

## Pulmonary Gas Exchange Effects of Nitroglycerin in Canine Edematous Lungs

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The authors determined the effects of nitroglycerin on pulmonary gas exchange in 11 anesthetized dogs with diffuse pulmonary edema induced by oleic acid injury. Measurements of venous admixture ( $\dot{Q}_{VA}/\dot{Q}_t$ ) and shunt ( $\dot{Q}_s/\dot{Q}_t$ ) using both oxygen and inert-gas-elimination methods were done before, during, and after nitroglycerin infusion, first during air ventilation and then during ventilation with 100 per cent oxygen. Nitroglycerin reduced mean blood pressure (MAP) approximately 30 per cent ( $P < 0.01$ ) during both air and oxygen ventilation. During air ventilation, nitroglycerin caused PVR to decrease by 29 per cent ( $P < 0.01$ ) but caused no change in PVR during oxygen ventilation.  $Pa_{O_2}$  decreased from  $64 \pm 8$  torr (mean  $\pm$  SD) to  $55 \pm 9$  torr ( $P < 0.01$ ) with nitroglycerin infusion during air ventilation. The decrease in  $Pa_{O_2}$  was primarily due to an increase in  $\dot{Q}_{VA}/\dot{Q}_t$  which increased from  $28 \pm 12$  per cent to  $36 \pm 14$  per cent (oxygen method) ( $P < 0.05$ ). Similarly, the inert gas  $\dot{Q}_{VA}/\dot{Q}_t$  increased from  $31 \pm 10$  to  $37 \pm 14$  per cent ( $P < 0.05$ ). During oxygen ventilation, the effect of nitroglycerin on gas exchange was similar in direction but less in magnitude. These results provide evidence that nitroglycerin may cause significant impairment of pulmonary gas exchange when abnormal lung function is present and  $Fi_{O_2}$  is low. The mechanism is most likely due to inhibition of hypoxic pulmonary vasoconstriction. (Key words: Anesthetic techniques: hypotension, induced, nitroglycerin. Lung: blood flow; edema; shunting; hypoxic vasoconstriction.)

IN RECENT YEARS, intravenous nitroglycerin (NTG) has been used to reduce systemic blood pressure in anesthetized patients.<sup>1-3</sup> Recently Fahmy<sup>3</sup> showed that intravenous nitroglycerin was associated with a reduction in  $Pa_{O_2}$  in anesthetized patients, (mean  $Pa_{O_2}$  decreased by 57 torr from 175 to 118 torr with an  $Fi_{O_2}$  of 0.40). These authors did not investigate the cause of the decrease in  $Pa_{O_2}$ . Hales *et al.*<sup>4</sup> have found that nitroglycerin inhibits hypoxic pulmonary vasocon-

striction (HPV) produced by ventilating dog lungs with nitrogen. Also, Mookherjee *et al.*<sup>5</sup> showed that sublingual nitroglycerin caused a small but significant increase in venous admixture ( $\dot{Q}_{VA}/\dot{Q}_t$ ) of 3.8 per cent in patients being evaluated for chest pain. Therefore, it is likely that nitroglycerin impairs pulmonary gas exchange by inhibiting HPV, resulting in increased flow to poorly ventilated or unventilated lung. Alternatively, because nitroglycerin is a potent venodilator,<sup>6</sup> it could increase  $\dot{Q}_{VA}/\dot{Q}_t$  and decrease  $Pa_{O_2}$  by causing a disproportionate increase in Thebesian vein and bronchial vein blood flow, *i.e.*, anatomic shunt.

If nitroglycerin impairs gas exchange by inhibiting HPV, this effect should be greatest in subjects with abnormal lungs breathing air in whom HPV returns ventilation-perfusion ratios towards normal. Although Kochukoshy *et al.*<sup>7</sup> and Hales *et al.*<sup>4</sup> found that nitroglycerin decreased  $Pa_{O_2}$  in patients with pulmonary disease, neither they nor others have reported the effects of nitroglycerin on pulmonary shunt ( $\dot{Q}_s/\dot{Q}_t$ ) or  $\dot{Q}_{VA}/\dot{Q}_t$  in such patients. In an earlier study we used an animal model of diffuse lung injury produced by oleic acid injection to determine the effects of sodium nitroprusside on gas exchange.<sup>8</sup> In the present study, we used the same model to examine the effects of intravenous nitroglycerin on pulmonary hemodynamics and pulmonary gas exchange during air and oxygen ventilation. We used the usual oxygen method of measuring changes in  $\dot{Q}_{VA}/\dot{Q}_t$  and  $\dot{Q}_s/\dot{Q}_t$  and also the multiple inert gas elimination technique, which can discretely measure intrapulmonary  $\dot{Q}_{VA}/\dot{Q}_t$  and separate intrapulmonary ( $\dot{Q}_s/\dot{Q}_t$ ) from other  $\dot{V}_A/\dot{Q}$  abnormalities.

