

Vasodilators Worsen Gas Exchange in Dog Oleic-acid Lung Injury

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The authors studied the effects of vasodilator treatment with either hydralazine or minoxidil on gas exchange and lung water accumulation over a 5-h period in canine oleic acid-induced pulmonary edema. Thirty dogs were given intravenous oleic acid 1 day prior to study to produce a stable, diffuse lung injury. On the day of study, one group of animals was given minoxidil, a potent systemic and pulmonary vasodilator. A second group was given hydralazine, a potent systemic vasodilator but weak pulmonary vasodilator, and a third group was not treated. Hemodynamic and gas exchange variables were assessed prior to treatment, and again after 5 h of treatment. Both drugs caused an increase in cardiac output and a decrease in peripheral vascular resistance. Minoxidil increased venous admixture from 17 ± 4 to $55 \pm 6\%$ ($P < 0.05$), whereas hydralazine-treated dogs had a smaller increase, from 26 ± 5 to $47 \pm 6\%$ ($P < 0.05$), and untreated animals did not show a significant change. Lung water increased $27 \pm 12\%$ in the untreated animals over the course of the study, $43 \pm 18\%$ in the hydralazine animals, and $60 \pm 16\%$ ($P < 0.05$ vs. untreated) in the minoxidil animals. The authors conclude that adverse effects may result from peripheral vasodilators in animals with permeability pulmonary edema, but the extent and severity of these effects may vary, depending on the drugs' effects on the pulmonary circulation. (Key words: Lung; edema; hypoxic pulmonary vasoconstriction; water. Pharmacology: hydralazine; minoxidil.)

USING SYSTEMIC VASODILATORS for afterload reduction and consequent maximization of cardiac output and oxygen transport may be desirable in the treatment of acute respiratory failure. We tested the hypothesis that vasodilators adversely affect gas exchange in established permeability edema, with the effects more profound if the vasodilator also acts to inhibit hypoxic pulmonary vasoconstriction.

The pulmonary vasoconstrictor response to hypoxia (HPV) results in pulmonary hypertension when global lung hypoxia is present, but primarily causes flow diversion away from abnormal lung in the presence of regional hypoxia.¹ When the abnormality is regional, the HPV response acts to preserve ideal matching of perfusion and ventilation.

We hypothesized that the presence of an inhibitor of HPV in an animal whose lung includes areas of altered permeability would worsen gas exchange. We further hypothesized that an increase in lung edema could occur in the absence of any change in pulmonary artery pressure or left ventricular filling pressure, because microvascular pressure might increase due to inhibition of HPV with subsequent decreased precapillary resistance.

Oleic-acid injured dogs were studied 24 h after the initiation of the injury. This produces increased permeability in multiple areas of the lung while leaving some areas relatively normal.² In addition, this model, unlike acute oleic-acid injury, remains relatively stable over the course of a day.³

We studied the effects on this model of two systemic vasodilators, hydralazine and minoxidil. We chose these two vasodilators because of their markedly different effects on the pulmonary vascular response to hypoxia. Minoxidil virtually ablates the HPV response within 2 to 3 h of administration,^{4,5} whereas hydralazine has little effect on that response.⁶

Methods

We studied 30 mongrel dogs weighing a mean of 21.8 ± 0.6 kg. Animal care followed institutional guidelines for animal experimentation. All animals were brought to the laboratory on the morning prior to study, their tracheas were intubated, and the dogs were anesthetized with halothane while thermistor-tipped pulmonary artery and carotid artery catheters were placed. When they were fully awake, the animals were given 0.08 ml/kg of oleic acid over 5 min *via* the right atrial port of the pulmonary artery catheter and were then returned to their cages overnight.

On the morning of the study, dogs were anesthetized with 30 mg/kg of pentobarbital. Following tracheal intubation, they were mechanically ventilated at a fractional inspired O₂ concentration ($F_{I_{O_2}}$) = 0.5 to achieve a $P_{a_{CO_2}}$ = 30–35 mmHg. Pancuronium was administered as needed to prevent spontaneous respiratory efforts.

Baseline measurements were made of arterial and venous blood gases, pulmonary and systemic arterial pressure, pulmonary artery wedge pressure, and lung water.

