Acute Cardiopulmonary Effects of Nitroglycerin in Canine Oleic Acid Pulmonary Edema

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In a canine model of acute respiratory failure, the authors investigated acute cardiopulmonary effects of nitroglycerin (TNG) and compared the results with those obtained after phlebotomy. Oleic acid increased intrapulmonary shunt (Qs/Qt) from 7.4 to 31% ($P < 0.001$) and decreased ($P < 0.01$) cardiac output (CO). In the presence of assumed low-pressure pulmonary edema, TNG was infused to decrease mean blood pressure ($\overline{BP}$) by 40%; this was associated with a 26% decrease ($P < 0.05$) in CO. Qs/Qt increased from 31 to 42% ($P < 0.01$). There was a slight increase ($P < 0.01$) in pulmonary vascular resistance (PVR) with TNG, and mean pulmonary artery pressure ($\overline{PAP}$) decreased ($P < 0.05$). In contrast, when CO was decreased by a similar amount with phlebotomy, mean Qs/Qt did not significantly change. There were similar changes in PVR and $\overline{PAP}$ and mixed venous O_2 tension with TNG and phlebotomy. Accordingly, current results rule out increased flow, increased $P\overline{v}_{O_2}$, and mechanical alterations in pulmonary vascular pressures as contributory to the increase in Qs/Qt with TNG. Alternatively, the increase in Qs/Qt with TNG may be explained by a direct pharmacologic decrease in pulmonary hypoxic vasoconstriction and/or by nonspecific pharmacologic effects. (Key words: Hypoxia: shunt. Lungs: shunt; vascular resistance. Pharmacology: nitroglycerin.)

IN PATIENTS with established left ventricular (LV) failure, acute cardiopulmonary effects of nitroglycerin (TNG) are well described.[1] TNG decreases mean blood pressure ($\overline{BP}$), mean pulmonary artery pressure ($\overline{PAP}$), and right and left ventricular filling pressures.[2] In these patients, cardiac output (CO) remains constant or increases,[1,2] and pulmonary and systemic vascular resistance (PVR and SVR) usually decrease.[1,2] Alternatively, acute cardiopulmonary effects of TNG have only recently been investigated in models of acute respiratory failure.[3] In a recent study of canine oleic acid pulmonary edema, intravenous TNG decreased mean BP and increased CO.[3] PVR decreased, but biventricular filling pressures remained constant. While effects of TNG on intrapulmonary shunt (Qs/Qt) were not reported, since CO increased and arterial O_2 tension decreased with TNG, if oxygen consumption remained constant, then Qs/Qt must have increased. The increase in Qs/Qt could be explained by decreased hypoxic pulmonary vasoconstric-

tion secondary to increased CO and thus increased mixed venous O_2 tension ($P\overline{v}_{O_2}$) and/or to direct pharmacologic effects of the drug.[4] On the other hand, in another recent study, CO and Qs/Qt remained constant when $\overline{BP}$ decreased 30% with TNG.[5] Because of the conflicting effects, the current study was designed to investigate acute cardiopulmonary effects of TNG in a canine model of oleic acid induced acute respiratory failure and to test the hypothesis that Qs/Qt would increase with TNG.

Methods

Six mongrel dogs (20–30 kg) were anesthetized with pentobarbital (30 mg/kg) and supplemented as required, *i.e.*, 2 mg/kg of pentobarbital was slowly infused (30 to 60 s) as required to prevent spontaneous ventilation. They were laid supine and ventilated (Harvard 607)® with 100% O_2 via an endotracheal tube. Tidal volume was 15 ml/kg and respiratory rate adjusted to maintain P_{CO_2} at 35–45 mmHg. A thermistor-tipped, flow-directed Swan-Ganz® catheter was inserted via the external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery where pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were obtained. Also, samples of mixed venous blood were obtained from this catheter. A second Swan-Ganz® catheter was similarly placed in the right ventricle to obtain measurements of right ventricular (RV) pressure. A catheter was placed in the abdominal aorta via the femoral artery. This catheter was used to obtain samples of arterial blood and to monitor the systemic arterial BP. All catheters were connected to Statham P23 ID® transducers leveled to the center of the chest. The output from all transducers was displayed on a 12-Channel Electronics for Medicine® oscillograph. A third Swan-Ganz catheter was positioned similarly to the first two in the RV, then withdrawn into the right atrium for injection of saline boluses for determinations of CO by computer (Columbus Instruments). These preparations usually were complete in less than 1 h, during which approximately 500 ml of 6% dextran was given to adjust PCWP to approximately 5 mmHg.

