables, and figures are presented as mean ± SE mean. A three-way statistical analysis of variance was employed to disclose any difference between the control situation and the repeated hypoxic challenges and if there was a potentiation of the HPV response. The patients, the inspired gas mixtures, and the repetition made up the three dimensions. This test also enabled an analysis of any interaction between the gas mixtures and the repeated challenges.

EXPERIMENTAL PROCEDURE

Both lungs were ventilated initially with 100% O_2 for at least a half hour to obtain steady state conditions. At the end of this period, the cardiac output was determined in triplicate; blood samples were collected for blood gas, saturation, and inert gas measurements; and expired gas

TABLE 1. Central Hemodynamics during Repeated Unilateral Hypoxic Challenges ($\bar{X} \pm$ SE)

	Heart Rate (beats/min)	Lung Blood Flow (l/min)			Mean Arterial Pressure (mmHg)	Mean Pulmonary Artery Pressure (mmHg)	Pulmonary Wedge Pressure (mmHg)	Pulmonary Vascular Resistance (mmHg × min × l⁻¹)	
		Total	Control Lung	Test Lung				Control Lung	Test Lung
Control 1	67 ± 3	4.84 ± 51	2.1 ± 0.2	2.7 ± 0.3	87.8 ± 7	11.8 ± 0.9	9.0 ± 0.6	1.52 ± 0.51	1.23 ± 0.42
Challenge 1	68 ± 3	5.33 ± 58	3.6 ± 0.4*	1.7 ± 0.4*	98.3 ± 15	18.2 ± 1.0*	8.2 ± 1.0	2.69 ± 0.25†	6.22 ± 1.28*
Control 2	61 ± 3	4.45 ± 38	2.1 ± 0.3	2.3 ± 0.2	83.3 ± 7	13.7 ± 0.7	9.3 ± 1.2	1.98 ± 0.34	1.80 ± 0.35
Challenge 2	68 ± 2	4.76 ± 35	3.1 ± 0.3*	1.7 ± 0.2*	84.6 ± 7	17.7 ± 1.0*	10.2 ± 1.4	2.40 ± 0.56†	4.65 ± 1.12*
Control 3	64 ± 3	4.48 ± 40	2.1 ± 0.3	2.4 ± 0.2	86.3 ± 8	15.5 ± 1.0	11.3 ± 1.2	2.03 ± 0.49	1.68 ± 0.37
Challenge 3	68 ± 4	4.72 ± 38	3.0 ± 0.1*	1.8 ± 0.3*	78.0 ± 8	18.2 ± 0.9*	11.0 ± 1.2	2.40 ± 0.51†	4.36 ± 0.85*

* Three-way analysis of variance: significant effect of hypoxic challenge, $P < 0.01$.

† Three-way analysis of variance: significant effect of hypoxic challenge, $P < 0.05$.

was collected for measurements of volume and determination of the ST 6 concentration. The test lung was rendered hypoxic by ventilation with 5% O_2 in nitrogen, while the other lung (control lung) was ventilated with oxygen. The measurements were repeated after 15 min. Two additional hypoxic challenges were performed during 15-min periods, each being preceded by a 15-min period of oxygen ventilation of both lungs.

Results

EFFECTS ON LUNG BLOOD FLOW

In the first control situation, cardiac output averaged 4.9 l/min. Fifty-seven per cent of the perfusion was distributed to the right (test) lung and 43% to the left (control) lung. Pulmonary artery mean and wedge pressures were within normal limits, the vascular resistance of the right and left lung being 1.23 and 1.52 mmHg × l⁻¹ × min, respectively. The systemic mean pressure was on the average 85 mmHg (table 1).

Ventilation of the test lung with 5% O_2 in nitrogen resulted in a 10% increase in cardiac output and a marked reduction in the fractional perfusion of the test lung, down to 31% of cardiac output. Pulmonary artery mean pressure increased by 54%, and the vascular resistance of the test lung increased fivefold. The vascular resistance of the control lung increased moderately, and the pulmonary wedge pressure, as well as the systemic pressure, were all essentially unaltered (table 1, fig. 1).

On restoration of the control state (100% oxygen to both lungs), the circulatory variables returned toward the same level as during the initial control period. Thus, the fractional perfusion of the test lung increased to 48% of the cardiac output, and the vascular resistance of that lung decreased to 1.80 mmHg × l⁻¹ × min.

