

Ventilation-Perfusion and Gas Exchange Effects of Sodium Nitroprusside in Dogs with Normal and Edematous Lungs

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This study was designed to investigate the mechanism by which sodium nitroprusside (SNP) decreases oxygenation by determining its effects on venous admixture (\dot{Q}_{VA}/\dot{Q}_t) and ventilation-perfusion distribution (\dot{V}_A/\dot{Q}) in animals with normal and abnormal lungs. SNP was infused into seven dogs anesthetized with pentobarbital. Mean blood pressure was decreased by 40 per cent during normal lung function and again after the production of diffuse pulmonary edema by intravenous administration of oleic acid. Measurements of blood-gas values, \dot{Q}_{VA}/\dot{Q}_t and \dot{V}_A/\dot{Q} by the inert-gas-elimination method were taken before, during, and after SNP infusion during ventilation with air and then during ventilation with 100 per cent oxygen in each pulmonary condition. SNP caused no change in cardiac output (\dot{Q}_t) during normal lung function or after the production of pulmonary edema. SNP had no effect on pulmonary gas exchange during normal lung function. During pulmonary edema and ventilation with air, SNP decreased P_{aO_2} from 71 ± 7 torr (mean \pm 1 SD) to 61 ± 11 torr ($P < .01$), and increased \dot{Q}_{VA}/\dot{Q}_t (oxygen method) from 20 ± 8 to 38 ± 18 per cent ($P < .01$). The increase in \dot{Q}_{VA}/\dot{Q}_t correlated well with a 28 per cent decrease in pulmonary vascular resistance (PVR) ($r = -.863$). During pulmonary edema with air and ventilation SNP increased \dot{V}_A/\dot{Q} maldistribution, but during ventilation with oxygen, SNP caused no significant change in \dot{Q}_t/\dot{Q}_t , PVR, or \dot{V}_A/\dot{Q} . The increase in \dot{Q}_{VA}/\dot{Q}_t and increases in perfusion to low \dot{V}_A/\dot{Q} regions seen only in animals with pulmonary edema during ventilation with air are compatible with the hypothesis that nitroprusside impairs pulmonary gas exchange by inhibiting hypoxic vasoconstriction, thus increasing \dot{V}_A/\dot{Q} maldistribution. (Key words: Anesthetic techniques, hypotension, induced, nitroprusside. Lung: blood flow; edema; shunting; hypoxic vasoconstriction; perfusion.)

THE SAFETY of controlled hypotension depends upon the maintenance of adequate oxygen delivery to various organs. Oxygen delivery in turn depends on both the maintenance of blood flow and the adequacy of arterial oxygenation. Sodium nitroprusside (SNP), a potent vasodilator, is frequently used to produce controlled hypotension. Some investigators¹⁻³ have

found that it has no effect on pulmonary gas exchange, while others have shown that SNP may decrease arterial oxygenation^{4,5} and increase venous admixture.^{6,7}

The purpose of this study was to elucidate the mechanism by which SNP impairs pulmonary gas exchange. We have previously shown that SNP decreases arterial oxygenation and increases intrapulmonary shunting (\dot{Q}_s/\dot{Q}_t) in the presence of regional atelectasis.⁸ We suggested that it acted directly to increase \dot{Q}_s/\dot{Q}_t by inhibiting hypoxic pulmonary vasoconstriction. Regional atelectasis, however, not only causes hypoxic vasoconstriction, but also produces hydrostatic gradients which, in the presence of pulmonary-artery hypotension, result in a disproportionate increase in vascular resistance of the ventilated lung.⁸ In the present study we used a model of diffuse pulmonary injury produced by oleic acid⁹ to investigate the effects of SNP on pulmonary gas exchange and \dot{V}_A/\dot{Q} . Oleic acid induces diffuse pulmonary edema and hypoxia but avoids the hydrostatic effects produced when hypoxia and hypoxic vasoconstriction are the result of regional atelectasis. If nitroprusside exerts its effects on oxygenation by inhibition of hypoxic vasoconstriction, then changes in gas exchange caused by SNP should depend on the presence of pre-existing pulmonary injury and the inspired oxygen concentration.

