

Hypoxia-induced Pulmonary Vasoconstriction in the Human Lung

The Effect of Isoflurane Anesthesia

Å. Jolin Carlsson, M.D.,* L. Bindsvlev, M.D.,† G. Hedenstierna, M.D.‡

The influence of isoflurane on hypoxic pulmonary vasoconstriction (HPV) was studied in eight subjects prior to elective surgery. The lungs were ventilated separately with a double-lumen endobronchial catheter. After oxygen ventilation of both lungs for 30 min during intravenous barbiturate anesthesia, the test lung was rendered hypoxic by ventilation with 8% O₂ in nitrogen. The control lung was ventilated continuously with 100% O₂. Isoflurane was added to the inspired gas, so that end-tidal concentrations of 1% and 1.5% were obtained. Cardiac output (\dot{Q}_T) 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 hypoxic challenge during intravenous anesthesia resulted in a reduction in the fractional perfusion of the test lung from 54% to 41% of \dot{Q}_T . Mean pulmonary arterial pressure increased by 46%, and pulmonary vascular resistance (PVR) of the test lung more than doubled. Arterial oxygen tension fell from 375 mmHg (50 kPa) to 101 mmHg (13.5 kPa). Adding isoflurane to the inhalation gas, first at a concentration of 1%, then 1.5%, caused no further significant change in the distribution of pulmonary blood flow, although six of the eight subjects showed a small increase in test lung blood flow at isoflurane 1.5%. There was no change in PVR or in any other circulatory variable. Arterial blood gases remained essentially unaltered. When the hypoxic challenge was discontinued, all variables returned to control values. It is possible that higher isoflurane concentrations would have caused a clear change in the blood flow distribution, but, at clinical concentrations, the effect of HPV in the human is all but immeasurable. (Key words: Anesthetic techniques: double lumen tube intubation. Anesthetics, volatile: isoflurane. Lung: blood flow; shunting; hypoxic pulmonary vasoconstriction.)

THERE HAVE BEEN several reports describing a local pulmonary vasoconstrictor response to hypoxia in conscious man with the effect of redistributing pulmonary blood flow from poorly to more adequately ventilated regions.¹⁻³ Investigations on animals have shown that, during intra-

venous anesthesia, efficient hypoxic pulmonary vasoconstriction (HPV) occurs.⁴⁻⁶ However, with inhalation anesthesia, the majority of studies indicate that HPV is inhibited or reduced.^{7,8} This suggests that inhalation anesthetics are not to be recommended in patients with pre-existing lung disease and in those who are to undergo lung surgery, since inhibition of HPV would predispose the patient to greater hypoxemia than might otherwise be the case.

However, there are also reports that HPV is not reduced, but remains unaltered during inhalation anesthesia.^{9,10} The divergent results might be due to the extent to which these agents inhibit HPV and/or to the influence of other hemodynamic changes concomitant with the anesthetic administration.

Recent reports studying the effect of isoflurane on HPV are similarly conflicting, ranging from no effect on HPV in dogs[§] and no decrease on arterial oxygenation during one-lung ventilation in patients undergoing thoracotomy¹¹ to inhibition of HPV in a dose-dependent manner in both dogs¹² and rats.¹³

In view of the increasing clinical use and value of isoflurane, the present study was undertaken to determine whether isoflurane influences the blood redistribution in the human lung during HPV under conditions of clinical anesthesia.

Patients and Methods

Eight subjects, five men and three women, were studied prior to elective surgery. Their mean age was 56 years (range 45-64), mean height 170 cm (range 158-178), and mean weight 71 kg (52-82). None of them had a history of chest disease. Three were moderate smokers (5-20 cigarettes/day). Clinical examination, chest x-ray, and ECG showed no abnormalities. The study was described in detail to all subjects, and their consent was obtained. The Ethics Committee of the Karolinska Institute had approved the study. There were no complications attributable to the investigation.