Animals were then given either minoxidil 1 mg/kg ($n = 12$), hydralazine 1 mg/kg ($n = 10$), or not treated ($n = 8$). Hydralazine animals were continued on an infusion of $0.05 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of the drug to compensate for its ongoing removal from the circulation *via* excretion and

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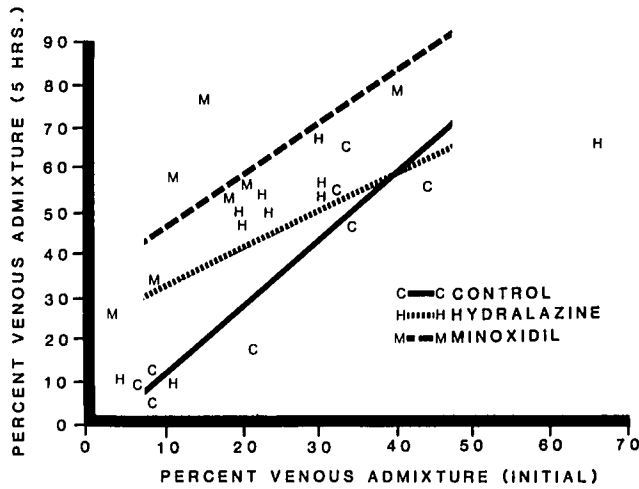


FIG. 1. Venous admixture at 5 h as a function of initial venous admixture. Minoxidil dogs = M; hydralazine = H; untreated = C. Least squares regression lines demonstrate that for any given initial value, minoxidil-treated animals tended to have the highest 5-h venous admixture ($P < 0.05$ by analysis of covariance).

metabolism. Minoxidil was not given by infusion, as it is not significantly excreted over 5 h. All measurements were then repeated at 5 h.

Lung water measurements were made in triplicate using the ice-water-indocyanine green technique and calculated with an Edwards® 9310 Lung Water Computer.⁷ Immediately following the 5-h measurements, the animals were killed, and the lungs were exsanguinated by passive drainage of blood. The lungs were then weighed, and the left lower lobe was removed for gravimetric analysis by the method of Pearce *et al.*⁸

Pulmonary vascular resistance (PVR) and total systemic

resistance (TSR) were calculated by the following formulas:

$$\text{PVR in dyn} \cdot \text{s} \cdot \text{cm}^{-5} = \frac{(P_{pa} - P_{paw}) \times 80}{Q_t}$$

$$\text{TSR in dyn} \cdot \text{s} \cdot \text{cm}^{-5} = \frac{P_a \times 80}{Q_t}$$

where P_{pa} is mean pulmonary artery pressure; P_{paw} is pulmonary artery wedge pressure; and P_a is systemic arterial pressure.

Venous admixture was calculated from blood gases using the standard Berggren equation and the computer program of Ruiz *et al.*⁹

Comparison between baseline and 5-h results (within groups) were made using Student's *t* test for paired data.¹⁰ Comparisons of the effects of treatment were made using analysis of covariance to control for the variability in baseline values.¹¹

Results

Data presented are for surviving animals only: four animals in the minoxidil group did not survive to 5 h ($P < 0.05$ vs. hydralazine and controls by Fisher's exact test). All animals developed pulmonary edema after receiving oleic acid and prior to any drug. Lung water values varied widely (range 10.1–36.3 ml/kg), but all animals had substantially higher values than our previously established normal laboratory value of 4–6 ml/kg.

Venous admixture (\dot{Q}_{VA}/\dot{Q}_T) also demonstrated a wide range (fig. 1). The tendency to lower initial values for lung water and \dot{Q}_{VA}/\dot{Q}_T in the minoxidil group is accounted for by the elimination from data analysis of the four nonsurvivors in that group. Because the sickest an-

TABLE 1. Hemodynamic Data

	Untreated (n = 8)		Hydralazine (n = 10)		Minoxidil (n = 8; survivors only)	
	Baseline	5 h	Baseline	5 h	Baseline	5 h
Cardiac output ml · kg ⁻¹ · min ⁻¹	165 ± 14	184 ± 18	154 ± 18	219 ± 18*†	147 ± 18	249 ± 29*†
Mean blood pressure mmHg	124 ± 8	132 ± 12	115 ± 10	107 ± 7†	123 ± 23	78 ± 6*†
Pulmonary artery pressure (mean) mmHg	15 ± 1	16 ± 2	12 ± 1	18 ± 1*	13 ± 2	5 ± 2
Pulmonary artery wedge pressure mmHg	1.8 ± 0.6	1.9 ± 0.4	1.8 ± 0.4	3.1 ± 0.6	0.7 ± 0.2	1.7 ± 0.4
Pulmonary vascular resistance dyn · sec · cm ⁻⁵	318 ± 23	305 ± 32	263 ± 16	270 ± 23	300 ± 40	211 ± 35*†
Total systemic resistance dyn · sec · cm ⁻⁵	2,889 ± 325	2,797 ± 296	3,027 ± 277	2,038 ± 198*†	3,271 ± 295	1,192 ± 119*†

* $P < 0.05$ versus baseline by paired *t* test.

