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Effects of posture on blood flow diversion by hypoxic pulmonary vasoconstriction in dogs†

S. M. WALTHER, K. B. DOMINO AND M. P. HLASTALA

Summary

We used differential excretion of sulphur hexafluoride from the left and right lung to measure blood flow diversion by hypoxic pulmonary vasoconstriction (HPV) in the prone and supine positions in dogs ($n=9$). Gas exchange was assessed using the multiple inert gas elimination technique. Blood flow diversion from the hypoxic (3% oxygen) left lung was mean 70.7 (SD 11.2) % in the supine compared with 57.0 (12.1) % in the prone position ($P<0.02$). The supine position was associated with increased perfusion to low $\dot{V}_A/\dot{Q}$ regions ($P<0.05$). The increased flow diversion with hypoxia in the supine position was associated with more ventilation to high $\dot{V}_A/\dot{Q}$ regions ($P<0.05$). We conclude that flow diversion by hypoxic pulmonary vasoconstriction is greater in the supine position. This effect could contribute to the variable response in gas exchange with positioning in patients with ARDS. (*Br. J. Anaesth*. 1998; **81**: 425–429).

Keywords: lung, blood flow; hypoxia; ventilation, hypoxic response; position, effects; model, dog

Hypoxic pulmonary vasoconstriction (HPV) is one mechanism by which matching of ventilation and perfusion takes place. Pulmonary arteries constrict progressively when exposed to hypoxia.[1] Local oxygen tension in small arterioles (approximately less than 500 μm in diameter) is determined mainly by oxygen tension in alveolar gas. Thus when hypoxic gas enters distal air spaces, vasoconstriction diverts, flow to other, presumably better oxygenated, lung regions. The main determinants of this redistribution of flow are, apart from local oxygen concentration, interactions between arterial, alveolar and interstitial pressures, as outlined in the zonal perfusion model of Hughes and colleagues.[2] However, this model has been challenged by a growing number of observations that show large isogravitational perfusion heterogeneity[3–6] and lack of, or minimal, gravitational gradients in the prone position.[5–8] Detailed studies of pulmonary perfusion suggest increased conductance to flow in dorsal lung regions.[9] The reason for this dorsal flow bias could be differences in ventral–dorsal vasoreactivity inherent in the microvasculature[10] or regional differences in branching anatomy.[11]

The tendency of dorsal lung regions to accept more flow enhances gravitational redistribution of perfusion in the supine position. Increased dorsal flow conductance may balance the influence of gravity in the prone position, thus promoting more uniform flow distribution that is typically seen in the prone position.[5 12] We hypothesized that the mechanisms responsible for this asymmetric response to positioning might interact differently with HPV in the prone and supine positions. As many studies show improved gas exchange with prone positioning of patients with ARDS[13–16] or obesity,[17] we speculated that this might result, in part, from more efficient matching by HPV of perfusion to ventilation in the prone position. This notion was explored using a dog split lung model in which the left lung was subjected to hypoxia (3% oxygen), and the right lung ventilated with 100% oxygen for the entire experiment. In this study, we found more hypoxic diversion of blood flow, assessed using the multiple inert gas elimination. technique (MIGET), in the supine compared with the prone position.

Materials and methods

ANIMAL PREPARATION AND PHYSIOLOGICAL MEASUREMENTS

The study was approved by the University of Washington Animal Care Committee. We used nine dogs (mean weight 20.8 (SD 1.8) kg). They were fasted overnight but had free access to water. A peripheral vein was cannulated and anaesthesia was induced with pentobarbital 30 mg kg^{-1} i.v. and maintained with intermittent i.v. doses as required (30–90 mg every 20–30 min). The trachea was intubated orally and the lungs ventilated with a tidal volume of 15 ml kg^{-1}. A femoral artery catheter, pulmonary artery catheter via the external jugular vein, and a femoral venous catheter were inserted via peripheral cutdowns. Systemic arterial, pulmonary arterial, pulmonary arterial occlusion and airway pressures were measured continuously and recorded on a Western Graphic Mach 12 data-management system DMS 1000 with Validyne amplifiers (Irvine, CA, USA). Vascular pressures were zeroed to the mid-chest level. Body temperature was maintained at 38±1°C using heating lamps

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and pads. Thermodilution cardiac outputs ($\dot{Q}_T$) were obtained in triplicate (Edward's SAT-2 Cardiac Output Computer, Santa Ana, CA, USA).

