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Pulmonary Vasodilator Effects of Nitroglycerin and Sodium Nitroprusside in Canine Oleic Acid-induced Pulmonary Hypertension

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The hemodynamic effects of nitroglycerin (TNG) and sodium nitroprusside (SNP) were studied in a canine model of pulmonary hypertension. Oleic acid administration resulted in pulmonary hypertension with a 133% increase in pulmonary vascular resistance (PVR), a 40% increase in mean pulmonary artery pressure (MPAP), and a 28% decrease in cardiac output (CO). In this model, subsequent TNG administration increased CO 40%, decreased PVR 43%, and decreased MPAP 12%; pulmonary hemodynamics during TNG administration were not significantly different from those prior to oleic acid administration. SNP produced systemic hypotension but did not alter either PVR or MPAP and increased CO only 14%. The efficacy of TNG in this model may relate to its ability to dilate preferentially the pulmonary vascular bed. (Key words: Anesthetic techniques: hypotensive, nitroglycerin, nitroprusside. Blood pressure: hypertension, pulmonary. Lung: blood flow; damage; intravascular pressures; vascular resistance. Pharmacology: nitroglycerin; nitroprusside.)

SYSTEMIC ARTERIAL VASODILATOR THERAPY with agents such as sodium nitroprusside (SNP), hydralazine, and prazosin has an established role in the acute and chronic management of disease states associated with elevated systemic vascular resistance (SVR).[1–3] In contrast, the role of pulmonary arterial vasodilator therapy in the management of disease states associated with elevated pulmonary vascular resistance (PVR) such as adult respiratory distress syndrome, chronic obstructive pulmonary disease, primary pulmonary hypertension, and chronic pulmonary emboli remains limited. The limited role of pulmonary vasodilator therapy reflects the lack of a safe, effective agent.

Over the past several decades, many agents have been evaluated as pulmonary vasodilators. These include acetylcholine,[4] tolazoline,[5] isoproterenol,[6] phentolamine,[7] hydralazine,[8] diazoxide,[9] verapamil,[10] prostaglandin E_1,[11] and nifedipine.[12] Although each of these agents has been effective in one or several patients, none of these agents has gained widespread clinical use as a pulmonary vasodilator. Currently, the most frequently used agent for the acute treatment of pulmonary hypertension is SNP.[13–15]

Although SNP may be a pulmonary vasodilator, both animal studies[16–20] and clinical studies[21–24] suggest that the effects on the pulmonary circulation occur only at doses which dramatically decrease SVR. The use of such a drug in disease states associated with severe pulmonary hypertension is likely to be complicated by systemic hypotension. The ideal pulmonary vasodilator should be effective at doses which do not severely decrease SVR. Unlike SNP, nitroglycerin (TNG) dilates systemic capacitance vessels at doses which do not affect systemic arteriolar resistance vessels.[25,26] Several animal and clinical studies suggest that TNG is an effective pulmonary vasodilator.[27–32] We recently have compared the effects of SNP and TNG in four patients with chronic pulmonary hypertension.[33] TNG increased cardiac output 61%, decreased PVR 50%, and decreased mean pulmonary artery pressure (MPAP) 16%. In contrast, SNP decreased systemic blood pressure and SVR without affecting cardiac output, PVR, or MPAP. We explained the increase in cardiac output which occurred with TNG as resulting from pulmonary vasodilation and a decrease in right ventricular afterload.

In view of the marked heterogeneity of patients with pulmonary hypertension, we decided to compare these two drugs in an animal model. Most animal models of pulmonary hypertension have either extreme variability or high mortality.[34] Diffuse lung injury caused by administration of oleic acid results in a reproducible model of respiratory distress syndrome with pulmonary hypertension.[35] Using this model, we find that TNG but not SNP decreases PVR, decreases MPAP, and increases cardiac output.

Methods

Eight adult mongrel dogs, weighing 13–35 kg, were studied. After an overnight fast animals were anesthetized with 8.8 mg/kg ketamine, im, followed by 30 mg/kg sodium pentobarbital, iv. Animals were intubated with a cuffed endotracheal tube and mechanically ventilated with 100% oxygen at a rate of 12 breaths/min and a tidal volume of 15–20 ml/kg. Anesthesia was maintained by continuous pentobarbital infusion at a rate of 5–10 $mg \cdot kg^{-1} \cdot h^{-1}$, sufficient to prevent spon-

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TABLE 1. Hemodynamic Variables Prior to Oleic Acid Administration and before and after Administration of TNG and SNP