§ Saidman LJ, Trousdale FR: Isoflurane does not inhibit hypoxic pulmonary vasoconstriction. (Abstract) ANESTHESIOLOGY 59:A 472, 1982.

* Research Fellow, Department of Anesthesia, Karolinska Hospital.

† Associate Professor, Department of Anesthesia, Karolinska Hospital.

‡ Associate Professor, Department of Clinical Physiology, Huddinge Hospital.

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Address reprint requests to Dr. Hedenstierna: Department of Clinical Physiology, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

ANESTHESIA

Premedication consisted of morphine (0.14 mg/kg) and scopolamine (0.06 mg/kg) administered intramuscularly about 1 h before induction of anesthesia. To avoid depression of the HPV-response in the control situation, anesthesia was induced with thiopental (250–300 mg).⁴ Muscle relaxation was achieved with pancuronium bromide (0.1–0.2 mg/kg). Fentanyl (0.1–0.2 mg) was given intravenously for pain relief. Repeated doses of thiopental (50 mg/20 min) were given to maintain anesthesia during control measurement until isoflurane was commenced. Isoflurane was administered to both lungs. The isoflurane vaporizers, one for each lung, were adjusted so that end-tidal concentrations of first 1% and then 1.5% were obtained. The isoflurane concentration was measured by an electrochemical gas analyzer (EMMA[®], Gambro-Engström).

VENTILATION

After induction of anesthesia and muscle relaxation, intubation was performed with a double-lumen left bronchial catheter (Portex Twin Lumen Tube[®], size 5.5–6). 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 positive end-expiratory pressure of 10 cm H₂O (0.98 kPa); any leak to the opposite lung was detected by a balloon attached to the proximal end of its tube connection. The proximal ends of the double-lumen tube were connected to a specially designed Engström ventilator with two separate bag-in-box circuits and pressure-operated non-rebreathing valves. Compressed air was delivered to both bag-in-box chambers by the same piston. In this way, the respiratory frequency remained equal and essentially synchronous in both circuits, with an inspiration: expiration ratio of 1:2 and a frequency of 12 breaths/min. Tidal volume was evenly distributed between the two lungs. Each circuit was fed from an independent flow meter dispensing 100% O₂, or a gas mixture of 92% nitrogen and 8% O₂ 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 non-rebreathing valve and sampled in a bag. The volume was measured with a spirometer (Gould, Godart Expirograph[®]).

The experimental set-up is shown in figure 1. All subjects were studied while they were in the supine position, and ventilated with equally large tidal volumes to both lungs to obtain an arterial PCO₂ of about 35–40 mmHg. All volumes were converted to BTPS.

Hemodynamic. A triple-lumen, thermistor-tipped balloon catheter (Swan-Ganz[®] No 7F) was introduced percutaneously by a sleeve technique into a medial cubital

