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INFLUENCES OF HYPERCAPNIA ON CARDIAC FUNCTION IN THE NEWBORN LAMB¶

This study is affectionately dedicated to Harry Greene, who among his many interests was an enthusiastic shepherd. Although his sheep primarily represented friends, food and fertilizer, he also appreciated the contribution which this species has made to a better understanding of the first great challenge that we all must meet.

There is an abundance of evidence which suggests that hypercapnia impairs the performance of isolated heart-lung preparations, and that this is primarily consequent to diminished contractility of the myocardium.[1-7] Patterson[8] showed that the cardiac depressant effect of CO_2 could be prevented largely by the addition of epinephrine. In intact adult dogs acidosis produced by CO_2 retention causes striking stimulation of the sympathoadrenal system, manifested by large increases in circulating epinephrine and norepinephrine, as well as increased blood pressure, anuria, and elevated blood glucose levels.[9] Metabolic acidosis with similar levels of arterial pH (approximately 7.0) produced by lactic acid infusion failed to elicit these manifestations of increased sympathoadrenal activity. They appeared only after sufficient acid was given to reduce the arterial pH to less than 6.9. Circulatory failure was not evident with either respiratory or metabolic acidosis until the arterial pH fell below 6.6.[9]

It is clear from the foregoing findings that hypercapnia diminishes myocardial contractility in the isolated heart-lung preparation, presumably by producing an intracellular acidosis.[2,7,9] In animals with intact autonomic function, on the other hand, evidence for activation of the sympathoadrenal system,[9] and observations which show that the cardiac depressant effect of CO_2 may be inhibited by the infusion of catecholamines,[6,8] suggest that the intact animal may be highly resistant to respiratory acidosis. This assumption is not supported by the findings of Boniface and Brown.[1]

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The present study was designed to evaluate the effects of hypercapnia on myocardial contractility in the newborn, and to assess the contributions of the sympathoadrenal system to the preservation of cardiac function under these conditions. A preliminary report on these findings has appeared.[10]

METHODS

Sixteen term lambs varying in age from 8 hours to 11 days were studied. They were lightly anesthetized with thiopental sodium (15 mg/kg., intravenously), followed by the administration of alpha glucochloralose (30 mg/kg.) approximately 15 minutes later. Small supplemental doses of chloralose were given if necessary.

The animals were prepared for measurement of left ventricular function using a preparation similar to that previously described.[11] The trachea was intubated and a midline thoractomy was performed. The lungs were ventilated with a Harvard respiratory pump. Heparin (5 mg/kg.) was given intravenously and the descending thoracic aorta was cannulated (Fig. 1). Left ventricular output (minus coronary flow) was measured with a Shipley-Wilson rotameter. Arterial pressure could be controlled with an adjustable constant pressure reservoir. Cardiac output was altered by augmenting venous

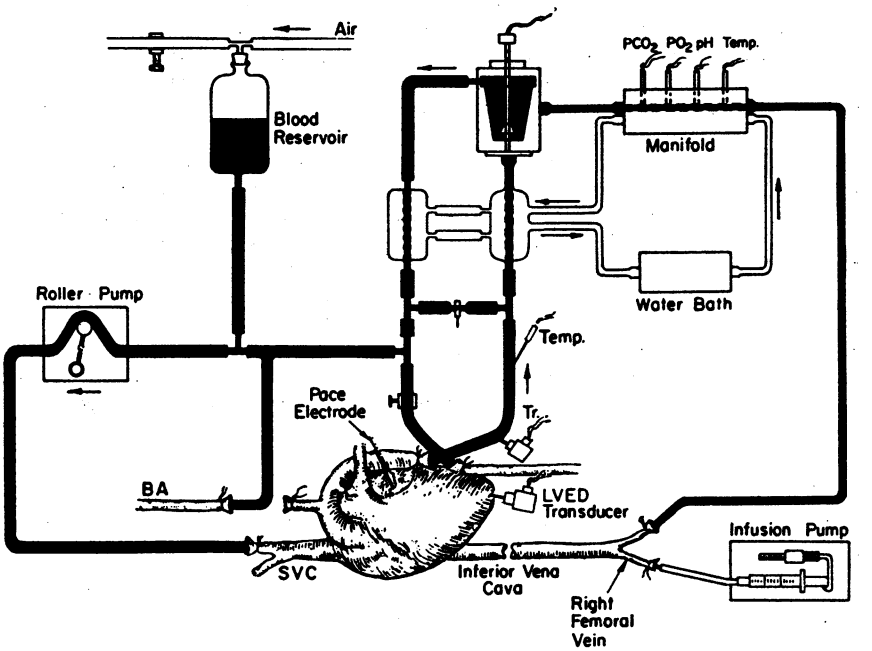

FIG. 1. Schema for measurement of ventricular performance in the lamb. Left ventricular output measured with Shipley-Wilson rotameter. TR = Sanborn transducers; TEMP. = temperature probe; MANIFOLD = Jewett flow-through electrode assembly; BA = brachiocephalic artery. Haake water bath in continuity with heat exchangers and electrode assembly to maintain thermal homeostasis. Sarns roller pump to alter venous return to the heart. Air pressurized blood reservoir for maintaining arterial pressure constant. Ductus arteriosus ligated.

