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Effects of Hypercapnia on Myocardial Contractility in Piglets[1] (41754)

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Abstract. The effects of acute hypercapnia on cardiac contractility and their dependence on adrenergic pathways were studied in 27 piglets anesthetized with pentobarbital (30 mg/kg, ip). Aortic pressures and flow, and heart rate were held constant; atropine was used to produce parasympathetic blockade. Hypercapnia was achieved by addition of CO_2 to the respirator. In the control group ($N = 7$) the first derivative of left ventricular (LV) pressure (dP/dt_{max}) increased significantly following induction of severe hypercapnia ($P_aCO_2 > 80$ mm Hg; pH < 7.00). There were no significant changes in LV end diastolic pressure. The magnitude of the positive inotropic responses was unaltered by ganglionic blockade with tetraethylammonium chloride (100 mg) ($N = 5$). In contrast, no change in LV dP/dt_{max} was observed during hypercapnia in piglets ($N = 15$) subjected to β-adrenoreceptor blockade with practolol (4 mg/kg). Our findings indicate that the increased cardiac contractility during acute severe hypercapnia is not dependent upon the integrity of the neural reflex system. Rather, it is due to adrenal release of catecholamines into the circulation. These animals are highly resistant to the intrinsic cardiac depressant action of hypercapnic acidosis.

Contractile performance of the heart during acute hypercapnia has been studied in several models. It is clear that severe hypercapnia diminishes the contractility of isolated heart preparations (1–4). This negative inotropic effect is reduced by infusion of catecholamines (5). Accordingly, in intact animal preparations severe hypercapnia activates the sympathoadrenal system (5, 6), and this largely compensates for the intrinsic depressant action on the myocardium (7, 8). Stimulation of cardiac adrenergic receptors may be consequent to release of transmitter from sympathetic nerve endings in myocardium, to endogenous catecholamines, or secondary to increased concentrations of circulating catecholamines. The latter may result from reflexly induced release from the adrenal medulla and peripheral adrenergic nerve endings, or by direct action of CO_2 or H^+ on these tissues (5, 6, 9). The relative importance of direct activation of the sympathoadrenal system during hypercapnia, as contrasted with reflexly mediated activity, is not fully resolved.

It has been shown that the maximal capacity for sympathetic regulation during stress is not completely reached at the time of birth, and undergoes further development postnatally (10, 11). Gootman *et al.* (11) have found that the pressor response of piglets to diencephalic electrical stimulation is sharply diminished or absent during hypercapnia, in contrast with adults. No differences were observed during normocapnia. This suggests that centrally mediated adrenergic support of the heart during hypercapnia may be limited in the neonate. The present investigation was designed to test the hypothesis that autonomic neural pathways are less important than circulating catecholamines for sympathetic stimulation of the neonatal heart during exposure to hypercapnic stress.

Methods. Studies were carried out in 27 piglets of mixed breed and both sexes. They varied in age from 10 to 65 days. Each animal was anesthetized with sodium pentobarbital (30 mg/kg, ip). The preparation has been described in detail elsewhere (12). In brief, the trachea was exposed and intubated. The chest was opened in the midline and ventilation was maintained with a Harvard constant-volume, positive-pressure respiratory pump. The ductus arteriosus was ligated and heparin (1000 Units) was given intravenously to prevent clotting in the recording catheters and extracorporeal system. The thoracic aorta was

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cannulated and cardiac output was measured with a Biotronex extracorporeal transducer and electromagnetic flowmeter system. Aortic flow was then passed through a heat exchanger and returned to the descending aorta and the brachiocephalic artery. Rectal temperature was maintained at 37 ± 1°C. The left subclavian artery was ligated. Systemic flow and aortic pressure were controlled by a roller pump and an adjustable constant pressure reservoir in the extracorporeal circuit, respectively (Fig. 1). The extracorporeal system was primed with freshly drawn heparinized (600 units/100 ml) donor blood.

