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Effect of β-Adrenergic Receptor Blockade on Responses to Acute Hypoxemia in Lambs

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ABSTRACT. We studied the effects of β-adrenergic receptor blockade on general circulatory and metabolic responses to moderate (FIO_2 = 0.09) acute hypoxemia in newborn (protocol 1) and 3-wk-old (protocol 2) lambs, and on regional blood flow distribution in newborn lambs (protocol 1). Via a left thoracotomy we placed an electromagnetic flow transducer around the ascending aorta and inserted various vascular catheters. After 2 days of recovery, the lambs were studied. In protocol 1, we measured cardiovascular variables and regional blood flow distribution during control conditions, after 45 min of acute hypoxemia, and after 0.5 mg/kg of propranolol during acute hypoxemia. In protocol 2, we measured cardiovascular variables during control conditions and after 45 min of acute hypoxemia with and without propranolol pretreatment. In both groups, propranolol limited the increase in cardiac output and heart rate caused by hypoxemia, and thus decreased oxygen delivery. However, propranolol also decreased oxygen consumption so that pulmonary arterial pO_2 was either higher (protocol 1) or the same (protocol 2) as during acute hypoxemia alone. Neither metabolic acidosis nor hypothermia ensued. In protocol 1, propranolol decreased renal, carcass, and most importantly, myocardial blood flows. However, myocardial O_2 consumption also fell, coronary sinus pO_2 increased, and blood was redistributed toward the subendocardium, suggesting that myocardial perfusion improved. Thus, β-adrenergic receptor blockade during acute moderate hypoxemia may have a beneficial effect by reducing total body and myocardial oxygen demand in excess of the reduction in oxygen delivery. (*Pediatr Res* 23: 229–234, 1988)

Acute hypoxemia induces profound changes in oxygen delivery and consumption in the fetus, newborn, and adult, although the changes at each age are substantially different. When exposed to moderately low inspired oxygen concentrations, the adult dog maintains total body oxygen delivery, by increasing heart rate and cardiac output (1). In contrast, the fetal sheep develops bradycardia and a reduced combined ventricular output, severely decreasing oxygen delivery (2, 3). The newborn lamb responds similarly to the adult dog, but the percentage increase in heart rate and cardiac output is less, and total body oxygen delivery does fall (4). The lesser response in the newborn may be explained by its proportionally greater resting cardiac output and heart rate (5), which limit its capacity to respond to stress. All three age groups redistribute blood flow in order to maximize regional oxygen delivery to vital organs (1–4).

Not only are there major differences in oxygen delivery in animals of different ages exposed to acute hypoxemia, but there are also major differences in oxygen consumption. The adult dog maintains oxygen consumption unchanged until hypoxemia becomes severe, at which time consumption decreases and metabolic acidemia and decompensation rapidly ensue (1). In contrast, the newborn lamb is able to decrease oxygen consumption substantially despite a large increase in cardiorespiratory work; acidemia does not develop unless hypoxemia is severe (FIO_2 = 0.06) and consumption is reduced by at least 30% (4). This ability of the newborn to decrease oxygen consumption during brief periods of hypoxemia without metabolic decompensation may be explained by the large proportion of metabolic activity that is directed toward nonvital processes. Specifically, growth accounts for about one-third of the calories expended by the newborn lamb (4), and suppression of the metabolic activity directed toward growth may not induce anaerobic metabolism and metabolic decompensation.

The dramatic circulatory adaptations to acute hypoxemia are mediated through many mechanisms, but sympathetic stimulation is clearly important. Whereas sympathetic stimulation is beneficial to the adult because it substantially increases heart rate and cardiac output, it is less beneficial to the newborn, which has a lesser capacity to increase heart rate and cardiac output because of a high resting β-adrenergic state (6). Moreover, sympathetic stimulation is deleterious because it increases metabolic activity and thus oxygen demand. We postulate that blockade of β-adrenergic stimulation during acute moderate hypoxemia may be beneficial to the newborn because it might decrease oxygen demand in excess of oxygen delivery. We therefore devised protocol 1 presented below, in which we determined the effects of β-adrenergic receptor blockade using propranolol during acute moderate hypoxemia in the newborn lamb: we measured general cardiovascular variables, total body oxygen delivery and consumption, and regional blood flow and metabolism.