return with a pump-operated arteriovenous by-pass which permitted blood to be pumped from the flowmeter circuit to the external jugular vein. In order to assure that all aortic flow was diverted through the rotameter the ductus arteriosus was ligated, and the brachiocephalic artery was ligated near its origin and separately cannulated for passive perfusion from the rotameter circuit (Fig. 1). The extracorporeal tubing, flowmeter and reservoir were primed with freshly drawn heparinized (5 mg/100 ml.) maternal sheep blood.

Pressures were measured within the aortic arch and left ventricular chamber with Sanborn transducers. The maximal rate of rise of left ventricular pressure (dP/dt max.) was computed by an RC differentiating circuit with a time delay of 0.286 msec. Blood temperature was continuously measured with a Yellow-Springs probe and telethermometer and maintained at 38 ± 1°C. by employing a suitable circulating warm water bath heat exchanger system (Fig. 1). Continuous measurements of arterial pH, P_{O_2} and P_{CO_2} as well as blood temperature were obtained from a Jewett flow-through electrode assembly, which has been described elsewhere.[13] These measurements were checked frequently with an Instrumentation Laboratories pH, P_{CO_2} and P_{O_2} system. Heart rate was maintained constant by electrical pacing of the left atrium. The pressures, heart rate, cardiac output, ventricular dP/dt and arterial P_{CO_2} were recorded on a Sanborn 358 direct writing recorder.

Arterial carbon dioxide tension was altered by the admixture of CO_2 to room air with a suitable gas mixing device and introducing this mixture into the respirator. When used in conjunction with the Jewett flow-through assembly the desired arterial P_{CO_2} values could be achieved without difficulty. To assure full oxygenation the gas mixture was usually augmented with small amounts of oxygen to maintain the arterial P_{O_2} near 100 mm Hg.

Ventricular function curves were plotted relating stroke volume and mean ejection rate to left ventricular end-diastolic pressure while mean aortic pressure and heart rate were held constant. In order to permit quantitative comparison the stroke volume, mean ejection rate, and dP/dt max. at left ventricular end-diastolic pressure of 10 cm H_2O were computed and used as indices of contractility. Myocardial responses to acute hypercapnia were studied in lambs with autonomic function intact, and in lambs subjected to beta-adrenergic blockade with propranolol (0.25 mg/kg.). Beta blockade was assumed to be adequate when the responses to isoproterenol (1 μg) injected intravenously were abolished. Selected experiments were done in two additional lambs to study the effects of acute hypercapnia during norepinephrine infusion and during hypoxia.

RESULTS

Influences of acute hypercapnia on left ventricular performance in lambs with autonomic function intact.

The results from nine tests with eight lambs who were not subjected to adrenergic blockade are tabulated in Table 1. None of the animals manifested significant reduction of cardiac performance when the arterial P_{CO_2} was increased to values as high as 100 mm Hg, with a concomitant reduction of pH to 6.88. The mean values of all measurements were slightly higher during hypercapnia. For the groups as a whole elevation of the mean P_{CO_2} from 24 (± 1.9 SE) to 75 (± 6.3 SE) mm Hg with an associated

TABLE 1. CONTROL LAMBS. RESPONSES TO ACUTE HYPERCAPNIA

Lamb	Age	SV_{10}			MER_{10}			dP/dt			P_{CO_2}			pH		
		Control	↑CO_2	Control	Control	↑CO_2	Control	Control	↑CO_2	Control	Control	↑CO_2	Control	Control	↑CO_2	Control
#1 7 kg.	11	4.70	5.00	4.60	44.0	48.2	41.0	5000	6200	7000	22	44	26	7.23	7.03	7.14
		4.54	4.54	3.52	36.0	38.6	30.8	7200	8680	6300	22	60	23	7.33	7.01	7.40
#2 5 kg.	4	3.82	3.84	2.92	35.6	36.6	27.5	3500	3400	2900	25	60	30	7.42	7.16	7.40
#3 3.7 kg.	4	3.04	3.10	3.10	23.1	25.8	24.4	5500	4370	5160	20	72	29	7.36	7.01	7.42
#4 1.8 kg.	3	2.90	2.82	2.70	17.0	18.8	16.0	2800	2740	2500	33	100	31	7.35	6.99	7.49
#5 3.1 kg.	3	2.90	3.04	2.56	25.0	23.3	21.3	3500	4000	3250	32	72	22	7.32	7.10	7.52
#11 5.4 kg.	1	5.86	5.97	5.80	31.7	33.6	29.0	3550	3360	3330	21	82	25	7.44	6.99	7.36
#13 3.8 kg.	2	4.45	4.55	4.05	30.0	32.3	27.0	3050	3300	2850	26	100	30	7.41	6.88	7.38
#14 4.6 kg.	8 hrs.	5.90	5.46	5.94	33.9	34.2	33.9	3510	3240	3300	15	84	20	7.45	6.93	7.45
Mean		4.23	4.26	3.91	30.7	32.4	27.9	4180	4370	4070	24	75	26	7.37	7.01	7.40
S.D.		1.17	1.13	1.29	8.0	8.8	7.2	1436	1900	1650	5.7	19	4	.07	.03	.10
S.E.		.39	.38	.43	2.7	2.9	2.4	479	633	550	1.9	6.3	1.3	.02	.01	.03
P		N.S.	.05<p<.1		N.S.	<.01		N.S.	N.S.		<.001	<.001		<.001	<.001	