After ensuring steady state conditions (stable $\overline{BP}$, $\overline{PAP}$, RV pressures) for approximately 10 min, baseline measurements (CO, RV pressure, $\overline{BP}$, $\overline{PAP}$, PCWP, and heart rate [HR]) were obtained during a 5-s breath-hold at functional residual capacity (FRC). Immediately following these measurements, arterial and mixed venous

TABLE 1. Effects of Oleic Acid on Cardiopulmonary Function (values are mean ± SD)

	CO (l·min⁻¹)	SV (ml)	RVEDP (mmHg)	PAP (mmHg)	$\overline{BP}$ (mmHg)	PCWP (mmHg)	HR (beats·min⁻¹)	PVR (mmHg·l⁻¹·min)	SVR (mmHg·l⁻¹·min)	Pao₂ (mmHg)	Pvo₂ (mmHg)	Qs/Qt (%)	pHa
Baseline	3.9 ± 1.5	25 ± 10	1 ± 0.5	13 ± 5	133 ± 24	5 ± 2	160 ± 17	2.3 ± 1	38 ± 16	528 ± 27	55 ± 7	7.4 ± 1.9	7.38 ± 0.03
After oleic acid	2.5 ± 0.6*	16 ± 4*	2 ± 1.6	14 ± 3	130 ± 21	4 ± 2	154 ± 36	4.1 ± 1‡	54 ± 13‡	144 ± 121‡	43 ± 6‡	31 ± 12‡	7.31 ± 0.07

* $P < 0.01$ compared with baseline.
† $P < 0.05$ compared with baseline.

‡ $P < 0.001$ compared with baseline.

blood samples were taken for subsequent analysis and shunt calculations.

After completion of baseline measurements, a pulmonary capillary leak was created by infusing oleic acid (0.09 ml/kg) into the right atrium. The infusion took place during a 20-s breath-hold at FRC. Following oleic acid, normal saline (60 ml/h) was continously infused. Ninety to 120 min after oleic acid and after ensuring a stable preparation, a second set of measurements was obtained (C1). The preparation was considered stable if $\overline{BP}$, $\overline{PAP}$, RVP, PCWP, CO, and arterial O_2 tension varied less than 10% on two consecutive measurements obtained 10 min apart. Following C1 measurements, TNG (range, 60–800 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused at a rate sufficient to reduce mean arterial pressure by approximately 40%. While this dose is larger than that given to patients, it was similar to that required by other investigators in a canine study to produce a similar change in BP.[3] Subsequently, a third set of measurements was obtained after steady state conditions had been present for approximately 10 min (TNG). Then, TNG was discontinued, and approximately 45 min later, a fourth set of measurements was obtained (C2a). The latter set of measurements was obtained after ensuring a stable preparation as described above. In all dogs, TNG decreased CO. In the last four dogs (four of six), a fourth set of measurements (C2b) was followed by phlebotomy to decrease CO the same amount as during TNG infusion (300–500 ml blood was removed). Then a fifth set of measurements was obtained during steady state conditions. Subsequently, the heparinized autologous blood was reinfused to return CO to prephlebotomy levels, and final measurements (C3) were obtained during steady state conditions. To assess effects of oleic acid, TNG and phlebotomy on cardiopulmonary function values were compared (paired t test) with preceding conditions, i.e., measurements obtained during TNG infusion were compared with C1 measurements, and values obtained following phlebotomy were compared with C2b measurements. To determine that there were no effects of time on our preparations and to confirm stability, variables in control conditions (1, 2b, 3) were assessed via a two-way analysis of variance, where the

two factors were dogs and control conditions. All data are expressed as mean ± standard deviation.

Blood gases and pH were measured with a Model 165/2 Blood Gas Analysis® (Corning, Medford, Massachusetts) immediately after collection. Arterial P_{CO_2} was maintained between 35 and 45 mmHg by adjusting ventilatory rate and sodium bicarbonate (range, 20–50 mEq) was given as required to treat metabolic acidosis and maintain arterial pH greater than 7.25. The oxygen electrode was calibrated with blood exposed to oxygen tensions from 20 to 700 mmHg on a tonometer, and measured values were corrected using the tonometer factor. Hematocrits were measured using an Autocrit II® centrifuge (Clay Adams, Parsippany, New Jersey). No correction was made for trapped plasma. Arterial and mixed venous oxygen contents (CO_2) were calculated using the formula CO_2 = (hematocrit/3 × 1.34 × % saturation) + (P_{O_2} × 0.003). When arterial O_2 tension was less than 140 mmHg, per cent saturation was determined using the nomogram of Rossing and Cain[6]; otherwise saturation was assumed to be 100%. Right to left shunt (Qs/Qt) was calculated according to the equation: $Qs/Qt = (Cc'_{O_2} - Ca_{O_2})/(Cc'_{O_2} - C\overline{v}_{O_2})$, where Cc'_{O_2} = hematocrit/3 × 1.34 × % saturation + (0.003 × PA_{O_2}). Stroke volume (SV) was calculated according to the formula: SV = CO/HR, PVR (mmHg·l⁻¹·min) was calculated as (PAP − PCWP)/CO, and SVR (mmHg·l⁻¹·min) as (BP − RVEDP)/CO.

