β -Adrenergic Influence on Increased Myocardial Oxygen Consumption during Hypoxemia in Awake Newborn Lambs

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ABSTRACT. The purpose of this investigation was to determine the role of increased β -adrenergic activity in regulating the increase in myocardial oxygen consumption that occurs during hypoxemia in unanesthetized newborn lambs. Through a left thoracotomy, fluid-filled catheters were placed in the ascending aorta, coronary sinus and left atrium, a pressure transducer was introduced into the left ventricle, and pacing wires were sutured onto the left atrium. The lambs were studied 3 d later by making intermittent measurements of aortic and coronary sinus blood oxygen saturations and Hb concentrations, left ventricular myocardial blood flow, cardiac output, heart rate, left atrial and aortic blood pressures, the maximal first derivative of left ventricular pressure, aortic and coronary sinus blood oxygen contents, the arteriovenous difference of oxygen across the left ventricular myocardium, myocardial oxygen consumption, and external cardiac work (aortic mean blood pressure times cardiac output). In nine lambs with an intact β -adrenergic nervous system (group 1), the above measurements were made during a control period and during hypoxemia ($\text{FiO}_2 = 0.08\text{--}0.10$) with spontaneous tachycardia. In another group of 12 lambs (group 2), the measurements were made during a control period, after β -blockade (1.5 mg/kg intravenous propranolol) with pacing at the control heart rate, during hypoxemia with pacing at the control heart rate, and during hypoxemia with pacing-induced tachycardia. In the group 2 lambs, β -blockade completely inhibited the increase in heart rate, maximal first derivative of left ventricular pressure, cardiac output and cardiac work that occurred during hypoxemia in the group 1 lambs that had an intact β -adrenergic nervous system. In contrast, by comparing the results in groups 1 and 2, it is evident that β -blockade inhibited no more than 75–80% of the increase in myocardial oxygen consumption that occurred during hypoxemia in the group 1 lambs with an intact β -adrenergic nervous system. This study demonstrates that β -adrenergically mediated increases in heart rate, left ventricular contractility, and external cardiac work account for no more than 75–80% of the increase in myocardial oxygen consumption during hypoxemia in unanesthetized newborn lambs. The factor(s) that are responsible for the residual increase in myocardial oxygen consumption remain to be determined. (*Pediatr Res* 25:585–590, 1989)

Abbreviations

LVEDP, left ventricular and diastolic pressure
dP/dt, first derivative of left ventricular pressure
LV, left ventricle

Acute hypoxemia has important effects on the developing myocardium. We have demonstrated previously that myocardial oxygen consumption increased by 30–40% during moderate hypoxemia ($\text{FiO}_2 = 0.08\text{--}0.10$) in unanesthetized newborn lambs (1). To understand the underlying mechanism, we reasoned that hypoxemia also has been associated with β -adrenergically mediated increases in several of the hemodynamic determinants of myocardial oxygen consumption. Thus, we postulated that increased β -adrenergic activity would be an important regulator of the increase in myocardial oxygen consumption that occurs during hypoxemia (2–7).

Previous studies have demonstrated that myocardial oxygen consumption increased during hypoxemia in β -adrenergically blocked anesthetized newborn lambs and mature dogs (8, 9). However, all of these experimental animals were studied under the influence of β -blockade. Thus, there is no information using the same experimental preparation with and without β -blockade that would permit a quantitative estimation of the role of the β -adrenergically mediated augmentation of cardiovascular function on the increase in myocardial oxygen consumption during hypoxemia. Furthermore, the previous studies were performed under the influence of anesthesia and acute surgical preparation, which can have significant effects on β -adrenergic function (10). Thus, the purpose of this study was to evaluate the role of the increased β -adrenergic activity in regulating the increase in myocardial oxygen consumption during hypoxemia in newborn lambs that were not under the influence of anesthesia or acute surgical preparation.