A Kottmeier double-lumen endobronchial tube (Les Wilkins Co., Seattle, WA, USA) was inserted via a subcricoid tracheostomy. Complete lung isolation was verified by the absence of air bubbles escaping from one limb of the endobronchial tube when the other was hyperinflated, and the absence of cross-contamination when the lungs were ventilated separately with helium. Both lungs were ventilated synchronously with a Harvard dual-piston ventilator (South Natick, MA, USA) with separate gas breathing systems. The inspired gas mixture was adjusted using a Cameron GF-5 Gas Flowmeter (Port Aransas, TX, USA). Inspired, mixed-expired and end-tidal P_{CO_2} and P_{O_2} were measured with a Mass spectrometer (Perkin Elmer, Medical Gas Analyzer Instrumentation Laboratories 1302) and corrected for body temperature. Right and left tidal volumes were set at 9 and 6 ml kg^{-1}, respectively, and were adjusted to yield equal airway pressures of 10–15 cm H_2O. Ventilatory frequency was adjusted to yield normocapnia. The lungs were hyperinflated every 30 min to prevent microatelectasis.

MULTIPLE INERT GAS ELIMINATION TECHNIQUE

The multiple inert gas elimination technique (MIGET) was used to assess pulmonary gas exchange[18 19] and the fraction of blood flow to the left and right lungs.[20] A solution of six inert gases (sulphur hexafluoride, ethane, cyclopropane, halothane, diethyl ether and acetone) dissolved in 5% dextrose was infused into the femoral vein catheter at a rate of 3 ml min^{-1} for 1 h before starting any measurements. Inert gas partial pressures were measured in duplicate blood samples collected simultaneously from the pulmonary and femoral arteries and in mixed expired gas. Exhaled gas specimens were maintained at >40°C before analysis to avoid condensation and loss of high solubility gases.

Concentration of inert gases were measured using a gas chromatograph (Varian 3300, Walnut Creek, CA, USA) equipped with a flame ionization detector and an electron capture detector. The gas extraction method of Wagner, Naumann and Laravuso[21] was used to determine the concentration of inert gases in the blood samples.

STUDY PROCEDURE

Before beginning the study, the animals were "primed" with 3–4 hypoxic challenges. After demonstration of a stable HPV response by consistent increases in mean pulmonary artery pressure and stable arterial blood-gas tensions with left lung hypoxia, the study began. The right lung was ventilated with an $F_{I_{O_2}}$ of 1.0 throughout the study. The left lung was ventilated with an $F_{I_{O_2}}$ of 1.0 (hyperoxia) or 0.03 (hypoxia) in random order. Inspired carbon dioxide ($F_{I_{CO_2}} = 0.03$) was added to the left lung inspired gas mixture during hypoxia, and to both lungs ($F_{I_{CO_2}} = 0.01$–0.02) during hyperoxia to prevent cyclical variations in the HPV response caused by alveolar hypocapnia. Animals were studied in the supine and prone positions in random order. Blood-gas tensions, collection of mixed expired gas samples and haemodynamic measurements were obtained after a stabilization period of 20 min in each phase.

CALCULATIONS AND STATISTICAL ANALYSIS

Pulmonary blood flow to each lung was calculated by the Pick principle for the inert gas with the lowest solubility in blood, sulphur hexafluoride (SF_6):

$$\dot{Q}_R = (\dot{V}_R x P_R(\text{exp})_{SF6})/\lambda_{SF6}\ (P(\text{v})_{SF6}) - P(\text{a})_{SF6})$$

$$\dot{Q}_L = (\dot{V}_L x P_L(\text{exp})_{SF6})/\lambda_{SF6}\ (P(\text{v})_{SF6}) - P(\text{a})_{SF6})$$

