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The Effects of Tolazoline on the Distribution of Cardiac Output in Normoxemic and Hypoxemic Lambs

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Summary

We measured cardiac output and its distribution (microspheres), blood gases and pH, heart rate, and pulmonary and aortic pressures in three groups of 1- to 3-day-old lambs.

Group I consisted of six animals who had these measurements made during both control (normoxemic) and hypoxemic (Pa_{O_2} 25 ± 3 mm Hg) periods. Hypoxemia increased the pulmonary artery pressure 70% ($p < 0.01$). This elevation in pulmonary arterial pressure lasted as long as the animals were hypoxemic (90 min). Hypoxemia had no effect on cardiac output, mean systemic arterial pressure, heart rate, or the rate-pressure product of the left ventricle. Blood flow to the heart increased an average of 228% ($p < 0.05$); flow to the brain increased 233% ($p < 0.05$); flow to the skin decreased 35% ($p < 0.05$) after 60 and 90 min of hypoxemia. Blood flow to the remaining organs was uneffected by hypoxemia.

Group II consisted of four animals who were given 1, 5, and 10 mg/kg/h of tolazoline (Priscoline) intravenously while normoxemic. There was no effect on the pulmonary arterial pressures or blood gases and pH. Tolazoline (5 and 10 mg/kg/h) reduced systemic arterial pressures an average of 22% ($p < 0.05$). Tolazoline (1 mg/kg/h) reduced blood flow to the spleen 48% and that to the brain by 20% and increased flow to the body 32% ($p < 0.05$). Five mg/kg/h of tolazoline decreased renal and brain blood flow 35 and 20%, respectively ($p < 0.05$) while that to the body and liver increased 26 and 48% ($p < 0.05$). Tolazoline (10 mg/kg/h) returned splenic, body, and brain flow to control levels, and decreased renal blood flow further (48%) ($p < 0.05$). Tolazoline had no effect on the left ventricular rate-pressure-product.

Group III was given 1, 5, and 10 mg/kg/h of drug while the animals were hypoxemic (Pa_{O_2} 29 ± 4 mm Hg). The mean systemic arterial blood pressures decreased 20% with 5 and 10 mg/kg/h of tolazoline ($p < 0.05$), but tolazoline did not change mean pulmonary arterial pressure. Tolazoline had no effect on the left ventricular rate-pressure products. Cardiac output increased 47% with hypoxemia, but it was unaltered by the addition of tolazoline. Blood flow to the heart increased 300% and that to the brain 200% with hypoxemia and remained at these levels with infusing tolazoline. Flow to the remaining tissues was constant. Five mg/kg/h of tolazoline increased cardiac flow further (560% of control). Ten mg/kg/h maintained the high cardiac flow seen with 5 mg/kg/h infusions of tolazoline, decreased that to the kidneys 33%, and increased flow to the lower body 67%. These data indicate that tolazoline does not decrease the pulmonary hypertension caused by hypoxemia and that tolazoline does little to alter the effect of hypoxemia on the distribution of blood flow.

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At birth, there is an abrupt decline in the pulmonary arterial pressure, despite an increase in pulmonary blood flow (25). This decrease in pulmonary vascular resistance is attributed to alveolar expansion, an increase in the alveolar P_{O_2} and a decrease in alveolar P_{CO_2} (4), and possibly to the clearance of lung water (3). However, the pulmonary arterial pressure does not decrease to normal in some cases.

Regardless of the cause, persistence of pulmonary hypertension is usually attended by significant hypoxemia, and by intrapulmonary or extrapulmonary right-to-left shunting, or both. Because of this, numerous ventilatory maneuvers and vasodilating agents have been used in an attempt to decrease pulmonary arterial pressure and restore arterial oxygenation. Tolazoline is one such drug that has had extensive clinical use. However, the results have been quite variable. In some cases, infusion of tolazoline is attended by a marked fall in pulmonary arterial pressure and increase in arterial P_{O_2}. In others there has been no improvement or a worsening of the patient's condition (5, 11, 15). Of additional importance is the fact that the use of tolazoline has been associated with numerous untoward effects, including gastrointestinal bleeding, renal failure, intracranial hemorrhage, and systemic hypotension (12, 24, 26, 27).