Variable	Pre-Oleic	Base-TNG	Final-TNG	Base-SNP	Final-SNP
CO (l/min)	3.91 ± 0.30	2.88 ± 0.41	4.04 ± 0.44†§	2.78 ± 0.27	3.16 ± 0.28*
HR (beats/min)	130 ± 8	122 ± 7	116 ± 7	122 ± 6	131 ± 8
SV (ml/beat)	31 ± 3	23 ± 3	35 ± 3†‡	24 ± 3	25 ± 4
PVR (dyn·s·cm^{-5})	139 ± 29	355 ± 60	203 ± 33†‡	292 ± 31	306 ± 42
MPAP (mmHg)	11.0 ± 1.5	16.1 ± 1.7	14.2 ± 1.6*	14.6 ± 2.0	16.3 ± 2.3
PAWP (mmHg)	5.4 ± 2.0	4.9 ± 1.9	4.8 ± 1.8	5.1 ± 1.7	4.4 ± 1.8
SVR (dyn·s·cm^{-5})	2,758 ± 286	3,577 ± 549	1,398 ± 137†	3,088 ± 339	1,714 ± 141†
MAP (mmHg)	128 ± 6	112 ± 5	68 ± 2†	103 ± 5	67 ± 2†
CVP (mmHg)	2.8 ± 1.3	2.8 ± 1.4	2.9 ± 1.3	2.4 ± 1.4	2.4 ± 1.2
Pa_{O_2} (mmHg)	511 ± 39	79 ± 13	52 ± 6†‡	93 ± 17	113 ± 27

Values are means ± SEM of eight subjects.
* $P < 0.05$ compared with baseline of same drug; † $P < 0.01$.
‡ $P < 0.05$ compared with Final-SNP; § $P < 0.01$.
Abbreviations: CO = cardiac output; HR = heart rate; SV = stroke volume; PVR = pulmonary vascular resistance; MPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; SVR = systemic vascular resistance; MAP = systemic mean arterial pressure; CVP = central venous pressure; and Pa_{O_2} = systemic arterial oxygen tension.

taneous respirations. Systemic artery and triple-lumen thermistor-tipped pulmonary artery catheters were inserted by cutdown procedures on the femoral artery and vein. A central venous catheter was introduced via the right external jugular vein.

A baseline hemodynamic profile (see below) and arterial blood gas were obtained. Oleic acid (Eastman Kodak) in a dose of 0.10 ml/kg was administered as a bolus injection through the central venous catheter. Previous experiments have demonstrated that hemodynamic variables become stable within two hours after oleic acid administration and remain stable for at least an additional four hours. For the first two hours after oleic acid, normal saline was administered as needed to maintain hemodynamic stability. For the remainder of the experiment, normal saline was administered at 50 ml/h.

A second hemodynamic profile and arterial blood gas were obtained two hours after oleic acid administration. Dogs then received either SNP (Nipride; Roche) or TNG by continuous infusion. TNG was prepared by dissolving 0.6-mg tablets (Lilly) in 5% dextrose solution to a final concentration of 1.2 mg/ml; TNG was administered via Anesthesia Venoset (Abbott) tubing. Initial dose of SNP was 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$; initial dose of TNG was 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. These doses did not have significant hemodynamic effects in any of the dogs; dogs require significantly higher doses of both drugs compared with humans. Ten minutes after beginning each dose, a repeat hemodynamic profile was obtained and the dose was doubled. This process was repeated until the systemic mean arterial pressure fell below 70 mmHg; the infusion rate then was held constant for 20 minutes and a final hemodynamic profile and arterial blood gas were obtained. The infusion then was terminated. One hour later, a new baseline hemodynamic profile and arterial blood gas were obtained and the other drug was tested.

Hemodynamic profiles consisted of systemic mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), mean pulmonary artery wedge pressure (PAWP), and cardiac output (CO). Cardiac output was recorded as the mean of three determinations by thermodilution technique, each using 10 ml of iced normal saline; the Edwards Laboratories 9520A Cardiac Output Computer was used. Systemic vascular resistance (SVR) in dyn·s·cm^{-5} was calculated as (MAP − CVP) × 80/CO; pulmonary vascular resistance (PVR) was calculated as (MPAP − PAWP) × 80/CO.

Results are expressed as means ± SEM of the eight dogs. Statistical analysis was by Student's paired t test and by standard linear regression analysis with $P < 0.05$ considered significant.