MATERIALS AND METHODS

Experimental preparation. We performed a left thoracotomy under halothane anesthesia on 21 Western lambs at 2–6 d after birth when they weighed 5.1 ± 0.4 kg. Using techniques described previously, pacing wires (#5633 hookup wire, Cooner Wire Co., Chatsworth, CA) were sutured to the left atrial appendage, fluid-filled catheters (inside diameter of 0.10 cm; outside diameter of 0.15 cm) were placed in the ascending aorta, left atrium, and coronary sinus; and a pressure transducer catheter (#PC-350, Millar Instruments, Houston, TX) was inserted in the left carotid artery and manipulated into the LV (1). Separate catheters were placed into a leg vein and artery and advanced to the distal

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inferior vena cava and the abdominal aorta, respectively. All catheters and wires were tunneled subcutaneously to the left posterior chest and protected by a nylon-mesh jacket. The wounds were sutured and the lambs recovered with their ewes.

Experimental protocols. At 3 d after surgery, the lambs were blindfolded and placed in a nylon-mesh support sling. We began a continuous recording of heart rate, LVEDP, aortic blood pressure, and dP/dt. Arterial and coronary sinus blood withdrawals were made at selected intervals (see below) for the measurement of blood gases, oxygen saturations, and Hb concentrations. Myocardial blood flows and cardiac outputs were measured intermittently with the radionuclide-labeled microsphere technique (11). Rectal temperatures were measured with a thermistor; they varied randomly and minimally throughout each study. Ambient temperature was maintained between 23.3 and 25.0°C.

The β -adrenergic nervous system was left intact in nine of the lambs (group 1; *i.e.* no β -blockade) in which we made the above measurements during a control period and during arterial hypoxemia (Fig. 1). These lambs differ from the previous study (1) in that carbon dioxide was not added to the gas mixture (see below). In the other 12 lambs (group 2), we repeated sequential sets of the above measurements during a control period, after complete β -blockade while pacing the left atrium at the control heart rate, during hypoxemia with pacing at the control heart rate, and during hypoxemia with pacing at 250–260 bpm. This

rate was used because it was the average heart rate during hypoxemia in lambs in this age group with an intact β -adrenergic nervous system (1, 12).

Measurements were made at the end of each 30-min control period, 15 min of the propranolol administration, at the end of each 30-min period of hypoxemia, and after 3 min of atrial pacing. Each period of hypoxemia lasted 30 min and was produced by placing the lambs in an environment of 8–10% oxygen with the balance as nitrogen. β -blockade was produced with 1.5 mg/kg of intravenous propranolol. The adequacy of β -blockade was tested after the end of each experiment by assessing the effect of a 0.2 μ g/kg bolus of intravenous isoproterenol on heart rate and left ventricular dP/dt (see Table 1). Any increase in heart rate or dP/dt was considered to indicate incomplete β -blockade throughout the experiment. A single study was performed in each lamb with one of the above protocols. The lambs were killed with euthanasia solution after the completion of each experiment. Correct placement of catheters were verified at necropsy. Thus, the group 1 lambs were studied for 60 min and the group 2 lambs were studied for 78 min. We do not believe that the difference in the duration of the studies has contributed independently to the results because our previously published data have demonstrated that the study variables are stable for these durations (13).

Measurements and calculations. PO_2 , PCO_2 , and pH were measured with a blood gas analyzer (model 158, Corning Instruments, Medfield, MA). All values for PO_2 were corrected to 39°C, the average body temperature of sheep (14). Oxygen saturations and Hb concentrations were measured with a spectrophotometric technique (Radiometer OSM2, Copenhagen). Blood oxygen contents were calculated using a capacity factor of 1.36 mL of oxygen/g of Hb (14).