Results

Table 1 illustrates effects of oleic acid on cardiopulmonary function. There was a large decrease ($P < 0.01$) in CO with oleic acid. Corresponding to the fall in CO, SVR increased ($P < 0.05$) and mixed venous O_2 tension ($P\overline{v}_{O_2}$) decreased ($P < 0.001$). Mean BP and $\overline{PAP}$ remained constant with oleic acid, and PVR increased ($P < 0.05$). Also, oleic acid substantially increased Qs/Qt ($P < 0.001$), and, corresponding to the increase in shunt, there was a large fall in Pa_{O_2} ($P < 0.001$).

Acute cardiopulmonary effects of TNG are illustrated in table 2. As discussed under Methods, TNG was infused at a rate sufficient to reduce $\overline{BP}$ approximately

TABLE 2. Effects of Nitroglycerin and Phlebotomy on Cardiopulmonary Function in Canine Oleic Acid Pulmonary Edema (values are mean ± SD)

	CO (l·min⁻¹)	SV (ml)	RVEDP (mmHg)	PAP (mmHg)	$\overline{BP}$ (mmHg)	PCWP (mmHg)	HR (beats·min⁻¹)	PVR (mmHg·l⁻¹·min)	SVR (mmHg·l⁻¹·min)	Pa_{O_2} (mmHg)	Pv_{O_2} (mmHg)	Qs/Qt (%)	pH$_a$	No. of Dogs
Control 1 (after oleic acid)	2.5 ± 0.6	16 ± 6	2 ± 1.6	14 ± 3	130 ± 21	4 ± 2	154 ± 36	4.1 ± 1	54 ± 13	144 ± 121	43 ± 6	31 ± 12	7.31 ± 0.07	6
Nitroglycerin	2.0 ± 0.3*	14 ± 3*	−1 ± 3	12 ± 4*	83 ± 8†	2.2 ± 1.8*	150 ± 36	4.9 ± 1.6†	44 ± 4†	106 ± 99*	40 ± 7	42 ± 14‡	7.30 ± 0.04	6
Control 2a (45 min after TNG)	2.7 ± 0.8	18 ± 7	−1 ± 3	14 ± 3	116 ± 21	3.7 ± 1.6	151 ± 39	4.1 ± 0.9	48 ± 16	124 ± 94	42 ± 6	31 ± 7.8	7.33 ± 0.04	6
Control 2b (prephlebotomy)	2.7 ± 0.9	20 ± 9	−2 ± 2	14 ± 2.4	118 ± 27	3.8 ± 1.7	140 ± 19	3.9 ± 0.8	46 ± 16	135 ± 97	41 ± 7	31 ± 8.1	7.34 ± 0.01	4
Phlebotomy	2.0 ± 0.6†	14 ± 6*	−2 ± 2	11.5 ± 1.3*	103 ± 10	2.3 ± 1.9*	148 ± 23	4.8 ± 1.5	56 ± 13*	143 ± 119	37 ± 9	28 ± 5	7.33 ± 0.03	4
Control 3 (transfusion)	2.8 ± 0.8	21 ± 8	−1 ± 2	15 ± 3.3	121 ± 33	4.0 ± 2.2	137 ± 19	4.0 ± 0.6	47 ± 16	125 ± 82	41 ± 9	32 ± 3.8	7.30 ± 0.03	4

* $P < 0.05$ compared with preceding control.
† $P < 0.001$ compared with preceding control.
‡ $P < 0.01$ compared with preceding control.

40%. TNG decreased ($P < 0.05$) CO 20%, from 2.5 to 2.0 l·min⁻¹. In all dogs, CO was sequentially measured as the dose of TNG increased, and a transient increase in CO was not observed. Biventricular filling pressure tended to decrease with TNG. PCWP decreased from 4.0 to 2.2 ($P < 0.05$) and RVEDP decreased insignificantly. While there was a small decrease ($P < 0.05$) in SVR with TNG, PVR increased ($P < 0.05$) slightly.