change of pH from 7.37 (± .02 SE) to 7.01 (± .01 SE) caused no significant change in the mean values for SV_{10}, MER_{10} or dP/dt_{10}. Reduction of the arterial P_{CO_2} to near control values was followed by a small reduction in the mean values, but only the change in MER_{10} was clearly significant ($p<.01$). Thus, acute hypercapnia in lambs with intact autonomic function failed to diminish myocardial contractility. Representative ventricular function curves from a 4-day old lamb are shown in Figure 2.

Hemodynamic evidence which suggests that acute hypercapnia may produce adrenergic stimulation of the myocardium is evident from the tracings shown in Figure 3. This shows segments of record obtained at equivalent levels of cardiac output before, during, and following exposure to acute hypercapnia. With aortic pressure and heart rate held constant, elevation of the arterial P_{CO_2} from 20 to 60 mm Hg caused no change of end-diastolic

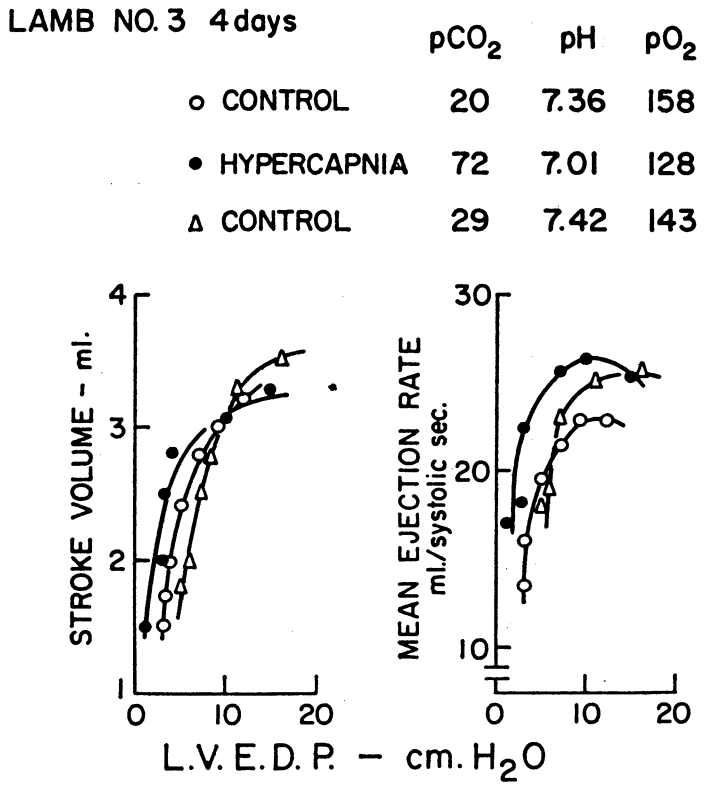

FIG. 2. Left ventricular function curves relating stroke volume and mean ejection rate to left ventricular end-diastolic pressure (LVEDP). During acute hypercapnia the curves show little change from the controls. Heart rate and mean aortic pressure constant.

pressure of the left ventricle, but there was widening of the diastolic interval, a reduction of the duration of ejection from 120 to 105 msec., and the dP/dt max. increased from 6700 to 8500 mm Hg/sec. With reduction of the P_{CO_2} from 60 to 23 mm Hg (right panel) the end-diastolic pressure rose from 8 to 14 mm Hg, the duration of ejection increased to 120 msec. and the dP/dt fell to 6,000 mm Hg/sec.

