

Effect of Sodium Nitroprusside on Cardiovascular Function and Pulmonary Shunt in Canine Oleic Acid Pulmonary Edema

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The authors investigated the acute effects of nitroprusside on intrapulmonary shunt (Q_s/Q_t), cardiac output, and left ventricular function in dogs with normal lungs, and again after they developed oleic acid pulmonary edema. Before oleic acid, nitroprusside reduced pulmonary capillary wedge pressure (PCWP) and stroke volume, and there were no changes in Q_s/Q_t . Ninety minutes after oleic acid, PCWP, Q_s/Q_t , and systemic vascular resistance increased and stroke volume decreased. Then nitroprusside increased cardiac output by 35 per cent and increased Q_s/Q_t from 12 to 18 per cent. After oleic acid, stroke volume increased on nitroprusside from 18 to 23 ml ($P < 0.05$) despite reduced preload, as PCWP decreased from 10.4 to 4.4 torr on nitroprusside ($P < 0.05$). Increased stroke volume may be explained by the reduction in resistive afterload, as nitroprusside reduced systemic vascular resistance from 60 to 34 torr·l⁻¹·min. To the extent that canine oleic acid pulmonary edema represents low pressure edema in patients, nitroprusside is a potential treatment to reduce PCWP, pulmonary microvascular pressure, and pulmonary edema while maintaining cardiac output. (Key words: Blood pressure; peripheral vascular resistance. Heart: afterload reduction; cardiac output. Lung: gas exchange; shunt; vascular permeability; vascular resistance. Pharmacology: nitroprusside.)

IN PATIENTS WITH HEART FAILURE, the administration of sodium nitroprusside increases cardiac output and reduces left ventricular filling pressure.¹⁻³ A significant number of patients with no known heart disease have reduced cardiac output and stroke volume at normal or increased pulmonary capillary wedge pressure (PCWP) during treatment for hypoxemic respiratory failure.⁴ Conceivably, nitroprusside therapy of this mild left ventricular dysfunction would reduce PCWP without reducing stroke volume. By reducing pulmonary vascular pressure, such a cardiovascular effect potentially treats the low pressure pulmonary edema attributed to increased pulmonary vascular permeability in these patients.⁵ Indeed, a four-hour infusion of nitroprusside did reduce the low pressure pulmonary edema induced by intravenous oleic acid in dogs.⁶ In that study, PCWP was reduced from 11 to 6 torr by nitroprusside, yet stroke volume and cardiac output increased. These hemodynamic effects of nitroprusside differ from those in normal dogs⁷ and from those in another study of canine oleic

acid pulmonary edema,⁸ in which cardiac output and stroke volume decreased and PCWP was not reduced during brief infusions of nitroprusside. Furthermore, intrapulmonary shunt (Q_s/Q_t) increased in dogs treated with nitroprusside for four hours,⁶ but it did not change during a brief infusion of the drug.⁸

To resolve these conflicting reports, we designed this study to describe the acute effects of nitroprusside on Q_s/Q_t , on cardiac output, and on the relationship between PCWP and stroke volume. Based on our previous study⁶ we asked two main questions about the potential therapeutic value of a brief infusion of nitroprusside in canine oleic acid pulmonary edema. Does nitroprusside reduce PCWP and increase stroke volume, and what is the net effect of increased cardiac output and increased shunt on arterial oxygenation? We emphasize that the cardiovascular and shunt effects of nitroprusside in canine oleic acid edema are not synonymous with nitroprusside effects in clinical low pressure edema. Rather, these results provide insight into potential mechanisms of action of nitroprusside in one model of low pressure pulmonary edema which may guide clinical trials.

Methods

Seven mongrel dogs (20-30 kg) were anesthetized with pentobarbital (30 mg/kg) and supplemented as required. They were artificially ventilated (20 ml/kg) in the lateral decubitus position with 100 per cent O₂ via tracheostomy tube. A catheter was placed in the femoral artery to obtain arterial blood and monitor systemic arterial blood pressure (BP) by connecting it to a Statham® P23 AC pressure transducer. A thermistor-tipped flow-directed Swan-Ganz catheter was inserted via the external jugular vein and positioned with pressure monitoring in a branch of the pulmonary artery where pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure were reproducibly obtained by connecting it to a Statham® P23 BB pressure transducer. All vascular pressures were referenced to the center of the chest. Samples of mixed venous blood were also obtained via this catheter. A second Swan-Ganz catheter was passed similarly into the right ventricle and withdrawn under pressure monitoring to the right atrium for injection of saline boluses during cardiac output (CO) determinations. The thermal dilution curve was recorded on a separate, single channel recorder and was analyzed by computer (Columbus Instruments). The outputs from all transducers were displayed on an 8-channel Hewlett Packard® os-

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cillograph. These preparations were usually completed in less than one hour, during which about 300 ml normal saline were infused to achieve adequate hydration. After ensuring an adequate level of anesthesia the experiment was begun, and saline infusion (30 ml/h) was continued throughout the study.