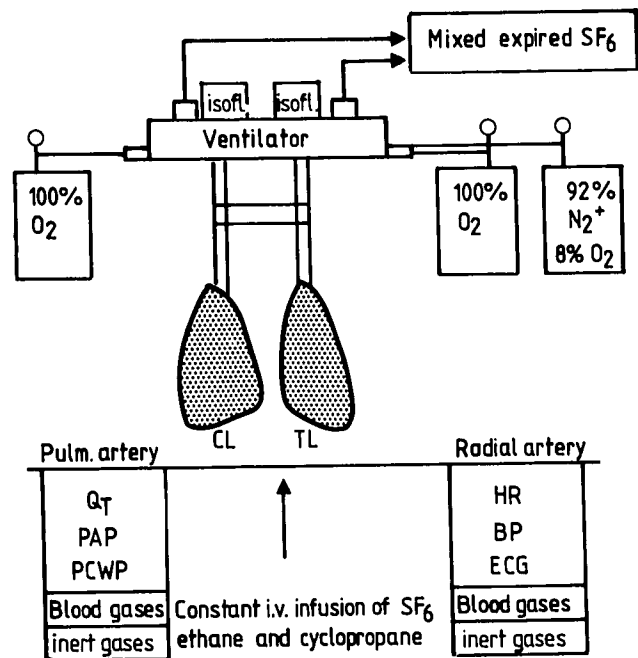


FIG. 1. A graphic display of the experimental procedure. The lungs were ventilated with either 100% O₂ (both lungs; control situation) or 100% O₂ (control lung, CL) and 92% nitrogen + 8% O₂ (test lung, TL). Two isoflurane vaporizers were used for administering the anesthetic (top figure). An infusion of SF₆, ethane and cyclopropane continued throughout the experiment, the gas concentrations in mixed venous and systemic arterial blood together with the expired SF₆ concentration from each lung being determined by gas chromatography. Measurements of vascular pressures and blood gases were also made. QT = cardiac output; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; HR = heart rate; BP = blood pressure.

vein, and was advanced to the pulmonary artery under continuous monitoring of ECG and pressure. Cardiac output was determined by thermodilution. The thermal indicator was 10 ml of 5.5% glucose at 0–2° C, injected into the right atrium. Cardiac output was derived from the mean of three consecutive measurements (Cardiac Output Computer 9520 A[®], Edwards Lab.). The radial artery was cannulated for pressure recordings and blood sampling, and a central venous catheter was introduced percutaneously for infusion of inert gas. All pressures were recorded with pressure transducers (No 840, Microelectronics), the signal being fed into an amplifier (Hellige). The transducers were calibrated against a saline manometer.

Regional perfusion and shunt. To assess the distribution of blood flow to the two lungs and to calculate the shunt, a mixture of three poorly soluble gases (SF₆, 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 inert gas concentrations were measured in a gas chromatograph (Sigma 3[®], Perkin-

TABLE 1. Central Hemodynamics During Hypoxic Pulmonary Vasoconstriction and Isoflurane Anesthesia (Mean ± SE)

| | Heart rate (Beats/Min) | Both Lungs | Lung Blood Flow (l/Min) Control Lung | Test Lung | Fractional Perfusion (%) | | Mean Arterial Pressure (mmHg) | Mean Pulmonary Arterial Pressure (mmHg) | Pulmonary Wedge Pressure (mmHg) | Pulmonary Vascular Resistance (mmHg × min × l ⁻¹) | |
|----------------------|---------------------------|-------------|--|--------------|--------------------------|-------------|-------------------------------------|---|--|--|--------------|
| | | | | | Control Lung | Test Lung | | | | Control lung | Test lung |
| Control | 71.4 ± 4.3 | 4.52 ± 0.44 | 2.06 ± 0.21§ | 2.46 ± 0.24 | 45.5 ± 1.5§ | 54.5 ± 1.5 | 74.3 ± 4.5 | 9.1 ± 1.4 | 5.3 ± 0.8 | 2.18 ± 0.75 | 1.64 ± 0.38 |
| Hypoxia | 69.5 ± 3.6 | 4.47 ± 0.38 | 2.61 ± 0.23*§ | 1.86 ± 0.25* | 59.0 ± 3.3*§ | 41.0 ± 3.3* | 72.0 ± 4.5 | 12.7 ± 2.8† | 6.8 ± 1.5† | 2.70 ± 1.20† | 3.68 ± 1.28* |
| + isoflurane 1% | 69.3 ± 3.0 | 4.46 ± 0.28 | 2.62 ± 0.22*§ | 1.84 ± 0.20* | 59.2 ± 3.8*§ | 40.8 ± 3.8* | 65.3 ± 3.75† | 13.3 ± 2.6† | 6.8 ± 1.6† | 2.93 ± 1.17† | 4.26 ± 1.54* |
| Hypoxia | 71.1 ± 3.3 | 4.25 ± 0.28 | 2.41 ± 0.15*§ | 1.84 ± 0.17* | 57.0 ± 1.9*§ | 43.0 ± 1.9* | 61.5 ± 4.5† | 13.8 ± 2.6† | 7.5 ± 0.8† | 2.89 ± 1.18† | 3.90 ± 1.33* |
| + isoflurane 1.5% | 61.6 ± 6.2 | 3.69 ± 0.28 | 1.52 ± 0.22 | 2.17 ± 0.22 | 41.0 ± 3.7 | 59.0 ± 3.7 | 72.8 ± 3.75 | 11.1 ± 2.1 | 7.5 ± 1.5 | 2.33 ± 1.08 | 2.03 ± 0.30 |
| Control (n = 6) | | | | | | | | | | | |