The causes of these untoward effects are unknown, but might be related to the effects of tolazoline on cardiac output and its distribution; this could be of particular concern during abnormal physiologic states such as hypoxemia. To our knowledge, the affect of tolazoline on cardiac ouput and its distribution has not been studied previously. Since these studies could not be done in humans, we examined the effects of tolazoline on intravascular pressures and on cardiac ouput and its distribution in normoxemic and hypoxemic 1- to 3-day-old lambs.

MATERIALS AND METHODS

Subjects. We studied 15 healthy, awake, intact, and unsedated lambs who were less than 4 days old (3.9 ± 0.4 kg). Four animals were used to evaluate the effects of hypoxemia and time on the model (Group I); four were used to evaluate the effects of tolazoline in normoxemic animals (Group II); and seven were used to evaluate the effects of tolazoline in hypoxemic animals (Group III).

Preparation. The lambs were blindfolded and placed in the lateral recumbent position on a table where they lay quietly.

Following injections of local anesthetic, catheters were inserted into a femoral artery and vein through a groin incision and into the left ventricle and ascending aorta through a carotid artery. A flow-directed catheter was inserted into the pulmonary artery via the right jugular vein. The arterial and ventricular catheters were connected to strain gauges (Statham P23DB) whose outputs were recorded on a Beckman Dynagraph.

Protocol. When the vital signs were stable for 15 to 30 min, we measured arterial blood gases and pH_a (Radiometer, Copenhagen, Denmark) and the intravascular pressures, and determined cardiac ouput and its distribution with 15-μm radioactive microspheres (23). Cardiac ouput was determined by summing the blood flow to all of the organs. The spheres were injected into the left ventricle and their concentration in blood was measured by simultaneously withdrawing blood from the ascending and descending aorta for 1 or 1.5 min. Control measurements were made while the animals were breathing room air. Blood losses were replaced with maternal blood.

Hypoxemia control group (Group I). After completing the control measurements, we measured the intravascular pressures, cardiac output and its distribution, and blood gases and pH in four animals after 30, 60, and 90 min of hypoxemia (Pao_2 25 ± 3 to 32 ± 3 mm Hg). In these and subsequent animals, hypoxemia was produced by placing a large plastic bag over the lamb's head and snout and replacing a fraction of the inspired air with nitrogen. After completing the measurements during hypoxemia, the animals were again studied when normoxemic. These four lambs received no tolazoline and were used to assess the effects of hypoxemia *per se* and the stability of the preparation over time.

Tolazoline control group (Group II). After making the control measurements, we measured the intravascular pressures, cardiac ouput and its distribution, and blood gases and pH, during normoxemia plus tolazoline. We infused 1 mg/kg of tolazoline over 15 s and followed it with an infusion of 1, 5, and 10 mg/kg/h of tolazoline. Fifteen min after beginning the infusion of each dose of tolazoline, we repeated all of the measurements listed above. These lambs were used to assess the effects of tolazoline on cardiac ouput and its distribution in the normoxemic state.

Tolazoline plus hypoxemia (Group III). Following control measurements during normoxemia, we made the animals hypoxemic (Pao_2 23 ± 4 mm Hg, SD). Carbon dioxide was not added to the inspired gas to maintain a constant $Paco_2$. After 15 min of hypoxemia, the blood gases, intravascular pressures, and the cardiac output and its distribution were again measured. Next, we administered 1 mg/kg of tolazoline over 15 s and followed it with a continuous infusion of 1, 5, and then 10 mg/kg/h of the drug. Fifteen min after beginning the continuous infusion of each dose of tolazoline, and when the heart rate and mean arterial pressure were constant for at least 5 min, we remeasured the intravascular pressures, blood gases, pH, and the cardiac output and its distribution.