where $\dot{Q}_R$ and $\dot{Q}_L$ = right and left lung blood flow; $\dot{V}_R$ and $\dot{V}_L$ = right and left lung minute ventilation; $P_R(\text{exp})_{SF6}$ and $P_L(\text{exp})_{SF6}$ = partial pressure of SF_6 in mixed expired gas from the right and left lung; λ_{SF6} = Ostwald blood-gas partition coefficient of SF_6; $P(\text{v})_{SF6}$ and $P(\text{a})_{SF6}$ = Partial pressure of SF_6 in mixed venous and arterial blood. Blood flow to each lung was expressed as a fraction of total pulmonary blood flow. Left lung blood flow diversion during hypoxia was calculated as $(\dot{Q}_{\text{hyperoxia}} - \dot{Q}_{\text{hyperoxia}})/\dot{Q}_{\text{hyperoxia}}$ and expressed as percent.[22]

Concentrations of the six inert gases in mixed expired gas, pooled from both lungs, were used to assess changes in the ventilation/perfusion ($\dot{V}_A/\dot{Q}$) distributions predicted by the 50-compartment model of Wagner, Saltzman and West, and Evans and Wagner.[18 19] This model considers the lung to consist of 50 homogeneous compartments arranged in parallel, each with $\dot{V}_A/\dot{Q}$ values evenly spaced on a logarithmic scale. Inert gas shunt, deadspace, mean $\dot{V}_A/\dot{Q}$ ratios of $\dot{V}_A$ and $\dot{Q}$ distributions, percentage of $\dot{Q}$ to low $\dot{V}_A/\dot{Q}$ units ($\tilde{V}_A/\dot{Q}$ ratio 0.005–0.1), and percentage of $\tilde{V}_A$ to high $\tilde{V}_A/\dot{Q}$ units ($\dot{V}_A/\dot{Q}$ ratio 10–100) were calculated from the 50-compartment model.

Data were analysed by two-factor ($F_{I_{O_2}}$ and position) within-subjects analysis of variance. Significant differences determined from analysis of variance were analysed by calculating the least significant difference. Data are expressed as mean (SD). $P<0.05$ was considered significant.

Results

Right and left airway pressures, and left and right end-tidal carbon dioxide concentrations were not different between the conditions; the latter were within normal limits in both lungs (4.5–5.7%). There were no significant changes in Pa_{CO_2} and Pa_{O_2}; Pv_{O_2} did not change with position but decreased during hypoxia (table 1).

Mean pulmonary artery pressure increased significantly with hypoxia ($P<0.01$) but did not differ between positions when analysed by two-factor ANOVA. Pulmonary artery occlusion pressure and systemic artery pressure were unaffected by hypoxia but systemic artery pressure changed significantly with position. Cardiac output did not differ significantly between the conditions (table 1).

The proportion of total pulmonary perfusion flowing to the left lung during hyperoxia was not significantly different between the prone and supine positions (0.40 (0.05) and 0.39 (0.05), respectively). Left lung blood flow diversion by hypoxia was 57.0

Table 1 Blood-gas tensions and haemodynamics (mean (SD)). ***$P<0.001$ *vs* hyperoxia; †$P<0.05$, ††$P<0.01$ *vs* prone posture with same $F_{I_{O_2}}$

	Hyperoxia		Hypoxia	
	Prone	Supine	Prone	Supine
Arterial oxygen tension (mm Hg)	604 (21)	586 (30)	221 (97)***	259 (94)***
Arterial carbon dioxide tension (mm Hg)	38 (2)	39 (6)	39 (4)	42 (5)
Mixed venous oxygen tension (mm Hg)	78 (14)	72 (7)	61 (9)***	60 (7)***
Mean pulmonary artery pressure (mm Hg)	18 (4)	16 (4)	23 (5)***	20 (4)***
Pulmonary artery occlusion pressure (mm Hg)	7 (1)	12 (5)†	8 (4)	11 (3)
Mean systemic artery pressure (mm Hg)	147 (13)	125 (13)††	149 (11)	120 (11)††
Thermodilution cardiac output (litre min^{-1})	4.6 (1.6)	3.7 (1.0)	4.4 (1.5)	3.8 (0.8)