### Methods

Eleven adult mongrel dogs weighing  $23.0 \pm 2.7$  kg (mean  $\pm$  SD) were studied. Twenty-four hours prior to the study, the animals were anesthetized with pentobarbital, 30 mg/kg, iv. Under sterile surgical conditions a triple lumen pulmonary artery (thermodilution) and systemic arterial catheters were placed via an external jugular vein and forepaw arterial vessels, respectively. The animals were then allowed to recover from the anesthesia. To produce diffuse lung injury, 0.06-0.07 ml/kg oleic acid, followed by 20 ml of saline was infused via a Harvard<sup>®</sup> pump

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at 2 ml/min into the right atrial port of the pulmonary artery catheter. Twenty-four hours later the animals were reanesthetized with pentobarbital 30 mg/kg, iv. The trachea was intubated with a cuffed endotracheal tube and the animal placed in the prone position. The lungs were mechanically ventilated at a tidal volume of 12–15 ml/kg at a rate set to maintain the  $P_{aCO_2}$  at approximately 35 torr. Neither tidal volume nor respiratory rate was subsequently altered. Spontaneous respiration was prevented by iv succinylcholine, 5 mg·kg<sup>-1</sup>·h<sup>-1</sup>, and additional doses of iv pentobarbital (2–3 mg/kg) were administered every hour.

For the first part of the study,  $F_{I_{O_2}}$  was always 0.21. We postulated that using a  $F_{I_{O_2}}$  of 1.0 first would result in absorption atelectasis. If this atelectasis were to undergo gradual reversal by subsequently changing to an  $F_{I_{O_2}}$  of 0.21, then an effect on  $\dot{Q}_{VA}/\dot{Q}_I$  would be produced which might obscure the effect of nitroglycerin. Control measurements of vascular pressures and gas exchange were carried out and nitroglycerin, 1 mg/ml, in a glass syringe<sup>9</sup> was then infused intravenously with a Harvard<sup>®</sup> infusion pump in order to lower mean systemic arterial pressure (MAP) by approximately 30 per cent. After approximately 10 min at the reduced pressure, the measurements were repeated, and the nitroglycerin infusion was then stopped. The MAP was allowed to return toward the prenitroglycerin infusion value, which required approximately 45 min, and postinfusion measurements were done. The animals' lungs were then ventilated with 100 per cent oxygen ( $F_{I_{O_2}} = 1.0$ ) and the same procedure carried out as with  $F_{I_{O_2}} = 0.21$ .

Measurements consisted of systemic arterial, pulmonary arterial (PAP), pulmonary wedge (PAW) and airway ( $P_{aw}$ ) pressures, and thermodilution cardiac outputs ( $\dot{Q}_I$ ). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated as  $SVR = MAP \times 80/\dot{Q}_I$ , and  $PVR = (PAP - PAW) \times 80/\dot{Q}_I$  dyn·s·cm<sup>-5</sup>. Systemic arterial and pulmonary artery blood samples were drawn and immediately put in ice. Within 2–3 min the blood samples were analyzed for  $P_{O_2}$ ,  $P_{CO_2}$ , and pH using a blood-gas analyzer (Radiometer Model BMS 3 MK 2<sup>®</sup>).  $\dot{Q}_{VA}/\dot{Q}_I$ , during ventilation with room air, and  $\dot{Q}_S/\dot{Q}_I$ , during oxygen ventilation, were calculated using the standard oxygen method of Berggren with a program developed by Ruiz *et al.*<sup>10</sup> The dead space-to-tidal volume ratio ( $V_D/V_T$ ) was calculated using the Enghoff modification of the Bohr equation.