The interrelations of hypoxia and hypercapnia were studied and are illustrated by the ventricular function curves shown in Figure 4 from a lamb 4 days of age. In this animal with autonomic function intact reduction of the arterial P_{O_2} from 88 to 40 mm Hg while maintaining the P_{CO_2} at 30 mm Hg caused a shift to the left of the curves relating stroke volume and mean ejection rate to left ventricular end-diastolic pressure, indicating a positive inotropic response. When the arterial P_{O_2} was re-elevated to 140 mm Hg the ventricular function curves returned to original control positions. The P_{O_2} was then reduced to 43 mm Hg, and the P_{CO_2} increased from 38 to 90 mm Hg simultaneously. This was associated with a substantial reduction of ventricular performance, manifested by a reduction of stroke volume and

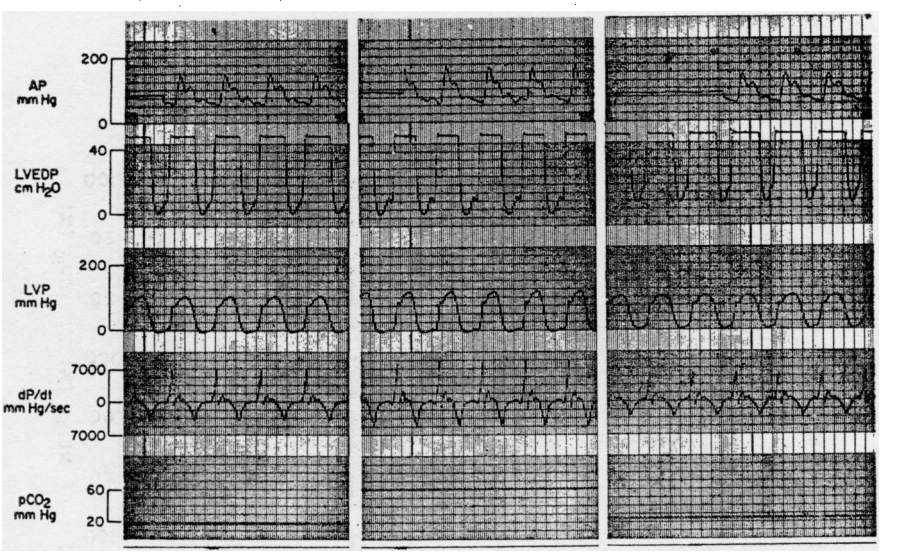

FIG. 3. Original tracing showing responses to acute hypercapnia. AP = aortic pressure; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure; dP/dt = maximal rate of rise of left ventricular pressure. Left panel—P_{CO_2} 20 mm Hg. Middle panel—P_{CO_2} 60 mm Hg. Right panel—P_{CO_2} 23 mm Hg. Positive inotropic response manifested by shortening of duration of ejection from 120 to 105 msec., widening of the diastolic interval and increase of dP/dt max. from 6700 to 8500 mm Hg/sec. (middle panel). Heart paced. Cardiac output 1100 ml/min. in all panels. Chart speed—100 mm/sec.

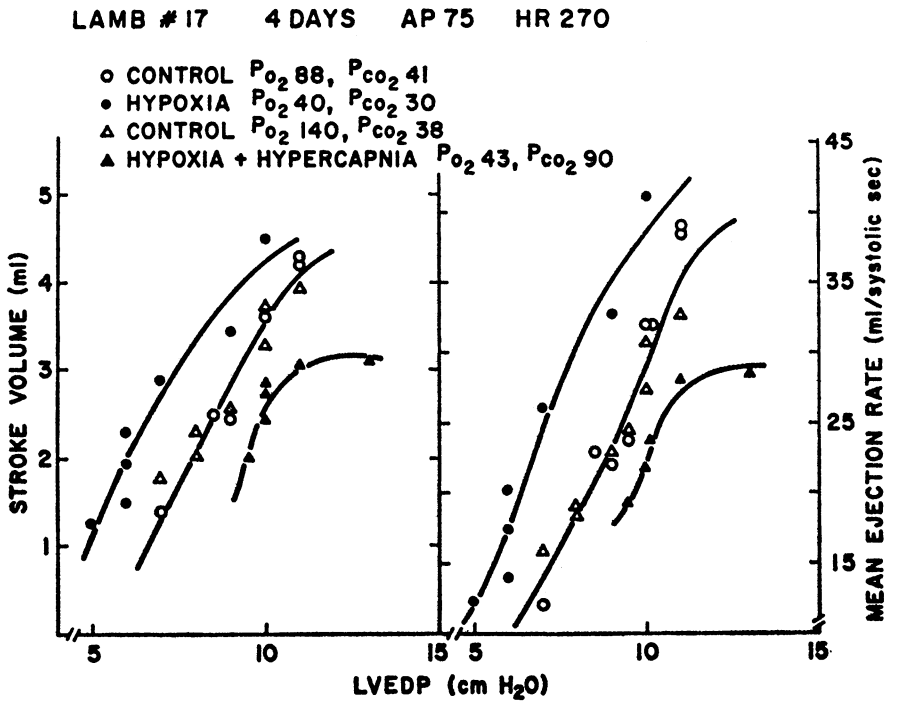

FIG. 4. Responses to hypoxia, and to combined hypoxia and hypercapnia. Aortic pressure (AP) and heart rate (HR) constant. Mild hypoxia caused a shift to the left of the curves. With essentially the same degree of hypoxia in the presence of hypercapnia the curves shifted to the right. See text for further discussion.