Materials and Methods

The effects of nitroprusside on gas exchange and \dot{V}_A/\dot{Q} were studied during four situations: normal lung function at inspired oxygen fractions ($F_{I_{O_2}}$) of .21 and 1.0, and impaired lung function at $F_{I_{O_2}} = .21$ and 1.0. Seven mongrel dogs (weights 20-40 kg) without evidence of pulmonary abnormalities, *i.e.*, fever, cough, or abnormal lung sounds, were studied. Each was anesthetized with pentobarbital, 30 mg/kg, iv. The trachea was intubated with a cuffed endotracheal tube and the dog placed in the prone position. The animal was then paralyzed with succinylcholine, 5 mg/kg, and the lungs ventilated with room air ($F_{I_{O_2}} = .21$) at a tidal volume of 12-15 ml/kg with a frequency sufficient to maintain P_{aCO_2} approximately 35 torr. Once established, ventilation was not adjusted again during the experiment. Using sterile surgical technique, pulmonary-artery (thermodilution)

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TABLE 1. Systemic Hemodynamic Values in Dogs before, during, and after Sodium Nitroprusside (SNP) Administration

	Normal Lungs						Pulmonary Edema					
	Air Ventilation			Oxygen Ventilation			Air Ventilation			Oxygen Ventilation		
	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP
Heart rate (beats/min)	159 ± 14	157 ± 18	159 ± 13	140 ± 58	171 ± 15	161 ± 13	151 ± 25	163 ± 17	163 ± 17	166 ± 24	182 ± 27	160 ± 22
\dot{Q}_t (l/min)	5.27 ± 1.22	5.18 ± 1.08	6.09 ± 1.74	6.29 ± 1.71	5.54 ± 0.94	7.05 ± 1.92	4.67 ± 1.79	4.53 ± 1.49	5.20 ± 1.91	5.24 ± 2.05	4.83 ± 2.16	5.33 ± 1.50
MAP (torr)	138† ± 13	63† ± 8	124 ± 8	127† ± 8	65† ± 7	113 ± 22	119† ± 14	64† ± 13	111 ± 8	115† ± 8	57† ± 13	103 ± 17
SVR (dyne.sec cm ⁻⁵)	2,198† ± 584	1,016* ± 252	1,746 ± 512	1,731† ± 523	916 ± 90	1,335 ± 339	2,316† ± 919	1,174* ± 206	1,880 ± 562	1,976† ± 698	1,028 ± 280	1,605 ± 568
Dose of SNP (μg/kg/min)		43 ± 18			64 ± 47			26 ± 16			26 ± 16	

Mean values ± 1 SD; n = 7. \dot{Q}_t = cardiac output; MAP = mean arterial pressure; SVR = systemic vascular resistance.

* .01 < P < .05 between successive values.
† P < .01 between successive values.

and systemic arterial catheters were placed via an external jugular vein and forepaw arterial vessels, respectively.

Initial studies were done at $F_{I_{O_2}}$.21. After control measurements of vascular pressures and gas exchange, SNP, .1 per cent, was infused with a Harvard infusion pump until mean arterial pressure (MAP) had decreased to approximately 60 torr. After 15 min at the decreased pressure, measurements were repeated. Nitroprusside infusion was then stopped and measurements were again repeated 20 min after the blood pressure returned to control levels.

Following measurements in dogs with normal lungs, the intravascular catheters were filled with heparin and covered with plastic protective dressings. The animals were allowed to recover from the effects of anesthesia for 24 hours. On the following day, diffuse pulmonary injury was produced by injecting oleic acid, .06–.07 ml/kg, into the right atrium. This dose of oleic acid produces a fairly predictable and stable noncardiogenic pulmonary edema, with the peak extent of injury occurring 24 hours after injection. § Therefore, 24 hours after oleic acid injection the animals were reanesthetized and the effects of nitroprusside again assessed, first at $F_{I_{O_2}}$.21 and then at $F_{I_{O_2}}$ 1.0 as previously described. Following studies of both normal lungs and those with pulmonary edema, the ability of the lung to respond to alveolar hypoxia was tested by ventilating the lungs with oxygen, 10 per cent, and observing the change in pulmonary vascular resistance (PVR).

