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# EFFECTS OF ANAESTHETICS ON THE PULMONARY CIRCULATION

J. B. EISENKRAFT

It is well established that general anaesthesia may impair gas exchange in the lung and that arterial hypoxaemia may occur as a result. Nunn [46] investigated the factors which influence the arterial oxygen tension ($Pa_{O_2}$) during halothane anaesthesia (1.0–1.5%) during spontaneous ventilation. He reported a calculated shunt of 14% of total pulmonary blood flow, as compared with a calculated shunt of only 1% in normal conscious supine subjects in whom the same measurement techniques had been used [47]. Nunn suggested that the large shunt found during anaesthesia was probably caused by increased perfusion of totally unventilated parts of the lung, and that maldistribution of ventilation:perfusion ratios caused that part of the total alveolar–arterial $Po_2$ difference which could not be accounted for by shunt. Thus regions of low ventilation:perfusion ratio, which have little effect on elimination of carbon dioxide, cause a marked impairment of oxygenation of the arterial blood [46].

Marshall and colleagues [34] studied pulmonary venous admixture before, during and after halothane in oxygen anaesthesia in 10 spontaneously breathing patients. The mean inspired tension of halothane was 0.8–1.1 kPa (approximately 0.9%). The percentage pulmonary venous admixture ($\dot{Q}s/\dot{Q}t$%) was 4.4% before anaesthesia, increasing to 12.1% and 14.8% at 40 min and 3 h of anaesthesia respectively, and 6.5% and 5.2% at 40 min and at 3 h after anaesthesia. These authors [34] concurred essentially with Nunn [46] and also concluded that, in their study, the postoperative hypoxaemia observed was the result, not of respiratory depression, but of residual effects of increased venous admixture which had developed during the anaesthetic.

All patients undergoing general anaesthesia show changes in lung mechanics, such as decreases in compliance and functional residual capacity, as well as changes in the distribution of ventilation [49]. Although these changes may contribute to the observed impairment of oxygenation, they do not provide a complete explanation, because similar changes in mechanics occur with both inhaled and i.v. anaesthetic drugs, yet inefficient oxygen exchange has been established only with the inhaled agents [35]. This suggests that inhaled agents exert a specific effect which tends to produce hypoxaemia. Interest has therefore been directed to the regulation of the pulmonary circulation during anaesthesia, and in particular to hypoxic pulmonary vasoconstriction (HPV). This is a homeostatic mechanism by which pulmonary blood flow is diverted away from hypoxic areas, thereby optimizing gas exchange.

## NORMAL MECHANISM OF HYPOXIC PULMONARY VASOCONSTRICTION

Hypoxic pulmonary vasoconstriction was described first in 1942 by Von Euler and Liljestrand [68], investigating pulmonary haemodynamic responses in the cat to changes in the inspired gas composition. Cats were anaesthetized with i.v. chloralose; systemic arterial pressure was measured from one carotid artery, while pulmonary arterial pressure was recorded via a cannula inserted directly into the pulmonary artery. The cats were studied during both spontaneous and positive pressure breathing. It was found that when they breathed an $F_{I_{O_2}}$ of 0.105 (10.5% oxygen in nitrogen), the pulmonary arterial press-

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ure invariably increased. Neither vagotomy nor stellate ganglionectomy influenced this response, which was thought to be a direct effect of hypoxia on the pulmonary vasculature. At $FI_{O_2}$ 1.0, pulmonary arterial pressure decreased. The authors concluded that the increase in pulmonary arterial pressure during hypoxia was the result of a direct effect on lung vessels, "thereby increasing the blood flow to better aerated lung areas which leads to improved conditions for the utilization of the alveolar air" [68].

While in the classic study of Von Euler and Liljestrand both lungs were rendered hypoxic, others have studied the effect of the size of the lung segment made hypoxic and the severity of the hypoxic stimulus on perfusion pressure and flow diversion. In one such study, six mongrel dogs were anaesthetized with pentobarbitone and electromagnetic flow probes were placed around the main, left and left-lower lobe pulmonary arteries [38]. Pressures were measured in the main pulmonary artery, left atrium and abdominal aorta. Following insertion of a Robertshaw left-sided bronchial tube, and a left lower lobe bronchotomy whereby a separate tube was placed to permit independent ventilation of the left lower lobe, ventilation of different sized segments of lung could be achieved [38].

The effects of changing $FI_{O_2}$ were observed in test lung segments of seven different sizes which corresponded to left lower lobe, upper lobe lingula, left lung, right lung, right lung plus left lower lobe, right lung plus left upper lobe lingula, and whole lung. In each experiment, the rest of the lung was ventilated with an $FI_{O_2}$ of 1.0, while HPV in the test segment was demonstrated by both increased perfusion pressure (mean pulmonary arterial pressure minus mean left atrial pressure) and diversion of blood flow away from the hypoxic test segment. It was found that changes in pulmonary perfusion pressure increased with the size of the hypoxic lung segment from 0 (smallest hypoxic segment) to approximately 2.2 times baseline when the whole lung was rendered hypoxic. The diversion of flow, as a percentage of the blood flow to the test segment under normoxic conditions, decreased as the size of the hypoxic segment increased. Flow diversion increased linearly as $Pa_{O_2}$ decreased in the range 17.3–3.7 kPa. In terms of both flow diversion and changes in perfusion pressure, the HPV response was predictable, continuous, and maximal at a predicted $Pa_{O_2}$ of 4.0 kPa [38]. Thus the HPV response caused an increase in perfusion pressure and blood flow diversion.

*Site for stimulation of HPV and its sensitivity*

Characteristics of the stimulus site for HPV have been studied *in vitro* using an isolated rat lung preparation [41]. The lungs were perfused and ventilated with separate control of $PA_{O_2}$ and $P\bar{v}_{O_2}$. The lungs were perfused with blood from donor rats and, with perfusion flow kept constant, HPV was measured as a change in perfusion pressure. Both the perfusate and the ventilating gas concentrations were varied between $FI_{O_2}$ values of 0.00 and 0.21 while the HPV responses were measured. In this study HPV was found to be a function of both $PA_{O_2}$ and $P\bar{v}_{O_2}$ and the relationship could be expressed as if the two combined to give a single oxygen tension ($Ps_{O_2}$) at the HPV stimulus site [41]. The relationship could be expressed mathematically as:

$$Ps_{O_2} = [(PA_{O_2})^{0.62} \times (P\bar{v}_{O_2})^{0.38}]$$

The $Ps_{O_2}$–HPV response curve was sigmoid, with a 50% response when both $PA_{O_2}$ and $P\bar{v}_{O_2}$ were 4.04 kPa, at which point $Ps_{O_2}$ was also 4.04 kPa. It was concluded also that $PA_{O_2}$ had a greater effect than $P\bar{v}_{O_2}$ as a result of oxygen exchange between gas in the alveoli and blood in small pulmonary arteries [41].