Left atrial and aortic blood pressures were measured with Statham P23Db transducers referenced to atmospheric pressure with 0 obtained at the midchest position. The left ventricular pressure transducer was calibrated by matching the LVEDP with the left atrial *a* wave, and the peak systolic pressure in the left ventricle with the peak systolic pressure in the ascending aorta. The dP/dt was measured with a Beckman 9879 differentiating circuit which was calibrated with a 3.18 Hz internal sine wave. The output of the differentiating circuit is linear to 100 Hz. A lead II electrocardiogram was recorded with adhesive electrocardiographic electrodes and a Beckman 9855 electrocardiographic coupler (Beckman Instruments Inc., Palo Alto, CA). Left atrial pacing was performed with a physiologic stimulator, using the minimum output necessary to stimulate the atrium (#SD9, Grass Instrument Co., Quincy, MA). All pacing was performed with 1:1 atrioventricular conduction.

Cardiac outputs and blood flows to the left ventricular free wall were measured as previously described with 15- μ m-diameter microspheres labeled with ^{57}Co , ^{114}In , ^{113}Sn , ^{85}Sr , ^{95}Nb , or ^{46}Sc (1, 11). During each left atrial injection of microspheres, reference samples were withdrawn continuously from the ascending thoracic aorta and the descending abdominal aorta into pre-weighed syringes for 2 min at a rate of 4 mL/min. Cardiac outputs were calculated by summation of the radioactivity of all systemic body parts (11). Total lung radioactivity was measured separately. To estimate left to right shunting of blood, we multiplied the ratio of lung radioactivity to total body radioactivity by 100%. As there is very little tissue shunting of 15- μ m-diameter microspheres (15), this calculation was used to detect the combination of bronchial blood flow and left to right shunting through peripheral organ beds, a patent atrial foramen ovale or a patent ductus arteriosus. Each sample contained at least 400 microspheres, thereby providing a statistical accuracy of $\pm 10\%$ (16). There was no more than 10% variability in flows between paired cerebral hemispheres and kidneys, thereby demonstrating adequate mixing of microspheres within the circulation (11).

We calculated the arteriovenous difference of oxygen across the left ventricular free wall and left ventricular myocardial

Fig. 1. The effect of β -adrenergic blockade on ascending aortic (CaO_2) and coronary sinus ($CcsO_2$) blood oxygen content, the arteriovenous difference of oxygen across the left ventricular myocardium (A-CS O_2 difference), myocardial blood flow, and myocardial oxygen consumption during hypoxemia ($FiO_2 = 0.08$ – 0.10). "Intact ANS lambs" ($n = 9$) indicates lambs with an intact β -adrenergic nervous system, *i.e.* those studied without β -blockade. " β -blocked lambs" ($n = 12$) were given 1.5 mg/kg of intravenous propranolol. For this group, left atrial pacing was used to maintain the control heart rate during "propranolol" and "hypoxemia." "Hypoxemia/HR" indicates continued hypoxemia with pacing-induced tachycardia at 250–260 bpm. LV = left ventricular myocardium. * = $p < 0.01$ and + = $p < 0.05$ compared to the previous treatment within the group.

Table 1. *Effect of isoproterenol in lambs with an intact β -adrenergic nervous system and in β -blocked lambs**

	Intact β -adrenergic lambs (group 1)		β -blocked lambs (group 2)		
	Control	Isoproterenol	Control	Propranolol	Isoproterenol
Heart rate (bpm)	185 $\pm$ 10	269 $\pm$ 14†	191 $\pm$ 11	169 $\pm$ 10‡	169 $\pm$ 10
LEVDP (mm Hg)	5.0 $\pm$ 0.7	3.6 $\pm$ 0.5‡	4.7 $\pm$ 0.6	7.8 $\pm$ 0.9‡	7.1 $\pm$ 0.8
Maximal dP/dt (mm Hg/s)	4126 $\pm$ 344	7246 $\pm$ 634†	4248 $\pm$ 402	3210 $\pm$ 390‡	3168 $\pm$ 390

* Values are means $\pm$ SEM. Isoproterenol was given intravenously as a bolus of 0.2 μ g/kg. Propranolol was given intravenously as a 1.5 mg/kg over 1–2 min. Results indicate the maximal change after drug administration. The isoproterenol test was performed in the β -blocked lambs after the conclusion of each hypoxemia experiment.