Vascular pressures and thermodilution cardiac output (\dot{Q}_t) values were measured during each control and SNP treatment period. Systemic arterial, pulmonary arterial (PAP), and airway (P_{airway}) pressures were monitored continuously and pulmonary wedge pressures (PAW) were monitored intermittently. Systemic vascular resistance (SVR) in dyne.sec cm⁻⁵ was calculated using the formula $SVR = MAP \times 80/\dot{Q}_t$. Pulmonary vascular resistance (PVR) was calculated as $PVR = (\overline{PAP} - PAW) \times 80/\dot{Q}_t$. Systemic arterial and pulmonary arterial blood samples were drawn, placed in ice, and analyzed for P_{O_2} , P_{CO_2} , and pH on a blood-gas analyzer (Radiometer, Model BMS3 MK2). Arterial blood samples were measured within 2–3 min after collection to minimize errors in P_{O_2} measurement. The analyzer was calibrated with 100 per cent oxygen prior to measuring arterial blood samples with expected P_{O_2} values greater than 300 torr and calibrated with room air prior to determining blood-gas values of the remaining arterial and mixed venous blood samples. P_{O_2} values were multiplied by a factor of 1.04 to correct for the difference between blood and gas calibration. Hemoglobin (Hb) was measured using a Co-oximeter (Instrumentation Laboratories, Model IL182) calibrated for dog hemoglobin. Hb saturation was determined from the blood-gas values using a program developed by Ruiz *et al.*¹⁰ and modified for use in dogs.¹¹ Arterial and mixed venous blood oxygen content values were determined from blood-gas, saturation, and Hb values where content = per cent saturation × Hb × 1.34 + 0.0031 P_{O_2} . \dot{Q}_{VA}/\dot{Q}_t during air

§ Modell HI, Cheney FW: A stable pulmonary edema model in dogs (abstr). Am Rev Resp Dis 115(4):358, 1977.

¹¹ Ruiz BC, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida: Personal communication.

ventilation and \dot{Q}_s/\dot{Q}_T during ventilation with oxygen were calculated using the standard oxygen method. The dead space-to-tidal volume ratio (V_D/V_T) was calculated using the Enghoff modification of the Bohr equation.

The multiple-inert-gas-infusion technique of Wagner *et al.*¹¹ was used to measure the effect of nitroprusside on \dot{V}_A/\dot{Q} . A mixture of six gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone) with different blood-gas solubilities dissolved in saline solution was infused into a leg vein continuously at a rate of approximately 3 ml/min, beginning at least 30 min before the first measurements. Samples of arterial blood, mixed venous blood, and mixed expired gas were collected at the same time as the other measurements and blood sampling were done. Blood and expired gas samples were analyzed for their relative gas concentrations using a gas chromatograph (Beckman, Model GC 72-5) with a flame ionization detector and electron-capture detector (Analog Technology). The retention (P_A/P_V) *vs.* solubility and the excretion (P_E/P_V) *vs.* solubility curves were then plotted, using methods described previously.¹² These curves reflect the particular distribution of ventilation-perfusion ratios that produce them. Retention and excretion plots were also converted by computer analysis to distributions reflecting the relationship between perfusion and ventilation as a function of \dot{V}_A/\dot{Q} ranging from 0.005 to 100, as well as shunt (\dot{V}_A/\dot{Q} less than .005) and dead space (\dot{V}_A/\dot{Q} greater than 100.0).¹³ Derived \dot{V}_A/\dot{Q} distributions were used to calculate predicted arterial blood-gas values. The inert gas venous admixture

was calculated using the standard oxygen method from the predicted blood-gas values.

The data were analyzed by two-way analysis of variance, followed by multiple-comparison procedures comparing all pairs of means by the Newman-Keuls test.¹⁴ Changes in P_{aO_2} values, however, were compared using Student's *t* test for paired data rather than analysis of variance because of the alinear relationship between P_{O_2} and oxygen content. The inert gas elimination data were analyzed by Student's *t* test for paired data. Because of technical problems, inert gas values were measured during pulmonary edema and air ventilation in seven dogs, but in only six dogs in each of the other three situations. Unless otherwise noted, only the significant effects of SNP in comparison with control values are reported.

Results

Nitroprusside produced similar effects on systemic hemodynamics in normal and oleic acid-injured lungs at both $F_{I_{O_2}}$.21 and $F_{I_{O_2}}$ 1.0 (table 1). There was no significant effect on heart rate (HR) or \dot{Q}_l . There were, however, significant decreases in mean arterial pressure (MAP) of approximately 50 per cent and of SVR of approximately 45 per cent in each situation. After oleic acid had been administered, the dose of SNP necessary to decrease MAP to the same values as in normal lungs decreased by about 50 per cent.