*Atelectasis and HPV*

Under normal circumstances, when a lung is made atelectatic, blood flow to that lung is decreased. The relative contribution of passive mechanical forces *vs* HPV as mechanisms for reducing blood flow in atelectatic lung were studied in a dog model [1]. Selective atelectasis of the left lower lobe caused lobar blood flow (measured using an electromagnetic flow probe) to decrease 59% from control. Re-expansion and ventilation of the left lower lobe with a mixture of 95% nitrogen in carbon dioxide, which would terminate any mechanical effect, resulted in no significant increase in lobar flow. Ventilation of the lobe with 100% oxygen, which would terminate any stimulation of HPV, increased lobar blood flow to control values. It was therefore concluded that the major mechanism whereby blood flow to atelectatic lung is decreased is HPV [1]. A similar conclusion was reached by Miller and colleagues [43], who studied an anaesthetized, open-chest dog model in which the whole left lung was made atelectatic. In this study left lung

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blood flow during hyperoxic conditions was calculated by multiplying cardiac output by the fractional carbon dioxide excretion from the left lung. Left lung blood flow during hypoxic ventilation or atelectasis was calculated from blood oxygen contents using a blood mixing equation [43].

In those regions of the lung that are atelectatic, the stimulus for HPV is the $P\bar{v}_{O_2}$. In a study using intact dogs, Domino and colleagues [26] found that the blood flow reduction observed in atelectatic lung was a function of $P\bar{v}_{O_2}$. Approximately 50% of blood flow was diverted away from atelectatic lung when $P\bar{v}_{O_2}$ was low (3.2 kPa) or normal (6.1 kPa). When $P\bar{v}_{O_2}$ exceeded 13.3 kPa, blood flow was not diverted away from atelectatic lung and lung blood flow was nearly that expected under normoxic conditions. The authors also concluded that the contribution of mechanical factors in reducing blood flow to atelectatic lung in the open chest situation was small [26].

The exact mechanism of the HPV response remains to be determined, but it is believed to be accounted for by each smooth muscle cell in the pulmonary arterial wall responding to the oxygen tension in its vicinity [41]. It has been observed that the smooth muscle in the pulmonary arterial wall depolarizes and develops spontaneous electrical activity in response to hypoxia and other contractile stimuli [28, 31]. Increased calcium channel activity may be important in the mechanism of HPV because BAY K8644, a $Ca^{2+}$-channel potentiator, enhances HPV, while nifedipine diminishes it [66]. Other studies have been directed towards determining whether HPV occurs mainly in alveolar or extra-alveolar vessels. The results suggest that the site of HPV varies among species, but is predominantly observed in precapillary arteries [16].

*Effect of HPV on arterial oxygenation*

Hypoxic pulmonary vasoconstriction can have a significant effect on $Pa_{O_2}$. If flow diversion occurs when part of a lung is made hypoxic, $Pa_{O_2}$ should be greater than if there were no HPV. The relationship between $Pa_{O_2}$ and the amount of lung

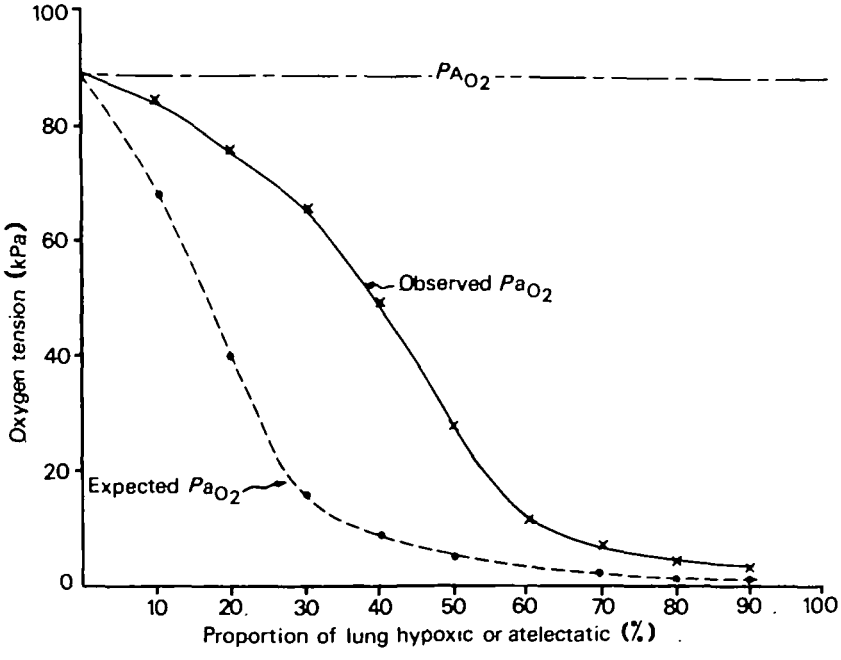


FIG. 1. Role of hypoxic pulmonary vasoconstriction (HPV) in preserving arterial oxygen tension ($Pa_{O_2}$) in dogs, assuming $Pa_{CO_2}$ = 5.33 kPa, $(Ca_{O_2} - C\bar{v}_{O_2})$ = 5 ml $dl^{-1}$ and haemoglobin = 14 g $dl^{-1}$. Lung is ventilated with 100% oxygen while increasing proportions of lung are subjected to hypoxia or atelectasis. In the absence of HPV the expected $Pa_{O_2}$ would follow the dashed line, whereas in the presence of an active HPV response the observed $Pa_{O_2}$ is maintained closer to the solid line. (Adapted from [38] by permission of the American Physiological Society and the author.)

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tissue made hypoxic (fig. 1) shows that, when little of the lung is hypoxic, HPV has little effect on $Pa_{O_2}$ because in this situation the shunt is small [2, 36, 37]. If most of the lung is hypoxic, effective flow diversion is not possible and it becomes irrelevant, in terms of $Pa_{O_2}$, whether the hypoxic lung region has HPV or not. In the latter case active HPV would, however, increase pulmonary vascular resistance and thereby increase the work of an already hypoxic heart [2].

When the amount of lung tissue made hypoxic is intermediate, there may be a large difference between the $Pa_{O_2}$ expected with normal HPV compared with that in its absence. Such a situation may exist during one-lung anaesthesia for thoracic surgery, when an active HPV response can increase $Pa_{O_2}$ from potentially dangerously low arrhythmogenic values to higher and safer ones. Thus, during studies of one-lung ventilation, shunt through the non-ventilated lung is usually about 25% of the cardiac output, in contrast to the 40–50% which might be expected if blood flow to the collapsed lung continued as if to a ventilated lung [2].

This brief overview of normal HPV has demonstrated the value of this homeostatic mechanism and how impairment of it may result in arterial hypoxaemia.

## EFFECTS OF ANAESTHETICS ON HPV

The effects of anaesthetic agents on HPV were first described by Buckley and colleagues [17]. Using a dog model they found that nitrous oxide increased the HPV response, but that 0.5% halothane, which had no significant effect on cardiac output, abolished HPV [17]. There have been many subsequent studies of the effects of anaesthetics on HPV. All manner of ingenious preparations, methods and species have been used and the results have frequently been inconsistent. Benumof [2] has classified the preparations used for these studies as *in vitro*, *in vivo* non-intact, *in vivo* intact, and human studies. This useful classification will be followed here.

### *Inhaled Anaesthetic Agents*

#### In vitro *preparations*

The first extensive studies of the effects of inhaled agents on HPV were by Sykes and colleagues [59, 63]. They studied isolated cat and dog lung preparations perfused at constant flow using a special perfusion circuit and ventilated with either normoxic or hypoxic gas mixtures. They found that the pressor response to hypoxaemia could be elicited for up to 5 h and that it was inhibited by halothane, trichloroethylene and diethyl ether added to the inhaled gas mixture.