Results

The final dose of SNP ranged from 4–64 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the total dose of SNP did not exceed 2 mg/kg in any dog. The final dose of TNG ranged from 256–1,024 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Hemodynamic measurements and arterial oxygen tension prior to administration of oleic acid, prior to administration of each drug, and during administration of the final dose of each drug are presented in table 1. Cardiac output was decreased significantly after oleic acid administration. TNG increased cardiac output in all eight dogs. Mean cardiac output increased 40% with TNG but only 14% with SNP; the increase with TNG was significantly greater than with SNP. The final cardiac output with SNP was significantly lower than the cardiac output prior to oleic acid administration; the final cardiac output with TNG

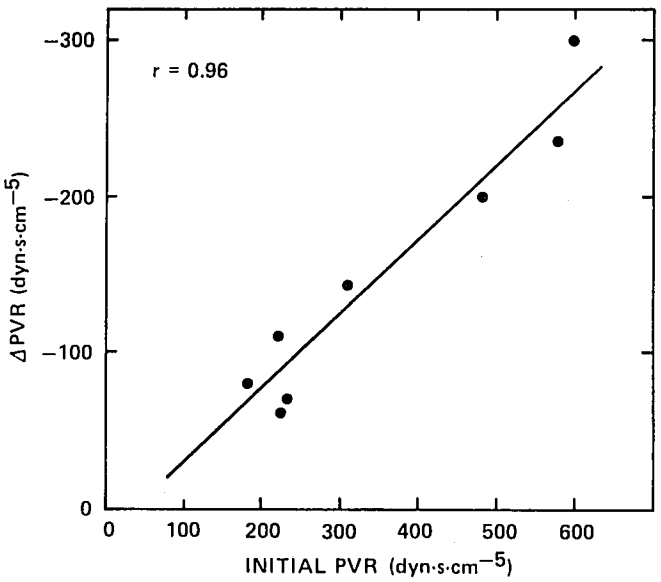

FIG. 1. Change in pulmonary vascular resistance (ΔPVR) in dyn·s·cm^{-5} during nitroglycerin (TNG) administration as a function of initial PVR prior to TNG. The regression line is y = 15 − 0.47x; r = 0.96; $P < 0.001$.

was similar to the cardiac output prior to oleic acid administration.

There were no significant changes in heart rate but there was a trend towards decreased heart rates with TNG and increased heart rates with SNP. Stroke volume was decreased significantly after oleic acid administration. TNG increased stroke volume 50%; stroke volume was not affected by SNP. The final stroke volume with TNG was significantly higher than with SNP and was not significantly different from the value prior to oleic acid administration.

Pulmonary vascular resistance (PVR) was increased significantly after oleic acid administration. TNG decreased PVR in all eight dogs. TNG resulted in a 43% decrease in PVR; SNP resulted in a nonsignificant 5% increase in PVR. The final PVR with TNG did not differ significantly from the initial PVR prior to oleic acid administration; the final PVR with SNP was significantly higher than the PVR prior to oleic acid administration. The decrease in PVR which occurred with TNG was highly correlated with the PVR prior to TNG administration (fig. 1); subjects with the highest PVR prior to TNG administration had the greatest decreases in PVR with TNG.

Mean pulmonary artery pressure (MPAP) was increased significantly after oleic acid administration. TNG decreased MPAP 12%; SNP resulted in a nonsignificant 12% increase in MPAP.

Systemic mean arterial pressure (MAP) was decreased significantly and systemic vascular resistance (SVR) was increased significantly after oleic acid administration. Both TNG and SNP resulted in decreases in MAP and SVR in all dogs; there were no significant differences in these effects between the two drugs. Neither drug resulted in a significant change in central venous pressure or pulmonary artery wedge pressure.

Arterial P_{O_2} was decreased markedly after oleic acid administration. TNG resulted in a further decrease in P_{O_2}; SNP resulted in a nonsignificant increase in P_{O_2}. The P_{O_2} with TNG was significantly lower than that with SNP.

Discussion

In this animal model oleic acid produced diffuse lung injury, resulting in pulmonary hypertension, hypoxemia, and decreased cardiac output. TNG increased cardiac output 40% and stroke volume 50% and decreased PVR 43%; MPAP, SVR, and MAP all decreased. Doses of SNP which resulted in a similar decrease in MAP (a clinically relevant endpoint) did not affect stroke volume, PVR or MPAP and increased cardiac output by only 14%.