The two additional hypoxic challenges, with 15 min of oxygen respiration in between, resulted in similar redistributions of the pulmonary blood flow. The fractional perfusion of the test lung decreased to 35% during the second challenge and to 37% during the

third challenge. Thus, no potentiation of the redistribution of blood flow from the hypoxic lung was noted during the succeeding challenges. Rather, mean changes in individual lung blood flow and vascular resistance tended to be smaller with each challenge.

An increase in pulmonary artery mean pressure between the control states was observed. However, no significant interaction between gas mixtures and repetition, using three-way analysis of variance, was seen.

EFFECTS ON GAS EXCHANGE

During the initial control state with 100% oxygen, Pa_{O_2} averaged 353 mmHg and Pa_{CO_2} was normal (table 2). The venous admixture was as high as 18.6% of cardiac output, and the shunt, calculated from the inert gas retention, was only slightly smaller.

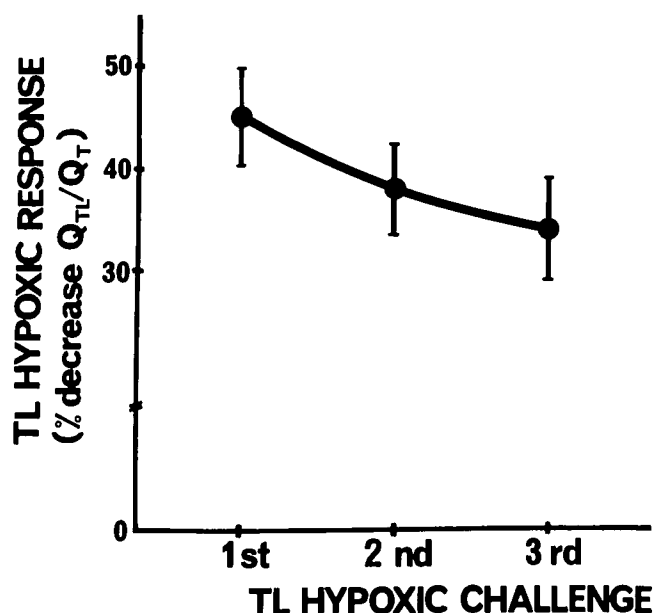The hypoxic challenge caused a marked decrease in

FIG. 1. Test lung (TL) hypoxic response (percentage decrease $\dot{Q}_{TL}/\dot{Q}_T$) as a function of repeated intermittent hypoxic challenges.

TABLE 2. Arterial Blood Gases (Pa_{O_2}, Pa_{CO_2}), Venous Admixture, Inert Gas Shunt during Repeated Unilateral Hypoxic Challenge ($\bar{X} \pm SE$)

	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	Venous Admixture (% cardiac output)	Inert Gas Shunt (% cardiac output)
Control 1	353 ± 18	37 ± 3	18.6 ± 2.1	14.9 ± 4.7
Challenge 1	79 ± 12*	39 ± 3	40.4 ± 5.0*	25.1 ± 2.8
Control 2	326 ± 38	37 ± 4	17.9 ± 2.3	14.7 ± 5.1
Challenge 2	74 ± 8*	38 ± 4	42.4 ± 4.1*	12.6 ± 2.6
Control 3	374 ± 19	36 ± 5	16.7 ± 2.4	15.5 ± 3.1
Challenge 3	71 ± 9*	36 ± 2	45.5 ± 5.3*	16.2 ± 4.6

* Three-way analysis of variance: significant effect of hypoxic challenge, $P < 0.01$.

Pa_{O_2} to around 79 mmHg, Pa_{CO_2} being maintained around 39 mmHg. Venous admixture increased to 40%, and the inert gas shunt was unaltered (the inert gases being eliminated by nitrogen-ventilated areas as well as by oxygen-ventilated ones).

On restoration of the control state, the venous admixture and Pa_{O_2} returned to the initial control values, and the inert gas shunt and Pa_{CO_2} remained unaltered.

The second and third hypoxic challenges showed decreases in Pa_{O_2} and increases in the venous admixture similar to those of the first challenge. Thus, there were no significant differences between the three hypoxic challenges.

Discussion

This study shows that hypoxic challenge of one lung in the intravenously anesthetized human subject causes a maximum vasoconstrictor response within the first 15 min and that this response cannot be potentiated by repeated challenges. These observations conflict with results obtained in open chest dogs. Possible causes of this difference will be discussed in the following paragraphs after a few comments on the methods.