Similar results were found by Bjertnaes [10], who perfused isolated rat lungs with blood at a constant volume pulsatile inflow and used change in inflow pressure as a measure of HPV. In this study, the lungs were ventilated with normoxic and hypoxic gas mixtures, with and without potent inhaled agents. The results showed a dose-related reversible inhibition of HPV with diethyl ether, halothane and methoxyflurane [10].

Marshall, Lindgren and Marshall [40] used a similar isolated rat lung model to study the effects of halothane, enflurane and isoflurane on HPV. All three agents were found to depress HPV in a dose-related manner. The concentrations in MAC units (adjusted for rats) at which a 50% inhibition of HPV occurred (the $ED_{50}$) were 0.47, 0.60 and 0.56 for halothane, isoflurane and enflurane, respectively, and neither the ED values nor the slopes of the dose–response curves were significantly different among the agents. It was therefore concluded that they inhibit HPV with essentially identical potencies.

An isolated rat lung preparation has also been used to study the effects of potent inhaled agents on the vascular resistance in atelectatic lungs [15]. Two pairs of isolated rat lungs were perfused in series at constant flow. One preparation was made atelectatic by airway occlusion, while ventilation of the other preparation using a hypoxic mixture (2% oxygen) resulted in an increase in vascular resistance in both preparations. Administration of halothane, enflurane or ether to the atelectatic lung via the ventilated preparation caused a dose-dependent reversible reduction of vascular resistance. The same reduction in resistance occurred when the perfusate $Po_2$ was increased. Thus halothane, enflurane and ether reduced the vascular resistance in the isolated perfused hypoxic atelectatic lung [15].

In all of the above studies [10, 15, 40, 59, 63], HPV was measured as a change in perfusion pressure during constant flow, and hypoxia was induced and the potent agent introduced by ventilation of the isolated perfused lungs.

#### In vivo *non-intact preparations*

The effects of inhaled anaesthetic agents (isoflurane, fluroxene, halothane, nitrous oxide) were

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studied in a dog model in which the left lower lobe had been isolated for separate ventilation [5]. Electromagnetic flow probes were placed around the main and left lower lobe pulmonary arteries, and the pulmonary arterial and left atrial pressures were measured directly. The limitations of flow meters have been discussed elsewhere [53]; in particular, to have good contact between probe and vessel, the probe must constrict the vessel, thereby decreasing its conductance and potentially altering both flow distribution and perfusion pressure of the lobe under study. Changes in left lower lobe blood flow in relation to total cardiac output were studied in response to ventilation of the lobe with normoxic and hypoxic (nitrogen) gas mixtures, with and without the addition of potent inhaled anaesthetic agents [5]. Selective ventilation of the left lower lobe with nitrogen alone (i.e. hypoxia) resulted in a 53% reduction in blood flow to the lobe. Responses to lobar hypoxia were re-measured during the administration of potent inhaled agents at 1 and 2 MAC concentrations, both to the left lower lobe and to the rest of the lung. Isoflurane and fluroxene inhibited lobar HPV by 50% at 2 MAC. Nitrous oxide (0.3 MAC) caused a slight but significant inhibition, while halothane and enflurane caused slight but non-significant changes in lobar HPV. Administration of anaesthetics to the whole lung produced almost identical effects on HPV as when administration was confined to the test lobe alone [42]. It was concluded that nitrous oxide, isoflurane and fluroxene locally inhibit HPV and thereby increase total venous admixture, while halothane and enflurane do not have this effect [5]. Indeed, halothane slightly enhanced HPV in that study. Interestingly, in a subsequent report from the same laboratory and using the same dog model, it was found that HPV was unaffected during both light and deep isoflurane anaesthesia [52]. The authors were unable to explain why their results were at variance with those reported previously [5, 42].

The above results also differed from those obtained using *in vitro* preparations. Possible sources of difference may be related to the methods used to measure HPV. In the *in vitro* studies [10, 15, 40, 59, 63], lungs were perfused at constant flow and the HPV response measured by changes in pressure. In the *in vivo* non-intact models, electromagnetic flowmeters were used to assess changes in blood flow to the hypoxic lobe or lung. Other differences in methods used in the *in vitro* and *in vivo* non-intact preparations include presence (or absence) of perfusion pulsations, perfusion fluid composition, baroreceptor reflexes, absence of bronchial blood flow (which abolishes all central and autonomic nervous activity in the lung), chemical and humoral influences, lymph flow influences and the use of different species [2].

### In vivo *intact preparations*

Sykes and his co-workers used an intact dog model to study the effects of nitrous oxide and halothane on HPV [60, 62]. In this model, each lung was ventilated separately but synchronously, one with 100% oxygen and the other with 100% oxygen or a test gas mixture. The HPV response was assessed by measuring the redistribution of blood flow between the two lungs. This was achieved using an infusion of xenon-133 into the inferior vena cava and measuring the mixed expired concentration of xenon emanating from each lung. In these studies the ratio of blood flows between the two lungs was deemed to be equal to the ratio of xenon counts between the two lungs. In one study [62], one lung was ventilated with nitrogen or nitrous oxide while the other was ventilated with 100% oxygen. The results showed that the vasoconstrictor response to nitrous oxide was less than that to nitrogen, and that this difference occurred in the absence of changes in pulmonary arterial pressure, pulmonary capillary wedge pressure or cardiac output. Interestingly, in this study there were no significant differences between $Pa_{O_2}$ values during unilateral hypoxia with nitrogen and those with nitrous oxide, even though blood flow to the hypoxic lung was greater during ventilation with the latter. One possible explanation for this observation was that nitrous oxide caused a decrease in $\dot{V}/\dot{Q}$ ratio in the hypoxic lung, causing less oxygen to be extracted from mixed venous blood during passage through the lung and tending to offset the effects of increased shunt on $Pa_{O_2}$ [62]. Using a similar model, Sykes and colleagues [60] found that there was no significant alteration of the HPV response by halothane in 0.5–1.5% inspired concentrations.

Naeije and colleagues [45] compared halothane, enflurane and isoflurane in intact dogs ventilated (both lungs) in mildly hyperoxic conditions and challenged with short periods (10 min) of hypoxia ($FI_{O_2} = 0.1$). Arterial pressures were monitored via pulmonary arterial and abdominal aortic

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catheters. The three agents produced similar haemodynamic changes, but only isoflurane inhibited hypoxia-induced increases in pulmonary vascular resistance which were associated with a slight deterioration in arterial oxygenation in both normoxic and hypoxic conditions. This occurred at 0.5, 1.0, and 1.5 MAC isoflurane [45]. In this study, changes in pulmonary vascular resistance index were used as a measure of HPV activity, based upon which only isoflurane inhibited the response. Such studies in intact animals are obviously subject to numerous confounding variables as a result of other changes in the cardiorespiratory systems and errors associated with their measurement.

Overall, the findings of the *in vivo* intact studies are in general agreement with those of the *in vivo* non-intact, but differ from those of the more easily controllable *in vitro* studies. The discrepancies among results are attributable to many factors associated with the type of preparation used. Thus *in vitro* studies utilized denervated lungs, deprived of bronchial and lymphatic circulations, and usually perfused with non-pulsatile flows. Species differences may also be important.