$\dot{V}_A/\dot{Q}$  distributions were determined using the multiple inert gas elimination technique of Wagner *et al.*<sup>11</sup> A mixture of six inert gases (SF<sub>6</sub>, ethane, cyclopropane, halothane, diethyl ether, and acetone)

dissolved in saline was continuously infused into a peripheral vein at 3 ml/min for a minimum of 30 min before the first sampling period. Samples of arterial blood, mixed venous blood, and mixed expired gas were collected when other measurements and blood sampling were done. Inert gas concentrations in blood and expired gas samples were determined using gas chromatography (Beckman Model GC-72-5<sup>®</sup>) with a flame ionization detector and electron capture detector (Analog Technology). Derived  $\dot{V}_A/\dot{Q}$  distributions were determined using methods described previously.<sup>12</sup> Derived  $\dot{V}_A/\dot{Q}$  distributions and the  $F_{I_{O_2}}$  were used to calculate the predicted arterial blood-gas values. The measured mixed venous blood-gas values and the predicted arterial blood-gas values were then used to calculate the inert gas venous admixture (inert gas  $\dot{Q}_{VA}/\dot{Q}_I$ ) and shunt (inert gas shunt) using the standard oxygen method.

The data were analyzed using analysis of variance techniques, except that  $P_{aO_2}$  values were compared using Student's *t* test because of the alinear relationship between  $P_{O_2}$  and oxygen content.

## Results

### AIR VENTILATION (TABLES 1–4)

During nitroglycerin infusion, there was a significant decrease in MAP, SVR and  $\dot{Q}_I$  (table 1). The 18 per cent decrease in  $\dot{Q}_I$  ( $P < 0.01$ ) was associated with a 10 per cent decrease in stroke volume ( $P < 0.05$ ) and an insignificant decrease in heart rate. Nitroglycerin also caused a 35 per cent decrease in PAP ( $P < 0.01$ ) but no change in PAW (table 2). In spite of the decrease in  $\dot{Q}_I$ , PVR decreased by 26 per cent.

$P_{aO_2}$  decreased by 9 torr during nitroglycerin infusion ( $P < 0.01$ ) (table 3). The decrease in  $P_{aO_2}$  was primarily due to an increase in  $\dot{Q}_{VA}/\dot{Q}_I$  (oxygen method). The mean increase in  $\dot{Q}_{VA}/\dot{Q}_I$  (oxygen method) was 8 per cent ( $P < 0.05$ ) with a range of –5 to +30 per cent (fig. 1). There was a similar increase in the inert gas  $\dot{Q}_{VA}/\dot{Q}_I$  ( $P < 0.05$ ). There was no correlation between increases in  $\dot{Q}_{VA}/\dot{Q}_I$  and decreases in PVR ( $r = 0.271$ ). The inert gas  $\dot{Q}_S/\dot{Q}_I$  representing flow to completely unventilated lung, did not increase significantly (table 4).

### OXYGEN VENTILATION (TABLES 1–4)

Nitroglycerin caused similar decreases in MAP and SVR (27 per cent and 26 per cent, respectively) but no change in  $\dot{Q}_I$  (table 1). PAP decreased by 19 per cent but there was no change in PAW (table 2). When ventilation was changed from air to oxygen, PVR decreased by 29 per cent, but was unchanged

TABLE 1. Systemic Hemodynamic Effects of Intravenous Nitroglycerin (NTG) in Pulmonary Edema

	Air Ventilation			Oxygen Ventilation		
	Pre-NTG	NTG	Post-NTG	Pre-NTG	NTG	Post-NTG
Heart rate (beats/min)	180 ± 26	166 ± 28	180 ± 32	188 ± 30	184 ± 26	190 ± 25
$\dot{Q}_t$ (l/min)	3.45 ± 0.69	2.84 ± 0.64	3.35 ± 0.64	3.21 ± 0.63	3.20 ± 0.63	3.36 ± 0.58
MAP (torr)	135 ± 26	90 ± 21	116 ± 28	123 ± 24	90 ± 19	116 ± 27
SVR (dyn·s·cm <sup>-5</sup> )	3,252 ± 557	2,496 ± 553	2,921 ± 694	3,118 ± 603	2,303 ± 618	2,813 ± 754
Dose of NTG (μg·kg <sup>-1</sup> ·min <sup>-1</sup> )		167 ± 44			178 ± 32	

Values are means ± 1 SD; n = 11;  $\dot{Q}_t$  = cardiac output; MAP = mean arterial pressure; SVR = systemic vascular resistance.