Samples of arterial and mixed venous blood were obtained simultaneously for subsequent analysis and shunt calculations. Hemodynamic measurements (CO, BP, PAP, PCWP, heart rate [HR]) were then recorded during a 10-S breath hold at FRC. After the completion of baseline measurements, nitroprusside (range 2–8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), was infused via the femoral vein catheter to reduce mean BP approximately 20 per cent. Five minutes after blood pressure was reduced to this stable level, a complete second set of measurements were obtained and designated NP. Then nitroprusside was discontinued and five minutes after BP had returned to control levels, a third set of measurements were obtained. To control for effects of time, the values of the first and third measurements were averaged, and compared with the NP values.

To create a pulmonary capillary leak, oleic acid (0.08 ml/kg) was infused into the right atrium over 30 seconds. After a 90-min interval the previous sequence of measurements was repeated. In addition, a second infusion of nitroprusside was given, measurements were repeated (NP₂), and after the drug was discontinued a final set of measurements were obtained. Since each set of measurements obtained during nitroprusside was bracketed by control measurements, the mean of those control measurements was compared to the intervening measurements on nitroprusside. Statistics were applied using Student's paired *t* test.

Arterial and mixed venous blood samples were analyzed for P_{O_2} , P_{CO_2} , and *pH* using a Corning® blood-gas analyzer (model 165/2) immediately after collection. The oxygen electrode was calibrated with blood exposed to oxygen tensions from 20 to 700 torr on a tonometer and measured values were corrected using the tonometer factor. Arterial and mixed venous oxygen contents ($C\bar{v}_{\text{O}_2}$) were measured directly using a carbon monoxide scrubbing technique.⁹ Right to left shunt (Q_s/Q_t) was calculated according to the equation $Q_s/Q_t = (C\bar{c}'_{\text{O}_2} - C\bar{a}_{\text{O}_2}) / (C\bar{c}'_{\text{O}_2} - C\bar{v}_{\text{O}_2})$, where $C\bar{c}'_{\text{O}_2} = C\bar{a}_{\text{O}_2} + 0.003 (P_{\text{bar}} - 47 - P_{\text{aCO}_2} - P_{\text{aO}_2})$ when arterial O_2 saturation is 100 per cent. Pulmonary vascular resistance (PVR) was calculated as $\text{PVR} = (\text{PAP} - \text{PCWP})/\text{CO}$, and systemic vascular resistance ($\text{SVR}) = \text{BP}/\text{CO}$.

Results

The cardiopulmonary effects of nitroprusside in dogs with normal lungs are illustrated in table 1. Mean BP was reduced approximately 22 per cent (145 to 114 torr). Cardiac output, pulmonary artery pressure, pulmonary

TABLE 1. Effects of Nitroprusside on Hemodynamics and Gas Exchange in Dogs with Normal Lungs

	Control	NP
BP (torr)	145 ± 11*	114 ± 13
CO (l/min)	3.9 ± 1.0	4.0 ± 1.9
HR (beats/min)	143 ± 22*	189 ± 26
SV (ml)	28.1 ± 8.5*	21.3 ± 5
PCWP (torr)	6.6 ± 1.3*	4.6 ± 2.1
PAP (torr)	15.7 ± 2	14.3 ± 1.8
PVR (torr·l ⁻¹ ·min)	2.5 ± 1.1	2.7 ± 0.9
Q _s /Q _t (per cent)	6.4 ± 1.3	6.7 ± 1.7