In addition to the primary purpose of this study, we addressed two secondary issues. Because hypoxemic episodes are frequently treated with propranolol in the older infant with tetralogy of Fallot we wished to determine whether its effects were similar in the older lamb. We postulated that this may not be so, because moderate hypoxemia is somewhat less well tolerated (4). In addition, we wished to determine whether the effects of propranolol were similar whether given before or after induction of hypoxemia. Both of these questions were addressed in protocol 2 presented below.

MATERIALS AND METHODS

We performed two separate experimental protocols for this study. In protocol 1 we studied 10 newborn lambs (7 ± 6 days)

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and determined the effects of β-adrenergic receptor blockade during moderate hypoxemia (9% oxygen in nitrogen) on general cardiovascular variables, total body oxygen consumption and delivery, regional blood flow, and myocardial metabolism. We performed protocol 2 on 12 older lambs (26 ± 16 days), to determine whether the general response to propranolol is similar in the older infant and whether that response is similar when propranolol is given before induction of hypoxemia. The lambs were of normal weight (protocol 1: 5.6 ± 1.7 kg, protocol 2: 8.7 ± 2.4 kg) and had normal hemoglobin concentrations for age (protocol 1: 9.6 ± 3.0 g/dl, protocol 2: 7.7 ± 1.8 g/dl).

Surgical preparation. Under general anesthesia with 0.5–0.7% halothane in oxygen, each lamb was ventilated with a Harvard respiratory pump. Catheters were inserted into a pedal artery and vein and advanced to the descending aorta and inferior vena cava, respectively. These catheters were used for intravenous fluid administration and blood gas and pressure monitoring during surgery and the recovery period. After additional local anesthesia (1% lidocaine HCl) a thoracotomy was performed in the third or fourth left intercostal space, and the pericardium was incised over the pulmonary artery. A precalibrated electromagnetic flow transducer (C & C Instruments, Culver City, CA) was applied around the ascending aorta just above the coronary arteries. Polyvinyl catheters were placed in the left atrium and main pulmonary artery directly, and placed in the ascending aorta and superior vena cava via the internal thoracic artery and vein, respectively. In protocol 1, a polyvinyl catheter was also placed in the coronary sinus via the hemiazygous vein. An 8F polyvinyl catheter was placed in the left pleural cavity to remove air and fluid during the recovery period and the chest was closed in layers. All vascular catheters were filled with heparin and were led along with the chest drainage catheter and flow transducer cable to the left flank of the lamb. The lamb was extubated and observed in a specially designed recovery area. When it was able to stand and cardiovascular variables had returned to near normal values the lamb was returned to its ewe.

Experimental protocol. General. Each lamb was allowed to recover for at least 2 days before study so that cardiovascular function could return to normal (7). All studies were performed with the lamb blindfolded, resting quietly in a sling, and supported in the upright position. Room temperature was maintained at 25° C. A loosely fitting plastic bag was placed over the lamb's head to collect expired gas for continuous measurement of oxygen consumption (8). Pressures, heart rate, and ascending aortic flow were recorded continuously.

Protocol 1. After a period of stabilization, pressures, heart rate, oxygen consumption, and ascending aortic blood flow were recorded. Blood samples (1.0 ml) were collected from the pulmonary artery, ascending aorta, and coronary sinus for measurement of blood gases, hemoglobin oxygen saturation, and hemoglobin concentration. The coronary sinus catheter functioned in only seven of the 10 lambs. For measurement of regional blood flow distribution, radionuclide-labeled microspheres of 15 μm diameter were then rapidly injected into the left atrium while reference blood samples were withdrawn from the ascending and descending aorta at a rate of 7 ml/min for 1.25 min.

After these control measurements in room air, a gas mixture containing 9% oxygen in nitrogen was administered through the plastic bag, as described previously (4). After 45 min of hypoxemia, the measurements were repeated. During hypoxemia the presence of any significant right to left shunt through the foramen ovale or ductus arteriosus was excluded by the indicator-dilution technique. Indocyanine green was injected into the inferior vena caval catheter while descending aortic blood was sampled through a cuvette densitometer.