\*  $P < 0.01$  between adjacent values.

during infusion of nitroglycerin. With nitroglycerin, there was a decrease in  $P_{aO_2}$  of 18 torr ( $P < 0.05$ ) but no significant change in  $\dot{Q}_s/\dot{Q}_t$  measured by the oxygen method (table 3). The inert gas  $\dot{Q}_s/\dot{Q}_t$ , however, showed a small but significant increase of 3 per cent (table 4).

### Discussion

Oleic acid infusion produces marked  $\dot{V}_A/\dot{Q}$  maldistribution.<sup>8</sup> In atelectatic and low  $\dot{V}_A/\dot{Q}$  areas, alveolar hypoxia is produced during air breathing, activating HPV. The intensity of HPV present depends upon the severity of  $\dot{V}_A/\dot{Q}$  maldistribution in each animal and the  $F_{IO_2}$ . HPV is greater during air than oxygen breathing when alveolar hypoxia is

more intense. During oxygen ventilation, HPV is likely present only in areas of complete atelectasis (*i.e.*, intrapulmonary shunt). In addition, Forrest *et al.*<sup>13</sup> have found that the intensity of HPV for any degree of alveolar hypoxia is variable from animal to animal. Approximately 60 per cent of dogs have a medium to high intensity of pulmonary vascular response while 40 per cent are low responders.<sup>13</sup> Similarly, in humans, Fowler and Read<sup>14</sup> found that only two-thirds of patients with normal lungs react to alveolar hypoxia with pulmonary hypertension. A vasoactive drug that inhibits HPV should thus produce a greater effect on pulmonary gas exchange in subjects with higher than normal levels of venous admixture and especially those that are strong HPV reactors.

TABLE 2. Pulmonary Dynamic Effects of NTG

	Air Ventilation			Oxygen Ventilation		
	Pre-NTG	NTG	Post-NTG	Pre-NTG	NTG	Post-NTG
$\overline{PAP}$ (cm H <sub>2</sub> O)	23 ± 8	15 ± 5	25 ± 10	16 ± 6	13 ± 6	15 ± 6
$\overline{PAW}$ (cm H <sub>2</sub> O)	2 ± 3	2 ± 3	2 ± 3	1 ± 3	1 ± 3	1 ± 3
PVR (dyn·s·cm <sup>-5</sup> )	502 ± 187	372 ± 103	546 ± 195	358 ± 136	297 ± 138	336 ± 169
$P_{aw}$ (cm H <sub>2</sub> O)	13 ± 3	13 ± 3	13 ± 3	13 ± 3	13 ± 3	13 ± 3
$V_D/V_T$	0.39 ± 0.08	0.46 ± 0.12	0.43 ± 0.14	0.48 ± 0.11	0.56 ± 0.11	0.43 ± 0.16

Values are means ± 1 SD; n = 11;  $\overline{PAP}$  = mean pulmonary artery pressure;  $\overline{PAW}$  = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance;  $P_{aw}$  = peak airway pressure;

$V_D/V_T$  = dead space-to-tidal volume ratio.

\*  $P < 0.01$  between adjacent values.

TABLE 3. Pulmonary Gas Exchange Effects of NTG

	Air Ventilation			Oxygen Ventilation		
	Pre-NTG	NTG	Post-NTG	Pre-NTG	NTG	Post-NTG
$\dot{Q}_s/\dot{Q}_t$ (per cent) or $\dot{Q}_{VA}/\dot{Q}_t$ (per cent) (O <sub>2</sub> method)	28 ± 12	36 ± 14	31 ± 10	17 ± 7	18 ± 9	19 ± 8
	*					
Pa <sub>O<sub>2</sub></sub> (torr)	64 ± 8	55 ± 9	60 ± 7	407 ± 118	389 ± 117	387 ± 111
	†			*		
Paco <sub>2</sub> (torr)	32 ± 4	32 ± 5	36 ± 9	38 ± 8	40 ± 9	38 ± 10
		*		†		
pH <sub>a</sub>	7.35 ± 0.02	7.32 ± 0.03	7.31 ± 0.03	7.31 ± 0.05	7.28 ± 0.06	7.29 ± 0.08
	†			†		
P $\bar{V}$ O <sub>2</sub> (torr)	41 ± 6	37 ± 5	38 ± 6	62 ± 5	61 ± 9	62 ± 9
	†					
P $\bar{V}$ CO <sub>2</sub> (torr)	37 ± 5	39 ± 6	45 ± 9	45 ± 9	47 ± 10	47 ± 13
		*				
pH $\bar{v}$	7.32 ± 0.03	7.29 ± 0.03	7.28 ± 0.04	7.27 ± 0.07	7.24 ± 0.07	7.24 ± 0.09

Values are means ± 1 SD; n = 11; a = arterial;  $\bar{v}$  = mixed venous.  
\* 0.01 < P < 0.05 between adjacent values.