A 15-gauge needle was passed through the apex into the left ventricular cavity and used to obtain pressure traces. Full ventricular and high-gain diastolic pressure traces were recorded. Aortic and ventricular pressure measurements were made with Sanborn transducers, using the midlevel of the heart as zero reference. The first derivative of LV pressure (dP/dt_{max}) was obtained by a differentiating circuit incorporated in the carrier preamplifier. Cardiac frequency was controlled by electrically pacing the left atrium with a Grass SD-5 stimulator, set 5–10% faster than the intrinsic rate. The pressures, aortic flow, heart rate, and LV dP/dt measurements were recorded simultaneously on a multichannel oscilloscope (Hewlett-Packard 7758B System) at chart speeds of 0.5 or 100 mm/s.

All animals were given atropine (1 mg, iv) to obviate possible reflex changes in ventricular contractility due to parasympathetic interaction (13). Ganglionic blockade was produced by giving 100 mg tetraethylammonium chloride (TEAC), iv. β-Adrenoreceptor blockade was achieved by administration of practolol (4 mg/kg, iv). This dose completely eliminated the positive inotropic responses to a 0.5-μg/kg, iv bolus of norepinephrine.

Hypercapnia was produced by admixing room air with CO_2 and O_2 using a Simet gas mixing device. This mixture was introduced into the respirator to yield the desired level of P_aCO_2. Steady-state equilibrium was achieved within about 2 min.

Arterial blood samples were obtained for measurement of blood gases and pH (Instrumentation Laboratories system) at appropriate intervals. All data were analyzed by standard

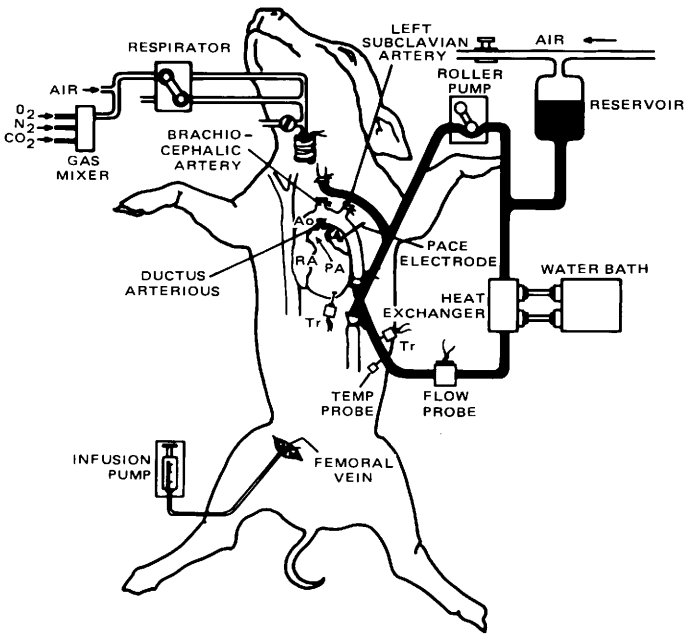

FIG. 1. Schematic representation of open-chest preparation for control and measurement of left ventricular performance in the piglet. Ductus arteriosus and left subclavian artery were ligated. AO, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium; TR, transducer. See text for detailed description.

statistical methods (14), and differences were considered significant at $P < 0.05$.

Results. Original traces from a representative experiment are shown in Fig. 2 and illustrate changes in cardiac dynamics before and 15 min following introduction of high CO_2. With arterial PO_2 in the normal physiological range, increasing arterial PCO_2 from 23 (Fig. 2A) to 83 mm Hg (Fig. 2B) resulted in a concomitant reduction of arterial pH from 7.43 to 7.00. This elicited a large increase of cardiac adrenergic stimulation, as indicated by a doubling of LV dP/dt_{max}, widening of the diastolic interval, and a reduction in left ventricular end diastolic pressure (LVEDP). It should be noted that heart rate, aortic pressure and flow were held constant throughout this and all experiments to be reported.