Propranolol, 0.5 mg/kg, was then administered intravenously and, after another 15 min, the measurements were repeated. The lamb was then returned to room air and all measurements other than microsphere injection were repeated at 15 and 30 min.

Protocol 2. After a period of stabilization, pressures, heart rate, oxygen consumption, and ascending aortic blood flow were recorded. Blood samples were collected from the ascending aorta and pulmonary artery for measurement of blood gases, hemoglobin oxygen saturation, and hemoglobin concentration, and hypoxemia was then induced. The hemodynamic variables and blood samples were measured at 5, 15, 30, 45, and 60 min of hypoxemia. These variables all stabilized by 30 min of hypoxemia. The data obtained at 45 min of hypoxemia are presented herein so that qualitative comparisons with protocol 1 can be made. The same experiment was performed on a different day, except that, before we induced hypoxemia, 0.5 mg/kg of propranolol was administered intravenously and repeated every 30 min. These two experiments were performed in random order. No microsphere studies were performed in this protocol because it rapidly became apparent that the general cardiovascular response to propranolol was nearly identical to that seen in protocol 1. It was decided that the difficulty in performing such studies in these larger animals exceeded the likelihood of finding significant differences in redistribution of blood flow in the absence of differences in general cardiovascular responses.

Measurements and calculations. Vascular catheters were connected to Statham p23Db pressure transducers (Statham Instruments, Oxnard, CA) and the signals were recorded on a Beckman direct writing recorder (Beckman Instruments, San Jose, CA). Heart rate was recorded continuously by a cardiotachometer triggered from the arterial pressure pulse or aortic phasic flow tracing. Ascending aortic blood flow was recorded continuously on the Beckman recorder via a Statham SP 2002 electromagnetic flowmeter. Blood gases were measured at 39° C on a blood gas analyzer (Radiometer, Copenhagen, Denmark), and hemoglobin concentration and oxygen saturation were measured on a Radiometer OSM2 hemoximeter. Blood oxygen contents were calculated from oxygen saturation and hemoglobin concentration assuming a hemoglobin binding capacity of 1.35 ml/dl. Cardiac output was determined by the Fick method from the measured oxygen consumption and the pulmonary arterial and ascending aortic oxygen contents. After completion of the study, the lamb was killed with an overdose of intravenous sodium pentobarbital.

For protocol 1, the tissues were prepared for microsphere analysis using the technique of Heymann *et al.* (9). Each organ was dissected, weighed, and incinerated, and radioactivity of each isotope was measured. The heart was dissected as described by Rouleau *et al.* (10) into right and left ventricular free wall, septum, and atria; each ventricle was separated into an inner, middle, and outer layer. Each organ or segment of organ had a minimum of 400 microspheres, thus assuring the flow measurement was accurate to within 10% (95% confidence limits) (9).

Oxygen delivery to each organ was calculated as the product of organ blood flow and arterial oxygen content. Left ventricular oxygen consumption was calculated by the Fick method from the formula

$$LV\ VO_2 = QLV \times (C_{AO} - C_{CS})O_2$$

where QLV is flow to the left ventricular free wall, C_{AO} is ascending aortic oxygen content, and C_{CS} is coronary sinus oxygen content. Myocardial extraction coefficient was calculated as the ratio of arteriovenous oxygen content difference divided by arterial oxygen content.

Analysis. Means and SDs were calculated for the absolute values of the general cardiovascular and metabolic data for both protocols. For the microsphere data from protocol 1, the mean and SD of the percent change from control were calculated. We used a paired *t* test to compare data between hypoxemia alone and hypoxemia during β-adrenergic blockade within each protocol. Differences were considered significant at $p \leq 0.05$ except for organ blood flows, which, because of the multiple organs evaluated, were considered to be different when $p \leq 0.01$. We did not compare data between control and hypoxemia alone, because such a comparison was not part of the study design. We thus did not need to perform a Bonferroni correction, as we had only one experimental intervention. No statistical comparison

of the effects of propranolol can be made between the two protocols, because the age of the animals, their numbers, and the protocols were different. All data in the text, tables, and figures are presented as mean ± 1 SD.