† $p < 0.001$ compared to previous treatment within the group. For the lambs with an intact β -adrenergic nervous system, $n = 9$; for the β -blocked lambs, $n = 12$.

‡ $p < 0.01$ compared to previous treatment within the group.

Table 2. *Blood gas data in lambs with intact β -adrenergic nervous systems and in β -blocked lambs**

	Intact β -adrenergic nervous system lambs (group 1)		β -blocked lambs (group 2)			
	Group	Hypoxemia	Control	Propranolol	Hypoxemia	Hypoxemia/T
Arterial						
PO ₂ (torr)	77 $\pm$ 2	27 $\pm$ 1†	75 $\pm$ 2	77 $\pm$ 2	27 $\pm$ 1†	26 $\pm$ 2
pH	7.44 $\pm$ 0.02	7.54 $\pm$ 0.02‡	7.45 $\pm$ 0.02	7.45 $\pm$ 0.01	7.55 $\pm$ 0.02‡	7.56 $\pm$ 0.02
PCO ₂ (torr)	39 $\pm$ 1	29 $\pm$ 1†	38 $\pm$ 1	37 $\pm$ 2	28 $\pm$ 1†	29 $\pm$ 1
O ₂ saturation (%)	96.3 $\pm$ 0.4	48.4 $\pm$ 0.6†	97.5 $\pm$ 0.5	96.9 $\pm$ 0.5	45.2 $\pm$ 0.6†	45.0 $\pm$ 0.5
Hb (g/dL)	10.3 $\pm$ 0.4	10.5 $\pm$ 0.3	10.6 $\pm$ 0.5	10.6 $\pm$ 0.4	11.3 $\pm$ 0.5	11.2 $\pm$ 0.5
Coronary sinus						
PO ₂ (torr)	24 $\pm$ 1	16 $\pm$ 1†	24 $\pm$ 2	24 $\pm$ 2	15 $\pm$ 2†	14 $\pm$ 1
pH	7.42 $\pm$ 0.01	7.52 $\pm$ 0.02‡	7.42 $\pm$ 0.02	7.41 $\pm$ 0.02	7.53 $\pm$ 0.01‡	7.54 $\pm$ 0.02
PCO ₂ (torr)	44 $\pm$ 1	32 $\pm$ 1†	45 $\pm$ 2	45 $\pm$ 2	31 $\pm$ 1†	30 $\pm$ 1
O ₂ saturation	29.9 $\pm$ 0.5	17.7 $\pm$ 0.5‡	30.9 $\pm$ 0.4	30.1 $\pm$ 0.4	18.1 $\pm$ 0.5‡	18.4 $\pm$ 0.5
Hb (g/dL)	10.5 $\pm$ 0.4	10.8 $\pm$ 0.4	10.9 $\pm$ 0.5	10.8 $\pm$ 0.4	11.1 $\pm$ 0.4	11.0 $\pm$ 0.5

* Values are means $\pm$ SEM. Hypoxemia was produced with an environmental oxygen concentration of 8–10%. In the β -blocked lambs, measurements during “propranolol” and “hypoxemia” were obtained while pacing the left atrium at the control heart rate. Measurements during “hypoxemia/T” were obtained while pacing the left atrium at 250–260 bpm. For the lambs with an intact β -adrenergic nervous system, $n = 9$; for the β -blocked lambs, $n = 12$.

† $p < 0.001$ compared to the previous treatment within the group.

‡ $p < 0.01$ compared to the previous treatment within the group.

