Cardiac Output and Postganglionic Sympathetic Activity during Acute Respiratory Alkalosis

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The effects of acute respiratory alkalosis on the cardiovascular system (particularly cardiac output) and spontaneous activity of postganglionic sympathetic nerves in anesthetized dogs has been examined. Fifteen experiments were performd on ten dogs. Reducing mean Pa_{CO_2} from 39.7 to 18.3 mm Hg without changing ventilation decreased both stroke volume and cardiac output ($P < 0.05$). Simultaneously with reduction in cardiac output, spontaneous postganglionic activity diminished. Alterations in cardiac output and postganglionic activity were reversed when the animal was returned to normocapnia. The authors conclude that a reduction in sympathetic nervous system activity contributes to the reduction of cardiac output observed during respiratory alkalosis.

RESPIRATORY ALKALOSIS is frequently encountered in modern anesthetic practice. Intentional hyperventilation during intracranial surgery and mechanical ventilation of postoperative patients are two potential sources of respiratory alkalosis. Further, to circumvent the possibility of respiratory acidosis, many patients are hyperventilated during surgery, especially in the presence of muscle relaxants and controlled ventilation.

The effect of respiratory alkalosis on cardiac output is still controversial, although Dale[1] published experimental evidence relative to this state almost half a century ago! He concluded that respiratory alkalosis resulted in decreases in blood pressure and cardiac output. Recently, some investigators[2, 3, 4, 5] have found cardiovascular effects associated with respiratory alkalosis that confirm Dale's earlier findings, while others[6, 7] have observed no significant change. Even when respiratory alkalosis is accepted as responsible for cardiovascular alteration, the role of the sympathetic nervous system has not been determined. The purpose of this study was to investigate the effect of respiratory alkalosis on cardiac output, while simultaneously monitoring spontaneous postganglionic activity of sympathetic nerves.

Methods

Ten unpremedicated mongrel dogs (weighing 10–15 kg) were used. Following induction with intravenous sodium thiopental (Pentothal) (15–20 mg/kg) and tracheal intubation, anesthesia was maintained with nitrous oxide and oxygen (4:1). The lungs were mechanically ventilated with a Starling pump through a Fink nonrebreathing valve. To prevent movement, decamethonium iodide (Syncurine), 3–4 mg, was injected intravenously and repeated as required.

A catheter was placed in the endotracheal tube to measure alternately end-tidal carbon dioxide concentration and intratracheal pressure. Through catheters (polyethylene tubing #240) placed in the arch of the aorta via the femoral artery and in the right atrium via the right jugular vein, pressures were measured with Statham pressure transducers and recorded on a Grass Model 5-B polygraph. The catheters were also used to inject drugs and dye and to sample blood. A Yellow Springs Tele-Thermometer monitored esophageal temperature, maintained at 38 ± 0.5 C by using a warming–cooling blanket.

The celiac ganglion was exposed, utilizing a left flank retroperitoneal approach, and a postganglionic fiber was placed carefully on bipolar platinum electrodes and covered with

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paraffin oil. Nerve activity was transmitted from the electrodes to a Grass Dual P 9 AC preamplifier. The amplified signal was displayed on a Tektronix type 565 dual-beam oscilloscope with a 2 A 61 differential amplifier. A Grass kymographic camera was used to photograph the action potentials, and semiquantitation of electrical activity was accomplished by integrating the nerve action potential with a Grass 5 P 3 EMC (0.2-sec time constant) integrator preamplifier, to give a cumulative tracing indicative of total activity. In eight experiments, data for statistical evaluation of changes in sympathetic activity were collected planimetrically from the area described by the recorded integration of nerve action potentials. These were subjected to Student's t test for dependent samples.

Proof that the action potentials recorded were those of postganglionic sympathetic nerves was obtained by the intravenous injection of trimethaphan (Arfonad), 0.75 mg/kg, at the conclusion of the experiment. Immediate cessation of nervous activity was taken as evidence that the nerve was postganglionic.

Cardiac output was measured by the dye-dilution technique. Freshly prepared cardio-green dye was injected into the right atrium during the expiratory phase of respiration. Dye concentration was measured by means of a Beckman Cardio-Densitometer in series with a Harvard constant-withdrawal pump. The resultant dye curve was integrated with a disc integrator and cardiac output calculated by forward triangulation. Blood samples were reinjected into the dog after calibration and cardiac output determinations.

After the animal was prepared, ventilation was adjusted to a rate of 24/min with a tidal volume of 500 ml. The inhaled gas mixture consisted of either 20 per cent oxygen–80 per cent nitrous oxide or 77 per cent nitrous oxide–3 per cent carbon dioxide and 20 per cent oxygen. The latter mixture was found to produce a normal end-tidal carbon dioxide concentration and Pa_{CO_2} approximately 40 mm Hg. Prior to measuring cardiac output, duplicate samples of blood were obtained for measurement of Pa_{CO_2}, Pa_{O_2} and pH_a with an Instrumentation Laboratories blood-gas analyzer. Blood loss was 25–75 ml and fluid replacement consisted of 300–500 ml of Ringer's lactate solution.