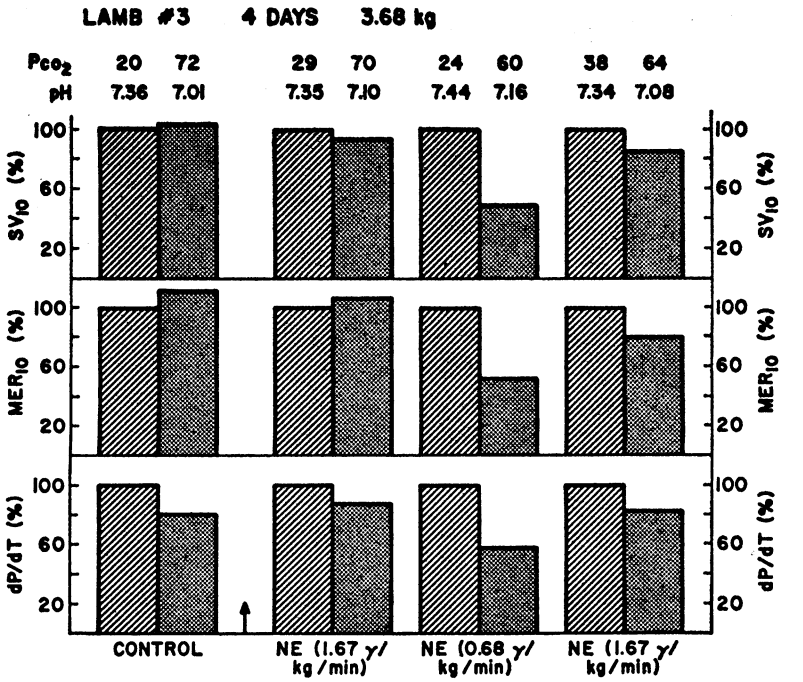

FIG. 5. Responses to acute hypercapnia early in the experiment (control) and during exogenous infusion of norepinephrine (NE) in differing amounts following failure of nervous system function (arrow). SV_{10} = stroke volume, MER_{10} = mean ejection rate and dP/dt_{10} = maximal rate of rise of ventricular pressure at left ventricular end-diastolic pressure 10 cm H_2O.

mean ejection rate for a given left ventricular end-diastolic pressure. Thus, hypercapnia in a reflexic animal, which might be expected to cause no reduction of ventricular performance with full oxygenation, produced substantial depression of contractility with concomitant hypoxemia.

Further evidence that depression of cardiac function during acute hypercapnia may be prevented by beta-adrenergic stimulation was obtained from the experiment shown in Figure 5. In this lamb with autonomic function intact elevation of the P_{CO_2} to 72 mm Hg (pH 7.01) caused little change of SV_{10} or MER_{10} and a slight reduction of dP/dt max. Sometime later in the experiment evidence for loss or depression of nervous system function appeared, which was manifested by loss of the eyelid reflex, reduction of the intrinsic heart rate from 260 to 200/minute, loss of the respiratory response to hypercapnia and the appearance of cardiac depression on exposure to elevated arterial P_{CO_2}. An infusion of norepinephrine (1.67 μg/kg/min.) was begun. During this infusion hypercapnia (P_{CO_2} 70 mm Hg, pH 7.10) failed to produce cardiac depression, and the performance values were virtually identical to the initial control values. The norepinephrine infusion rate was then reduced to 0.68 μg/kg/min. and the response to hypercapnia again tested. This caused severe depression of all the measurements of left ventricular performance. The rate of norepinephrine infusion was again returned to 1.67 μg/kg/min., and the reduction of cardiac performance on exposure to hypercapnia was substantially less.

Responses to acute hypercapnia following beta-adrenergic blockade.

Six lambs, 1½ to five days of age, were subjected to beta-receptor blockade with propranolol and the responses to acute hypercapnia were studied in 13 tests. Ventricular function curves from a representative animal are shown in Figure 6. Elevation of the arterial P_{CO_2} from 22 to 66 mm Hg caused a downward shift of the curves relating stroke volume and mean ejection to left ventricular end-diastolic pressure. When the P_{CO_2} was subsequently reduced to 32 mm Hg there was partial return of the curves toward the original control position.