Nitroprusside had no effect on PAP in normal animals, but decreased PAP significantly during pulmonary edema at both levels of $F_{I_{O_2}}$ (table 2). There was no significant effect on PAW. PVR was decreased significantly only during pulmonary edema and venti-

TABLE 2. Pulmonary Dynamic Values in Dogs before, during, and after Sodium Nitroprusside (SNP) Administration

	Normal Lungs						Pulmonary Edema					
	Air Ventilation			Oxygen Ventilation			Air Ventilation			Oxygen Ventilation		
	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP
\overline{PAP} (cm H ₂ O)	17 ± 3	14 ± 2	18 ± 4	18 ± 4	13 ± 2	17 ± 3	21† ± 5	15* ± 6	20 ± 6	19* ± 5	14 ± 4	17 ± 5
PAW (cm H ₂ O)	5 ± 2	4 ± 2	4 ± 2	5 ± 2	4 ± 1	4 ± 3	2 ± 2	0 ± 1	2 ± 2	2 ± 2	1 ± 2	2 ± 2
PVR (dyne.sec cm ⁻⁵)	179 ± 38	156 ± 31	192 ± 41	175 ± 34	139 ± 18	158 ± 33	366* ± 148	262 ± 137	313 ± 113	279 ± 92	251 ± 100	221 ± 77
P_{airway} (cm H ₂ O)	8 ± 1	9 ± 1	9 ± 2	9 ± 1	8 ± 1	9 ± 1	15 ± 4	15 ± 6	15 ± 4	14 ± 4	14 ± 4	14 ± 4
V_D/V_T	.56 ± .08	.61 ± .07	.52 ± .08	.58 ± .09	.63 ± .08	.59 ± .09	.56 ± .11	.62 ± .10	.58 ± .10	.59 ± .13	.66 ± .08	.61 ± .10

Mean values ± 1 SD; n = 7. \overline{PAP} = mean pulmonary arterial pressure; PAW = pulmonary-artery wedge pressure; PVR = pulmonary vascular resistance; P_{airway} = peak airway pressure; V_D/V_T

= dead space-to-tidal volume ratio.
* .01 < P < .05 between successive values.
† P < .01 between successive values.

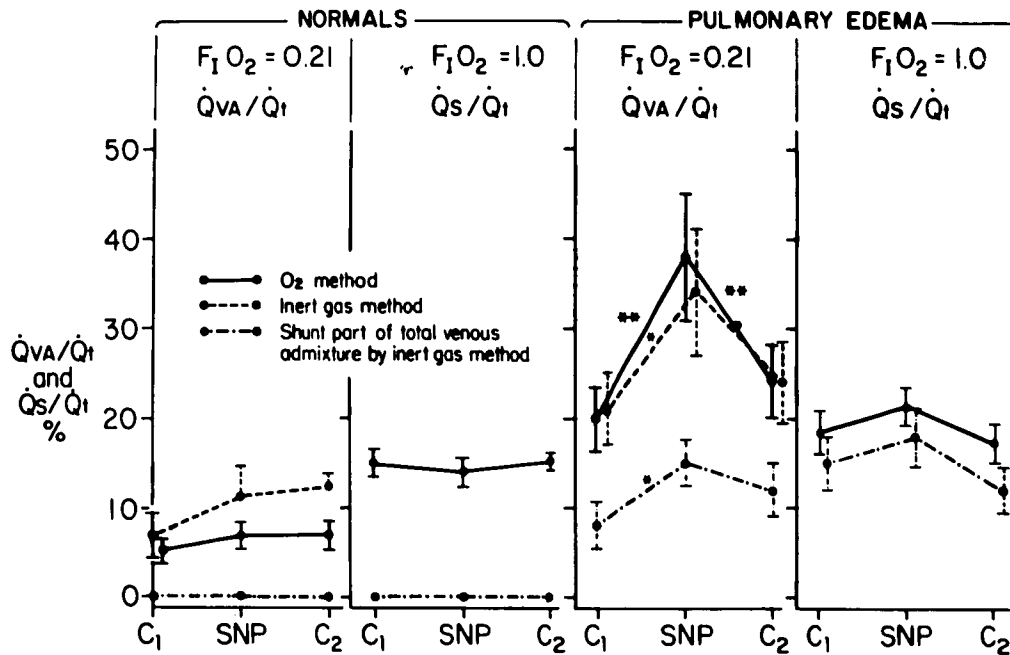


FIG. 1. Effects of SNP on \dot{Q}_{VA}/\dot{Q}_I and \dot{Q}_S/\dot{Q}_I under the different experimental conditions. Mean values \pm SE, $n = 7$; * $0.01 < P < 0.05$ between values, ** $P < 0.01$ between values.

lation with air. When the animals were ventilated with oxygen, 10 per cent, at the end of the experiment, PVR increased significantly by 52 per cent (170 ± 15 to 259 ± 43 dyne.sec cm^{-5}) during pulmonary edema. In none of the situations was there a significant change in airway pressure or V_D/V_T .