### *Site of inhibition of HPV by potent inhaled anaesthetic agents*

This question has been addressed by Bjertnaes, Hauge and Torgrimsen [14], who used an isolated rat lung preparation. They studied the inhibition of a standardized HPV response during the administration of halothane via the airways, the pulmonary artery by normal anterograde perfusion of the preparation, and the pulmonary veins by retrograde perfusion of the preparation. Halothane inhibited HPV most effectively when administered via the airways, less when presented to the arterial, and least when presented to the venous segments of the pulmonary vasculature. It was therefore concluded that HPV is inhibited by halothane at some extravascular site on the arterial side of the pulmonary vasculature, functionally closer to the alveoli than to the responding vessels [14].

### *I.v. Anaesthetic Agents*

Bjertnaes [10] used an isolated perfused rat lung model (in which profound depression of HPV had been observed with potent inhaled agents) to study the effects of i.v. agents, including fentanyl, pentazocine, ketamine, droperidol, diazepam, thiopentone and pentobarbitone, each of which was administered via the perfusion circuit. In doses which produced clinically useful concentrations in the perfusate solution, none of these agents was recorded to have any effect on HPV.

Because potent inhaled agents had been shown to depress HPV maximally when given via the airways [14], Bjertnaes, Hauge and Kriz [13] also examined the effect on HPV of nebulized fentanyl given via the airways compared with via the perfusion circuit, in the isolated rat lung model. No inhibition of HPV was seen with fentanyl via either route of administration.

In an *in vivo* non-intact preparation (left lower lobe dog lung model) in which nitrous oxide, isoflurane and fluroxene (but not halothane) had been shown to inhibit HPV, no such inhibition was found with the administration of thiopentone, ketamine, pethidine, lignocaine or chlorpromazine [5].

Lumb and colleagues [30] used an intact dog model (*in vivo* intact) to compare shunt fractions ($\dot{Q}s/\dot{Q}t\%$) during ketamine infusion with those during halothane anaesthesia. They reported a consistently lower $\dot{Q}s/\dot{Q}t\%$ with ketamine, and claimed that no factor other than the anaesthetic agents could account for this difference. They concluded that ketamine resulted in better maintained HPV than did halothane anaesthesia.

Thus, based upon the findings of the *in vitro*, *in vivo* non-intact, and *in vivo* intact animal model studies, it is generally considered that inhaled anaesthetics inhibit HPV, whereas i.v. agents do not [12].

### *Studies in Humans*

Studies in humans are perhaps of greatest significance because the clinical relevance of HPV is of greatest interest to anaesthetists. Such studies, however, are the most difficult to perform and to control for confounding variables.

### *Perfusion scan studies*

Pulmonary perfusion scanning (scintigraphy) has been used to evaluate the effect of inhaled agents on human HPV. Bjertnaes [11] studied two groups of young male volunteers who were scheduled to undergo surgery on the periphery (not abdominal or thoracic). The subjects underwent arterial cannulation for monitoring of arterial blood-gas tensions, $Pa_{O_2}$ in particular. Baseline $Pa_{O_2}$ values were obtained with the patients awake and breathing room air. Under i.v. anaesthesia (thiopentone, fentanyl, pancuronium),

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unilateral hypoxia was induced in both groups by ventilating the test lung with 100% nitrogen and the other with 100% oxygen using a double-lumen bronchial (Carlens) tube.

In each group of subjects the period of unilateral hypoxia was divided into two sequences, one with and one without a potent inhaled anaesthetic (halothane or diethyl ether). In 10 subjects (group A) inhaled anaesthesia was administered during the second sequence, and in seven subjects (group B), inhaled anaesthetics were administered during the first sequence. The distribution of blood flow to the test lung during air breathing and following each of the two sequences of unilateral hypoxia was assessed by lung scintigraphy. Thus one lung was made hypoxic and $Pa_{O_2}$ values were followed until they stabilized, at which time blood flow diversion as a result of HPV was thought to be maximal and sustained. An i.v. injection of isotope-labelled albumin was made so that the macroaggregates would be distributed to and trapped in the lungs, according to the differential pulmonary blood flow. The inhaled agent was then introduced (group A) or withdrawn (group B) and the $Pa_{O_2}$ values followed until another steady state was achieved. At this time, a second injection of macroaggregates, labelled with a different isotope, was made so that subsequent scanning could provide information on pulmonary blood flow distribution at both times of interest. In group A, hypoxia caused the median test lung blood flow distribution to decrease from 49% of total pulmonary flow (two lungs, $FI_{O_2} = 0.21$) to 25% (i.v. anaesthesia, unilateral hypoxia). After ipsilateral inhaled anaesthesia was added, blood flow increased to 34% of total pulmonary flow. This increase was significant for both diethyl ether and halothane subgroups. Blood flow distribution to the test lung during the first period of unilateral hypoxia was significantly greater during diethyl ether or halothane administration (group B) than during i.v. anaesthesia alone (group A). The inhibitory effect of the two inhaled anaesthetics on this response to hypoxia was observed at clinically used blood concentrations of these agents. It was concluded that diethyl ether and halothane inhibit HPV in humans and that this contributes to the development of arterial hypoxaemia during anaesthesia [11]. The scintillation perfusion scans obtained during the various stages of the study appeared to provide fairly convincing evidence that HPV does occur in humans.

*One-lung anaesthesia studies*

One situation in which HPV would be helpful is in patients undergoing one-lung anaesthesia for thoracic surgery. In this situation the target lung is collapsed (in contrast to being ventilated with nitrogen) and the other lung is ventilated. A number of studies have attempted to draw conclusions about the effects of anaesthetics on HPV from measurements made during one-lung anaesthesia.

Weinreich, Silvay and Lumb [69] used a continuous infusion of ketamine in 110 patients undergoing one-lung anaesthesia. They postulated that, because ketamine has positive effects on the cardiovascular system and is an i.v. agent with no inhibitory effect on HPV, it should produce improved oxygenation. They found that none of their 110 patients had a $Pa_{O_2}$ of less than 9.3 kPa when $FI_{O_2}$ was 1.0, compared with other studies [65, 67] in which halothane was used and 15–25% of the patients had a $Pa_{O_2}$ less than 9.3 kPa with $FI_{O_2} = 1.0$ [65, 67]. Although the Weinreich study had no control group, the authors suggested that ketamine provides a satisfactory alternative to the potent volatile agents for one-lung anaesthesia [69].

Rees and Gaines [48] compared a ketamine–oxygen technique with an enflurane (1–3% inspired concentration) technique in 24 patients undergoing one-lung anaesthesia. The $Pa_{O_2}$ and $Qs/Qt$% values were compared between the two groups of 12 patients studied. No significant differences in $Pa_{O_2}$ or $Qs/Qt$% were found, but stroke volume index, left ventricular stroke work index and cardiac index were all significantly greater with ketamine. These results suggested that ketamine afforded no advantage, in terms of $Pa_{O_2}$ or $Qs/Qt$%, over enflurane during one-lung anaesthesia.