All animals were killed with an overdose of barbiturate and potassium chloride. Their organs were removed and ashed as previously described (23). Data were compared by repeated measures and the Bonferroni test for differences between groups (10).

RESULTS

Blood gases, pH_a, and intravascular pressures. Blood gases, pH_a, and intravascular pressures of the control and the test animals are given in Tables 1–3. In Group I, the Pao_2 and $Paco_2$ decreased and the pH rose with the onset of hypoxemia ($p < 0.01$) and were constant for the remainder of the hypoxemic period (90 min). The mean systemic arterial pressure of Group I was unchanged by hypoxemia. Mean pulmonary artery pressures, on the other hand, increased significantly with the onset of hypoxemia and remained elevated as long as the animals were hypoxemic. When the animals again breathed room air for 15 min, their blood gases and pH and their mean systemic and pulmonary arterial pressures all returned to control levels, indicating that the preparation was stable during the 90-min period of hypoxemia. This was also the duration of our studies in the lambs given tolazoline.

In Group II (normoxemia plus tolazoline), there was no significant change in blood gases, pH, pulmonary artery pressures, heart rate, or left ventricular rate-pressure-product with the infusion of tolazoline (Table 2). The mean systemic arterial pressures descreased ($p < 0.05$) with the infusion of 5 and 10 mg/kg/h of tolazoline.

In Group III, the heart rates, mean intravascular pressures, blood gases, and pH values were within normal limits for animals of this age during the normoxemic period (19, 21) (Table 3). The mean pulmonary artery pressure increased from 27 ± 4 mm Hg

Table 1. *The effects of hypoxemia on arterial blood gases, pH, intravascular pressures and rate-pressure product**

	Pao_2 (mm Hg)	$Paco_2$ (mm Hg)	pH	MAP (mm Hg)	MPAP (mm Hg)	HR (bpm)	RPP (mm Hg·bpm)
Normoxemia	80 ± 8	39 ± 3	7.42 ± .01	108 ± 12	30 ± 7	184 ± 15	19,872 ± 298
Hypoxemia							
30 min	25 ± 3†	33 ± 4†	7.48 ± .06†	90 ± 15	51 ± 5†	175 ± 18	15,750 ± 263
60 min	29 ± 2†	30 ± 3†	7.44 ± .01	95 ± 14	54 ± 7†	195 ± 17	18,525 ± 277
90 min	32 ± 3†	34 ± 3†	7.39 ± .01	125 ± 12	56 ± 7†	191 ± 15	23,875 ± 307
Normoxemia	84 ± 7	39 ± 5	7.40 ± .02	112 ± 13	28 ± 6	180 ± 20	21,082 ± 358

* MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate; RPP, rate-pressure product; bpm, beats/min. Values are means ± SD.

† Significantly different from normoxemia at the $p < 0.05$ level.

Table 2. *The effects of tolazoline on arterial blood gases, pH, intravascular pressures, and rate-pressure product of normoxemic lambs**

	Pao_2 (mm Hg)	$Paco_2$ (mm Hg)	pH	MAP (mm Hg)	MPAP (mm Hg)	HR (bpm)	RPP (mm Hg·s)
Normoxemia (no drug)	71 ± 7	40 ± 3	7.41 ± 0.04	87 ± 14	27 ± 4	222 ± 33	19,158 ± 2,833
Normoxemia + tolazoline (mg/kg/h)							
1	65 ± 8	40 ± 3	7.40 ± 0.02	84 ± 9	27 ± 1	267 ± 30	22,515 ± 3,333
5	62 ± 1	42 ± 2	7.38 ± 0.02	76 ± 15†	27 ± 1	282 ± 37	21,695 ± 6,774
10	66 ± 7	45 ± 6	7.35 ± 0.06	61 ± 19†	27 ± 3	269 ± 23	16,610 ± 5,867

* MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; HR, heart rate; RPP, rate-pressure product; bpm, beats/min.

† Significantly different from no drug ($p < 0.05$).