Table 3. *Hemodynamic data in lambs with an intact β -adrenergic nervous system and in β -blocked lambs**

	Intact β -adrenergic nervous system lambs (group 1)		β -blocked lambs (group 2)			
	Control	Hypoxemia	Control	Propranolol	Hypoxemia	Hypoxemia T
Heart rate (bpm)	192 $\pm$ 4	259 $\pm$ 4†	188 $\pm$ 5	188 $\pm$ 5	188 $\pm$ 5	256 $\pm$ 2‡
LEVDP (mm Hg)	5.3 $\pm$ 0.6	4.1 $\pm$ 0.7‡	4.6 $\pm$ 0.5	8.2 $\pm$ 0.7‡	7.9 $\pm$ 0.8	5.7 $\pm$ 1.0‡
Maximal dP/dt (mm Hg/s)	4337 $\pm$ 397	7330 $\pm$ 756†	4462 $\pm$ 347	3168 $\pm$ 225‡	3196 $\pm$ 263	3858 $\pm$ 316‡
Aortic mean blood pressure (mm Hg)	85 $\pm$ 3	84 $\pm$ 3	80 $\pm$ 2	78 $\pm$ 3	76 $\pm$ 2	78 $\pm$ 2
Cardiac output (mL/min/kg)	243 $\pm$ 16	273 $\pm$ 14‡	245 $\pm$ 15	230 $\pm$ 10‡	228 $\pm$ 11	230 $\pm$ 10
LV work (product of cardiac output and aortic mean blood pressure (mm Hg $\times$ mL/min/kg)	20.9 $\pm$ 1.6	24.5 $\pm$ 2.1‡	20.1 $\pm$ 1.2	17.8 $\pm$ 0.9‡	17.6 $\pm$ 0.8	17.3 $\pm$ 1.1

* Values are mean $\pm$ SEM. Hypoxemia was produced with an environmental oxygen concentration of 8–10%. In the β -blocked lambs, measurements during “propranolol” and “hypoxemia” were obtained while pacing the left atrium at the control heart rate. Measurements during hypoxemia/T were obtained while pacing the left atrium at 250–260 bpm. For the lambs with intact β -adrenergic nervous systems, $n = 9$; for the β -blocked lambs, $n = 12$ compared.

† $p < 0.001$ compared to the previous treatment within the group.

‡ $p < 0.01$ compared to the previous treatment within the group.

oxygen consumption as described previously (1). Left ventricular work was estimated as the product of aortic mean blood pressure and cardiac output.

The mean $\pm$ SEM was calculated for each variable. Significant,

within-group differences were determined with analysis of variance for repeated measurements for group 2 (β -blocked) lambs where we compared four groups of measurements, and with paired t tests for the group 1 lambs (intact β -adrenergic nervous

systems) where we compared two groups of measurements (17). When an ANOVA produced a computed *F* ratio which exceeded the critical *F* ratio at $p = 0.05$, the modified *t* test was used to identify the treatment(s) that were significantly different (18). Comparisons between group 1 and 2 lambs were made with unpaired *t* tests.

RESULTS

The administration of propranolol to normoxic group 2 lambs had no statistically significant independent effect on the arterial or coronary sinus blood gases, oxygen saturations or Hb concentrations (Table 2). Propranolol administration was associated with small but reproducible and statistically significant reductions in myocardial blood flow and myocardial oxygen consumption (Fig. 1).