Rogers and Benumof [50] theorized that, if inhaled anaesthetics significantly inhibit HPV in humans and all other factors which might influence $Pa_{O_2}$ remain "relatively constant", the administration of inhaled anaesthetics during one-lung ventilation should decrease $Pa_{O_2}$. They therefore measured $Pa_{O_2}$ before, during and after the administration of halothane or isoflurane to 20 patients undergoing thoracotomy under i.v. anaesthesia and one-lung ventilation. Ten patients received halothane and 10 isoflurane. Within each of those groups, five patients received ketamine and five methohexitone as the i.v. anaesthetic.

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The procedure involved five stages:
Stage 1 = Two-lung ventilation, i.v. anaesthesia.
Stage 2 = One-lung ventilation, i.v. anaesthesia.
Stage 3 = Discontinue i.v. agent, start inhaled agent, one-lung ventilation.
Stage 4 = Discontinue inhaled agent, restart i.v. agent, one-lung ventilation.
Stage 5 = Two lung ventilation, i.v. anaesthesia.

The results showed no significant differences in $Pa_{O_2}$ between stages 2 and 3, or between 3 and 4, in both the halothane and isoflurane groups. There was, however, a small (but not statistically significant) decrease in both cardiac index and pulmonary arterial pressure with the administration of the inhaled agent in both the halothane and isoflurane groups. These authors [50] considered that other variables tending to affect $Pa_{O_2}$ had remained "fairly constant" throughout and concluded that the inhaled agents at about 1 MAC do not significantly affect HPV in humans.

Carlsson and colleagues studied HPV in humans whose lungs were exposed to enflurane [20] or isoflurane [18] anaesthesia, comparing the responses with those obtained during i.v. barbiturate anaesthesia. In these studies, patients' lungs were ventilated separately using a double-lumen tube. The test lung was made hypoxic by ventilation with 6–8% oxygen in nitrogen, while the other lung was ventilated with 100% oxygen. Cardiac output was determined by thermodilution and distribution of blood flow between the lungs was assessed from the elimination of continuously infused sulphur hexafluoride ($SF_6$), a poorly soluble inert gas. Application of the hypoxic challenge resulted in decreased blood flow to the test lungs, and the subsequent addition of 2% enflurane [20] or 1.0–1.5% isoflurane [18] caused no significant change in the distribution of pulmonary blood flow. When the hypoxic challenge was discontinued, all variables returned to control values. These findings suggested that, in the concentrations used, enflurane and isoflurane have no measurable effect on HPV in humans.

In the isoflurane study [18], however, hypoxic lung blood flow did increase (but not significantly) at an end-tidal isoflurane concentration of 1.5%. This suggested that isoflurane might have a slight effect on HPV which might perhaps have been better revealed by a more hypoxic challenge (< 8% oxygen) [18]. In addition, measurements were made after 15-min periods of breathing a new gas mixture. This was considered reasonable because a previous study (from the same group) had concluded that the hypoxic challenge to one lung in an i.v. anaesthetized human subject elicited a maximum vasoconstrictor response within the first 15 min and that this response could not be potentiated by repeated challenges [8]. Furthermore, there was no further potentiation or diminution of the HPV response during a 60-min period of hypoxia [19].

These studies [8, 18–20] used $SF_6$ elimination as an indicator of differential lung blood flow. This method for separate lung blood flow measurement has been compared with the use of electromagnetic flowmeters and elimination of carbon dioxide in dogs in which one lung was made hypoxic by ventilation with 8% oxygen or 100% nitrogen [21]. There was good correlation between flows measured by the probe and by $SF_6$ methods. Poor results were obtained with the carbon dioxide elimination method, which could be explained by its dependence on the $\dot{V}/\dot{Q}$ ratio and the effect of $Pa_{O_2}$ on the carbon dioxide binding capacity of blood. The carbon dioxide output method could also over-estimate blood flow to an hypoxic lung as a result of the increased alveolar–capillary carbon dioxide gradient [67]. Although the carbon dioxide elimination method has been claimed to be reliable [9], it is considered by the reviewer to be inaccurate and its errors not easily corrected. The use of an inert poorly soluble gas such as $SF_6$ is considered preferable for measuring differential lung blood flows [21]. From a practical point of view, however, elimination of carbon dioxide is readily measured in most laboratories and clinical settings, whereas relatively few centres have the facilities to measure $SF_6$ concentrations.

Benumof, Augustine and Gibbons [4] questioned if failure to detect an effect of isoflurane on HPV in humans in two previous studies [18, 50] might have been the result of the relatively short duration of exposure to the inhaled agent, so that clinically relevant tissue concentrations were not achieved. They therefore studied the effect of inhaled anaesthetics on $Pa_{O_2}$ and $Qs/Qt$% by first establishing a long duration of inhaled anaesthesia ($F_{I_{O_2}} = 1.0$; end-tidal values $\geq 1$ MAC for 1 h) with stable one-lung collapse and then, while keeping one lung atelectatic, discontinuing the inhaled agent and introducing i.v. agents (fentanyl, diazepam, thiopentone). In this study, the mean (SD) values for $Pa_{O_2}$ during one-lung ventilation with halothane were much lower than those with isoflurane (15.5 (8.1) *vs* 30.9 (12.9) kPa), which

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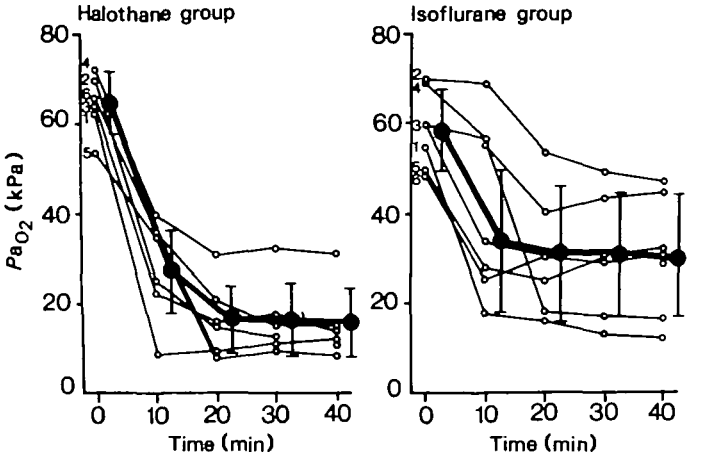


FIG. 2. Serial $Pa_{O_2}$ measurements (mean (SD)) during conversion from two-lung ventilation to one-lung ventilation at time 0 in six individual patients (1–6) in both the halothane and isoflurane groups. The mean $Pa_{O_2}$ value at the end of two-lung ventilation and just before beginning one-lung ventilation is the same as the first mean $Pa_{O_2}$ value in figure 3, and the last (40-min) mean one-lung ventilation $Pa_{O_2}$ value is the same as the second mean $Pa_{O_2}$ value in figure 3. (Adapted from [4] by permission of the author and publisher.)