(control) to 51 ± 6 mm Hg when the animals were hypoxemic ($p < 0.01$). When tolazoline was infused, it did not reduce the pulmonary arterial pressure, nor did it change the heart rate, blood gases, or pH from those during hypoxemia alone (Table 3). The left ventricular rate-pressure products were unchanged by either hypoxemia or hypoxemia plus tolazoline.

In all three groups of animals, blood drawn from the ascending aorta and femoral artery had the same Pa_{O_2}. Therefore, we assumed that there was no right-to-left shunting of blood through the ductus arteriosus.

Tissue blood flow (ml/100 g/min). Table 4 shows the effects of hypoxemia and time on the blood flow (ml/100 g/min) in Group I. Brain flow was increased significantly above control throughout the hypoxemic periods. It returned towards control levels when the animals were made normoxemic at the end of the study. Skin flow was decreased after 90 min of hypoxemia and during the return to normoxemia. Blood flow to the heart increased during hypoxemia but, because of large standard deviations, the changes were not statistically significant. Cardiac ouput increased significantly. There was no significant change in flow to the other organs.

Table 5 shows the effects of tolazoline on organ blood flow (ml/100 g/min) in Group II (tolazoline and normoxemia). One mg/kg/h tolazoline increased blood flow to the carcass. The same dose decreased blood flow to the spleen and brain, despite an increase in cardiac ouput. Five mg/kg/h decreased gut, kidney, and brain blood flow ($p < 0.05$). Flow to the liver and body were increased ($p < 0.05$). Ten mg/kg/h of tolazoline increased splenic flow further and increased pulmonary flow. Renal flow was similar to that at 5 mg/kg/h of tolazoline. Gut, body, and brain flows returned to control levels.

Table 6 shows the effects of tolazoline on the blood flow (ml/100 g/min) of Group III (hypoxemia plus tolazoline). The flow to the heart tripled and that to the brain doubled with the onset of hypoxemia. One mg/kg/h of tolazoline maintained the flow to heart and brain at levels attained with hypoxemia alone but did not increase it further. Five mg/kg/h of tolazoline increased myocardial flow further while maintaining cerebral flow at levels achieved with hypoxemia alone. Lung flow increased. Ten mg/kg/h of tolazoline maintained blood flow to the brain and heart at those levels seen with infusion of 5 mg/kg/h. Renal blood flow decreased below control levels, and flow to the lower body increased.

DISCUSSION

Pulmonary hypertension usually decreases pulmonary blood flow and causes right-to-left shunting of blood through the ductus arteriosus and/or the foramen ovale in neonates. This leads to hypoxemia. Tolazoline is the drug most commonly used to try to reduce the pulmonary vascular resistance of such patients and increase their pulmonary blood flow. Unfortunately, tolazoline is effective in doing so in only about half of the patients, probably because it has multiple pharmacologic effects (1, 12–14, 29, 31). As a consequence, the effect of this drug on the pulmonary vascular resistance and pressure depends on which of its several pharmacologic effects predominates. At present we are unable to tell *a priori* which one will do so.

Our studies indicate that tolazoline has no effect on the pulmonary artery pressures of either normoxemic or hypoxemic animals. This finding has previously been reported in humans and animals (6, 24, 28). Although pulmonary vascular resistance

Table 3. *The effects of tolazoline on arterial blood gases, pH, intravascular pressures, and rate-pressure product of hypoxemic lambs*[*]

	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH	MAP (mm Hg)	MPAP (mm Hg)	HR (bpm)	RPP (mm Hg·bpm)
Normoxemia	76 ± 6	38 ± 3	7.42 ± 0.03	81 ± 9	27 ± 4	190 ± 20	15,390 ± 2,165
Hypoxemia	23 ± 3†	29 ± 4†	7.45 ± 0.06	72 ± 8	51 ± 6†	245 ± 24†	17,640 ± 1,983
Hypoxemia + tolazoline (mg/kg/h)							
1	29 ± 4†	28 ± 4†	7.43 ± 0.06	73 ± 8	54 ± 2†	263 ± 24†	19,199 ± 2,305
5	28 ± 2†	28 ± 3†	7.38 ± 0.10†	63 ± 5†	56 ± 5†	258 ± 24†	16,254 ± 2,321
10	26 ± 2†	28 ± 4†	7.38 ± 0.08†	66 ± 8†	52 ± 8†	254 ± 29†	16,764 ± 2,016

[*] MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; HR, heart rate; RPP, rate-pressure product; bpm, beats/min.
† Significantly different from normoxemic control ($p < 0.05$ level).