The reductions in arterial PO_2 , blood oxygen saturations, and blood oxygen contents during hypoxemia were similar during all of the periods in the two groups of lambs (Table 2 and Fig. 1). Although all periods of arterial hypoxemia in both groups of lambs were partially compensated by reductions in coronary sinus blood oxygen contents, these increases in myocardial oxygen extraction were insufficient to prevent significant reductions in the arteriovenous difference of oxygen across the left ventricle (Fig. 1). Hypoxemia also produced statistically significant increases in myocardial blood flow in both groups of lambs that were greater than the reductions in the arteriovenous difference of oxygen, so that myocardial oxygen consumption increased during hypoxemia with or without β -blockade (Fig. 1). However, the increases in myocardial blood flow and oxygen consumption during hypoxemia were much less in the group 2 β -blocked lambs than in the group 1 lambs with an intact β -adrenergic nervous system (Fig. 1). This was apparent when studied at the control heart rate or during pacing induced tachycardia ($p < 0.01$ for both variables at either heart rate; Fig. 1). Myocardial oxygen consumption in the group 1 lambs increased 37.9% during hypoxemia from a control mean value of $792 \mu\text{mol}/\text{min}/100 \text{ g LV}$. In contrast, myocardial oxygen consumption increased 9.0% during hypoxemia with control heart rate pacing from a mean value of $752 \mu\text{mol}/\text{min}/100 \text{ g LV}$ after propranolol with control heart rate pacing. Therefore, β -blockade prevented 76% of the increase in myocardial oxygen consumption that occurred in the group 1 lambs with an intact β -adrenergic nervous system.

The administration of propranolol to the normoxic group 2 lambs increased LEVDP; whereas maximal dP/dt, cardiac output, and LV work decreased (Table 3). β -blockade in the group 2 lambs also prevented the increases in heart rate ($p < 0.001$), dP/dt ($p < 0.005$), cardiac output ($p < 0.01$), and cardiac work ($p < 0.01$) that occurred during hypoxemia in the group 1 lambs with an intact β -adrenergic nervous system (Table 3). In the β -blockade lambs, the addition of tachycardia to hypoxemia was associated with reduction in LEVDP and an increase in dP/dt, but there was no significant change in cardiac output or cardiac work (Table 3).

The adequacy of β -blockade was demonstrated in each lamb by measuring the chronotropic and inotropic responses to an $0.2\text{-}\mu\text{g}/\text{kg}$ bolus of intravenous isoproterenol at the end of each study. Pretreatment of group 2 lambs with $1.5 \text{ mg}/\text{kg}$ of intravenous propranolol completely prevented the tachycardia ($p < 0.001$) and the increase in the maximal dP/dt ($p < 0.005$) during isoproterenol that occurred in the group 1 lambs with an intact β -adrenergic nervous system (Table 1).

There were no significant changes in the percentage of total body radioactivity that was trapped in the lungs. In the group 1 lambs with an intact β -adrenergic nervous system, the ratio of lung to body radioactivity was $2.1 \pm 0.11\%$ during the control period and $2.2 \pm 0.14\%$ during hypoxemia. In the group 2 lambs the ratio was $1.9 \pm 0.17\%$ during the control period, $2.1 \pm 0.18\%$ after propranolol with control heart rate pacing, $1.8 \pm 0.15\%$

during hypoxemia with control heart rate pacing, and $2.0 \pm 0.12\%$ during hypoxemia with rapid atrial pacing.

DISCUSSION

Methodologic considerations. Surgery and anesthesia may have important independent effects on β -adrenergic activity as well as on the responses to several stresses (10). However, as Sidi *et al.* (19) have demonstrated previously that newborn lambs routinely achieved a full cardiovascular recovery from the effects of halothane anesthesia, thoracotomy and instrumentation by 2–3 d after surgery, the results of the present study should have been relatively free of these potentially confounding effects. Thus, we were able to isolate the role of the β -adrenergic system in modulating several of the individual determinants of myocardial oxygen consumption in a neonatal preparation.

Our model of hypoxemia in lambs *in vivo* should be distinguished from *in vitro* models of tissue hypoxia such as are produced in muscle baths. β -blockade has been shown to minimize tissue hypoxia and to inhibit myocardial creatine kinase release, intracellular calcium accumulation, the depression of mitochondrial oxygen consumption, and the increase in resting tension that occur during reduced oxygen tension in perfused mature rabbit hearts *in vitro* (20). This mechanism is unlikely to have been operative *in vivo* in the present study because we previously demonstrated that a 50% reduction in arterial blood oxygen saturation augmented myocardial oxygen consumption and function (1); there was no evidence that this level of hypoxemia produced myocardial hypoxia in our previous study or in others (1, 6, 8, 12).