Arterial pH, PO_2, and PCO_2 values obtained at specified time intervals from animals in the four experimental groups are listed in Table I. After 5 min of exposure to high CO_2, all piglets developed severe hypercapnia and acidosis. These conditions remained relatively stable throughout each experiment. Changes in left ventricular contractile performance in the four groups are summarized in Fig. 3. Average changes in LV dP/dt_{max} are expressed as percent of pre-hypercapnia control values. Average initial values for LV dP/dt_{max} and

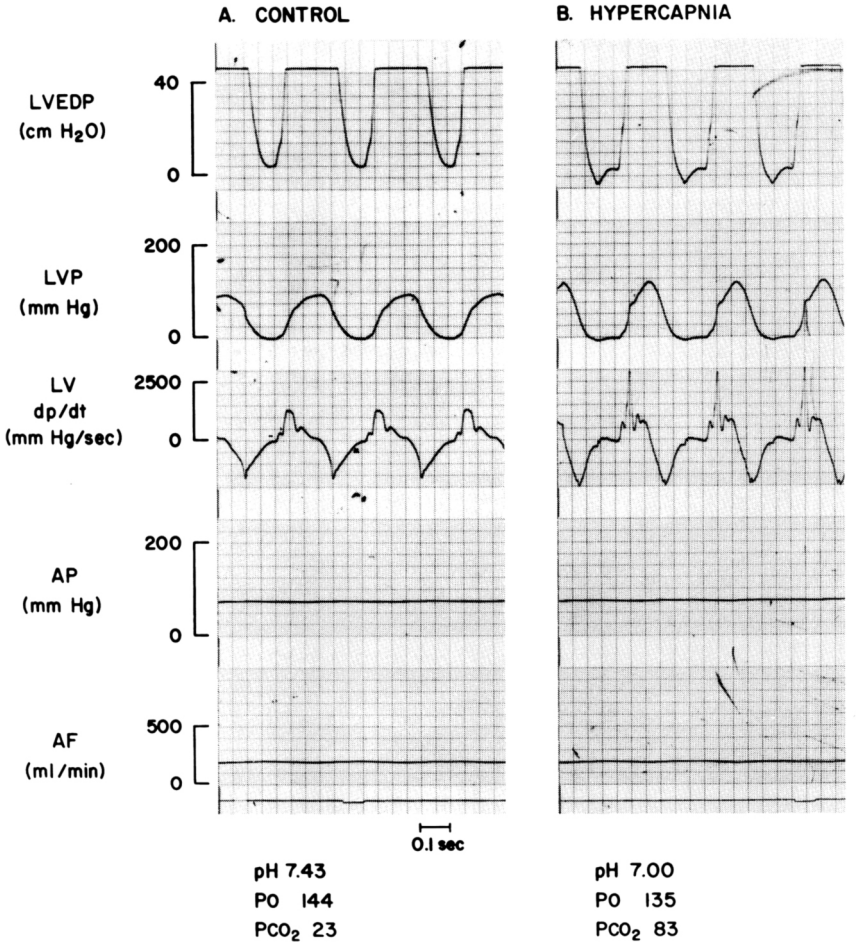

FIG. 2. Original traces from a 2-week old piglet (No. 801; body wt 4.1 kg) obtained following parasympathetic blockade with atropine. Fifteen minutes after initiation of hypercapnia (B) there was a large increase in LV dP/dt_{max} and reduction in left ventricular end diastolic pressure (LVEDP). Heart rate, aortic pressure (AP) and flow (AF) were kept constant.