During normal lung function, nitroprusside caused no change in either \dot{Q}_{VA}/\dot{Q}_I or \dot{Q}_S/\dot{Q}_I at the different inspired oxygen levels (fig. 1, tables 3 and 4). When $F_{I_{O_2}}$ was increased from .21 to 1.0 during normal lung function, \dot{Q}_S/\dot{Q}_I was increased and markedly higher

than the inert gas shunt. The increased \dot{Q}_S/\dot{Q}_I value may have been due to difficulty in accurately measuring high $P_{a_{O_2}}$ values.¹⁵ Once the animals had pulmonary edema and were breathing room air, nitroprusside caused significant increases in \dot{Q}_{VA}/\dot{Q}_I . The oxygen method value went from 20 to 38 per cent and the inert-gas venous-admixture method value from 21 to 34 per cent. There was also a significant increase in the inert gas shunt component, which went from 8 to 15 per cent. There was a highly significant negative correlation between \dot{Q}_{VA}/\dot{Q}_I (oxygen method) and

TABLE 3. Pulmonary Gas Exchange Effects in Dogs before, during, and after Sodium Nitroprusside (SNP) Administration

	Normal Lungs						Pulmonary Edema					
	Air Ventilation			Oxygen Ventilation			Air Ventilation			Oxygen Ventilation		
	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP
\dot{Q}_S/\dot{Q}_I (per cent) or \dot{Q}_{VA}/\dot{Q}_I (per cent)	6 ± 4	7 ± 3	7 ± 3	15 ± 4	14 ± 5	15 ± 4	20† ± 8	38† ± 18	24 ± 10	18 ± 7	21 ± 6	17 ± 7
$P_{a_{O_2}}$ (torr)	94 ± 8	93 ± 7	95 ± 11	541 ± 21	542 ± 29	538 ± 26	71† ± 7	61* ± 11	68 ± 9	427* ± 94	352* ± 107	421 ± 103
$P_{a_{CO_2}}$ (torr)	32 ± 3	33 ± 7	33 ± 5	31 ± 10	35 ± 7	37 ± 9	31 ± 5	35 ± 5	33 ± 3	33 ± 3	38 ± 7	40 ± 8
pH_a	7.39 $\pm .06$	7.36 $\pm .07$	7.37 $\pm .07$	7.41 $\pm .10$	7.35 $\pm .06$	7.34 $\pm .06$	7.37 $\pm .05$	7.33 $\pm .07$	7.35 $\pm .06$	7.35 $\pm .06$	7.31 $\pm .10$	7.29 $\pm .10$
$P\bar{V}_{O_2}$ (torr)	46 ± 8	46 ± 9	49 ± 9	75 ± 24	72 ± 21	75 ± 23	42 ± 7	43 ± 8	44 ± 6	62 ± 16	63 ± 14	65 ± 15
$P\bar{V}_{CO_2}$ (torr)	37 ± 3	37 ± 5	37 ± 4	38 ± 7	41 ± 8	43 ± 7	39 ± 6	41 ± 7	41 ± 6	39 ± 6	48 ± 8	49 ± 9
pH_v	7.37 $\pm .05$	7.34 $\pm .06$	7.35 $\pm .07$	7.36 $\pm .08$	7.32 $\pm .07$	7.32 $\pm .06$	7.34 $\pm .05$	7.31 $\pm .07$	7.31 $\pm .07$	7.31 $\pm .05$	7.29 $\pm .08$	7.28 $\pm .08$

Mean values ± 1 SD; $n = 7$; $a =$ arterial; $\bar{v} =$ mixed venous.
* $.01 < P < .05$ between successive values.

† $P < .01$ between successive values.