Table 4. *The effects of hypoxemia on cardiac output and organ blood flow (ml/min/100 g of tissue)*

	Cardiac output (ml/min)	Heart	Brain	Kidney	Gut	Liver	Spleen	Skin	Carcass	Lung
Normoxemia	1480 ± 423	414 ± 605	59 ± 39	278 ± 28	114 ± 45	23 ± 9	287 ± 451	20 ± 18	20 ± 17	137 ± 138
Hypoxemia										
30 min	1863 ± 368*	1064 ± 461*	140 ± 10*	274 ± 41*	118 ± 10	47 ± 19	346 ± 224	9 ± 14	24 ± 13	116 ± 105
60 min	1505 ± 536*	882 ± 212*	128 ± 31*	214 ± 11*	107 ± 3	27 ± 16	193 ± 6	15 ± 7	25 ± 10	97 ± 82
90 min	1725 ± 385*	945 ± 299*	136 ± 61*	153 ± 72*	75 ± 33	28 ± 31	132 ± 204*	13 ± 2*	32 ± 6	20 ± 1
Return to control	1329 ± 13	382 ± 37	95 ± 10	253 ± 126	118 ± 28	27 ± 12	205 ± 194	13 ± 2*	19 ± 1	36 ± 5*

* Significantly different from normoxemia ($p < 0.05$).

Table 5. *Effects of tolazoline on cardiac and organ blood flow (ml/min/100 g of tissue) of normoxemic lambs*

	Cardiac output (ml/min)	Heart	Brain	Kidney	Gut	Liver	Spleen	Skin	Carcass	Lung
Normoxemia (no drug)	979 ± 137	55 ± 16	72 ± 6	226 ± 77	84 ± 4	27 ± 40	443 ± 185	13 ± 7	19 ± 3	83 ± 81
Normoxemia + tolazoline (mg/kg/h)										
1	1209 ± 142*	69 ± 23	58 ± 10*	234 ± 23	70 ± 17	59 ± 34	230 ± 120*	12 ± 5	25 ± 2*	88 ± 51
5	1119 ± 127	78 ± 33	58 ± 3*	146 ± 75*	53 ± 18*	40 ± 25*	381 ± 191	9 ± 0.2	24 ± 2*	119 ± 46
10	1272 ± 22	76 ± 25	77 ± 5	139 ± 27*	91 ± 2	13 ± 7	625 ± 5*	15 ± 5	17 ± .7	158 ± 26*

* Significantly different from normoxemia ($p < 0.05$).

Table 6. *The effects of tolazoline on cardiac output and organ blood flow (ml/min/100 g of tissue) of hypoxemic lambs*

	Cardiac output (ml/min)	Heart	Brain	Kidney	Gut	Liver	Spleen	Skin	Carcass	Lung
Normoxemia	956 ± 75	149 ± 53	65 ± 20	251 ± 54	125 ± 34	49 ± 87	263 ± 163	11 ± 7	16 ± 4	164 ± 115
Hypoxemia	1404 ± 132*	446 ± 78	131 ± 41*	235 ± 81	123 ± 49	52 ± 60	224 ± 210	11 ± 6	20 ± 8	153 ± 141
Hypoxemia + tolazoline (mg/kg/h)										
1	1313 ± 62*	521 ± 421*	132 ± 37*	196 ± 59	100 ± 41	36 ± 20	171 ± 108	8 ± 4	23 ± 8	277 ± 247
5	1500 ± 240	833 ± 486*†	159 ± 50*	209 ± 119	123 ± 61	44 ± 13	210 ± 185	11 ± 10	31 ± 22	372 ± 196*†
10	1478 ± 190	710 ± 350*	113 ± 14*	169 ± 55*†	136 ± 61	48 ± 13	224 ± 355	10 ± 10	30 ± 15†	294 ± 120