† $P < 0.05$ for change over 5 h when compared with untreated by analysis of covariance.

TABLE 2. Gas Exchange Data

	Untreated (n = 8)		Hydralazine (n = 10)		Minoxidil (n = 8; survivors only)	
	Baseline	5 h	Baseline	5 h	Baseline	5 h
PaO ₂ mmHg	135 ± 26	118 ± 26*	114 ± 23	92 ± 25*	126 ± 15	62 ± 9*†
PvO ₂ mmHg	51 ± 4	49 ± 5	46 ± 3	45 ± 3	45 ± 2	43 ± 5
pH	7.33 ± .02	7.33 ± .02	7.36 ± .01	7.32 ± .02	7.39 ± .02	7.33 ± .03
Wet/dry ratio		7.58 ± 0.42		8.12 ± 0.33		8.45 ± 0.57

PvO₂ = mixed venous blood oxygen.
* P < 0.05 versus baseline by t test.

† P < 0.05 versus untreated by analysis of covariance, controlling for baseline values.

imals in this group died from hypoxemia, the remaining data are skewed toward the less affected animals.

HEMODYNAMIC EFFECTS

Untreated animals maintained their baseline cardiac output at the end of 5 h, whereas animals both in the minoxidil and hydralazine groups increased their cardiac outputs (table 1). Both drugs caused substantial peripheral vasodilation, although minoxidil caused a greater decrease in the calculated systemic resistance (P < 0.05) (table 1).

Calculated pulmonary vascular resistance remained unchanged in the untreated and hydralazine groups, but decreased from 300 ± 40 to 211 ± 35 dyn · sec · cm⁻⁵ in the minoxidil-treated animals. Pulmonary artery pressure remained unchanged in the minoxidil and untreated groups, but increased in hydralazine-treated animals.

GAS EXCHANGE

Arterial oxygen tension decreased in all three groups, but there was no significant difference in the decrease between the untreated (135 ± 26 to 118 ± 26 mmHg) and the hydralazine treated (114 ± 23 to 92 ± 25 mmHg) animals. However, the minoxidil animals demonstrated a dramatic decline (table 2) in PaO₂, from 126 ± 15 to 62 ± 9 mmHg (P < 0.05 vs. untreated). Venous admixture increased 39% in the untreated animals (P = 0.06), nearly doubled in the hydralazine group (P < 0.05) and more than tripled in minoxidil dogs (P < 0.01) (fig. 1). When the final venous admixture was assessed as a function of the initial venous admixture, minoxidil treatment resulted in a significantly higher final value as compared with hydralazine or no treatment (P < 0.05 by analysis of covariance).

LUNG EDEMA

Measured lung water increased by a mean of 27 ± 12% (P = 0.10) over the course of the experiment in untreated animals, 43 ± 18% in hydralazine-treated animals (P

< 0.05), and 60 ± 16% in minoxidil-treated animals (P < 0.01) (fig. 2). Minoxidil-treated, but not hydralazine-treated, animals had a significantly greater increase in lung water than did the control group (P < 0.05).

Discussion

This study was designed to assess the effects of two different vasodilators, one an inhibitor of HPV, in the intact animal with established permeability edema.