METHODOLOGIC CONSIDERATIONS

The fractional perfusion of each of the two lungs can be studied by measuring the excretion of a continuously infused, poorly soluble gas. The less soluble the gas, the less its elimination will be affected by variations in the ventilation–perfusion ratio. Sykes et al.[8] studied the regional distribution of the pulmonary blood flow by the infusion of ^{133}Xe (blood–gas partition coefficient: 0.18). Because of its low solubility, 95% of the ^{133}Xe is taken up by the alveoli and eliminated via the airways, provided that there is normal ventilation–perfusion matching and no shunt. The SF6 is even less soluble; its blood–gas partition coefficient is 0.006, and 99% is removed from the pulmonary capillary bed. SF6 therefore is even more suitable for measurements of fractional pulmonary blood flow.[9] However, the blood not coming

into contact with ventilated alveoli will retain its SF6, and the measured perfusion distribution therefore will reflect the nonshunted blood flow. The magnitude of the shunt can be estimated reasonably well by measuring the retention of SF6 (i.e., the arterial to mixed venous blood ratio). In the present study the determination of the magnitude of the shunt has been made even more precise by using three inert gases of low solubility, thus allowing extrapolation of the retention to even lower blood gas partition coefficients.[5] The unaltered inert gas shunt during hypoxic challenge indicates that there was no increased perfusion of nonventilated regions (e.g., atelectases) during the challenge. It therefore seems reasonable to assume that the fractional inert gas shunt was distributed evenly between the two lungs both during hyperoxia and hypoxia and that the fractional perfusion distribution between the lungs would have been much the same even if the shunt blood flow had been included.

POTENTIATION OF HPV

The first report on potentiation of the pulmonary vasoconstrictor response with repeated intermittent hypoxia was published in 1977 by Unger et al.[10] They rendered both lungs hypoxic in dogs and noted a successive increase in pulmonary artery pressure with repeated hypoxic challenges.

Lobar hypoxic pulmonary vasoconstriction was studied in an open-chest dog model by Pirlo et al.,[3] and an increased vasoconstrictor response was observed on repeated hypoxic challenges. The results have been questioned, however, because prior to the measurements there had been a recent history of blood vessel manipulations that may have interfered with the normal response to the hypoxic challenges.[2] The potentiation of the vasoconstrictor response by repeated challenges was reproduced by Benumof[4] in the open-chest dog model even after 2–2.5 h of rest before the tests. On the other hand, Chen et al.[11] found that the vasoconstrictor response in closed-chest dogs was maximal at

the first hypoxic challenge. Thus, the manipulation of the pulmonary blood vessels may be of importance even after a few hours of rest. Another difference between the two dog studies was that the "left lower lobar" vasoconstrictor response was studied in the open-chest dogs while a "whole lung" response was studied in closed-chest dogs. A multiple inert gas elimination technique and radioactive microspheres were used to demonstrate that the degree of decrease in blood flow with bronchial obstruction diminished as the volume of obstructed lung increased in intact dogs.[12]

HPV IN MAN

A number of investigators have demonstrated diversion of the blood flow from the hypoxic lung during unilateral hypoxic ventilation in awake humans.[13-16] None of these papers mention potentiation of HPV with time, nor with repeated hypoxic challenges. Very few investigations of the effect of unilateral hypoxia and blood flow diversion in anesthetized human subjects have been published. Bjertnaes[17] was the first to demonstrate a blood flow diversion of 21.5% (range 11.5–31%) from the hypoxic lung during one-lung hypoxia in intravenously anesthetized humans, which was abolished by adding diethyl ether or halothane to the inspired gas. The magnitude of the HPV response was the same as that found in the present study. Potentiation of the hypoxic pulmonary vasoconstrictor response with time or through repetition was not reported by Bjertnaes.[17]

CONCLUDING REMARKS

Hypoxic challenge of one lung in intravenously anesthetized human subjects elicited a maximum vasoconstrictor response and redistribution of pulmonary blood flow within the first 15 min without potentiation by repeated challenges. This response pattern was the same as and of similar magnitude to that seen in closed-chest dog experiments on repeated one-lung hypoxic challenges and differed from the increasing vasoconstrictor response demonstrated in repeated lobar hypoxia in open-chest dogs. While repeated hypoxic challenges possibly may potentiate the vasoconstrictor response in small lung regions, it appears to be of no use in the initiation of one-lung ventilation in humans prior to thoracic surgery.

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