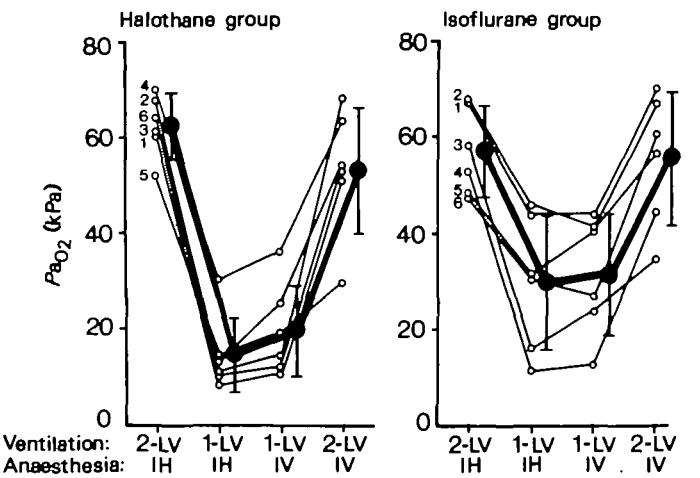


FIG. 3. $Pa_{O_2}$ values during the four experimental sequence steps in individual patients (1–6). Conversion from two-lung ventilation (2-LV) to one-lung ventilation (1-LV) during inhalation anaesthesia (IH) (first two values at left) in both groups caused a very large and significant decrease in $Pa_{O_2}$. Conversion from IH to i.v. anaesthesia (IV) during 1-LV (middle two values in both groups) caused a slight but significant increase in $Pa_{O_2}$ in the halothane group, and a very slight and non-significant increase in $Pa_{O_2}$ in the isoflurane group. Conversion from 1-LV to 2-LV during IV (last two values at right) caused a very large and significant increase in $Pa_{O_2}$ in both the halothane and isoflurane groups. (Adapted from [4] by permission of the author and publisher.)

was consistent with greater depression of HPV by halothane, compared with isoflurane (fig. 2). Discontinuing halothane and introducing i.v. anaesthesia during one-lung ventilation caused a slight but significant increase in $Pa_{O_2}$ (5.2 (3.9) kPa (fig. 3)) and decrease in $Qs/Qt$% (7 (2) % (fig. 4)). Discontinuing isoflurane caused a slight but non-significant increase in $Pa_{O_2}$ (1.7 (2.5) kPa) and decrease in $Qs/Qt$% (2 (2)%). The authors calculated that the atelectatic lung had active HPV and that the slight decrease in shunt and increase in $Pa_{O_2}$ when changing from inhaled to

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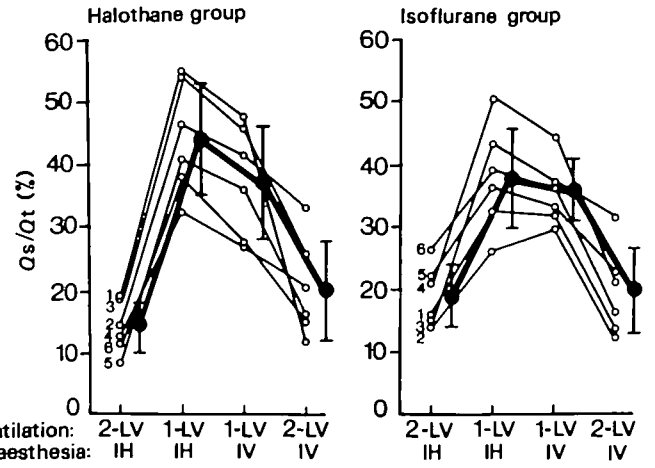


FIG. 4. Shunt ($Qs/Qt$) values during the four experimental sequence steps in six individual patients (1–6). Conversion from two-lung ventilation (2-LV) to one-lung ventilation (1-LV) during inhalation anaesthesia (IH) (first two values at left) in both groups caused a very large and significant increase in $Qs/Qt$. Conversion of IH to i.v. anaesthesia (IV) during 1-LV (middle two values) caused a slight but significant decrease in $Qs/Qt$ in the halothane group, and a very slight and non-significant decrease in $Qs/Qt$ in the isoflurane group. Conversion from 1-LV to 2-LV during IV (last two values at right) caused a very large and significant decrease in $Qs/Qt$ in both the halothane and isoflurane groups. (Reproduced from [4] by permission of the author and publisher.)

i.v. anaesthesia was consistent with the findings in animal studies [4]. They further concluded that, because continuous positive airways pressure (CPAP) to the non-dependent lung is usually effective in improving $Pa_{O_2}$ during one-lung anaesthesia, "the use of halogenated drugs in patients undergoing one-lung ventilation is no longer a significant issue" [4].

In subsequent correspondence concerning the above study, Marshall pointed out that the efficacy of CPAP in relieving hypoxaemia "does not mean the problem is solved" [33]. He concluded that the data of Benumof, Augustine and Gibbons [4] showed that hypoxaemia is a frequent cause of concern during one-lung ventilation, and that the choice of anaesthetic agent has a significant effect, halothane being associated with a large probability and greater incidence of hypoxaemia. He also suggested that the variability of the inhibition of HPV is probably different between halothane and isoflurane, being greater with isoflurane, and that, because the $Pa_{O_2}$ increased significantly when halothane was replaced with an i.v. agent, the choice of inhaled *vs* injectable agent may be important [33]. In response to the latter point, Benumof stated that his data did not support that conclusion because the patients who had the lowest $Pa_{O_2}$ during halothane/one-lung ventilation had the smallest increase in $Pa_{O_2}$ when changed to i.v. anaesthesia/one-lung ventilation, while those who had the greatest $Pa_{O_2}$ during halothane/one-lung anaesthesia had the largest increase in $Pa_{O_2}$ when switched to i.v. agent/one-lung anaesthesia [33].

### *Differences between the results from* in vitro *and* in vivo *studies*

In general the differences in results between the *in vitro* (clear inhibition of HPV by inhaled agents) and *in vivo* studies (no inhibition of HPV or difficult to demonstrate) are striking. This prompted the suggestion that other variables may have been obscuring the effects of HPV in the *in vivo* studies [37]. One such variable is cardiac output, which is altered to a markedly different extent by different inhaled agents. Marshall and Marshall [37] collected data from a large number of published studies and plotted the HPV ratio (defined as % flow to the hypoxic segment with anaesthetic/% flow without anaesthetic) as ordinate against cardiac output ratio (defined as cardiac output with anaesthetic/cardiac output without) as abscissa, measured at the same time (fig. 5). The regression line drawn through the points showed:

$$\text{Effect of anaesthetic on HPV ratio} = 0.46 + 0.83 \times (\text{cardiac output ratio}) \quad (r = 0.74).$$

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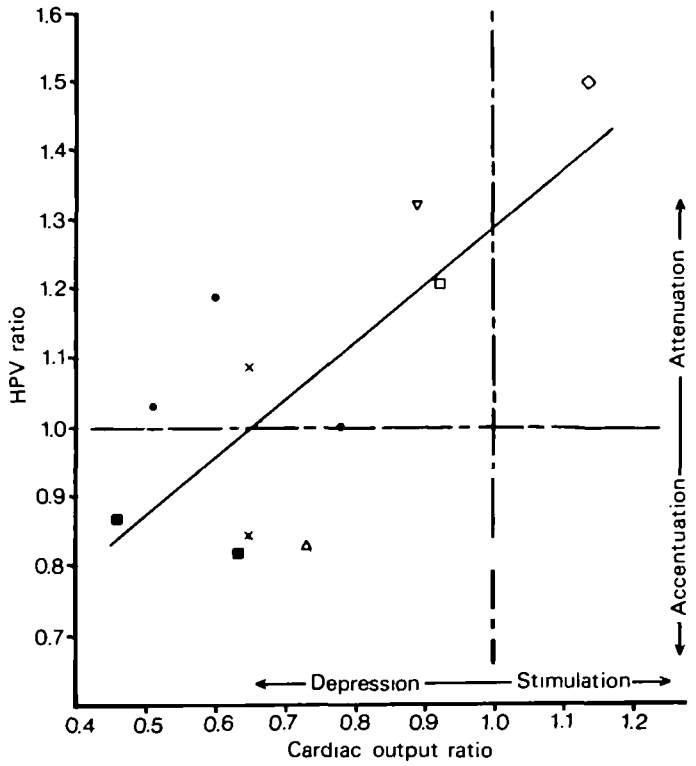