* Significantly different from control ($p < 0.05$).
† Significantly different from hypoxemia ($p < 0.05$).

was not determined, it is likely that it was little affected by tolazoline in the hypoxemic animals because pulmonary blood flow and pressure were similar to those present during hypoxemia alone. Tripp *et al.* (28) found that both pulmonary vascular resistance and pulmonary/systemic vascular resistance ratios of hypoxemic lambs increased during tolazoline infusion. They found an increase in the ratio of pulmonary to systemic artery pressures. We also found a rise in pulmonary/systemic arterial pressure ratio. Since the levels of cardiac ouput were similar during hypoxemia and hypoxemia plus tolazoline, it is likely that our animals had similar changes in pulmonary and peripheral vascular resistance to those reported by Tripp *et al.*

The hypoxemic lamb may not be the ideal model of the persistent pulmonary hypertension seen in infants because the two differ in their response to oxygen. Infants usually have little or no improvement in oxygenation and no reduction in pulmonary artery pressure with increasing the inspired oxygen concentration, even to 100% (6). Both pressure and oxygenation returned to normal when the inspired oxygen concentration of our lambs was increased to that of room air. We conclude from this that the pulmonary hypertension seen in infants with primary pulmonary hypertension is due to factors besides hypoxemic pulmonary arterial constriction alone.

Blood gases often worsen when tolazoline is administered to infants who have pulmonary hypertension (6, 22). There are several possible reasons for this. 1) There may be interference with hypoxemic pulmonary vasoconstriction in areas where the ventilation/perfusion ratio is low or zero, thereby increasing venous admixture. 2) Tolazoline may decrease systemic vascular resistance more than pulmonary vascular resistance and promote right-to-left shunting of blood through the foramen ovale. 3) Tolazoline may reduce systemic vascular resistance more than pulmonary vascular resistance, which, in the presence of a large patent ductus arteriosus, would allow right-to-left shunting through the ductus arteriosus. 4) Tolazoline might decrease cardiac output, which would decrease mixed venous oxygen tension. This would decrease Pa_{O_2}. In our study, the pulmonary arterial pressure was always less than the systemic pressure and the Pa_{O_2} values above and below the ductus arteriosus were equal; therefore, shunting did not occur through the ductus arteriosus. Cardiac ouput was always at or above control levels when tolazoline was administered. Since tolazoline did not affect aortic oxygen tension during hypoxemia, we conclude that tolazoline caused neither a redistribution of pulmonary blood flow nor a change in transatrial shunting.

We studied three groups of animals to define 1) the effects of hypoxemia without tolazoline, 2) the effects of tolazoline in normoxemic animals, and 3) the effects of tolazoline in hypoxemic animals. The first group of animals was used to define the effects of hypoxemia and of time. The variables measured were stable throughout the 90-min period of hypoxemia and returned to control levels with return to normoxemia. From this we conclude that the preparation was stable. Thus, changes in these variables with infusing tolazoline into hypoxemic animals would be due to tolazoline and not to hypoxemia or time *per se.*

The second group was used to determine the effects of tolazoline in normoxemic animals. Tolazoline increased cardiac output and decreased blood flow to the brain, kidney, carcass, and spleen. However, it is unlikely that these decreases in flow led to tissue hypoxemia because the animals were normoxemic and metabolic acidosis did not develop.

We did not include a group of animals to study the relationship between tolazoline and time because the smallest dose of drug was always given first.We expected, and found, that larger doses of drug would either not change or increase the effects seen with the smaller dose of drug. However, it would be useful to determine at a later date how long the effects of a dose of tolazoline last.

