A Hypoxic Pulmonary Vasoconstrictor Response in Dogs during and after Infusion of Sodium Nitroprusside

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The effect of sodium nitroprusside (SNP) on the pulmonary vasoconstrictor response to alveolar hypoxia was assessed by measuring the redistribution of blood flow in response to unilateral hypoxia. Ten dogs were anesthetized with thiopental and pentobarbital and a double-lumen endotracheal tube was inserted to permit separate ventilation of right and left lungs. Tidal volumes were maintained constant and redistribution of blood flow to each lung was followed by recording the radioactivity of mixed expired gas during the continuous intravenous infusion of 133Xe.

The pulmonary vasoconstrictor response was tested by ventilating the left lung with oxygen, 7 per cent, followed by 100 per cent nitrogen before, during and after an intravenous infusion of SNP. The experimental sequence was then repeated. Unilateral hypoxia consistently decreased blood flow to the hypoxic lung ($P < 0.02$), and there was no significant difference in flows during nonhypoxic conditions. Following infusion of SNP at a rate sufficient to decrease the mean arterial pressure to 80 torr there was a significant increase in flow ($P < 0.01$) to the nonhypoxic lung in response to both degrees of hypoxia. The second infusion of SNP blunted the pulmonary vasoconstrictor response to anoxia ($P < 0.001$), but the first infusion produced no significant blunting of response to either level of hypoxia. Arterial oxygen tension values increased significantly ($P < 0.05$) during hypoxic conditions following SNP infusion and were significantly decreased ($P < 0.05$) during the second infusion of SNP.

These results suggest that SNP may increase arterial hypoxemia by depressing the homeostatic diversion of blood flow away from hypoxic areas of the lung; on discontinuation of SNP, there may be an increased protective response to hypoxia. (Key words: Anesthetic techniques: hypotension, induced, sodium nitroprusside. Hypoxia: lung. Lung: blood flow; perfusion; vascular resistance.)

It has been clearly established that during localized alveolar hypoxia a response is evoked by which blood is diverted away from hypoxic areas to nonhypoxic areas of lung. It has been postulated that this mechanism may decrease arterial hypoxemia in patients with airway closure or pulmonary disease. This protective mechanism has been shown to be blunted by increased pulmonary vascular pressures and by certain anesthetic agents. Sodium nitro-

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Materials and Methods

Experiments were conducted on ten dogs of varied breeds, each weighing 14–26 kg. Each animal was anesthetized with thiopental, 20–30 mg/kg, iv, and pentobarbital, 10–20 mg/kg, iv. A cuffed endotracheal tube was passed and ventilation controlled mechanically. Cannulas were inserted for the measurement of arterial, pulmonary-artery and pulmonary capillary wedge pressures (Swan-Ganz catheter) and for arterial and mixed venous blood sampling. Additional catheters were inserted into the inferior vena cava for injection of indocyanine green, sodium nitroprusside, and xenon. A tracheostomy was then performed and a double-lumen tube passed. The cuff was inflated and the separation of the ventilation to each lung was checked by pressurizing each limb of the tube to +50 cm H₂O while the contralateral limb was connected to a tube dipping under the surface of water. Each limb of the double-lumen tube was connected to a nonrebreathing valve and separate second-stage ventilator circuit, which could be driven by the main ventilator at a frequency of 15 breaths/min (fig. 1). The tidal volume to each lung was adjusted to achieve an end-tidal carbon dioxide concentration of 4–4.5 per cent in each lung as measured by a continuous infrared analyzer (Hartmann and Braun URAS 4). 133Xenon dissolved in 50–100 ml of physiologic saline solution was continuously infused into the inferior vena cava at a rate of 1–2 mCi/hour, using a Braun continuous-infusion pump. The xenon was evolved continuously into alveolar gas and washed out by the tidal ventilation. The expired gas from each lung was passed through a fan-operated mixing unit into a glass coil situated within the collimator of a scintillation detector and the output from each

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Fig. 1. Ventilation circuit. The main ventilator drives two bellows in bottle systems. These aspirate the inspired gas from reservoirs and drive it through the nonrebreathing (collect) valves to the double-lumen tube. Expired gas passes to the mixing unit and scintillation detector.

detector was suitably processed to yield a continuous record of the radioactivity on each side on a potentiometric recorder 25 cm wide. Since tidal volumes were initially matched to blood flow and were then maintained constant throughout the experiment, the ratio of xenon counts between the two sides was proportional to the distribution of blood flow between the two lungs. Vascular and airway pressures were continuously recorded with strain gauges (Consolidated Electrodynamics) and a heated stylus recorder (Devices [M19]), while body temperature was measured with an esophageal probe and maintained close to 37°C by an operating table heater. Blood-gas values were determined in duplicate on two separate electrode systems (the ABL 12 and the standard Radiometer system, which were calibrated with standard gases and repeatedly checked by tonometered blood samples). Cardiac output was determined in triplicate by the indocyanine green dye-dilution technique, the curves being analyzed by the method of Simons and White.