FIG. 5. Effects of inhalation anaesthetics *in vivo*. Observed changes in HPV response with inhalation anaesthetics are compared with simultaneous changes in cardiac output; data have been standardized to allow comparison between studies. Cardiac output ratio = cardiac output with anaesthetic/cardiac output without anaesthetic. Control cardiac output in absence of inhalation agents is designated 1.0. The HPV response (HPV ratio) is indicated by comparing hypoxic segment flow with and without inhalation anaesthesia. If the anaesthetic has no effect, the value is 1.0; if the response to HPV is reduced, the value is $> 1.0$, and if response to HPV is enhanced, the value is $< 1.0$. Significant linear relationship of various studies is shown: anaesthetic action on HPV ratio = 0.46 + 0.83(cardiac output ratio); $r = 0.74$. These results suggest that changes in cardiac output in the presence of inhalation agents are an important influence on whether the response to HPV will appear to be increased or decreased. ● = Halothane [42, 60, 61]; ■ = isoflurane [52, 60]; △ = methoxyflurane [32]; □ = nitrous oxide [62]; ▽ = trichloroethylene [58]; ◇ = diethyl ether [61]; x = enflurane [42]. (Reproduced from [37] by permission of the American Physiological Society and the author.)

This relationship reveals that, in the presence of inhaled anaesthetics, the efficacy of HPV varies inversely with cardiac output. During inhalation anaesthesia, a direct inhibition of HPV may be offset by an enhanced responsiveness as a result of decreased cardiac output, with the result that flow diversion and gas exchange (as assessed by $Pa_{O_2}$) and, by inference, HPV may all appear to be unaffected (fig. 6).

Domino and colleagues [25] studied the influence of locally administered isoflurane on the regional HPV response over a range of cardiac outputs in closed-chest dogs. In this preparation the right lung was ventilated with either 100% oxygen or a hypoxic mixture. Various alveolar concentrations (0.0, 1.0 and 2.5 MAC) of isoflurane were administered to the left lung. Cardiac output was varied by opening and closing surgically created arteriovenous fistulae and the HPV response was measured by differential elimination of carbon dioxide, and by venous admixture. In this model, when the effects of different concentrations of isoflurane on $\dot{Q}s/\dot{Q}t$% during left lung hypoxia were studied under stable conditions of cardiac output, mixed venous and alveolar oxygen tensions, and pulmonary arterial and wedge

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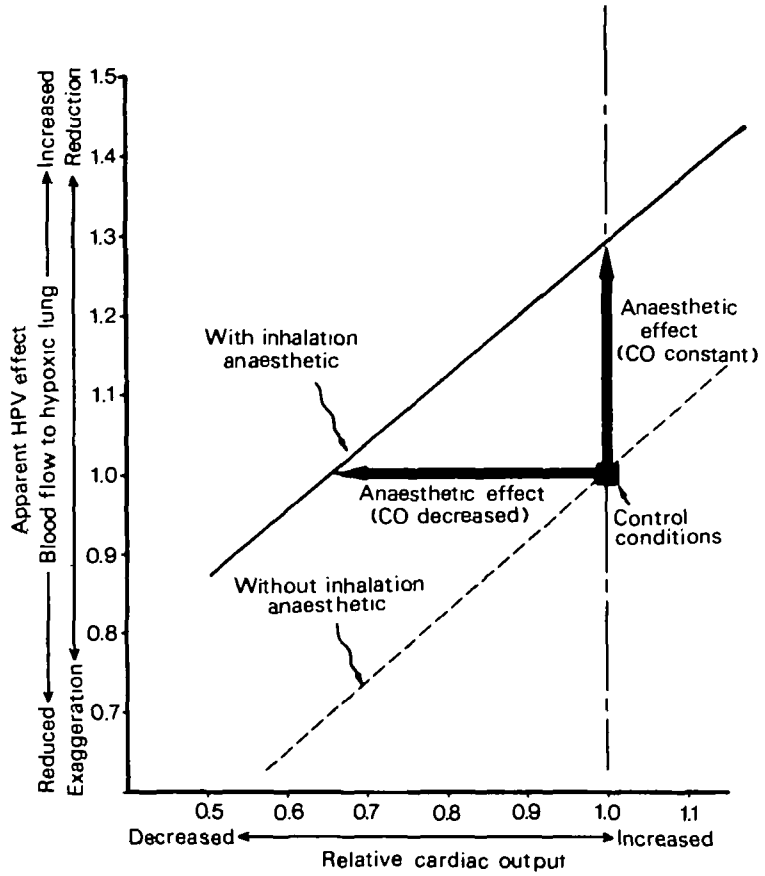


FIG. 6. Influence of inhalation anaesthetics on observed response to HPV. In the absence of inhalation anaesthetics, dashed line indicates changes of blood flow to a hypoxic lung region that occurs as total cardiac output (CO) changes according to predictions and experimental results. Solid line parallel to this shows the same relationship in the presence of inhalation anaesthetics. Vertical arrow demonstrates true reduction of HPV response associated with inhalation anaesthetics when CO is not changed. Horizontal arrow illustrates how action of anaesthetic agent simultaneously depresses HPV directly and enhances HPV through cardiac depression and leads to an apparently unchanged response to HPV. (Reproduced from [37] by permission of the American Physiological Society and the author.)

pressures, the results revealed a significant direct effect of the dose of isoflurane:

$$\%\ \text{depression of HPV} = [(22.8 \times \%\ \text{alveolar isoflurane}) - 5.3]$$

with an $ED_{50}$ of 2.4% isoflurane (alveolar concentration) for the response. These authors also demonstrated that, during left lung hypoxia, increasing the cardiac output caused an increase in both left lung blood flow and venous admixture. Thus, when many of the variables were kept constant, an inhibitory effect of isoflurane on HPV could be demonstrated in this *in vivo* intact model [25]. The interpretation of that study and its clinical implications were discussed elegantly by Benumof in an accompanying editorial [3].

The HPV–cardiac output relationship provides a plausible explanation for some of the discrepancies in results between the *in vivo* and *in vitro* studies and for the apparent lack of differences between the effects of i.v. and inhaled agents during one-lung anaesthesia in many of the human studies. Indeed, an increase in cardiac output, as may occur with some of the i.v. agents, might even be construed as being detrimental to the normal HPV response, and it could be argued that these agents should be avoided because of their indirect inhibitory effects on HPV. Clearly, many physio-

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logical variables must be considered when interpreting the effects of inhaled and i.v. anaesthetics on the pulmonary circulation, and on HPV in particular.