RESULTS

Protocol 1. Control variables of cardiovascular function and oxygen delivery, blood gases, and core temperature were normal (Table 1). Moderate hypoxemia caused arterial hemoglobin oxygen saturation to fall from 94 ± 4 to 50 ± 5%. Tachycardia (42% increase in heart rate) and hyperventilation ensued, pulmonary artery pressure more than doubled (140% increase), oxygen delivery decreased greatly (42%), but oxygen consumption decreased only modestly (15%) and core temperature did not change (Table 1). Blood flow to the myocardium (168%), brain (49%), and muscle and bone (18%) increased, whereas blood flow to the gastrointestinal tract (21%), kidneys (13%), and skin (29%) decreased (Fig. 1). Oxygen delivery to all organs and tissues thus decreased, except to the heart, which increased by 44% (Fig. 1). Vascular resistance decreased in the myocardium (63%) and the brain (35%), and increased all other organs and tissues (Fig. 2). Left ventricular rate-pressure product and oxygen consumption increased similarly (40 and 39%, respectively), in association with the large increase in blood flow (Fig. 3). Coronary sinus oxygen tension decreased by 55%, and there was a large reduction in the ratio of blood flow to the subendocardium *versus* subepicardium (inner-outer ratio) of both the left (from 1.18 ± 0.18 to 1.03 ± 0.16) and right (from 1.23 ± 0.15 to 1.01 ± 0.19) ventricles (Table 2).

When propranolol was given during hypoxemia, heart rate and cardiac output decreased to control values, which further decreased oxygen delivery to 85% of hypoxemic values (Table 1). However, oxygen consumption decreased similarly (to 78% of hypoxemic values) so that pulmonary arterial hemoglobin oxygen saturation and the arteriovenous oxygen content difference were not different from those obtained during hypoxemia alone (Table 1). Systemic arterial oxygen tension increased and blood pH and base deficit remained unchanged (Table 1). Blood flow and oxygen delivery to the myocardium, kidneys, and muscle and bone decreased significantly as compared to hypoxemia alone (Fig. 1). Total vascular resistance and resistances in the myocardium, kidney, and muscle and bone increased (Fig. 2). Despite the large decrease in left ventricular blood flow and oxygen delivery, left ventricular rate-pressure product and left ventricular oxygen consumption also decreased dramatically (to 61 and 59% of hypoxemic values, respectively) so that the inner-outer ratio of blood flow actually increased to control values and coronary sinus oxygen tension rose (Table 2). Right ventricular blood flow decreased significantly but did not return as near to its control value (Table 2).

We attempted to perform the same protocol on four of these lambs during severe hypoxemia (6% oxygen in nitrogen). Aortic oxygen tension decreased to 20 torr, and heart rate increased dramatically during hypoxemia. After propranolol was given, heart rate dropped drastically, metabolic acidosis rapidly ensued, and the lambs became very distressed. The studies were therefore abandoned and the lambs were returned to room air. Despite this, one lamb did not survive.

Protocol 2. Control variables of cardiovascular function and

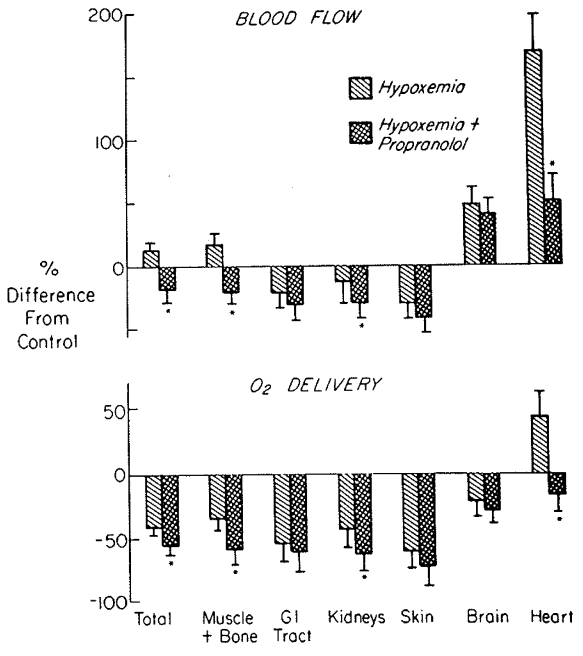

Fig. 1. Effects of hypoxemia (FIO_2 = 0.09) on blood flow and O_2 delivery to various tissues before and after propranolol (protocol 1, n = 7). *significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