TNG caused a marked deterioration in gas exchange, increasing Qs/Qt 35%, from 31 to 42% ($P < 0.01$). Corresponding to the increase in Qs/Qt, Pa_{O_2} decreased from 144 to 106 mmHg ($P < 0.05$). As illustrated in table 2, there was no deterioration with time in cardiopulmonary function, since all measured variables in C1 and C2a were similar and without significant differences by analysis of variance.

The lower half of table 2 depicts effects of phlebotomy. As discussed under "Methods," phlebotomy was performed in the last four dogs to attain the same decrease in CO that occurred with infusion of TNG.

In contrast to effects of TNG on Qs/Qt, when phlebotomy decreased CO from 2.7 to 2.0 l·min⁻¹ ($P < 0.01$), mean Qs/Qt did not significantly change. Corresponding to the slight change in Qs/Qt, there was a slight, nonsignificant increase in Pa_{O_2}. Note that both TNG and phlebotomy decreased ventricular filling pressures and $\overline{PAP}$s to a similar amount. Also, note that PVR and mixed venous O_2 tension were similar with both interventions.

All measured variables in C2b (phlebotomy baseline) and C3 were similar, and there were no differences by analysis of variance, indicating that our preparations were stable over time.

Discussion

The current study was designed to investigate acute cardiopulmonary effects of TNG in a canine model of acute respiratory failure. One objective was to test the hypothesis that Qs/Qt would increase with TNG.

As previously described,[3–5,7] oleic acid caused a marked deterioration in cardiopulmonary function. Ninety minutes after oleic acid, CO had decreased and intrapulmonary shunt had dramatically increased, from 7 to 31%. The deterioration in gas exchange with oleic acid is presumably explained by increased pulmonary vascular permeability and flooding of gas exchange units.

As in the experimental design, TNG infusion reduced $\overline{BP}$ 36%. Corresponding to the decrease in $\overline{BP}$, $\overline{PAP}$, CO, and mixed venous O_2, tension decreased and Qs/Qt increased. Since mixed venous O_2 did not increase with TNG, the deterioration in gas exchange cannot be explained by a decrease in pulmonary hypoxic vasoconstriction[4,8,9] because of this factor. Also, because $\overline{PAP}$

decreased with TNG, the increase in Qs/Qt cannot be explained by mechanical recruitment of previous non-ventilated nonperfused units.[10]

Since TNG was noted to decrease CO in the first two dogs studied, the subsequent four dogs underwent phlebotomy to match the fall in CO seen during TNG infusion. In this fashion, gas exchange could be compared in the presence or absence of TNG at identical CO.

Phlebotomy caused a decreased Qs/Qt in three of four dogs, and the mean Qs/Qt changed from 31 to 28% (P, NS). Similar results have been reported with alteration of CO in canine oleic acid pulmonary edema.[4,8] Smith et al.,[4] in a similar canine preparation, found that when phlebotomy decreased CO by 35%, Qs/Qt decreased from 44 to 36% (P < 0.05). In the current study, while phlebotomy did not significantly decrease Qs/Qt, this may be explained by the lesser fall in CO (26%). In contrast to the effects of phlebotomy on gas exchange, mean Qs/Qt significantly increased (P < 0.01), with TNG at a similar CO. The observation that PCWP and CO decreased equally with phlebotomy and TNG probably indicates that the decrease in CO with TNG was explained by redistribution of blood volume from the thorax to the systemic vascular, inducing "central hypovolemia."

As depicted in table 2, note that $\overline{PAPs}$ decreased an equal amount with TNG and phlebotomy. Since gas exchange tended to move in opposite directions with our two interventions, the above observations would indicate that the increase in Qs/Qt with TNG is probably not due to mechanical redistribution of blood flow to dependent, nonventilated units.

Most likely, the increase in Qs/Qt with TNG is explained by a direct decrease in pulmonary hypoxic vasoconstriction and/or nonspecific vasoactive effects of the drug resulting in increased perfusion to nonventilated lung units.

Colley et al.[5] investigated the acute cardiopulmonary effects of TNG in canine oleic acid pulmonary edema during ventilation with air and 100% O_2. During O_2 ventilation, TNG decreased $\overline{BP}$ and $\overline{PAP}$ but did not affect PVR, PCWP, CO, nor Qs/Qt.