The findings for the group are summarized in Table 2. Elevation of the mean P_{CO_2} from 24 (± 1.4 SE) to 73 (± 4.3 SE) mm Hg caused a highly significant reduction of SV_{10} ($p<.001$) and MER_{10} ($p<.01$). The dP/dt max. was not significantly different, however. While there was some tendency for improvement of ventricular performance when the P_{CO_2} was reduced to control values, this was variable, and in many tests there was little improvement or further deterioration (Table 2). Additional recovery was not observed in subsequent control curves.

TABLE 2. RESPONSES TO HYPERCAPNIA FOLLOWING BETA-ADRENERGIC BLOCKADE.

		SV_{10}			MER_{10}			dP/dt_{10}			P_{CO_2}			pH		
Lamb	*Age*	*Control*	*↑CO₂*	*Control*	*Control*	*↑CO₂*	*Control*	*Control*	*↑CO₂*	*Control*	*Control*	*↑CO₂*	*Control*	*Control*	*↑CO₂*	*Control*
#8	5	4.43	3.88	4.32	31.6	29.8	31.2	850	950	1040	24	75	29	7.39	7.06	7.41
6 kg.		3.04	1.34	1.47	21.7	10.1	11.3	700	500	570	34	64	34	7.36	7.18	7.39
		1.80	0.75	1.00	11.0	5.0	7.0	710	700	580	27	45	22	7.41	7.23	7.42
#9	1½	5.48	4.90	5.26	31.5	30.5	33.1	2740	3200	3000	21	66	27	7.39	7.14	7.38
4.5 kg.		5.26	4.26	4.72	33.1	29.9	32.0	3000	2900	3240	27	70	28	7.38	7.04	7.38
		3.78	2.20	2.10	27.9	16.0	16.8	1800	1220	1190	28	56	23	7.36	7.18	7.47
#10	5	4.65	4.10	4.33	29.1	27.3	28.9	2110	2180	2970	27	91	24	7.43	7.07	7.43
4.35 kg.		4.71	2.19	3.13	36.2	16.8	22.4	2970	2420	2660	20	100	26	7.48	6.99	7.35
		2.95	2.05	2.22	22.4	17.7	14.5	3130	1720	1500	18	94	24	7.48	7.02	7.45
#15	5	3.28	2.65	2.88	18.5	14.6	16.4	2630	1930	2540	22	66	32	7.43	7.10	7.36
3.5 kg.		3.38	3.02	2.65	18.6	17.4	13.9	2390	2320	2462	29	81	30	7.36	7.06	7.41
#19	2	5.23	4.05	2.43	26.2	20.5	12.7	2900	2000	1400	16	75	21	7.55	7.04	7.41
5.0 kg.																
#20	4	3.00	2.25	3.95	19.0	15.0	26.0	3370	3370	3560	23	67	23	7.20	7.14	7.35
3.5 kg.																
Mean		3.92	2.90	3.11	25.1	19.3	20.5	2254	1955	2055	24	73	26	7.40	7.10	7.40
S.D.		1.08	1.21	1.26	7.0	7.7	8.5	951	919	1043	5	15.4	4	.06	.07	.04
S.E.		.30	.33	.35	1.9	2.1	2.4	246	255	290	1.4	4.3	1.1	.02	.02	.01
P		<.001		>.2	<.01		>.2	>.9		>.9	<.001		<.001	<.001		<.001