Table 1. *Cardiovascular and metabolic data for protocol 1 (n = 10)*

	Control	Hypoxemia (45 min)	Hypoxemia + propranolol
Heart rate (beats/min)	196 ± 18	279 ± 27	184 ± 14*
Cardiac output (ml/kg/min)	267 ± 72	292 ± 67	231 ± 49*
Mean aortic pressure (mm Hg)	74 ± 5	72 ± 5	68 ± 4*
Mean PA pressure (mm Hg)	15 ± 4	36 ± 7	39 ± 9
Oxygen consumption (ml/kg/min)	14.6 ± 1.4	12.4 ± 1.7	9.7 ± 1.2*
AV O2 content difference (ml/dl)	5.3 ± 1.0	4.4 ± 0.7	4.7 ± 0.7
Systemic arterial			
pH	7.43 ± 0.03	7.45 ± 0.04	7.44 ± 0.06
pCO_2 (torr)	38 ± 2	28 ± 2	28 ± 3
Base deficit (mEq/liter)	1 ± 2	−4 ± 2	−5 ± 2
pO_2 (torr)	81 ± 7	28 ± 4	32 ± 4*
O_2 saturation (%)	94 ± 4	50 ± 5	54 ± 8
Pulmonary arterial			
pO_2 (torr)	31 ± 5	13 ± 3	17 ± 4*
O_2 saturation (%)	50 ± 12	17 ± 4	18 ± 5
Core temperature (°C)	39.3 ± 0.3	38.7 ± 0.3	38.6 ± 0.4

* Significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

oxygen delivery, blood gases, and core temperature were normal (Table 3). The response to hypoxemia (Table 3) was similar to that previously reported for lambs of similar age (4). Heart rate (51%), cardiac output (16%), and pulmonary artery pressure (93%) increased, hyperventilation developed, and systemic arterial pressure did not change. Oxygen consumption (16%) and arteriovenous oxygen content difference (27%) both decreased.

Prior treatment with propranolol significantly influenced the cardiovascular effects of hypoxemia (Table 3). Cardiac output and heart rate did not increase above control values and systemic arterial pressure fell. Only pulmonary arterial pressure increased to a similar extent as during hypoxemia alone. Although oxygen delivery was only 89% of that during hypoxemia alone, oxygen consumption decreased similarly (to 82% of hypoxemic values) and pulmonary arterial hemoglobin oxygen saturation and the arteriovenous oxygen content difference were not different.

DISCUSSION

We found that the circulatory and metabolic responses to acute moderate hypoxemia were similar in both the younger (protocol 1) and older (protocol 2) lambs to those we reported previously (3). The effects of β-adrenergic receptor blockade using propranolol were qualitatively similar whether given before induction of hypoxemia (protocol 2) or after induction (protocol 1). Propranolol did not abolish the hyperventilation response to hypoxemia (pCO_2 remained low in both groups of lambs, although CO_2 production was probably decreased so that the extent of ventilation was probably somewhat less), but did produce a marked fall, or prevented the expected increases, in heart rate and cardiac output, and systemic oxygen delivery fell dramatically. However, oxygen consumption also decreased during β-adrenergic blockade, and pulmonary arterial oxygen tension was actually higher than during hypoxemia alone in protocol 1. The higher pulmonary arterial oxygen tension in the absence of a change in hemoglobin oxygen saturation indicates that the hemoglobin oxygen dissociation curve shifted to the right. This may have been a direct effect of propranolol, which can release bound 2,3-diphosphoglycerate in the red blood cell and allow it to interact with hemoglobin (11). The lesser shift in the oxygen dissociation curve in the older lambs may be explained by the already rightward shifted curve relative to the newborn (5). In both groups, a right shift along with a similar or higher pulmonary arterial oxygen tension would allow the tissues a greater capacity to extract oxygen. It was not surprising, therefore, that metabolic acidosis did not ensue.