TABLE I. ARTERIAL pH, PO_2 AND PCO_2 VALUES DURING CONTROL AND HYPERCAPNIA

Groups	N	C	Hypercapnia (min) 5	10	15	20	25	30
A. pH (units)								
Control	7	7.38 ± 0.04	6.97 ± 0.02	6.92 ± 0.03	6.91 ± 0.02	6.91 ± 0.02	6.92 ± 0.01	6.92 ± 0.02
Ganglionic blockade	5	7.39 ± 0.04	6.90 ± 0.03	6.92 ± 0.03	6.89 ± 0.03	6.87 ± 0.01	6.88 ± 0.03	6.86 ± 0.03
β-blockade	9	7.35 ± 0.02	7.00 ± 0.05	6.96 ± 0.05	6.92 ± 0.04	6.90 ± 0.04	6.91 ± 0.04	6.92 ± 0.04
Ganglionic + β-blockade	6	7.47 ± 0.02	6.96 ± 0.04	6.91 ± 0.02	6.90 ± 0.02	6.88 ± 0.02	6.87 ± 0.02	6.87 ± 0.02
B. PO_2 (mm Hg)								
Control	7	144 ± 17	171 ± 17	170 ± 16	170 ± 17	168 ± 16	169 ± 16	169 ± 16
Ganglionic blockade	5	193 ± 24	182 ± 12	178 ± 13	178 ± 12	191 ± 16	195 ± 21	184 ± 16
β-blockade	9	131 ± 14	199 ± 30	211 ± 36	192 ± 30	190 ± 32	188 ± 33	188 ± 30
Ganglionic + β-blockade	6	186 ± 19	182 ± 17	181 ± 14	193 ± 15	186 ± 12	175 ± 13	164 ± 9
C. PCO_2 (mm Hg)								
Control	7	22 ± 1	79 ± 4	85 ± 4	90 ± 3	89 ± 2	87 ± 3	86 ± 3
Ganglionic blockade	5	24 ± 1	100 ± 5	98 ± 7	99 ± 9	105 ± 6	110 ± 7	110 ± 6
β-blockade	9	24 ± 2	77 ± 8	83 ± 5	81 ± 4	85 ± 5	84 ± 6	84 ± 5
Ganglionic + β-blockade	6	22 ± 2	96 ± 6	107 ± 6	117 ± 9	127 ± 8	121 ± 7	120 ± 7

Note. Values are means ± standard error of means. *N* = Number of animals. C = Control.

LVEDP in the control group were 2420 ± 181 (SE) mm Hg/sec and 4.0 ± 0.6cm H_2O, respectively. After 5 min of exposure to CO_2, LV dP/dt_{max} increased to 146.9 ± 14.4% of pre-hypercapnia values ($P < 0.001$). These values remained elevated, averaging 161.8 ± 12.4% of control at 15 min, and 147 ± 10.3% at 30 min. LVEDP did not change significantly during hypercapnia in this or the remaining three groups.

Ganglionic blockade with TEAC was employed to assess the effects of hypercapnia on reflexly mediated activation of the sympathoadrenal system. Mean control values for LV dP/dt_{max} and LVEDP following blockade were 1811 ± 89.7 mm Hg/sec and 3.4 ± 0.5 cm H_2O, respectively. Although measurements of LV dP/dt_{max} in animals given TEAC were significantly lower than in the control group ($P < 0.05$), the responses to hypercapnia did not differ. Within 10 min LV dP/dt_{max} rose to 162.9 ± 11.3% of pre-hypercapnia levels ($P < 0.001$). This elevation persisted for the full 30 min (Fig. 3).

In contrast with the two previous groups, there was no significant increase in LV dP/dt_{max} in animals with β-adrenoreceptor blockade following practolol (4 mg/kg). Similarly, β-blockade abolished the CO_2-induced positive inotropic responses in animals previously subjected to ganglionic blockade.

Discussion. The effects of hypercapnic acidosis on cardiac function differ depending on whether isolated or intact preparation are studied. It is clear from the present investigation that in the adrenergically intact piglet acute severe hypercapnia leads to substantial inotropic stimulation of the heart. This response is not altered by ganglionic blockade with TEAC, but is completely eliminated by β-adrenoreceptor blockade with practolol. Thus, direct adrenal catecholamine release is dominant in mediating the observed cardiac responses in these neonates. This conclusion is consistent with our recent hypoxia studies in the same species. We found that increased cardiac stimulation during hypoxia is dependent on the integrity of the adrenal glands, and there is minimal contribution from cardiac sympathetic neural activity (12).

It is well established in the literature that hypercapnia causes increased secretion of catecholamines from the adrenal glands (5, 6).