The failure of SNP to affect PVR is consistent with other animal studies. Using a similar model of canine oleic acid-induced pulmonary edema, Prewitt and Wood[16] found no change in PVR with SNP administration. Hill *et al.*[17] found no change in PVR with SNP administration in dogs with unilateral alveolar hypoxia despite a 50% decrease in SVR. Both Pace[18] and Colley *et al.*[19] demonstrated an effect of SNP on PVR only under conditions of hypoxic pulmonary vasoconstriction; even then, the decrease in SVR was larger than in PVR. Similarly, Sivak *et al.*[20] found the effects of SNP on PVR to depend upon the experimental conditions. Clinical studies suggest that SNP affects PVR only at doses which also affect SVR. Knapp and Gmeiner[21] reported that both SVR and PVR decreased to a similar extent when SNP was administered to patients with mitral stenosis, primary lung disease, or normal pulmonary artery pressures. Chatterjee *et al.*,[22] Pierpont *et al.*,[23] and Stephenson *et al.*[24] demonstrated decreases in PVR and SVR of similar magnitude when SNP was administered to patients with acute myocardial infarction, patients with left ventricular failure, or patients undergoing cardiac surgery.

In our animal model, TNG at tolerated doses was an effective pulmonary vasodilator. This finding is consistent with several other studies. Pinkerson *et al.*[27] demonstrated that TNG decreased PVR in dogs when cardiac output was maintained constant by bypassing either the left or the right ventricle. Similarly, Mentzer and Nolan[28] reported a 90% increase in pulmonary lobar blood flow with TNG when pulmonary artery pressure and left atrial pressure were held constant by a pul-

monary bypass circuit. In an oleic acid-induced model of pulmonary edema similar to the present experiment, Colley *et al.*[29] found that TNG decreased PVR 29% when ventilation was with room air but did not affect PVR when ventilation was with 100% oxygen. However, the pulmonary injury was less severe than in our model and the doses of TNG which they used did not result in as great a decrease in MAP. In clinical studies, Mookherjee *et al.*[30] demonstrated a 30% decrease in PVR and no change in SVR when sublingual TNG was administered to patients undergoing cardiac catheterization. Chick *et al.*[31] administered sublingual TNG to patients with chronic obstructive lung disease and observed a 15% decrease in PVR; similar to our study, the greatest decreases in PVR occurred in patients who initially had the highest PVR. Lappé *et al.*[32] reported a decrease in PVR when TNG was administered to three patients with respiratory failure. Overall, both our study and the literature suggest that TNG is a pulmonary vasodilator at doses which do not decrease MAP below acceptable levels.

The different hemodynamic patterns seen with TNG and SNP in this study are best explained in terms of preferential pulmonary *versus* systemic arterial dilation. TNG resulted in parallel decreases in PVR and SVR; SNP resulted in decreases in SVR without changes in PVR. In disease states with severe pulmonary hypertension, cardiac output may be limited by right rather than by left ventricular performance. If SVR decreases but PVR does not change, cardiac output will remain constant and MAP will decrease—this was the pattern seen with SNP. In contrast, TNG significantly decreased PVR at doses which affected SVR. The decrease in pulmonary resistance improved right ventricular performance; cardiac output therefore increased, helping to maintain MAP despite large decreases in SVR.

A portion of the decrease in PVR seen with TNG in this experiment was probably due to reversal of hypoxic pulmonary vasoconstriction, as evidenced by the significant decrease in Pa_{O_2} with TNG. In other studies, TNG was able to reverse hypoxic pulmonary vasoconstriction.[30,36] The mediators of pulmonary vasoconstriction are not completely understood.[37,38] It is not known if pharmacologic agents which reverse hypoxic pulmonary vasoconstriction are effective in reversing pulmonary vasoconstriction of other etiologies. If so, clinical use of such drugs in diseases with diffuse pulmonary vasoconstriction may result in improved pulmonary hemodynamics without the complication of hypoxia. In a study of four patients with chronic pulmonary hypertension, we found that TNG but not SNP was effective as a pulmonary vasodilator.[33] TNG increased cardiac output and decreased PVR and MPAP as in our animal model. SNP resulted in systemic hypotension at doses which did not alter PVR or MPAP. Most importantly, TNG did not affect Pa_{O_2} despite the 50% reduction in PVR.

The clinical use of pulmonary vasodilator therapy remains limited by the absence of a safe, effective drug. In general, drugs have been evaluated as pulmonary vasodilators because they are known to be potent systemic arteriolar dilators. These drugs are likely to preferentially decrease SVR over PVR and result in systemic hypotension when used in states of severe pulmonary hypertension. TNG is a potent systemic venodilator at doses which do not affect the systemic arteriolar bed. In this study, TNG had major pulmonary vasodilator effects at doses which resulted in acceptable levels of systemic blood pressure. The pulmonary vasodilator effects of TNG and the related long-acting nitrates warrant further animal and clinical investigation.

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