Changes in derived indices of left ventricular contractile function may reflect changes in loading conditions as well as changes in contractility (21, 22). Consistent with most pre-ejection phase indices, dP/dt is relatively independent of changes in afterload but varies directly with preload (21, 22). In this regard, the changes in dP/dt that occurred in the present study should accurately reflect directional changes in contractility because simultaneous measurements of LVEDP were constant or changed in the opposite direction to changes in dP/dt (21). Thus, although directional changes in dP/dt accurately reflect directional changes in left ventricular contractility, certain cases such as the reduction in LVEDP during hypoxemia with tachycardia in the group 2 β -blockade lambs (Table 3) may indicate that the simultaneous increase in dP/dt underestimates the actual increase in contractility.

Because we used left atrial pacing for part of the present study, we wanted to make sure that the unusual activation sequence did not produce left to right shunting of blood across the atrial foramen ovale as has been demonstrated in fetal lambs *in utero* (23). If present, such shunting could have altered several of the results. However, the constant low levels of lung radioactivity after left atrial injections of microspheres in both groups of lambs in this study suggest that the atrial foramen (and the ductus arteriosus) were functionally closed and did not allow any significant left to right shunting of blood in the 5- to 9-d-old lambs that we studied. Thus, it appears that the atypical activation sequence produced by left atrial pacing did not have any independent effect on the results in this study.

β -adrenergic mediated alterations in myocardial oxygen consumption during hypoxemia. Sidi *et al.* (24) recently described the effects of β -blockade on myocardial blood flow and oxygen consumption during environmental hypoxemia in unanesthetized newborn lambs. Their data and ours agree that, compared to control conditions, β -blockade prevents most but not all of the increase in myocardial blood flow during hypoxemia. Although the percentage reductions in oxygen and the myocardial arteriovenous differences of oxygen were remarkably similar in the two studies, the results of the two studies differed in that the present study found more of a residual increase in myocardial blood flow during hypoxemia with β -blockade in the group 2

lambs. This discrepancy in the amplitude of the myocardial blood flow response resulted in another difference between the studies. There was a residual increase in myocardial oxygen consumption during hypoxemia with beta blockade in the group 2 lambs in the present study, whereas Sidi *et al.* found similar levels to control conditions.

Although it is evident that the two studies differ in the myocardial blood flow and the calculated myocardial oxygen consumption responses, the cause of this discrepancy is not clear. The only apparent difference in the protocols is that we gave three times as much propranolol as Sidi *et al.* (24). Vlahakes *et al.* (25) have demonstrated an independent β -adrenergic influence on coronary vascular tone in dogs. However, if a similar influence is operative in newborn lambs and if Sidi *et al.* had produced an incomplete β -blockade, we would have expected a greater residual increase in myocardial blood flow in the lambs in the study of Sidi *et al.* Instead, we found the opposite result and cannot relate the above mentioned discrepant results to the different doses of propranolol.

Based on data from the present study, we may estimate the contribution of augmented β -adrenergic activity to the increase in myocardial oxygen consumption that occurs during hypoxemia. There was a 37.9% mean increase in myocardial oxygen consumption during hypoxemia in the group 1 lambs. In the group 2 β -adrenergically blocked lambs, there was a 9.0% mean increase in myocardial oxygen consumption when comparing the results after propranolol administration to the results during hypoxemia with heart rate maintained at control levels. Thus, it can be estimated that β -adrenergically mediated increases in contractility, external cardiac work and heart rate (which were constant in the group 2 lambs under these conditions) appear to account for no more than 75–80% of the total increase in the myocardial oxygen consumption during hypoxemia. This should be considered as a maximal estimate of the effect of the hemodynamic alterations because increased β -adrenergic activity may also influence myocardial oxygen consumption through primary metabolic alterations that could not be estimated independently in the present study (26). A further importance of our results is in the demonstration of a residual significant increase in myocardial oxygen consumption during hypoxemia in β -blocked lambs that were free of the effects of surgical instrumentation, thoracotomy, and anesthesia (10, 19).