The 24-h oleic-acid injury was studied because the injury is more stable over the initial few hours, yet there is still increased vascular permeability. Although the injury occurs in multiple areas of all lobes, the injury is patchy, sparing some areas of lung.² This is of importance to our study because it implies that HPV in injured areas can divert flow to uninjured areas and that inhibition of HPV

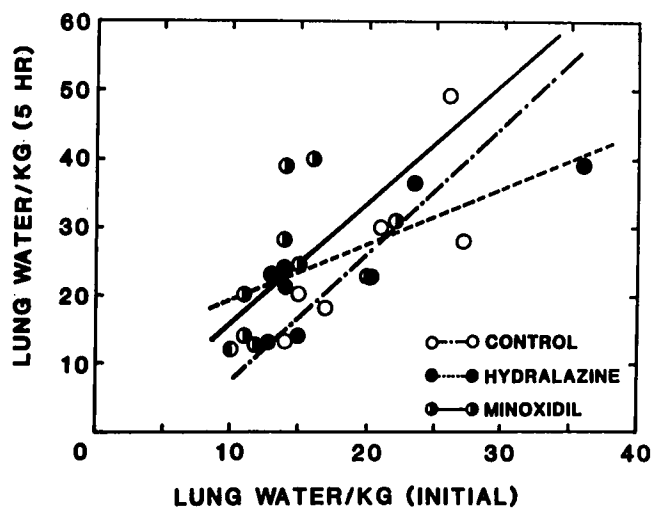


FIG. 2. Iced idocyanine green lung water at 5 h plotted as a function of the initial lung water. For any given value of initial lung water, minoxidil-treated animals have a higher predicted 5-h lung water. The regression line for minoxidil is significantly different from untreated (control) animals (P < 0.05 by analysis of covariance).

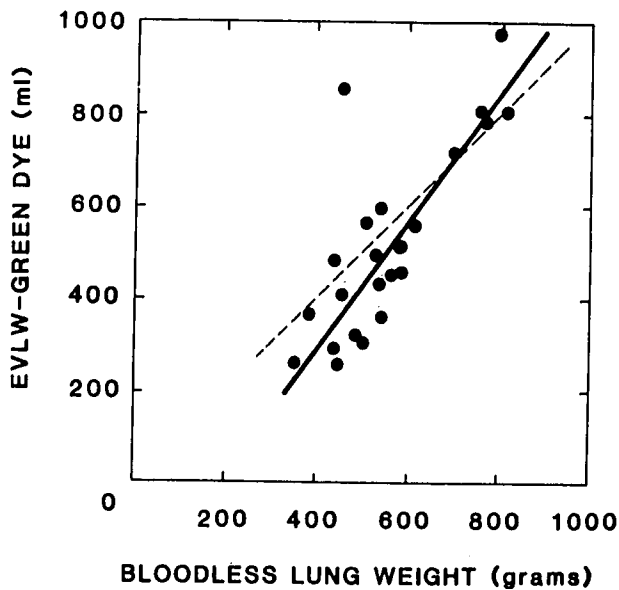


FIG. 3. Solid line represents least-square regression line for double indicator extravascular lung water (EVLW) versus postmortem bloodless lung weight ($r = 0.91$, $P < 0.001$). The outlier point at a bloodless lung weight of 450 g has been excluded from calculation of the line. The dashed line represents the line of identity.

will, therefore, change flow distribution, increasing the flow to injured areas.

The extent of the initial injury in the untreated and hydralazine groups was similar, based on lung water measurements and venous admixture. However, because of four deaths due to hypoxia from increased venous admixture in the minoxidil group, the baseline data (fig. 1) for the minoxidil group demonstrate a less severe degree of injury.

Both drugs resulted in an increase in cardiac output, whereas cardiac output remained stable in the untreated group. The doses of minoxidil and hydralazine were chosen, based on our laboratory experience, to achieve comparable increases. The increase in cardiac output after minoxidil may result from profound afterload reduction, with systemic resistance decreasing by over 64% ($P < 0.01$). Hydralazine produced a 33% decrease in systemic resistance ($P < 0.01$). Given the similar increases in cardiac output, hydralazine may, as suggested by other reports, have produced some direct cardiac inotropic effect.¹¹

At the end of 5 h, the lung water was similar in all three groups, yet the mean venous admixture was 55%

in the minoxidil group, far higher than in the untreated group ($P < 0.01$). This suggests that, for a given degree of lung edema, more blood flows to the injured areas during minoxidil treatment. This supports prior studies showing that minoxidil is a potent inhibitor of HPV.⁴

The relative effects of the two drugs on the pulmonary vasculature are demonstrated by the decrease in PVR from 300 ± 40 to 211 ± 35 $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$ in the minoxidil group as compared with no change in the hydralazine group. This resulted in no significant change in pulmonary artery pressure in the minoxidil group and a rise in mean pulmonary artery pressure from 12 ± 1 to 18 ± 1 mmHg ($P < 0.05$) in the hydralazine group.