† P < 0.01 between adjacent values.

HPV was present in this diffuse lung injury model as indicated by a 29 per cent decrease in PVR when ventilation was changed from air to oxygen in the absence of any change in  $\dot{Q}_t$ . Nitroglycerin caused a nearly identical decrease in PRV during air ventilation, but no change in PVR during oxygen ventilation. These results provide evidence that the sole effect of nitroglycerin on the pulmonary circulation was to inhibit HPV. The lack of correlation between changes in HPV and changes in  $\dot{Q}_{VA}/\dot{Q}_t$  was probably due to the effects of concomitant decreases in  $\dot{Q}_t$  on PVR.

During air ventilation, nitroglycerin caused a significant increase in  $\dot{Q}_{VA}/\dot{Q}_t$  measured by both the oxygen and inert gas methods and a significant fall in Pa<sub>O<sub>2</sub></sub>. The mean increase in  $\dot{Q}_{VA}/\dot{Q}_t$  (oxygen method) of 8 per cent was more than twice the mean increase found by Mookherjee *et al.*<sup>5</sup> in patients with normal lungs. The increase in inert gas  $\dot{Q}_{VA}/\dot{Q}_t$  indicates that the impairment in pulmonary gas exchange is due to increased flow to unventilated, *i.e.*, atelectatic and/or low  $\dot{V}_A/\dot{Q}$  lung areas, and not to an increase in flow through the Thebesian and bronchial veins. The inert gas  $\dot{Q}_s/\dot{Q}_t$  or shunt component of total venous admixture measured during air ventilation did not increase with nitroglycerin. Its failure to increase further defines the impairment

of gas exchange as due to increased flow to low  $\dot{V}_A/\dot{Q}$  lung areas. The shunt component measures flow to areas of completely unventilated lung. Areas of unventilated lung would be in the most severely damaged areas of lung. It is likely that vessels in these regions have a decreased ability to alter vascular tone

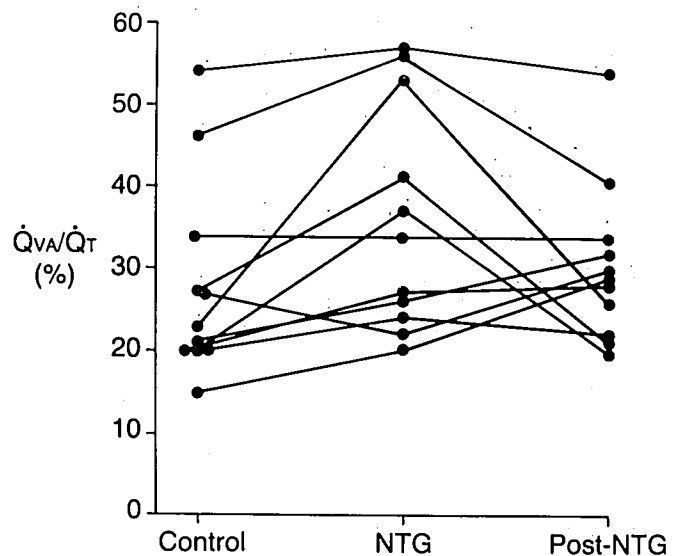


FIG. 1. Effect of NTG on  $\dot{Q}_{VA}/\dot{Q}_t$  (oxygen method) in individual dogs during air ventilation (n = 11).

TABLE 4. Ventilation-Perfusion Effects of NTG Determined by the Inert Gas Elimination Method

	Air Ventilation			Oxygen Ventilation		
	Pre-NTG	NTG	Post-NTG	Pre-NTG	NTG	Post-NTG
$\dot{Q}_{VA}/\dot{Q}_t$ (per cent)	31 ± 14	37 ± 14	31 ± 12	13 ± 12	16 ± 15	15 ± 12
		*	*	†		
$\dot{Q}_s/\dot{Q}_t$ (per cent) (Shunt component)	11 ± 12	12 ± 10	10 ± 8	13 ± 12	16 ± 15	15 ± 12
				†		

Values are means ± 1 SD; n = 11.