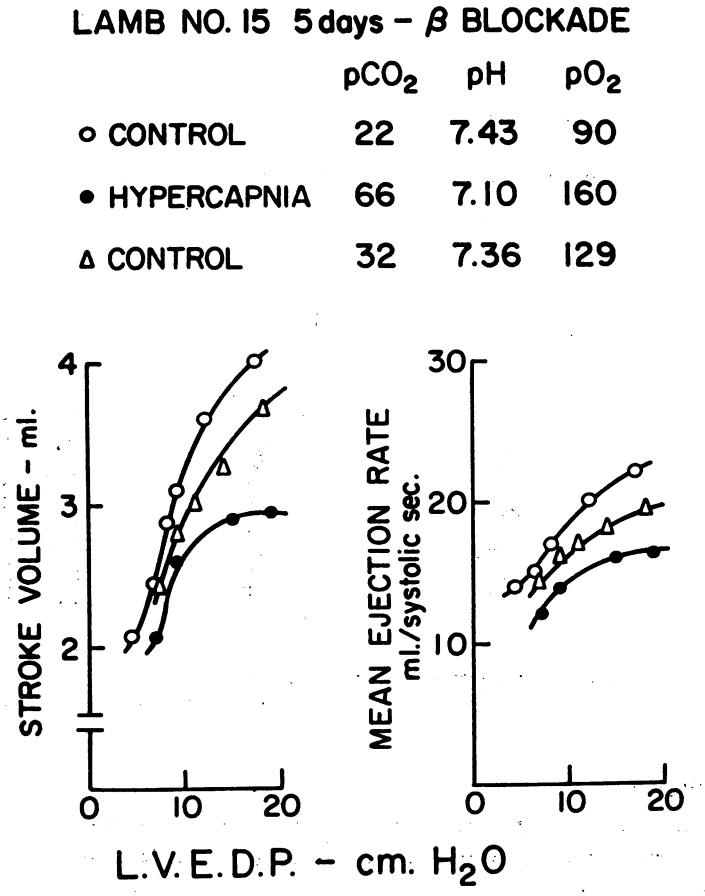

FIG. 6. Left ventricular function curves relating stroke volume and mean ejection rate to left ventricular end-diastolic pressure (LVEDP) following beta blockade with propranolol. During acute hypercapnia the curves are shifted to the right. Reduction of P_{CO_2} followed by partial return of curves to original control position.

The influences of hypercapnia on ventricular performance before and following beta-adrenergic blockade may be summarized in terms of percent change (Fig. 7). With autonomic function intact elevation of the arterial P_{CO_2} from 24 mm Hg (pH 7.39) to 75 mm Hg (pH 7.03) caused no significant change in any of the parameters of ventricular performance. The SV_{10} was 101%, the MER_{10} 106% and the dP/dt_{10} 104% of initial control values. With comparable hypercapnia in beta-blockaded animals the SV_{10} fell to 74%, the MER_{10} to 71% and the dP/dt_{10} to 87%. The differences between the two groups were significant for all of the three measurements of left ventricular performance.

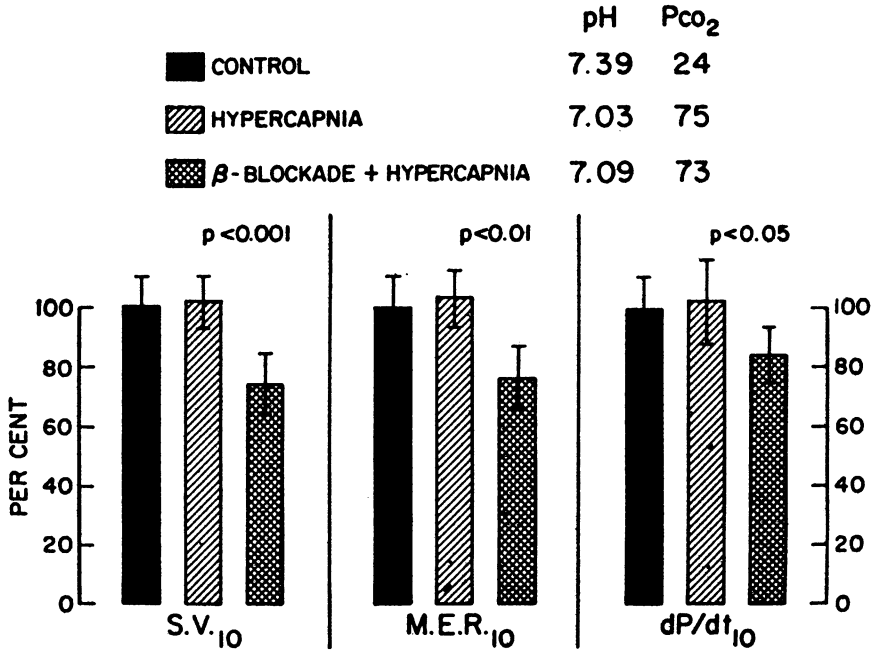

FIG. 7. Summary of responses to hypercapnia before and following beta blockade with propranolol in terms of percent of control values. Symbols same as Figure 5.

DISCUSSION

It may be concluded from this study that in the presence of a functioning sympathetic nervous system acute respiratory acidosis with arterial P_{CO_2} values up to 100 mm Hg does not cause significant depression of left ventricular performance in newborn lambs as early as eight hours following birth. If the lambs are first subjected to beta-receptor blockade with propranolol they behave much as isolated heart preparations,[8] and equivalent levels of hypercapnia consistently diminish myocardial contractility (Fig. 6). This is of interest not only because it demonstrates that the intrinsic effect of acute hypercapnia on the myocardium is to reduce its contractility, but in addition it suggests that the sympathoadrenal system is sufficiently developed in the early neonatal period to compensate for the intrinsic negative effects of this degree of hypercapnia.

It is likely that myocardial depression during hypercapnia in the isolated heart-lung preparation is consequent to the development of intracellular acidosis,[3,4,7] and this may be attributed to the fact that the cell membrane of cardiac muscle is freely permeable to CO_2.[7,18] Presumably the same

mechanism is responsible for diminished myocardial contractility observed during hypercapnia in lambs with beta blockade.