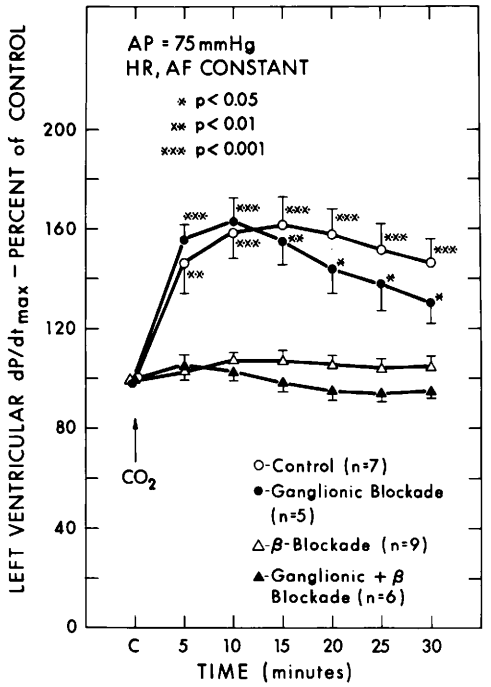

FIG. 3. Effects of hypercapnia on left ventricular dP/dt_{max}. Data expressed as percentage of values prior to initiation of hypercapnia. Vertical brackets, SEM. Heart rate (HR), aortic pressure (AP), and aortic flow (AF) constant.

Direct release of catecholamines has been reported to occur only when the blood pH falls below 6.8 (15, 16). However, Nahas *et al.* (17) have demonstrated increases in circulating plasma epinephrine and norepinephrine at arterial pH values of 6.9–7.1 and arterial PCO_2 levels between 96 and 103 mm Hg. These latter observations are consistent with our findings in the piglet (Table I and Fig. 3). These workers also found that there was no increase in catecholamine concentrations if the arterial blood pH of the animal was held in the normal range during hypercapnia using Tris buffer (18). The isolated perfused dog adrenal gland studies of Nahas and his associates (9, 19) suggest that H^+ is probably the dominant stimulus for adrenal medullary secretion rather than a direct effect of CO_2. At a pH of 6.81, the same increase in adrenal catecholamine output was produced when the arterial PCO_2 was either 34 or 150 mm Hg.

Although the main source of catecholamine secretion during hypercapnia is from the adrenal medulla, extraadrenal sites (such as sympathetic nerve endings) may also be involved (20). Goldman and Harrison (21) have demonstrated in rats that severe hypercapnia causes increased release of endogenous norepinephrine from the heart in both adrenalectomized and nonadrenalectomized animals. This augmented release of myocardial norepinephrine stores is engendered by both direct and reflexly mediated effects.

Electroneurographic recording techniques have shown a pronounced increase of cardiac sympathetic activity during hypercapnia in adult cats (22) and this persists following peripheral chemoreceptor denervation. Additional studies in adult dogs indicate that these responses probably take origin in the central nervous system (23). However, these findings do not apply to the neonatal piglet because ganglionic blockade failed to abolish the CO_2-induced positive inotropic responses (Fig. 3). It appears that there is minimal contribution from reflexly mediated sympathoadrenal stimulation during hypercapnia in this model. The increase in contractility is likely due to release of catecholamines from the adrenal glands into the blood stream, probably mediated by the action of H^+ on the medulla.

It may be concluded that adrenergic function is sufficiently developed in piglets of this age to produce vigorous responses to severe hypercapnic stress. Moreover, these hearts are remarkably tolerant to direct effects of respiratory acidosis. With comparable levels of hypercapnia, cardiac contractility in the β-blocked animals was not depressed from the control state. We have made similar observations in newborn lambs (7). These are also consistent with earlier studies with neonates which showed that metabolic acidosis does not reduce ventricular contractility, whereas the combination of acidosis and hypoxemia causes substantial depression (24, 25). This is in contrast with adult dogs in which elevation of arterial PCO_2 following β-blockade markedly depresses the maximum rate of rise of left ventricular pressure, and there is a concomitant increase in left ventricular end-diastolic pressure (26). Hypercapnic acidosis also diminishes ventricular force generation, as judged by a decline in LV systolic pressure (4), and this was attributed largely to elevated hydrogen ion concentrations. Thus, the neo-

natal heart appears to have much more resistance to high PCO_2. The basis for this phenomenon is not yet established.

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