Propranolol decreased oxygen delivery by inhibiting the tachy-

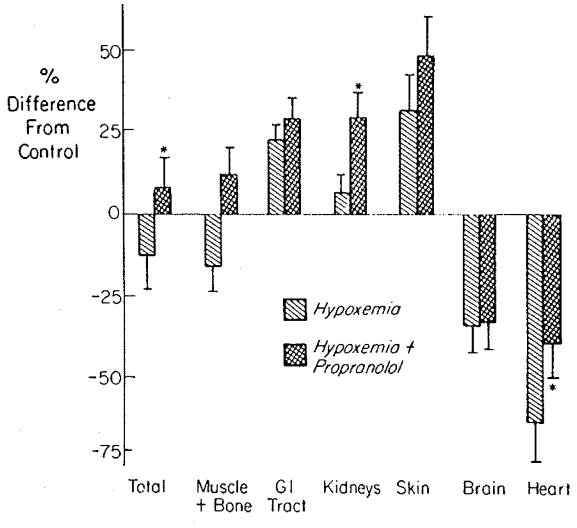

Fig. 2. Effects of hypoxemia (FIO_2 = 0.09) and hypoxemia with propranolol on total systemic vascular resistance and resistances across various vascular beds (protocol 1, n = 7). *significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

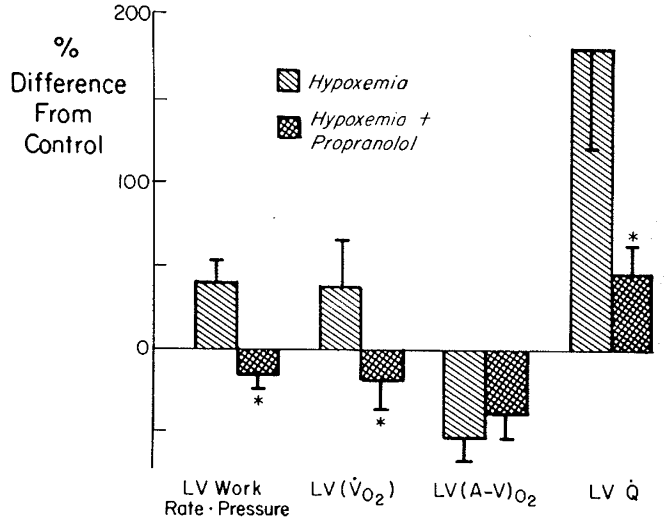

Fig. 3. Effects of hypoxemia (FIO_2 = 0.09) on left ventricular myocardial (*LV*) work, oxygen consumption (VO_2), arteriovenous oxygen difference [(A-V)O_2], and blood flow ($\dot{Q}$) before and after propranolol in seven lambs (protocol 1, n = 7). *significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

Table 2. *Myocardial blood flow and oxygen metabolism for protocol 1 (n = 7)*

	Control	Hypoxemia (45 min)	Hypoxemia + propranolol
Coronary sinus pO_2 (torr)	21 ± 3	13 ± 3	16 ± 4*
Coronary sinus O_2 saturation (%)	35 ± 6	14 ± 3	13 ± 3
Myocardial extraction coefficient	0.65 ± 0.04	0.69 ± 0.02	0.72 ± 0.03
Myocardial blood flow (ml/100 g/min)			
Left ventricle	213 ± 58	585 ± 153	296 ± 78*
Right ventricle	135 ± 32	587 ± 161	279 ± 59*
Septum	172 ± 44	582 ± 148	287 ± 64*
Inner-outer blood flow ratio			
Left ventricle	1.18 ± 0.18	1.03 ± 0.16	1.26 ± 0.19*
Right ventricle	1.23 ± 0.15	1.01 ± 0.19	1.16 ± 0.17*
Left ventricle O_2 consumption (m102/100 g/min)	13.3 ± 2.6	18.3 ± 3.4	10.3 ± 4.4*

* Significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

Table 3. *Cardiovascular and metabolic data for protocol 2 (n = 12)*

	No propranolol pretreatment		Propranolol pretreatment		
	Control 1	Hypoxemia (45 min)	Control 2	Propranolol	Hypoxemia + propranolol
Heart rate (beats/min)	167 ± 30	252 ± 33	170 ± 30	141 ± 23	153 ± 27*
Cardiac output (ml/kg/min)	187 ± 37	216 ± 41	199 ± 45	163 ± 35	176 ± 37*
Mean aortic pressure (mm Hg)	82 ± 10	78 ± 9	79 ± 7	77 ± 6	72 ± 6*
Mean PA Pressure (mm Hg)	15 ± 4	29 ± 12	15 ± 2	16 ± 4	27 ± 11
O2 consumption (ml/kg/min)	9.4 ± 3.0	7.9 ± 2.6	9.1 ± 2.6	8.8 ± 2.5	6.5 ± 1.8*
AV O_2 content difference (ml/dl)	4.7 ± 0.7	3.5 ± 0.3	4.4 ± 0.6	4.8 ± 0.8	3.7 ± 0.4
Systemic arterial					
pH	7.44 ± 0.03	7.47 ± 0.10	7.45 ± 0.02	7.44 ± 0.02	7.48 ± 0.08
pCO_2 (torr)	38 ± 2	25 ± 3	36 ± 2	35 ± 2	24 ± 2
Base deficit	2 ± 3	−5 ± 3	1 ± 2	0 ± 1	−5 ± 3
pO_2 (torr)	81 ± 5	32 ± 5	79 ± 7	80 ± 6	34 ± 5
O_2 saturation (%)	96 ± 4	46 ± 8	95 ± 4	95 ± 4	50 ± 7
Pulmonary arterial					
pO_2 (torr)	37 ± 4	14 ± 3	36 ± 6	32 ± 5	16 ± 3
O_2 saturation (%)	50 ± 11	16 ± 7	48 ± 8	42 ± 10	16 ± 4
Core temperature (°C)	39.4 ± 0.3	38.8 ± 0.3	39.5 ± 0.4	39.5 ± 0.4	38.7 ± 0.5

* Significantly different, hypoxemia + propranolol *versus* hypoxemia alone, $p \leq 0.05$.

cardia and increase in cardiac output that occurs during acute hypoxemia, and decreased oxygen consumption by an abolition of sympathetic nervous or catecholamine-induced stimulation of metabolism, including that of brown fat, occasioned by the hypoxemia (12). On balance, it appears that the beneficial effects of the decrease in oxygen consumption more than counterbalanced the deleterious effects of the decrease in oxygen delivery in the younger lambs (protocol 1), because pulmonary arterial oxygen tension increased and metabolic acidosis did not ensue, and at least counterbalanced the deleterious effects of the decrease in oxygen consumption in the older lambs (protocol 2), in which pulmonary arterial oxygen tension did not increase significantly and metabolic acidosis also did not ensue. In both groups, propranolol dramatically reduced oxygen consumption, by 22% in protocol 1 and 18% in protocol 2. This reduction in oxygen consumption could limit heat generation and cause core body temperature to fall. Although we did not see such a fall after propranolol, we studied the lambs only for a short time. During more prolonged hypoxemia core temperature could indeed fall and acidemia could then develop. Thus the beneficial effects of β-adrenergic blockade could be temporary.

Although propranolol had a strikingly similar overall effect on variables of general cardiovascular status and oxygen metabolism in the two groups of lambs, the mechanisms that initiated these effects may be quite different. Brown fat metabolism is stimulated under stress, but such stimulation is blunted during hypoxemia. Propranolol could decrease brown fat metabolism further, particularly in the younger lambs, which have a great deal of brown fat (13). Its effects on brown fat metabolism may be much more limited in the older lambs, in which much of the brown adipose tissue has been replaced by white (13). Also, the decrease in contractility and thus myocardial oxygen consumption may be quite different in the two groups of lambs, which function under very different contractile states at rest, and which respond quite differently to β-adrenergic blockade (6). Lastly, the extent to which sympathetic and other neurohormonal responses to hypoxemia are invoked may be quite different in the two age groups, so that the actions of propranolol may likewise be quite different.