The right lung was ventilated with 100 per cent oxygen throughout the experiment and the hypoxic vasoconstrictor response was assessed by measuring the diversion of blood flow in response to ventilation of the left lung with 7 per cent oxygen in nitrogen and with 100 per cent nitrogen. This test was performed before, during, and after the infusion of SNP and repeated during and after a second infusion of the drug. Blood-flow measurements were complemented by measurements of airway and vascular pressures, cardiac output, and blood-gas values when both lungs were being ventilated with oxygen and when 100 per cent nitrogen was being administered to the left lung.

The initial measurements of xenon counts, cardiac output, pressure and blood-gas values were initiated when stable conditions had been achieved after 20–30 min ventilation of each lung with oxygen. Oxygen, 7 per cent, was then administered to the left lung for 10 min and the xenon counts recorded. The ventilating gas to the left lung was then changed to nitrogen and 10 min later, a second complete set of measurements was obtained. Both lungs were then ventilated with oxygen and an infusion of SNP 0.02 per cent, was commenced. The infusion rate was adjusted to produce a mean arterial pressure of 80 torr. When conditions were stable, a third complete set of measurements was obtained. The hypoxic response was then tested as before and a fourth complete set of measurements obtained after 10 min of ventilation with nitrogen. The infusion was stopped, both lungs were ventilated with oxygen, and arterial pressure was allowed to increase. A fifth complete set of meas-
measurements was obtained when conditions had been stable for 20–30 min. The hypoxic sequence was repeated and the sixth full set of measurements was made during ventilation of the left lung with 100 per cent nitrogen. The infusion of SNP was then repeated, with a similar sequence of measurements during and after the infusion.

Statistical analysis was done by the two-sided t test. The differences between natural logarithms of right-to-left lung flow ratios at different stages of experimentation were analyzed. The logarithmic transformation tends to make such data approximately normally distributed, thus ensuring the applicability of the t test. P < 0.05 was regarded as significant.

Results

In the absence of hypoxic stimulus there was no significant change in the distribution of blood flow to each lung throughout the experiment. The unilateral administration of nitrogen consistently produced a significant diversion of blood flow away from the hypoxic lung (P < 0.02). A typical example of xenon counts in expired gases from each lung is shown in figure 2. However, the magnitudes of the responses to both degrees of hypoxia after the first drug administration were greater than the first set of control responses (P < 0.05) (fig. 3). The hypoxic responses recorded during the first period of SNP administration were significantly smaller than the responses during the second control period but not significantly different from those obtained in the first control period (fig. 3). The responses obtained during the second SNP administration were significantly different from those obtained during the third control period, but only the nitrogen response was significantly different from that in the second control period (fig. 3).

Unilateral administration of nitrogen always produced a significant decrease in PaO₂ (fig. 3). The second control period showed a significant increase in PaO₂ during unilateral hypoxia compared with the first control period and compared with values measured during both SNP infusions. After discontinuation of the second infusion of SNP there was a significant increase in PaO₂ during unilateral hypoxia (fig. 3). There was no significant difference among mixed venous oxygen tension (PvO₂) values during hypoxia at any stages of the experiment (fig. 3), nor were there any significant changes in cardiac output (Q) (fig. 4). Arterial blood CO₂ tension (PaCO₂) did not change during nonhypoxic conditions throughout the experiment, but it did increase significantly during unilateral hypoxia, except during the second control period. The R/L ratio of end-tidal CO₂ increased significantly during unilateral hypoxia. During the second control period there was a significant increase in R/L ratio of end-tidal CO₂ compared with the ratios during infusions of SNP. Excluding the second drug infusion,
pulmonary-artery pressure (P\textsubscript{PA}) increased in
response to hypoxia (fig. 4). SNP did not change P\textsubscript{PA}
from control, but after discontinuation of the in-
fusion there was a significant increase during hypoxia
(fig. 4). There was no change in pulmonary artery
wedge pressure (P\textsubscript{LW}) with infusion, but after SNP
was stopped there was a significant increase during
hypoxia compared with the initial control value.

Discussion

Administration of oxygen, 7 per cent, followed by
nitrogen, to one lung caused a stepwise decrease in
flow to the hypoxic lung, with compensatory increases
in flow to the opposite lung. The magnitude of this
response was significantly higher during the second
and third control periods than during the initial
period. During the initial infusion there was no
blunting of the vasoconstrictor response with 100 per
cent nitrogen, but there was a significant decrease in
diversion during administration of oxygen, 7 per cent,
compared with the first control value. Both periods of
SNP administration produced significant depression
of the response when compared with the second and
third control periods. The results were confirmed by
changes in the ratios of end-tidal CO\textsubscript{2} concentrations
and in \textit{P}_{\text{A}}O\textsubscript{2} values observed throughout the study.