PVR caused by nitroprusside in the animals with pulmonary edema during ventilation with air (fig. 2). During this situation only, nitroprusside increased the ventilation-perfusion maldistribution (figs. 3 and 4). The log standard deviation (log SD) of the perfusion distribution (an index of perfusion dispersion) increased, and there was an increase in the arterial-alveolar difference for each inert gas, indicating increased maldistribution of \dot{V}_A/\dot{Q} (table 4).

When the lungs with pulmonary edema were ventilated with oxygen, the initial control inert gas shunt value was 15 ± 7 per cent. While this value was not significantly different from the post-nitroprusside control value during ventilation with air, it was significantly higher than the prenitroprusside control value of 8 ± 7 per cent during ventilation with air. When nitroprusside was infused during pulmonary edema and ventilation with oxygen, there was no significant change in either oxygen or inert gas shunt values.

Nitroprusside produced no significant change in arterial or mixed venous blood-gas values during normal lung function at either $F_{I_{O_2}}$ (table 3). During pulmonary edema and ventilation with air, $P_{a_{O_2}}$ decreased significantly. During pulmonary edema and ventilation with oxygen, $P_{a_{O_2}}$ decreased significantly also, although there was no significant change in \dot{Q}_s/\dot{Q}_t or \dot{Q}_t .

Discussion

Nitroprusside in our study caused no change in $P_{a_{O_2}}$, \dot{Q}_{VA}/\dot{Q}_t or \dot{Q}_s/\dot{Q}_t in the normal lungs at either $F_{I_{O_2}}$. There was also no change in PVR when ventilation was changed from air to oxygen, suggesting the absence of significant amounts of hypoxic vasoconstriction. These observations are consistent with

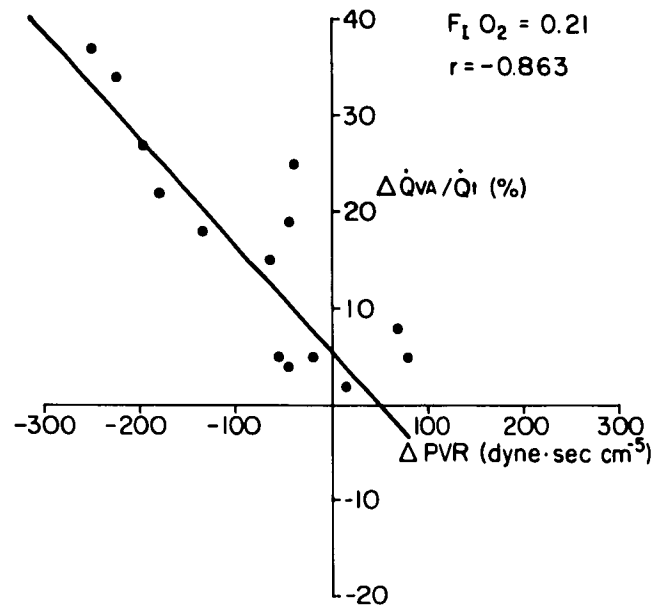


FIG. 2. Changes in \dot{Q}_{VA}/\dot{Q}_t vs. changes in PVR before and after SNP in seven dogs ventilated with $F_{I_{O_2}} = 0.21$ during pulmonary edema.

the findings that nitroprusside causes no change in gas exchange in anesthetized patients^{1,2} or dogs.³

In contrast to the lack of effect during normal lung function, SNP markedly impaired pulmonary gas exchange once pulmonary edema had been induced when the animals' lungs were ventilated with air. SNP caused significant decreases in $P_{a_{O_2}}$, marked increases in \dot{Q}_{VA}/\dot{Q}_t , and increases in perfusion to lung areas with low \dot{V}_A/\dot{Q} ratios. The log SD of the perfusion mode and the area under the arterial-alveolar difference-solubility curve were also increased. We have previously shown the latter index to be a useful quantifier of \dot{V}_A/\dot{Q} maldistribution.¹²

TABLE 4. Ventilation-Perfusion Effects of Sodium Nitroprusside (SNP) Determined by the Inert-gas-elimination Method