\* 0.01 < P < 0.05 between adjacent values.

† P < 0.01 between adjacent values.

and would be less likely to respond to nitroglycerin during either air ventilation or oxygen ventilation. This conclusion is supported by the observation that during oxygen ventilation, small changes in gas exchange were seen.  $Pa_{O_2}$  fell slightly and inert gas  $\dot{Q}_s/\dot{Q}_t$  increased slightly, but the increase in  $\dot{Q}_s/\dot{Q}_t$  measured by the oxygen method was not significant.

It is unlikely that the decrease in  $\dot{Q}_t$  seen during air ventilation following nitroglycerin in itself resulted in an alteration in  $\dot{V}_A/\dot{Q}$  maldistribution thus increasing  $\dot{Q}_{VA}/\dot{Q}_t$ . An acute decrease in  $\dot{Q}_t$  is usually associated with increased PVR and decreases in pulmonary shunting. Smith *et al.*<sup>15</sup> found that a hemorrhage-induced decrease in cardiac output of 35 per cent in animals with oleic acid lung injury reduced  $\dot{Q}_s/\dot{Q}_t$  from 29 to 22 per cent.

The reason nitroglycerin caused  $\dot{Q}_t$  to decrease during air ventilation, but not during oxygen ventilation is not clear. Nitroglycerin has been reported to cause decreases, increases, and no change in cardiac output.<sup>16</sup> These effects, however, have not been related to inspired oxygen concentrations but to the presence or absence of increased left ventricular end-diastolic pressure (LVEDP). In the present study, LVEDP values as reflected by PAW measurements, were low and essentially the same during air and oxygen ventilation. We speculate that the disparate effect of nitroglycerin on cardiac output observed in our study may have occurred because measurements on air ventilation always preceded those taken during oxygen ventilation. We thought that it was necessary for nitroglycerin to be infused first during air ventilation in order to avoid the residual effects of oxygen-induced absorption atelectasis on shunt and venous admixture. Early in the study during air ventilation, the level of anesthesia may have been deeper, and cardiovascular reflexes more impaired than later on during oxygen ventilation.

Only qualitative comparisons are possible between

the effects of nitroglycerin on pulmonary gas exchange found in the present study and the effects of nitroprusside found in the previous study.<sup>8</sup> It was not possible to produce the same degree of systemic hypotension with nitroglycerin as was done with nitroprusside. The degree of lung injury in the animals in both studies was, however, similar with values for  $\dot{Q}_{VA}/\dot{Q}_t$  of 20 per cent in the nitroprusside study, and 28 per cent in the present study. In addition, both nitroglycerin and nitroprusside caused a similar degree of reduction in PVR (29 per cent and 24 per cent reduction, respectively) during air ventilation and neither drug had a significant effect on PVR during oxygen ventilation. The mean increase in  $\dot{Q}_{VA}/\dot{Q}_t$  of 8 per cent (from 28 ± 12 to 36 ± 14 per cent) during air ventilation in this study is in contrast to the increase of 18 per cent (from 20 ± 8 to 38 ± 18 per cent) caused by nitroprusside in our previous study.<sup>8</sup> The difference in the effect of nitroglycerin and nitroprusside on  $\dot{Q}_{VA}/\dot{Q}_t$ , however, was not statistically significant by Student's unpaired *t* test. An examination of the effects of nitroglycerin on  $\dot{Q}_{VA}/\dot{Q}_t$  during air ventilation in individual animals (fig. 1) shows that nitroglycerin is fully capable of causing as large an increase in  $\dot{Q}_{VA}/\dot{Q}_t$  as is nitroprusside, but did so in fewer animals.

The clinician involved in administering a vasoactive drug such as nitroglycerin or nitroprusside, should realize that these agents are capable of adversely affecting pulmonary gas exchange and may produce a decrease in  $Pa_{O_2}$ . Increasing the  $Fi_{O_2}$  will minimize the effect. The decrease in  $Pa_{O_2}$  is not the result of an anatomic deterioration in lung structure, *i.e.*, increased atelectasis, and is readily reversible by discontinuing the drug infusion.

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