Previous studies in mature dogs have demonstrated that the major determinants of myocardial oxygen consumption in anesthetized mature dogs are contractility and wall stress, that external cardiac work and basal metabolism are quantitatively less important determinants, and that electrical activation accounts for less than 1% of myocardial oxygen consumption (3, 4, 27, 28, 29). Parmley and Tyberg (30) has estimated that contractility and wall stress each account for 30–40% of total myocardial oxygen consumption in the basal state whereas external cardiac work and basal metabolism each may account for 10–20%. Our results suggest that these estimates may be applicable for predicting the effects of alterations in these determinants on myocardial oxygen consumption in newborn lambs in that the β -adrenergically mediated increases in contractility and external cardiac work that occur during hypoxemia accounted for a highly significant increase in myocardial oxygen consumption (Fig. 1 and Table 3).

Considering the determinants of myocardial oxygen consumption as discussed above, it would appear that the residual increase in myocardial oxygen consumption during hypoxemia in the group 2 β -blocked lambs should have resulted from changes in wall stress or basal cellular metabolism. Our experiments were not designed to evaluate the contribution of changes in wall stress, but previous experiments in anesthetized mature dogs have demonstrated that myocardial oxygen consumption increased during hypoxemia even when wall stress was held constant (9). Thus, it appears that some of the residual increase in myocardial oxygen consumption during hypoxemia in the group

2 β -blocked lambs may have resulted from primary changes in cellular metabolism rather than from hemodynamic alterations. Previous investigations have suggested that a myocardial metabolic alteration could occur during hypoxemia through the use of alternative, less efficient, metabolic pathways that utilize the same substrates, or possibly from a shift in substrate selection (8, 31). Alternatively, the recent demonstration that adrenergically mediated alterations in myocardial lipid metabolism appear to be modulated by α - as well as β -adrenergic mechanisms may be pertinent to the present study because the use of propranolol in the lambs in this study would not have blocked an α -adrenergically mediated mechanism (26). Thus, it is possible that α -adrenergically mediated metabolic alterations were responsible for some of the residual increase in myocardial oxygen consumption in the group 2 lambs in this study. The present data do not permit an evaluation of this hypothesis.

The present study also demonstrates the dichotomy regarding the mechanism that regulates the development of tachycardia during hypoxemia and the mechanism that regulates the inotropic effect of tachycardia. The group 1 lambs with an intact β -adrenergic nervous system developed sinus tachycardia during hypoxemia whereas the group 2 β -blocked lambs had to be paced to prevent a reduction in sinus heart rate. This indicates that the tachycardia that normally develops during hypoxemia is mediated by increased β -adrenergic activity. However, our data demonstrating that contractility increased during pacing-induced tachycardia in the β -blocked lambs indicates that at least some of the inotropic effect of tachycardia is not β -adrenergically mediated (Table 3). These results are consistent with previous studies that have suggested that the inotropic effect of tachycardia is mediated by an increase in intracellular calcium concentration which occurs in association with a reduction in diastolic duration (32).

The present study demonstrates that β -adrenergically mediated increases in cardiac contractile function, work and heart rate are responsible for most but not all of the increase in myocardial oxygen consumption during hypoxemia in lambs. The factor(s) are responsible for the residual increase in myocardial oxygen consumption remain to be determined, although α -adrenergically mediated increases in basal myocardial metabolic activity remain as a distinct possibility.

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