In our study, TNG caused a similar decrease in $\overline{PAP}$ and $\overline{BP}$, however, CO and PCWP decreased and Qs/Qt and PVR increased when TNG was infused to reduce mean BP 36%. The different effects of TNG on PVR may be explained by its effects on CO, i.e., CO remained constant in their study and decreased in ours.

In contrast to current results and those of Colley et al.,[5] another study of canine oleic acid edema by Pearl et al.[3] reported that, when TNG decreased $\overline{BP}$ 39%, CO increased 40%. They found PVR and $\overline{PAP}$ decreased with TNG and PCWP remained constant. The decrease in PVR with TNG may be partially explained by the

increase in CO. While effects of TNG on Qs/Qt were not reported, since Pa_{O_2} decreased with TNG and CO increased, Qs/Qt probably increased.

The most striking difference reported in these studies was the inconsistent effects on CO. It is possible that the different effects on CO in the two studies reviewed and the current study were due, at least in part, to different effects of TNG on venous and arterial tone in the different animal preparations. In the study by Pearl et al., baseline PCWP was 4.9 mmHg and did not decrease with TNG suggesting no significant venodilation.[3] Similarly, in the study by Colley et al.,[5] PCWP was 1 mmHg before and during TNG infusion. In contrast, while baseline PCWP was 4 mmHg in our study, it decreased to 2.2 mmHg with TNG. Also, TNG had different effects on SVR and, hence, arterial tone. Resistance decreased 61% in the study by Pearl et al.,[3] 19% in the current study, and 26% in the study by Colley et al.[5] The large increase in CO in the former study may be partially explained by the different effects of TNG on arterial tone. We cannot explain the variable effect of TNG on vascular tone. It is possible that the differences in the anesthetic technique and/or the animal model may be involved.

While pentobarbital was used as the anesthetic in the three studies considered above, there were some differences in anesthetic technique. For example, in the study by Colley et al.,[5] after the initial bolus of pentobarbital (30 mg/kg), anesthesia was maintained by small additional pentobarbital doses (2–3 mg·kg^{-1}·h^{-1}) and a constant infusion of succinylcholine (5 mg·kg^{-1}·h^{-1}). In our study supplemental pentobarbital (2 mg/kg) was used only as required to suppress ventilation (approximately every 90 min). In contrast, in the study of Pearl et al.,[3] anesthesia was maintained by continuous pentobarbital infusion (5–10 mg·kg^{-1}·h^{-1}).

The differing cumulative doses of pentobarbital may have caused different degrees of barbiturate-induced myocardial depression in the three studies. The effects of TNG on CO have been demonstrated in humans to be dependent on the degree of underlying cardiac dysfunction.[1,2]

There were also some differences in the animal model. Colley et al. studied the effects of TNG 24 h after oleic acid and Qs/Qt prior to TNG was 17%.[5] In our study, TNG was given approximately 90 min after oleic acid, and initial Qs/Qt was 31%. Mechanical ventilation was similar between studies. In the study by Colley et al., tidal volume was 12 to 15 ml/kg with rate adjusted to maintain Pa_{CO_2} at approximately 35 mmHg.[5] We adjusted ventilatory rate to maintain Pa_{CO_2} between 35 and 45 mmHg, and tidal volume was 15 ml/kg. Pearl et al. set tidal volume at 15 to 20 ml/kg, and respiratory rate was 13 breaths/min.[3]

We have recently reported the acute cardiopulmonary effects of two doses of nitroprusside (NP) in canine oleic acid pulmonary edema.[11] In contrast to current results with TNG, the larger dose of NP decreased BP 20% and increased CO, $P\bar{v}_{O_2}$, and Qs/Qt. In the same study, a lower dose of NP decreased BP 8% and did not affect CO or gas exchange (Qs/Qt). We attributed the increase in Qs/Qt with the higher dose of NP to a decrease in pulmonary hypoxic vasoconstriction secondary to increased $P\bar{v}_{O_2}$ and/or increased CO *per se*.[12]

In contrast, in the current study, Qs/Qt increased with TNG, despite a decrease in CO and $P\bar{v}_{O_2}$. The results illustrate that in canine low-pressure pulmonary edema, TNG and NP have qualitatively different effects on cardiovascular performance. Further, the above comparison indicates that, while both drugs can increase Qs/Qt, they probably do so by different mechanisms.

The potential for adverse hemodynamic effects and deterioration of gas exchange when TNG is administered to animal models of acute lung injury raise caution for the use of TNG for humans with adult respiratory distress syndrome (ARDS).

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