Table 2 Gas exchange variables (mean (SD)). $\dot{V}A/\dot{Q}$=ventilation perfusion ratio. **$P<0.01$, ***$P<0.001$ *vs* hyperoxia; †$P<0.05$ *vs* prone posture with the same $F_{I_{O_2}}$

	Hyperoxia		Hypoxia	
	Prone	Supine	Prone	Supine
Mean $\dot{V}A/\dot{Q}$ of the perfusion distribution	0.88 (0.19)	0.75 (0.16)	0.67 (0.19)**	0.61 (0.18)**
Mean $\dot{V}A/\dot{Q}$ of the ventilation distribution	0.82 (0.35)	0.96 (0.34)	1.36 (0.33)***	1.37 (0.29)***
Shunt (%)	0.6 (0.9)	1.7 (1.3)	1.2 (1.5)	1.6 (1.9)
Perfusion to $\dot{V}A/\dot{Q}=0.005$–0.1 (%)	0.7 (1.6)	4.1 (3.4)†	1.0 (1.8)	5.5 (3.8)†
Ventilation to $\dot{V}A/\dot{Q}=10$–100 (%)	2.3 (3.1)	3.1 (3.4)	7.5 (3.9)***	13.8 (7.8)***†
Deadspace (%)	39.0 (5.0)	40.7 (6.5)	41.2 (2.4)	38.9 (6.3)

(12.1) % in the prone and 70.7 (11.2) % in the supine position ($P<0.02$, fig. 1). Inert gas shunt and deadspace did not change between conditions (table 2), Perfusion to regions with low $\dot{V}A/\dot{Q}$ ratios was larger in the supine than in the prone position ($P<0.05$), but there was no significant influence of $F_{I_{O_2}}$. Ventilation to regions with high $\dot{V}A/\dot{Q}$ ratios during hypoxia was higher in the supine than in the prone position ($P<0.05$, table 2).

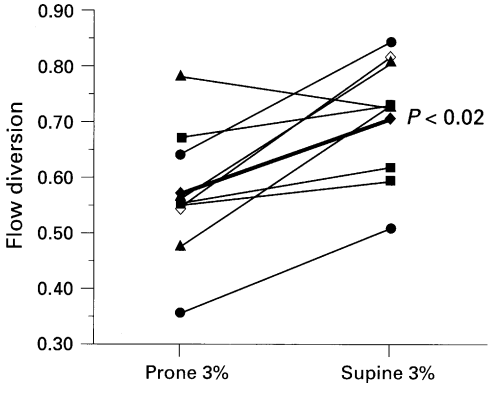

Figure 1 Individual effects of posture on blood flow diversion by left lung hypoxia (3% oxygen). Mean values are connected by a thick line.

Discussion

The important finding of this study was that redistribution of pulmonary blood flow by hypoxic vasoconstriction was more effective in the supine than in the prone position. Before considering the implications of these results, we discuss some of the limitations of the methods used in our experiment.

METHODOLOGICAL ISSUES

We used dogs to examine the hypothesis that the HPV response was position-dependent and might contribute to improved gas exchange in patients nursed in the prone position. Dogs are large enough to allow for invasive instrumentation and their HPV response has been characterized in great detail.[22–24] A major drawback is that dogs depend more on collateral ventilation than HPV in maintaining ventilation-perfusion matching.[25] However, it is likely that the basic mechanisms that determine flow diversion by HPV are similar in humans and dogs, as suggested by work showing marked similarity across different species.[23 24 26 27]

We measured blood flow to each lung by applying the Fick principle to the differential excretion of SF_6. This technique was found previously to provide an accurate non-invasive measure of pulmonary blood flow compared with invasive electromagnetometry.[20 28] Retention and excretion data from all six inert gases were used to describe the gas exchange function of the lungs according to the model of Wagner, Saltzman and West, and Evans and Wagner.[18 19]