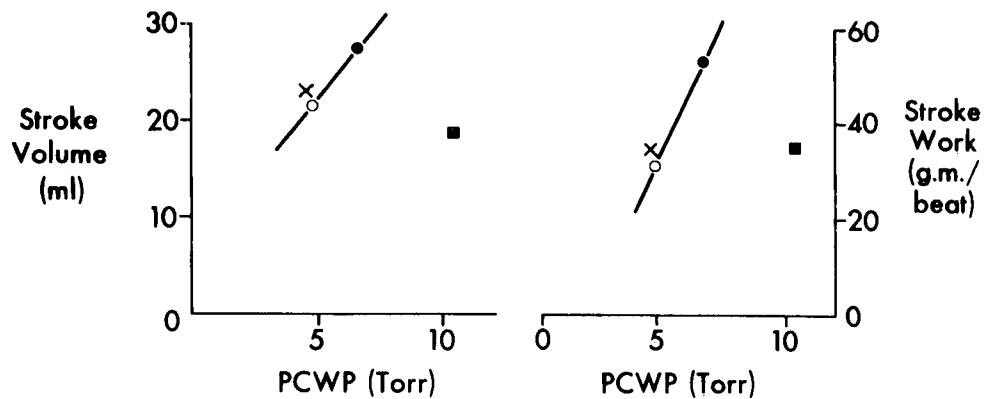
* Denotes significant difference ($P < 0.05$) from the corresponding NP values.

vascular resistance, and Q_s/Q_t were unchanged. Heart rate increased, so stroke volume (SV) fell from 28 to 21 ml ($P < 0.05$). There was a corresponding fall in PCWP from 6.6 to 4.5 torr ($P < 0.05$) on nitroprusside, suggesting that the fall in SV was associated with reduced left ventricular end-diastolic volume. These mean values of SV and PCWP are displayed in figure 1.

Comparison of control values in tables 1 and 2 reveals the effects of oleic acid edema. Ninety minutes after oleic acid (table 2), mean PCWP had increased from 6.6 to 9.2 torr ($P < 0.05$). Despite increased PCWP and unchanged blood pressure, cardiac output and stroke volume were reduced ($P < 0.05$). Mean CO and SV fell from 3.9 to 2.5 l/min and 28.1 to 20.1 ml, respectively. As illustrated in figure 1, oleic acid depressed the SV-PCWP relationship considerably. The depressed left ventricular function after oleic acid was associated with a large increase in systemic vascular resistance from 36.2 to 56.6 torr·l⁻¹·min ($P < 0.05$). Pulmonary artery pressure and pulmonary vascular resistance also increased in oleic acid pulmonary edema.

Table 2 presents the cardiopulmonary effects of two infusions of nitroprusside during oleic acid pulmonary edema. Both nitroprusside infusions increased cardiac output and stroke volume despite corresponding reductions in PCWP. For example, NP₂ increased CO from 2.4 to 3.5 l/min ($P < 0.05$), increased SV from 17.2 to 24.5 ml ($P < 0.05$), and reduced PCWP from 11.3 to 4.8 torr ($P < 0.05$). This effect of nitroprusside on PCWP and stroke volume is illustrated in figure 1. The values of nitroprusside lie close to the pre-oleic acid curve, indicating improvement in ventricular function with nitroprusside. An identical pattern was seen when stroke work was calculated and plotted against PCWP. This improvement in ventricular function was associated with a large reduction in mean systemic vascular resistance from 63 to 32 torr·l⁻¹·min on nitroprusside ($P < 0.05$) (table 2). Heart rate increased slightly during NP, but the increase in rate from control 2 to NP₂ (141 to 145 beats/min) was not significant (table 2). Accordingly, increased heart rate is an unlikely explanation of improved ventricular function on nitroprusside.

FIG. 1. Effect of nitroprusside infusion on the relationship between mean PCWP (abscissae) and mean stroke volume (left ordinate) and mean stroke work (right ordinate) in anesthetized dogs. Before oleic acid, PCWP, stroke volume, and stroke work decreased from control values (●) along normal Starling curves (continuous lines) to the values on nitroprusside (○). PCWP had increased 1.5 h after oleic acid, but stroke volume and work decreased (■). Then nitroprusside restored the pre-oleic acid Starling relationship by reducing PCWP but increasing stroke volume (X).



Mean pulmonary shunt doubled after oleic acid (tables 1 and 2), and arterial P_{O_2} decreased to 293 ± 149 torr. Compared to the corresponding average of values before and after each nitroprusside infusion, the drug increased Q_s/Q_t in all experiments. Mean Q_s/Q_t increased on NP₁ from 14.3 to 20.2 per cent ($P < 0.05$) and on NP₂ from 9.8 to 16.0 per cent ($P < 0.05$). Despite the large increase in Q_s/Q_t , Pa_{O_2} did not fall much because cardiac output and mixed venous P_{O_2} increased on nitroprusside (table 2).

Both nitroprusside infusions reduced PAP (table 2). Despite reduced pulmonary inflow pressures, pulmonary vascular resistance did not increase. Note that in all conditions, alveolar pressure P_A was zero, so both PAP and PCWP exceeded P_A except at the top (most lateral portion) of the lung, so most of the lung was in Zone III.