	Normal Lungs						Pulmonary Edema					
	Air Ventilation (n = 6)			Oxygen Ventilation (n = 6)			Air Ventilation (n = 7)			Oxygen Ventilation (n = 6)		
	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP	Pre-SNP	SNP	Post-SNP
Log SD perfusion	.470 ± .125	.611* ± .082	.467 ± .067	.601 ± .178	.551 ± .075	.508 ± .112	.722* ± .188	.950* ± .374	.691 ± .131	.800 ± .086	.948 ± .270	.652 ± .150
\dot{Q}_{VA}/\dot{Q}_t (per cent)	7 ± 7	11 ± 9	12 ± 5	0.0	0.1 ± 0.2	0.3 ± 0.6	21* ± 11	34* ± 19	24 ± 12	15 ± 7	18 ± 9	12 ± 6
Shunt (per cent)	0.0	0.0	0.0	0.0	0.1 ± 0.2	0.3 ± 0.6	8* ± 7	15 ± 7	12 ± 8	15 ± 7	18 ± 9	12 ± 6
a-A area (dimensionless)	.502 ± .144	.625 ± .140	.510 ± .103	.569 ± .176	.644 ± .193	.560 ± .160	.318† ± .192	.550* ± .234	.359 ± .141	.441 ± .207	.473 ± .247	.367 ± .163

Mean values ± 1 SD; log SD = log standard distribution of perfusion mode; a-A area = area under the arterial-alveolar difference-solubility curve.

* .01 < P < .05 between successive values.
† P < .01 between successive values.

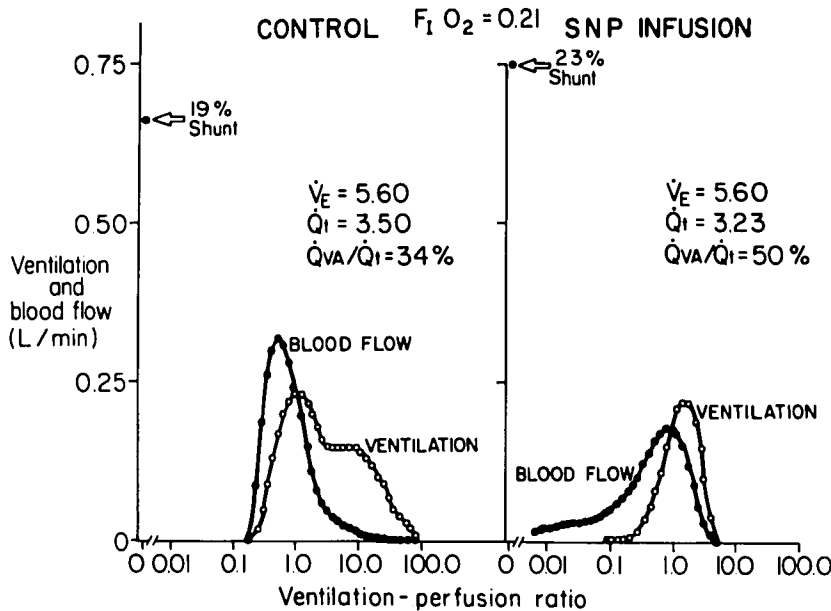


FIG. 3. Example of SNP increasing perfusion to low \dot{V}/\dot{Q} units while causing little effect on shunt flow in one dog with pulmonary edema. $F_{I O_2} = 0.21$. The inert-gas \dot{V}_D/\dot{V}_T increased, accounting for the apparent decrease in ventilation to high \dot{V}/\dot{Q} units.