POSITION RELATED EFFECTS ON HAEMODYNAMIC STATE

Higher mean pressures in the pulmonary and femoral artery were recorded in the prone compared with the supine position. Similar results, with higher

systemic arterial pressure in the prone position, have been reported in numerous investigations, including studies in human subjects.[13–15 29–32] The position-associated changes in vascular pressures could be explained in part by failure of the mid-chest level to reflect the true zero reference point in both positions. However, this is unlikely to be the sole mechanism as the use of a catheter in the right atrium as the true zero reference point still produced higher systemic pressure readings in the prone compared with the supine position in anaesthetized dogs.[30] We are not aware of any data that could shed light on the mechanisms responsible for these effects of position on haemodynamic state. It is possible that the heart was restricted by the lungs and its own weight in the supine position. It is equally likely that the prone position was associated with increased stimulation of the larynx and the airways by the tracheal tube, and hence increased sympathetic tone.

EFFECTS OF POSTURE ON BLOOD FLOW DIVERSION AND GAS EXCHANGE

The hypoxic left lung received a smaller fraction of cardiac output in the supine than in the prone position. Flow diversion by hypoxic vasoconstriction is an adaptive mechanism aimed at preserving gas exchange by directing perfusion away from lung segments with hypoxic gas. The efficiency of this response is influenced by the relative sizes of the hypoxic and hyperoxic parts of the lung.[22] The intensity of the response is a function of both alveolar and mixed venous oxygen tensions,[24 26] and it is also influenced by pH and carbon dioxide tension.[33] These factors were balanced between the prone and supine positions in our experiment, and the fraction of cardiac output to the left lung was similar in both positions, suggesting that the difference in flow diversion was caused by change in position. Flow diversion in the supine position was similar to previously published work,[22 28] although direct comparison with other studies is of limited interest because of the numerous factors that influence the response.

The factors responsible for reduced flow diversion in the prone compared with the supine position were not addressed specifically in our study. One mechanism, stated previously, is changes in haemodynamic state, particularly the increase in cardiac output that we and others have observed in the prone position. The results of Domino, Hlastala and Cheney are especially relevant in this respect.[28] In that study, cardiac output was increased by 85% using an external arteriovenous fistula during left lung hypoxia ($F_{I_{O_2}} = 0.04$) in supine dogs. The increase in blood flow was accompanied by a decrease from 63% to 48% in left lung hypoxic blood flow diversion. The results from that study suggest that the minute position-related changes in haemodynamic state that we observed cannot alone account for the posture-dependent alterations in flow diversion. Although speculative, it is possible that the asymmetry of the pulmonary circulation that normally balances the influence of gravity in the prone position[11] could account for the larger flow diversion in the supine position. The increased conductance to perfusion in dorsal lung regions[9] may work in concert with gravity by facilitating flow diversion in the supine position.

Data from retention and excretion of inert gases showed a significant increase in the fraction of ventilation to regions with high $\dot{V}_A/\dot{Q}$ ratios (10–100) during hypoxia, which is consistent with diversion of blood flow away from hypoxic lung regions. The increase in ventilation to these high $\dot{V}_A/\dot{Q}$ regions was significantly greater in the supine than in the prone position. This would normally be associated with less efficient gas exchange. However, it occurred under the conditions of the present experiment with split lungs, indicative of more effective separation of perfusion from ventilation in the supine than in the prone position. This observation is in agreement with perfusion data showing more efficient flow diversion in the supine position.

RELATIONSHIP TO THE CLINICAL SETTING

The split lung model can provide some valuable insights into the mechanisms that influence flow diversion by HPV, but cannot serve as a complete model of the complicated effects of HPV in diffuse lung pathology (i.e. ARDS). However, if the structure of the fractally branching pulmonary vasculature[11 34] plays a role in the observed effect, it is plausible that the same position-dependent influence exists on a smaller scale within each lung, with similar effects on the efficiency of regional gas exchange. This could have implications for patient care, among which posture-dependent effects of drugs that influence HPV can be expected. Less efficient flow diversion in the prone position may offset the beneficial influence of prone positioning on distribution of ventilation in ARDS, and thus explain why improvement in arterial oxygenation in the prone position is variable, and sometimes non-existent.[16]

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