Two/three way analysis of variance with orthogonal comparisons:

* Significant effect of hypoxia, P < 0.001

† Significant effect of hypoxia, P < 0.05

‡ Significant effect of isoflurane, P < 0.05

§ Significant difference between control and test lung, P < 0.001

Elmer). The SF₆ concentration ratio between the two lungs was assumed to reflect the perfusion ratio. 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 (arterial/mixed venous concentration ratio) of all three infused gases. Using an extrapolation method, the shunt was calculated as perfusion of lung regions with a ventilation-perfusion ratio of less than 0.005. The method is described in further detail elsewhere.^{14,15}

Blood gas analysis. Arterial and mixed venous oxygen and carbon-dioxide tensions, and pH, were measured by standard methods (equipment: BMS-3®, Radiometer). Oxygen saturation of the blood was measured by spectrophotometry (OSM-2®, Radiometer).

STATISTICS

Data given in the text, tables, and figures are presented as mean ± SEM. Two- and three-way analyses of variance were used together with orthogonal comparisons between 1) initial control situation and hypoxia, 2) hypoxic challenge without and with isoflurane, 3) isoflurane 1% and 1.5%, and 4) test and control lungs (blood flow only).

EXPERIMENTAL PROCEDURE

In the control situation, both lungs were ventilated with 100 O₂ for 30 min to achieve steady-state conditions. At the end of this period, cardiac output was determined in triplicate, blood samples were drawn for blood gas, saturation, and inert gas measurements from both arterial and mixed venous blood, and expired gas was collected for volume measurement and determination of the SF₆ concentration. After the steady-state period, the test lung was rendered hypoxic by ventilation with 8% O₂ in nitrogen, while the control lung was ventilated continuously with oxygen. Measurements and recordings were repeated 15 min after the start of low oxygen breathing, after which inhalation of isoflurane was commenced. Isoflurane was given at an end-tidal concentration of 1% in the first 15 min, followed by a 15-min period at 1.5%. The study was completed with a 15-min period of 100% O₂ administered to both lungs without isoflurane inhalation, the anesthesia being maintained by a dose of thiopental (50–100 mg).

Results

EFFECTS ON PULMONARY BLOOD FLOW

Hemodynamic values are shown in Table 1 and Figure 2. During oxygen breathing, 55% of cardiac output was distributed to the right (test) lung. Ventilation of the test

lung with 8% O₂ in nitrogen resulted in a 25% reduction of the fractional perfusion to 41% of cardiac output in 15 min (*P* < 0.01). Mean pulmonary arterial pressure increased by 45% (*P* < 0.01). The pulmonary capillary wedge pressure and the vascular resistance of the control lung increased slightly (*P* < 0.05), whereas the vascular resistance of the test lung more than doubled (*P* < 0.001). The mean systemic blood pressure remained essentially unchanged.

After isoflurane inhalation at 1%, no change in fractional test lung blood flow was noted. When the end-tidal isoflurane concentration was increased to 1.5%, test lung blood flow increased in six subjects and decreased in two subjects; the mean blood flow being 43% of cardiac output. This mean increase was not statistically significant. There was no significant change in total cardiac output. The mean pulmonary arterial pressure remained unchanged by the addition of isoflurane, as did the pulmonary capillary wedge pressure and the pulmonary vascular resistance of either lung. The mean systemic blood pressure dropped by 17% during isoflurane anesthesia. On restoration of the control situation (100% O₂ to both lungs and no isoflurane, n:6), the circulatory variables returned towards the same level as during the initial control period.