The third group was used to determine the effects of giving tolazoline to hypoxemic animals. This is the situation in which most infants are given tolazoline. The levels of cardiac output and myocardial blood flow present in hypoxemic animals given tolazoline were similar to those during hypoxemia alone (Group I). Instead of reducing cerebral and renal blood flow, as occurred when tolazoline was administered to normoxemic animals, tolazoline had no effect on flow to these organs when tolazoline was given to hypoxemic animals. Flow remained at levels present during hypoxemia alone. Thus, it appears that tolazoline does not interfere with the ability of these organs to regulate their blood flow. Organs such as the heart and brain meet their oxygen needs during hypoxemia primarily by increasing their blood flow and only minimally by increasing the extraction of oxygen from blood (15, 17, 21). Hypoxemia usually increases the oxygen requirements of the heart (as indicated by an increase in the rate-pressure product); (7) which increases the myocardial oxygen consumption (9, 17). We did not measure coronary sinus oxygen content in our studies and, therefore, cannot calculate myocardial oxygen consumption. However, the fact that the rate-pressure product was unaffected by hypoxemia and tolazoline suggests that the oxygen demands of the heart were being met.

In contrast to the heart and brain, organs such as the gut meet their oxygen requirements during hypoxemia by increasing the amount of oxygen extracted from the blood; blood flow remains constant or even declines (2). At some level of hypoxemia, the organ is unable to meet its oxygen requirements and its metabolic rate falls below the normoxemic value (7, 18). If tolazoline should alter the blood flow further or impair extraction of oxygen, then organ metabolism would be disrupted. We found no consistent change in blood flow to these organs when tolazoline was administered to hypoxemic lambs. Flows were similar to those present during hypoxemia alone. From our data, we cannot determine whether tolazoline interferes with oxygen extraction or oxygen uptake. However, it probably did not because metabolic acidosis did not occur. The rate-pressure product did not change when tolazoline was administered because decreases in blood pressure were offset by increases in heart rate. This suggests that myocardial oxygen consumption remained constant. Therefore, the increase in myocardial blood flow occurred in order to meet the increased volume of blood needed to provide normal oxygen delivery.

Tolazoline administration has been reported to have adverse effects on the gastrointestinal system of humans. Silverman *et*

al. (26) and Goetzman *et al.* (11) described gastrointestinal bleeding in patients who were treated with tolazoline for as little as 2 days. One per cent of children developed gastric ulcers and 79% gastrointestinal complaints when tolazoline was used in 663 patients to treat polio (26). These effects were dose related. Ahlquist *et al.* (1) reported increased gastric acid stimulation and augmented histamine contractions of the gut with tolazoline, effects which could be blocked by atropine. Our data show no reduction in gut blood flow (including stomach blood flow) when tolazoline was infused. If similar effects occur in humans, it is unlikely that the gastrointestinal complaints reported are due to reduced blood flow.

Tolazoline has also been reported to have effects on the renal system of infants. Oliguria and/or hematuria occurred in 7 of 46 and renal failure in 2 of 46 infants treated with this drug (11). In another study, renal failure and death occurred in 1 of 20 infants receiving tolazoline (22). The difficulty with studies of this kind is that the patients have been hypoxemic and often hypotensive for a period of time during the course of their illness. As a result, renal failure may be due to these causes and not tolazoline administration. Our animals showed a small but significant reduction in renal blood flow with the onset of hypoxemia but no further reduction in renal blood flow occurred until we gave 10 mg/kg/h of tolazoline. Therefore, it is difficult to account for the oliguria and/or renal failure reported in human infants on the basis of reduced renal blood flow, if infants and lambs respond to tolazoline similarly.

In summary, hypoxemia increases cardiac output and the blood flow to the heart and brain; it also decreases blood flow to the kidneys. Oxygen delivery is reduced to organs other than heart and brain with hypoxemia. The data also indicate that administering tolazoline to hypoxemic animals does not affect the distribution of blood flow caused by hypoxemia. Neither does it reduce the pulmonary artery pressure or improve oxygenation.

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