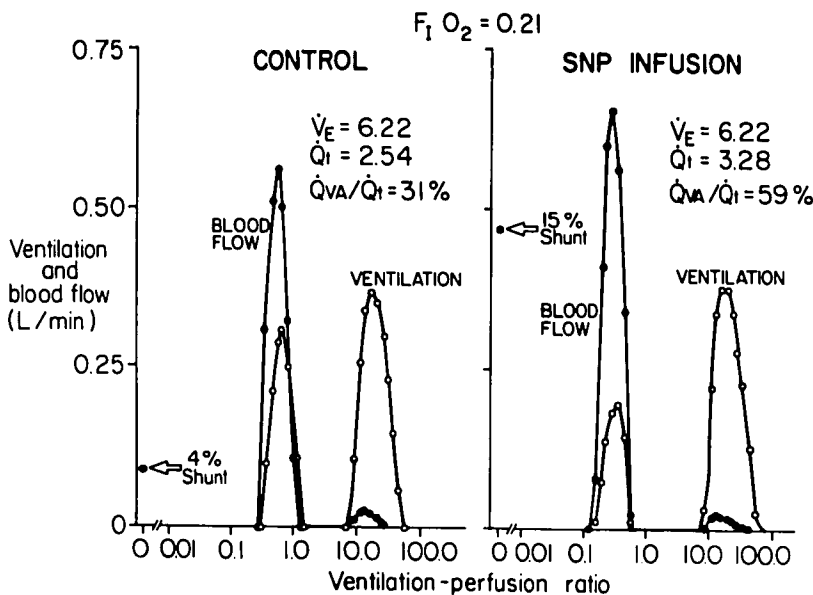


FIG. 4. Example of SNP increasing shunt flow and decreasing the mean \dot{V}/\dot{Q} of the perfusion mode in one dog with pulmonary edema. $F_{I O_2} = 0.21$. Note that there was no change in the symmetry of the perfusion mode. The bimodal ventilation pattern seen may have been due to positive-pressure ventilation as described by Dueck *et al.*¹⁶

The inverse relationship between PVR and \dot{Q}_{VA}/\dot{Q}_I in the animals with pulmonary edema during ventilation with air indicates that SNP has a disproportionate vasodilating effect on vessels perfusing hypoxic areas of the lung. These vessels are likely to have increased vascular tone due to hypoxic vasoconstriction. Previous studies have shown that the relaxant effect of nitroprusside on vascular smooth muscle is greatest on vessels undergoing active contraction. Arkin *et al.*** found that nitroprusside restored flow

to lung in which hypoxic vasoconstriction was induced by nitrogen ventilation. As in our study, Knapp *et al.*¹⁷ found that nitroprusside produced a greater decrease in PVR in patients with the highest values of PVR. Nitroprusside exerts a marked, dose-dependent relaxant effect on isolated bovine veins contracted by epinephrine, but little effect on relaxed bovine veins.¹⁸

When the animals with pulmonary edema were ventilated with oxygen, there was a small increase in the initial inert gas shunt value. This value was significantly higher than the pre-SNP control value during ventilation with air. A likely explanation is that oxygen caused some absorption atelectasis or release of hypoxic vasoconstriction, as found by Wagner *et al.*¹⁹

** Arkin DB, Wahrenbrock EA: Hypoxemia following nitroprusside administration: Effect of cardiac output and pulmonary autoregulation (abstr). American Society of Anesthesiologists, Annual Meeting, 1975, p 161.

in older human subjects breathing 100 per cent oxygen.

During pulmonary edema, when ventilation was with oxygen, SNP caused a significant decrease in $P_{a_{O_2}}$ even though there was no significant change in \dot{Q}_t or \dot{Q}_s/\dot{Q}_t . This is because small changes in arterial blood oxygen content cause large changes in $P_{a_{O_2}}$. The small decrease in arterial blood oxygen content was due to a combination of an insignificant decrease in \dot{Q}_t and an insignificant increase in \dot{Q}_s/\dot{Q}_t . The lack of effect of SNP on \dot{Q}_s/\dot{Q}_t probably occurred because inhalation of oxygen increased alveolar P_{O_2} to above the threshold for hypoxic vasoconstriction in poorly ventilated alveoli by diffusion. Another possibility is that the increase in mixed venous blood oxygen tension ($P\bar{v}_{O_2}$) reversed hypoxic vasoconstriction in unventilated areas. Both Barer *et al.*²⁰ and Bergofsky²¹ have shown that changes in $P\bar{v}_{O_2}$ in this range affect pulmonary vascular tone.

Selzer *et al.*⁵ concluded that nitroprusside decreased arterial blood $P_{a_{O_2}}$ by "opening of intrapulmonary shunts." In our study, however, no change in shunt flow occurred during normal lung function. Our results indicate that nitroprusside does not open anatomic intrapulmonary shunts, as the presence of such shunts should be unaffected by the extent of abnormality of the lung. Mookherjee *et al.*⁷ found that nitroprusside increased venous admixture in patients with congestive heart failure, and attributed the mechanism to the concurrent increase in cardiac output. In the present study nitroprusside increased venous admixture in the absence of a change in cardiac output. It is likely, then, that variation in cardiac output is not the primary mechanism by which nitroprusside changes venous admixture. The results of our study indicate that nitroprusside increases venous admixture by inhibiting hypoxic vasoconstriction, and that this effect can be minimized by increasing $F_{I_{O_2}}$. The extent to which nitroprusside impairs pulmonary gas exchange is dependent on the extent to which conditions favorable to the production of hypoxic vasoconstriction are present—namely, the relative magnitude of pre-existing pulmonary disease and $F_{I_{O_2}}$.

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