EFFECTS ON GAS EXCHANGE

During their initial control period with 100% O₂, PaO₂ averaged 377 mmHg, P \bar{v} O₂ 51 mmHg, and PaCO₂ 41 mmHg. The shunt calculated from the inert gas retention was as high as 20% of cardiac output (Table 2). The hypoxic challenge caused a reduction in PaO₂ to 101 mmHg (*P* < 0.001) and P \bar{v} O₂ to 39 mmHg (*P* < 0.001), with no change in PaCO₂. The inert gas shunt remained unaltered (the inert gases being eliminated by nitrogen-ventilated, as well as by oxygen-ventilated, areas). The addition of isoflurane during unilateral hypoxic breathing caused no further decrease in PaO₂ or P \bar{v} O₂, and PaCO₂ was unchanged. The inert gas shunt remained essentially unaltered.

Upon restoration of the control situation (no hypoxia, no isoflurane), PaO₂ and P \bar{v} O₂ returned towards the initial control values, and PaCO₂ and the inert gas shunt remained unchanged.

Discussion

HPV AND HYPOXIC STIMULI

We have used a hypoxic gas containing 8% O₂ in nitrogen, resulting in an inspired PO₂ of approximately 56 mmHg to the test lung, while the other lung received 100% O₂. This moderate hypoxic stimulus was used for safety reasons, in order not to create severe general hy-

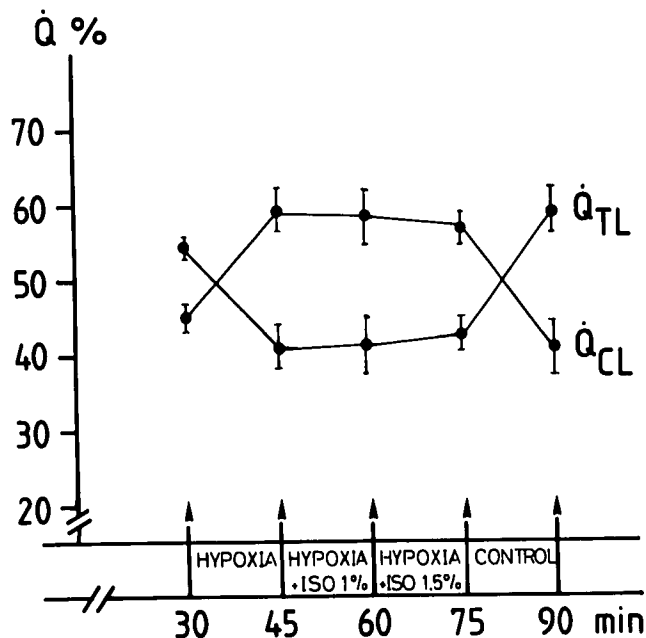


FIG. 2. The perfusion of the test lung (Q_{TL}) and the control lung (Q_{CL}) is the control periods and during hypoxia without and with isoflurane. Note the redistribution of pulmonary blood flow during hypoxia, indicating functioning hypoxic vasoconstriction (HPV) before and during isoflurane anesthesia.

poxemia. Despite this precaution, a PaO₂ of 59 mmHg was noted in one subject. The use of a moderate hypoxic stimulus will limit the magnitude of the HPV-response. Thus, the HPV-response, in our study, can be expected to approximate 50% of a maximal HPV-response.¹⁶ Since a single lung is capable of a 50% blood flow reduction,¹⁷ it can be expected that 8% O₂ to a lung would decrease blood flow to that lung by 25%. This is what we observed with our SF₆ elimination technique, fractional test lung blood flow being reduced from 54.5% to 41%.