*Potentiators of HPV*

While much of the previous research has addressed inhibition of HPV and its implications for clinical anaesthesia, more recent studies have investigated potentiators of this response.

Almitrine bimesylate, a respiratory stimulant, was found to improve $Pa_{O_2}$ in patients with chronic obstructive pulmonary disease, even in the absence of ventilatory stimulation [56, 64]. It has been shown to potentiate HPV in intact pentobarbitone-anaesthetized dogs [51], although another study in thoracotomized dogs failed to demonstrate such potentiation [22]. A study using high dose almitrine in a closed-chest unilateral hypoxic lung dog model (similar to that used by Domino and colleagues [25]) found that the drug caused non-specific pulmonary vasoconstriction which was maximal in those vessels having the least initial tone. Constriction was greatest in the lung ventilated with 100% oxygen, compared with the hypoxic lung. Blood flow was therefore diverted from the hyperoxic to the hypoxic lung, diminishing the efficacy of HPV in that lung. Hypoxic lung showed no further increase in vasoconstriction with almitrine and HPV was not enhanced in the hypoxic lung [23].

Hypoxic pulmonary vasoconstriction is reduced by prostacyclin ($PGI_2$, a potent vasodilator) and potentiated by leukotrienes [44]. Marshall, Kim and Marshall [39] used an isolated rat lung preparation to study the effects of halothane, ibuprofen (a cyclo-oxygenase inhibitor) and BW 755C (a lipoxygenase inhibitor) on the HPV response. They found that HPV was reduced by halothane (as shown previously); that inhibition of cyclo-oxygenase by ibuprofen potentiated HPV; and that when ibuprofen was present the attenuation of the HPV response by halothane was diminished. They also concluded that the products of the lipoxygenase pathway (leukotriene peptide) are essential for HPV, but this conclusion was not shared by Gottlieb and colleagues [27], who studied isolated ferret lungs. Species differences may therefore be of importance when considering the mechanism of HPV.

Lejeune and colleagues [29] studied the effects of 70% nitrous oxide on mean pulmonary arterial pressure (MPAP) – cardiac index relationships in 13 pentobarbitone-anaesthetized dogs with lungs ventilated alternately at $FI_{O_2}$ 0.3 or 0.1. Over a range of cardiac indices, hypoxia increased MPAP in seven "responder" dogs but did not affect MPAP in six "non-responder" dogs. In the latter group, HPV was restored by the administration of a cyclo-oxygenase inhibitor (acetylsalicylic acid 1 g i.v.). In responders, nitrous oxide partially inhibited HPV, while in non-responders with an HPV response restored by acetylsalicylic acid, nitrous oxide did not affect HPV. These findings suggest that the effects of nitrous oxide on the pulmonary vasculature depend upon pre-existing vascular tone and can be modulated by cyclo-oxygenase products of arachidonic acid metabolism. Inhalation anaesthetic agents stimulate release of arachidonic acid from cell membranes [57]. In the non-responder dogs treated with acetylsalicylic acid, increase in HPV by nitrous oxide can be explained by increased formation of vasoconstrictor leukotrienes from the increased amounts of precursor made available. If cyclo-oxygenase inhibitors will have any application for improving oxygenation during clinical anaesthesia has not yet been determined.

Scherer and colleagues [54] infused prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) into the pulmonary artery of an atelectatic lung of anaesthetized paralysed dogs and found that arterial and mixed venous oxygen tensions and calculated venous admixture during stable one-lung atelectasis could be improved. The proposed mechanism was an increase in HPV in the atelectatic lung. In a subsequent study, Scherer, Vigfusson and Lawin [55] found that, in terms of reducing venous admixture and improving arterial oxygenation during one-lung ventilation in dogs, both inflation of the balloon on a pulmonary arterial catheter lying in the artery supplying the atelectatic lung, and infusion of $PGF_{2\alpha}$ were equally effective. In both studies [54, 55] the dogs were anaesthetized with piritramide, an i.v. agent.

Chen and colleagues [24] studied the effect of i.v. $PGF_{2\alpha}$, administered as a continuous peripheral infusion, on the HPV response in a closed-chest dog model during left lung hypoxia. They found that $PGF_{2\alpha}$ caused vasoconstriction in both the right lung receiving 100% oxygen and the left receiving a hypoxic gas mixture, without significantly changing blood flow to either lung. Thus HPV was not enhanced by this non-specific increase in vasoconstriction. The authors con-

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cluded that, if $PGF_{2\alpha}$ is to be used to enhance oxygenation during one-lung anaesthesia, the infusion should be confined to the atelectatic lung, as in Scherer's studies. The efficacy of $PGF_{2\alpha}$ during the administration of potent inhaled anaesthetic agents has not yet been reported.

Bindslev, Cannon and Sykes [6] found that lignocaine restored normal HPV in a constant-flow, perfused left lower lobe dog lung preparation (*in vivo*, non-intact). Thus when the left lower lobe was ventilated with 100% oxygen or 7% oxygen in nitrogen, lignocaine had no effect on lobar PVR. Ventilation of the lobe with 7% oxygen in nitrous oxide decreased the response to hypoxia, while the addition of lignocaine restored lobar vascular resistance to a mean value similar to that observed during ventilation with 7% oxygen in nitrogen. Failure of lignocaine to increase lobar vascular resistance during ventilation with 100% oxygen, or 7% oxygen in nitrogen suggests that lignocaine acts directly at the site of HPV inhibition by nitrous oxide, and therefore at the site of alveolar hypoxia.

In a subsequent study [7] the same group found that lignocaine had no effect on lobar blood flow during lobar collapse (atelectasis) whether the right lung was ventilated with 50% oxygen in nitrogen or with 50% oxygen in nitrous oxide. Thus lignocaine reversed the depression of HPV produced by lobar *ventilation* with nitrous oxide. Failure to exert an effect on lobar vascular resistance during atelectasis was thought to be the result of absence of nitrous oxide-induced inhibition of HPV in the atelectatic lobe [7]. The effects of lignocaine on HPV which has been depressed by potent inhaled agents remain to be determined, as do the clinical implications of these observations.

## CONCLUSIONS

The effects of anaesthetic agents on the pulmonary circulation and on HPV in particular have been reviewed. Numerous models have been designed to study these effects and the results have not always been consistent, differences in methodology and difficulties in controlling confounding variables being the most likely reasons. In general, HPV is not directly inhibited by i.v. anaesthetic agents, but is directly inhibited by inhalation agents. Because of compensatory mechanisms that may be difficult to measure accurately (particularly in human subjects) the inhibition is usually, but not always, of little clinical consequence. Present consensus is that potent inhaled anaesthetic agents are not contraindicated for thoracic surgery requiring one-lung ventilation when active HPV is most desirable. Indeed, their use has been advocated because of their salutory effect on bronchomotor tone, high potency (allowing high inspired concentrations of oxygen) and rapid elimination [2]. There may, however, be some patients (particularly those with generalized lung abnormalities) in whom hypoxaemia may occur and in these subjects change to an i.v. agent should be considered [4, 33].

Potentiators of HPV remain at the experimental stage and have yet to be investigated in humans. As more is learned about the biochemical basis of HPV, potentiators may eventually offer real benefits to patients who develop hypoxaemia during general anaesthesia.

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