Depression of the hypoxic vasoconstrictor response
by SNP\textsuperscript{18,19,20,21} and by a number of inhalational anesthet-
ic agents has been observed in both animals and man,\textsuperscript{22,23,24}
although the mechanism is unknown. SNP may have a
direct effect on the pulmonary circulation. Calculated pulmonar-y vascular resistance when both
lungs were ventilated with oxygen was slightly greater
during both periods of SNP infusion than during the
three control periods. However, this would be
expected because cardiac output was decreased so that
fewer pulmonary vessels would have been perfused. It
has been suggested that SNP may act on the
precapillary vasculature,\textsuperscript{15} which is thought to be the
major site of hypoxic vasoconstriction. The cause of
increased hypoxic response after administration of
SNP is not clear, and the effect of time must be
considered. Nine dogs were exposed to 20 min of uni-
lateral hypoxia with nitrogen alternated with equal
periods of bilateral ventilation with oxygen for periods
of two to four hours; five dogs showed no difference in
magnitudes of diversion, while two showed increases in
diversion and in two there were decreases with time.

The effect of depression of the response on arterio-
oxygen tension is illustrated by the \textit{P}_{\text{A}}O\textsubscript{2} values found

\textsuperscript{\textsection} Arkin DB, Wahrenbrock EA: Hypoxemia following nitro-
prusside administration: Effect of cardiac output and pulmonary
autoregulation (abstr). American Society of Anesthesiologists

\textbf{Fig. 4.} Changes in cardiac output (Q), mean aortic pressure
(P\textsubscript{Ao}), mean pulmonary arterial pressure (P\textsubscript{PA}) and mean pulmonar-
y artery wedge pressure (P\textsubscript{LW}) at various stages of the experiment.
Results are means ± SEM.

in this study (fig. 2). During the control hypoxic
period, when diversion of flow was maximal, \textit{P}_{\text{A}}O\textsubscript{2} did
not decrease to below normal values. However, dur-
ing SNP infusion depression of the response was
associated with a decrease in \textit{P}_{\text{A}}O\textsubscript{2} although \textit{P}_{\text{V}}O\textsubscript{2} was
not significantly different from that existing during
the control hypoxic responses. The observed values of
\textit{P}_{\text{A}}O\textsubscript{2} during one-lung ventilation with nitrogen do not
give a fair indication of the values that would be ex-
pected if blood flow had been diverted from a non-
ventilated area of lung. During nitrogen ventilation
oxygen leaves the mixed venous blood so that the end-
pulmonary capillary oxygen tension (P\textsubscript{C}O\textsubscript{2}) in the
hypoxic lung is lower than mixed venous oxygen
tension. Under such circumstances P\textsubscript{C}O\textsubscript{2} depends on
the ventilation/perfusion ratio in the hypoxic lung.
When this is high, as it is during maximal diversion
of blood flow, P\textsubscript{C}O\textsubscript{2} is very low; when diversion is less,
P\textsubscript{C}O\textsubscript{2} is higher. During diversion the admixture of blood
having very low P\textsubscript{C}O\textsubscript{2} with blood from the oxygenated
lung will therefore tend to produce a lower \textit{P}_{\text{A}}O\textsubscript{2} than
would have been the case had P\textsubscript{C}O\textsubscript{2} equalled P\textsubscript{C}O\textsubscript{2}. Our
observed values of \textit{P}_{\text{A}}O\textsubscript{2} with diversion will thus under-
estimate the values likely to be found in the clinical
situation, although Benumof et al. concluded that the mechanism of a decrease in blood flow through atelectatic lung is mainly hypoxic pulmonary vasoconstriction, and that experiments performed utilizing ventilation hypoxia may also be applicable to atelectasis. Colley et al. found that SNP decreased P\textsubscript{A}\textsubscript{O\textsubscript{2}} and increased Q\textsubscript{A}/Q\textsubscript{S} by reversing the hypoxic pulmonary vasoconstriction. Our results would tend to confirm this conclusion, although our method cannot detect intrapulmonary shunt flows. The continuous-xenon-infusion technique for measuring the partition of blood flow between the lungs utilized in this study is dependent on ventilation/perfusion ratio. When this ratio is high, alveolar concentration of xenon is low, resulting in an increased washout of xenon. Low ventilation/perfusion ratios result in decreased washout and increased concentrations of xenon in end-pulmonary capillary blood. When tidal volume is kept constant and flow varies, as in this study, an increase in perfusion will result in an increased end-pulmonary capillary xenon concentration and an underestimation of actual flow. Conversely, when flows are decreased they will be overestimated.

The results of this study suggest that SNP depresses the protective response of hypoxic pulmonary vasoconstriction and, although this is unlikely to be of much importance in patients with normal lungs, it may well account for at least part of hypoxemia seen when SNP is administered to patients who have ventilation/perfusion inequalities resulting from anesthesia or pulmonary disease.

References


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