Despite the increase in pulmonary artery pressure in the hydralazine group, edema compared with baseline increased more in the minoxidil group over the 5 h. This is especially noteworthy because minoxidil does not even achieve peak effect in the first 2 h.¹² We hypothesize that the increase in edema in the minoxidil group compared with controls occurred because of a change in the microvascular pressure in injured areas. Despite constant pulmonary artery and pulmonary artery wedge pressures, microvascular pressure can increase if there is a decrease in precapillary resistance. Because the site of HPV is primarily arteriolar,¹³ and the site of fluid and protein leak in oleic-acid injury is the alveolar capillary,¹⁴ inhibition of HPV will increase hydrodynamic forces favoring leakage.

Alternative hypotheses for the greater increases in edema in minoxidil animals include a direct drug effect on permeability or a measurement artifact. A direct drug effect seems unlikely because the effect has not been reported during clinical trials of the drug,¹⁵ and no evidence of edema formation has occurred in normal dogs in our studies of the drug's effect on HPV.

We considered whether the increased edema could be an artifact of the iced indocyanine green lung water measurement technique. This technique has proven accurate except in the cases of severe alveolar flooding and reduced circulatory bed.¹⁶ To confirm this, we performed gravimetric determinations of extravascular lung mass with the measured extravascular lung water. A high degree of correlation was present (fig. 3), although there was a tendency throughout the range to underestimate the extent of edema. The tendency to underestimate gravimetric lung water existed equally in all three groups (table 3). The ratios of thermodilution of gravimetric lung waters were lowest for the minoxidil group but were not significantly different from each other, lending validity to our comparisons of the groups. The consistent underestimation of lung water may have been due to areas of severe alveolar flooding in which circulation was totally absent. Even so, the linearity of the relationship over the range studied supports the utility of this measurement in con-

TABLE 3. Ratio of Thermodilution to Gravimetric Lung Water By Group

Untreated	Hydralazine	Minoxidil
0.92 ± 0.08	0.99 ± 0.13	0.85 ± 0.07

firming the trends observed, although not for absolute quantitation of lung water.

Our finding that hydralazine increases cardiac output with relatively little effect on gas exchange as compared with other peripheral vasodilators confirms the findings of Harrison *et al.* in an acute oleic-acid dog model.¹⁷ However, while they found no deterioration in gas exchange after the drug, we found that hydralazine did adversely affect venous admixture. This difference may be a result of a difference in predrug ventricular filling pressures. In their study, relatively high, left-sided, predrug pressures (9 ± 1 mmHg) were reduced by hydralazine, whereas the relatively low pressures in our animals remained unchanged. Because even small changes in pulmonary venous pressure will affect edema in the face of increased permeability, the adequate gas exchange in their animals during hydralazine therapy may have occurred primarily because of the decreased left heart filling pressures.

The increase in edema with minoxidil in our study differs from several previous studies of vasodilators in acute lung injury.^{18,19} In each of these studies, presumed pulmonary microvascular pressure decreased. In the study of Broe *et al.*, using isolated lobes injured with hydrochloric acid, flow was held constant while sodium nitroprusside or isoproterenol was administered, causing pulmonary artery pressure to decrease.¹⁸ In the study of Prewitt *et al.*, the intact animals underwent oleic-acid injury, then were given nitroprusside, which markedly lowered pulmonary wedge pressure.¹⁹ In our study, the vasodilator did not alter significantly the pulmonary arterial or pulmonary wedge or microvascular pressures calculated by the formula of Gaar *et al.*,²⁰ yet edema increased. Our inability to measure microvascular pressure in the foci of lung injury makes it impossible to define the mechanism for worsening injury in these animals, but it seems likely that regional vasodilation due to HPV inhibition alters the microvascular pressure in the injured areas. Further support for this hypothesis comes from the studies of Foulke *et al.*, who found that nitroprusside did not decrease lung lymph production (*e.g.*, edema formation) in endotoxin-injured sheep, despite lower pulmonary arterial and wedge pressures.²¹ Their results, too, are explicable by alteration in regional microvascular pressures due to HPV inhibition.

We hypothesize that, while the use of vasodilators in permeability pulmonary edema may increase cardiac output, it may adversely affect gas exchange. Vasodilators with minimal effects on HPV, such as hydralazine, may be preferable in the face of respiratory failure.

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