Discussion

In canine oleic acid pulmonary edema, our brief infusions of nitroprusside reduced the normal PCWP by 6 torr and increased stroke volume. Such improved ventricular pumping function is similar to that described during vasodilator therapy of dogs or patients with heart failure.¹⁻³ It is quite different from the hemodynamic response in normal dogs^{7,8} or in dogs with unilateral atelectasis,¹⁰ where nitroprusside infusion reduced PCWP, stroke volume and cardiac output. Our results before oleic acid confirm and extend these previous studies, and are best explained by reduced left ventricular filling during nitroprusside infusion in dogs with a normal cardiovascular system. Ninety minutes after intravenous oleic acid, stroke volume and cardiac output were reduced despite increased PCWP. This mild left ventricular dysfunction resembles that reported in patients with hypoxemic respiratory failure.⁴ The response of ventricular pumping function to nitroprusside therapy in such patients is similar to our results after oleic acid, *vis.*, PCWP decreased and stroke volume and cardiac

output increased.¹¹ These considerations suggest that cardiovascular function in patients with low pressure pulmonary edema and dogs with oleic acid pulmonary edema responds favorably to nitroprusside therapy as it does in patients with heart failure.

Conceivably, left ventricular pumping function is depressed by oleic acid injury of the heart or by chemical mediators released from damaged lung. Alternatively, reduced stroke volume at increased PCWP may be due to increased systemic vascular resistance after oleic acid. Because nitroprusside returned both the systemic vascular resistance and the Starling relationship to the pre-oleic acid values, we prefer the latter explanation. Although similar stroke work at reduced PCWP signals increased ventricular contractility, nitroprusside does not increase contractility of ventricular muscle.¹² We propose that increased systemic vascular resistance after oleic acid impedes ventricular ejection and reduces stroke volume, and that nitroprusside reverses this process by lowering systemic vascular resistance to the pre-oleic acid level. In support of this notion, canine stroke volume doubled at a constant contractile state, end-diastolic volume and blood pressure when systemic vascular resistance was reduced by opening a systemic arterio-venous shunt.^{11,13} Though reduced systemic vascular resistance during nitroprusside infusion in canine oleic acid edema explains the increased stroke volume and reduced PCWP, it is possible that nitroprusside lowers PCWP and increases stroke volume by other mechanisms than reduced systemic vascular resistance in patients with low pressure pulmonary edema.

Our observation that acute nitroprusside infusion reduced PCWP and increased cardiac output in canine oleic acid edema differs from the results of another study. Colley *et al.*⁸ studied dogs 24 hours after oleic acid infusion when the low values of blood pressure and PCWP observed suggested hypovolemia. Then nitroprusside infusion reduced cardiac output and did not reduce PCWP. In contrast, we investigated the acute hemodynamic ef-

TABLE 2. Effects of Nitroprusside on Hemodynamics and Gas Exchange in the Presence of Oleic Acid Pulmonary Edema

	Control ₁	NP ₁	Control ₂	NP ₂
BP (torr)	147 ± 17.7*	114 ± 11	151 ± 18*	113 ± 12
CO (l/min)	2.6 ± 1.1	3.2 ± 1.3	2.4 ± 0.5*	3.5 ± 1.0
SVR (torr·l ⁻¹ ·min)	56.5 ± 13*	35.6 ± 11	63 ± 9*	32.3 ± 8
HR (beats/min)	133 ± 27*	150 ± 40	141 ± 32	145 ± 48
SV (ml)	20.1 ± 6.7	21.6 ± 8.2	17.2 ± 3.5*	24.5 ± 2.8
PCWP (torr)	9.2 ± 2.3*	4.0 ± 2.0*	11.3 ± 2.4*	4.8 ± 1.4
PAP (torr)	18.6 ± 2.8*	15.8 ± 2.7	20.8 ± 2.7*	16.8 ± 3.9
PVR (torr·l ⁻¹ ·min)	4.53 ± 3.8	4.55 ± 2.8	4.0 ± 2.2	3.8 ± 2.2
Pa _{O₂} (torr)	293 ± 149*	263 ± 167	354 ± 123*	305 ± 136
Pv _{O₂} (torr)	42.4 ± 4.4	43.6 ± 8.1	42.3 ± 3.2*	49.5 ± 6.9
Q _s /Q _t (per cent)	14.3 ± 5.6*	20.2 ± 10.3	9.8 ± 3.0*	16.0 ± 5.9

* Denotes significant difference ($P < 0.05$) from the corresponding NP value.

fects of nitroprusside 1.5 hours after oleic acid in dogs hydrated with 300 ml normal saline. One explanation of this difference is that nitroprusside is less effective in raising cardiac output and reducing PCWP when circulating blood volume is reduced.