Although adrenergic support during acute hypercapnia in the range of 75 to 100 mm Hg is usually sufficient to counter the intrinsic myocardial depressant effect of hypercapnia with adequate oxygenation, if the oxygen tension is low, acute hypercapnia may produce a substantial reduction of contractility (Fig. 4). These findings are consistent with those previously reported with the adult cat.[14] The most reasonable interpretation of these observations is that a moderate lack of oxygen may reflexly increase sympathetic activity while causing minimal intrinsic depression of contractile element function.[15] The net result is often an improvement in cardiac contractility,[16] and this is demonstrated in Figure 4. If, however, moderate hypoxia is accompanied by a significant intracellular acidosis, beta-receptor stimulation is inadequate to compensate for the combined intrinsic depressant effect, and cardiac function is reduced.

The possibility must also be considered that respiratory acidosis reduces the effectiveness of catecholamines to produce myocardial stimulation, whether released from nerve endings or from the adrenal glands.[17] It has been shown that lactic acidemia fails to diminish myocardial responsiveness to post-ganglionic sympathetic nerve stimulation in the adult dog[18] or the newborn lamb.[19] Previous studies have demonstrated no reduction of myocardial responsiveness to infused norepinephrine during lactic acidosis.[20] The suggestion that acidosis produced by hypercapnia may differ in this regard is supported by the observation that cardiac responses to efferent vagal stimulation during respiratory acidosis are enhanced, while those during equivalent acidosis produced by lactic acid infusion are unchanged.[21] Similar studies with sympathetic stimulation have shown no differences, however.[18] From these considerations it is unlikely that hypercapnia interferes significantly with the cardiac actions of norepinephrine.

Developmental changes in myocardial sympathetic innervation during the first few days following birth have been described in the newborn rabbit,[22] and the lamb (Friedman, *et al.*, unpublished observations); but in the calf this process is complete at the time of birth.[23] The morphological and biochemical changes in the lamb do not correlate with differences in myocardial responsiveness to reflex stimulation,[11] or to electrical stimulation of post-ganglionic sympathetic fibers.[19] It appears that cardiac sympathetic nerve function is well developed in this species at birth.

Although it has not been established whether neural or humoral mechanisms provide the predominant efferent adrenergic pathway in acute hypercapnia, it seems less likely that the latter is the major factor. The amount of norepinephrine that must enter the circulation to compensate for loss of

neural activity during hypercapnia (P_{CO_2} 75-100 mm Hg) appears to be on the order of 1 to 2 μg/kg/min. (Fig. 5). The data of Nahas and coworkers[24] from adult dogs suggest that the quantity of catecholamine (primarily epinephrine) which might be expected to be released from the adrenal glands under these conditions is much less than 1 μg/kg/min. Similar measurements in the lamb are not presently available, however.

Earlier studies in the adult cat have shown that cardiac sympathetic nerve discharge is enhanced during hypercapnia, and that this persists following peripheral chemoreceptor denervation.[25] Additional studies indicate that these responses probably take origin in the central nervous system.[26] There is evidence also that hypercapnia may directly stimulate sympathetic ganglia and perhaps other neural structures.[27,28] Applicability of these findings to the newborn lamb is not established, but it appears likely that adrenergic stimulation of the myocardium during hypercapnia is largely by neural pathways.[11,19]

SUMMARY

The influence of acute respiratory acidosis on left ventricular performance was studied in 16 lambs, 8 hours to 11 days of age. In eight control lambs, elevation of the arterial P_{CO_2} from 24 (pH 7.37) to 75 (pH 7.01) mm Hg was associated with no change of stroke volume (SV_{10}), mean ejection rate (MER_{10}), or dP/dt max (dP/dt_{10}) at a left ventricular end-diastolic pressure of 10 cm H_2O. These values were obtained under conditions of constant heart rate and aortic pressure, and indicate no change of myocardial contractility. Combined hypoxia and hypercapnia caused depression of cardiac performance. In six lambs subjected to beta-adrenergic blockade with propranolol, elevation of the P_{CO_2} from 24 (pH 7.40) to 73 (pH 7.10) mm Hg caused a highly significant reduction of SV_{10} ($p<.001$) and of MER_{10} ($p<.01$), and a less significant fall of dP/dt_{10} ($p<.05$). Following reduction of the P_{CO_2} to 26 mm Hg (pH 7.40) ventricular function remained depressed in most experiments. Continuous infusion of norepinephrine (NE) (1.67 μg/kg/min.) was sufficient to prevent cardiac depression in the absence of sympathoadrenal function. With lesser amounts (.68 μg/kg/min.) of NE there was depression of left ventricular performance during equivalent acute hypercapnia. It is concluded that sympathoadrenal function is sufficiently developed near the time of birth to largely compensate for the intrinsic negative inotropic effects of acute hypercapnia up to approximately 100 mm Hg P_{CO_2}.

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