TABLE 2. Arterial Blood Gases (PaO₂, PaCO₂), Mixed Venous Oxygen Tension (P \bar{v} O₂), and Inert Gas Shunt During Hypoxic Pulmonary Vasoconstriction and Isoflurane Anesthesia (X ± SE).

| | PaO ₂ (mmHg) | PaCO ₂ (mmHg) | P \bar{v} O ₂ (mmHg) | Inert Gas Shunt (% of Cardiac Output) |
|---------------------------|-------------------------|--------------------------|-----------------------------------|---------------------------------------|
| Control | 377 ± 44 | 41 ± 1.5 | 51 ± 4.5 | 19.9 ± 4.2 |
| Hypoxia | 101 ± 18* | 41 ± 2.3 | 39 ± 3.2* | 19.1 ± 4.4 |
| Hypoxia + isoflurane 1% | 103 ± 19* | 41 ± 2.3 | 40 ± 3.3* | 19.0 ± 3.8 |
| Hypoxia + isoflurane 1.5% | 102 ± 21* | 39 ± 1.5 | 39 ± 2.4* | 20.3 ± 4.7 |
| Control | 398 ± 53 | 39 ± 2.3 | 45 ± 1.5 | 17.8 ± 6.3 |

Two-way analysis of variance with orthogonal comparisons:
* Significant effect of hypoxia, *P* < 0.001

CONCENTRATION OF ISOFLURANE

Addition of isoflurane 1% and 1.5% end-tidal concentrations resulted in no statistically significant change in test lung blood flow. However, 6 of 8 patients increased their test lung blood flow at an end-tidal isoflurane concentration of 1.5%. The mean increase was not larger than 2–3% of cardiac output, but this small increase corresponds to an attenuation of the HPV-response by as much as 21%. Although the discussion is hypothetical and based on borderline changes, it nonetheless suggests a slight influence of isoflurane on HPV, which might have been better demonstrated had a more extreme hypoxic challenge been studied. Inhibition of the nondependent lung HPV-response by approximately 20% at 1 MAC isoflurane anesthesia was also demonstrated recently in dogs by Domino *et al.*,¹² using CO₂ elimination for measuring pulmonary blood flow. At 2 MAC, the inhibition seemed to be even larger. Attempts were made to study our patients at higher isoflurane concentrations, but the tests had to be discontinued because unacceptable hypotension ensued. This again underscores the difficulty inherent in human studies, requiring moderate hypoxic stimuli and moderate anesthetic concentrations.

The fact that contradictory results have been obtained in some animal studies on the blood flow distribution during hypoxia and isoflurane anesthesia may be a consequence of species differences and differences in anesthetic doses. Saidman (see above) found that the degree of hypoxic vasoconstriction in the dog lung remained the same, whether isoflurane was administered at an end-tidal concentration of 1.3% or of 2.6%. On the other hand, Mathers *et al.*⁹ reported that isoflurane inhibited HPV in dogs in a dose-dependent manner, both when administered locally to a hypoxic test lobe, and when administered to the whole lung. Marshall *et al.*¹³ also found a dose-dependent inhibition of HPV in isolated rat lung.

Finally, reduction of cardiac output and pulmonary arterial pressures can facilitate HPV by diminished mechanical interference, thus reducing shunt.¹⁸ Moreover, a change in P \bar{v} O₂, by either altered cardiac output or metabolic demand, may change the magnitude of the HPV-response.¹⁹ There are thus several variables which, if they change during the experiments, may interfere with the HPV-response. In the present study, cardiac output did not change to any significant degree on hypoxic stimulus or when isoflurane was added to the inspirate, nor did P \bar{v} O₂ change during the study.

The results imply that isoflurane might be indicated for anesthesia in the presence of lung disease or during one-lung ventilation for lung resection, since arterial oxygenation might be better preserved than would be the case with an anesthetic that more effectively inhibits HPV.

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