The different effects of nitroprusside on cardiac output in these two studies may account for the different effects on pulmonary shunt. Colley *et al.* had previously observed that nitroprusside increased Q_s/Q_t in dogs with unilateral atelectasis and attributed this effect to reduced alveolar hypoxic vasoconstriction during nitroprusside infusion.¹⁰ When Q_s/Q_t did not increase on nitroprusside in oleic acid edema, they speculated that alveolar hypoxic vasoconstriction was less effective in edematous lung units during oxygen breathing.⁸ Yet our dogs were also ventilated with O₂, and had a large increase in shunt during acute nitroprusside infusion. Conceivably, the increase in cardiac output we observed is the cause of increased Q_s/Q_t . Indeed, several studies report increased Q_s/Q_t when cardiac output increases in canine oleic acid edema.^{14,15} This effect of increased cardiac output on shunt might be explained by preferential pulmonary vascular recruitment in nonventilated regions. Alternatively, part of the Q_s/Q_t in edema is in fact a diffusion defect made worse by shortened pulmonary transit time when cardiac output increases, or increased cardiac output increases the edema.

Nitroprusside caused a large fall in PCWP and a smaller fall in pulmonary artery pressure (see table 2). The reductions in vascular pressure relative to alveolar pressure would have caused the lungs to change from a Zone III state before nitroprusside (PAP 20, PCWP

10, P_A 0) to Zone II/Zone III conditions during nitroprusside infusion (PAP 16, PCWP 4, P_A 0). Permutt *et al.*¹⁶ demonstrated in isolated perfused lungs that when lungs are in a Zone II/Zone III state, relatively small reductions (1–2 torr) in PAP are associated with large increases in pulmonary vascular resistance due to derecruitment of lung vessels. This explanation is supported in oleic acid edema by the data of Smith *et al.*,¹⁴ who observed that pulmonary vascular resistance doubled when phlebotomy reduced cardiac output, PCWP, and PAP. In our study, nitroprusside caused a similar reduction in PAP and PCWP, but pulmonary vascular resistance did not increase. One explanation is that nitroprusside blocked vasoconstriction in edematous lung regions, thereby increasing Q_s/Q_t and obscuring the effect of vascular derecruitment on pulmonary vascular resistance.

Note that the pulmonary vasodilator effect of nitroprusside need not prefer edematous nonventilated lung regions if the increased Q_s/Q_t observed on nitroprusside is due to increased cardiac output *per se*. Our data do not allow a distinction between selective vasodilation and a primary effect of increased cardiac output on Q_s/Q_t . Because Colley *et al.*⁸ did not demonstrate increased Q_s/Q_t during nitroprusside infusion in canine oleic acid edema when cardiac output did not increase, we infer that selective pulmonary vasodilation in nonventilated lung regions by nitroprusside is not responsible for increased Q_s/Q_t . Rather, increased Q_s/Q_t on nitroprusside is due to the associated increase in cardiac output observed in our study but not in theirs. This is supported by studies in dogs having oleic acid confined to one lower

lobe in which nitroprusside infusion and increased cardiac output did not redistribute pulmonary blood flow to the edematous lobe.¹¹ Accordingly, the reduction in PaO_2 on nitroprusside is small because the contribution of increased Q_s/Q_t to arterial hypoxemia is offset by the increased in mixed venous O_2 content when cardiac output is increased.

We previously demonstrated that a 4-hour infusion of nitroprusside reduced PCWP by 5 torr and pulmonary edema by 50 per cent in dogs with oleic acid edema.⁶ In that study, cardiac output and pulmonary shunt were much greater on nitroprusside than in another group of dogs in which phlebotomy reduced PCWP and edema by a similar amount. The present study confirms and extends these observations by demonstrating that acute nitroprusside infusion in canine oleic acid edema causes a reversible and reproducible increase in Q_s/Q_t and cardiac output at reduced PCWP. We attribute the improved left ventricular function to reduced systemic vascular resistance on nitroprusside, and we attribute increased Q_s/Q_t to increased cardiac output rather than to the pulmonary vasoactivity of nitroprusside. These results and conclusions suggest that nitroprusside therapy is one way to achieve the lowest wedge pressure at which an adequate cardiac output can be maintained in the treatment of low pressure pulmonary edema. Although oleic acid edema was studied because it is a convenient model of low pressure edema, it is obviously different from clinical low pressure edema so our conclusions require an adequate clinical trial.

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