Propranolol also altered the effects of acute hypoxemia on regional blood flow distribution, as studied in the younger lambs. Although cerebral blood flow did not change significantly, suggesting that it is regulated by local factors rather than β-adrenergic vasodilatation, blood flow to the gut, kidney, and the peripheral circulation did decrease and resistance did increase, probably resulting from abolition of the vasodilatory effect of β-adrenergic stimulation. Although oxygen delivery to these organs thus decreased, we assume that oxygen consumption also decreased and that fractional extraction remained relatively unchanged. This has been demonstrated in the hindlimb (representing skeletal muscle) of the acutely hypoxemic adult dog (14), in which oxygen consumption decreased by about 30% at the same level of hypoxemia as we induced. Moreover, the oxygen excess during recovery was less than the accumulated deficit, indicating that, even in the adult, suppression of nonessential oxygen metabolism can occur. In studies in fetal lambs, we have shown that in many organs such as the liver (15), kidney and hindleg (16), oxygen delivery and consumption are linearly related during hypoxemia. We cannot extrapolate these findings to our study, in which propranolol was given during hypoxemia. The relationship between oxygen delivery and demand are quite complex: whereas the driving force during hypoxemia may be the decrease in delivery, thereby inducing a decrease in utilization, the driving force during superimposed β-adrenergic blockade may be a decrease in oxygen demand, secondarily invoking a decrease in delivery.

We did determine the effects of β-adrenergic blockade during hypoxemia on myocardial oxygen delivery and consumption. Propranolol markedly decreased the elevated myocardial blood flow seen during acute hypoxemia alone, thus decreasing oxygen delivery considerably. However, myocardial oxygen consumption also decreased markedly, probably because of the decrease in heart rate, aortic pressure, and intrinsic contractility directly caused by propranolol. Thus coronary sinus oxygen saturation remained unchanged and, because of the rightward shifted hemoglobin oxygen dissociation curve, coronary sinus oxygen tension actually increased. This increase in coronary sinus oxygen tension suggests that the myocardium had a greater capacity to extract more oxygen than during hypoxemia alone. This is corroborated by the inner-outer blood flow ratios during hypoxemia alone and after propranolol was administered. The subendocardium is more subject to decreases in myocardial perfusion

than is the subepicardium, so that ischemia causes blood flow to be distributed away from the subendocardium and toward the subepicardium, thus reducing the inner-outer ratio (10). During hypoxemia the inner-outer ratio did decrease, suggesting that ischemia was present. After propranolol was administered, the ratio returned to control values, suggesting that propranolol appeared to alleviate the ischemia. This may be explained by the decrease in heart rate caused by propranolol. Subendocardial blood flow occurs almost exclusively during diastole, which is a greater proportion of the cardiac cycle at slower heart rates. In addition, propranolol may have decreased myocardial oxygen consumption to such an extent that ischemia would be less likely to occur.

These studies indicate that β-adrenergic receptor blockade is beneficial in abolishing the deleterious effects of sympathetic stimulation during acute moderate hypoxemia in the newborn lamb. Although oxygen delivery is reduced during β-adrenergic blockade, oxygen consumption is also reduced. This is particularly striking in the myocardium, where the very high blood flow and suggestion of subendocardial ischemia are reversed. In addition, the hemoglobin oxygen dissociation curve is shifted to the right, facilitating oxygen extraction. Although this is not always advantageous during hypoxemia (*e.g.* when alveolar oxygen tension is decreased a left shifted curve may facilitate oxygen uptake to a greater extent than a right shifted curve would facilitate release), it would be advantageous in infants with cyanotic heart disease and normal alveolar oxygen tension, in whom oxygen uptake is relatively unaffected by the position of the oxygen dissociation curve. The benefits of propranolol occurred without metabolic acidemia or hypothermia during our brief study, and may explain its beneficial effects in infants with hypoxic spells associated with tetralogy of Fallot. During prolonged or very severe hypoxemia, however, propranolol may be dangerous: nonshivering thermogenesis may be excessively impaired during prolonged hypoxemia, and marked bradycardia with a profound decrease in cardiac output may occur during severe hypoxemia. The application of these data to the clinical setting must therefore be used with great caution.

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