Each experiment consisted of a series of three observations of all parameters. Initially, normocapnic data were obtained after 20 minutes of hyperventilation with a gas mixture containing sufficient carbon dioxide to maintain Pa_{CO_2} within a normal range. The hypocapnic data were obtained 20 minutes after removing carbon dioxide from the inhaled gas. The animal was then ventilated with the initial gas mixture and a second set of normocapnic values obtained. The two sets of normocapnic data were averaged and compared with the data obtained during hypocapnia. Fifteen experiments were completed in ten animals.

Results

The data obtained during normocapnia and hypocapnia are presented and averaged in table 1. Reducing the mean carbon dioxide tension from 38.7 to 18.3 mm Hg was associated with significant ($P < 0.05$) decreases in cardiac output and stroke volume. Heart rate and peripheral resistance increased while blood pressure decreased during respiratory alkalosis; however, these changes were not significant.

Spontaneous postganglionic sympathetic activity occurred as bursts of action potentials with a frequency of approximately two bursts per second. The nature of postganglionic sympathetic activity reported herein is in agreement with that described by others.[8, 9, 10] A decrease in arterial carbon dioxide tension had little effect on burst frequency; however, it was associated with a decrease in duration and amplitude of electrical activity occurring during each burst. In the multifiber preparation, the decreased amplitude and duration of each burst were felt to be due to a decrease in the number of postganglionic fibers synchronously active. The decrease in recorded deflections of the integrated sympathetic activity, which is a semiquantitative summation of the total electrical potentials occurring during a burst, furnished evidence which substantiates an interpretation of decreased total activity. The mean changes in sympathetic activity were almost precisely proportional to the changes in Pa_{CO_2} (table 2). Decreases in cardiac output were a reflection of the decrement in sympa-

TABLE 1. Comparison of the Cardiovascular Effects of Normocapnia and Hypocapnia in Ten Dogs (Fifteen Experiments).

Dog and Experiment		P_{aCO_2} (mm/Hg)	pH	Cardiac Output (l/min)	Mean Aortic Pressure (mm/Hg)	Heart Rate	Systemic Resistance $\left(\frac{\text{dynes-sec}}{\text{cm}^5}\right)$	Stroke Volume (ml)
1A	N	35	7.35	2.29	126.5	165	4,405	13.9
	H	17.5	7.60	1.82	112.0	171	4,924	10.6
1B	N	38.5	7.34	1.92	124.5	173	5,115	11.2
	H	18.5	7.58	1.54	118.0	186	6,116	8.3
2A	N	43.5	7.35	2.62	129.0	123	3,932	21.3
	H	26.0	7.48	1.41	118.0	140	6,632	10.1
2B	N	41.0	7.36	2.33	127.5	124	4,360	18.8
	H	21.0	7.51	2.27	123.0	162	4,334	14.0
3A	N	37.0	7.32	4.43	127.0	156	2,292	28.4
	H	16.0	7.51	3.48	124.5	168	2,411	20.7
4A	N	39.3	7.34	1.85	133.5	157	5,752	11.9
	H	17.5	7.64	1.77	105.0	123	4,741	14.4
4B	N	39.5	7.33	1.71	136.0	150	6,356	11.4
	H	14.0	7.65	1.45	135.0	105	7,431	13.8
5A	N	38.8	7.35	1.85	126.0	100	5,449	18.5
	H	20.0	7.54	1.86	140.0	90	6,015	20.7
6A	N	37.7	7.28	2.16	105.0	164	3,885	13.2
	H	15.0	7.54	1.81	85.0	198	3,749	9.1
6B	N	40.7	7.26	2.01	124.0	165	3,930	12.2
	H	14.5	7.56	1.57	103.0	204	5,236	7.7
7A	N	42.5	7.37	3.69	106.5	178	2,296	20.7
	H	22.5	7.57	2.44	110.0	152	3,600	16.0
7B	N	37.5	7.40	3.77	106.5	167	2,248	22.6
	H	25.5	7.54	3.72	120.0	165	2,578	22.5
8A	N	34.0	7.35	2.82	123.0	189	3,486	14.9
	H	13.0	7.65	2.83	117.5	197	3,330	14.4
9A	N	38.0	7.31	1.90	127.0	175	5,336	10.9
	H	14.0	7.60	1.85	127.5	185	5,535	10.0
10A	N	38.0	7.27	3.95	94.0	140	1,902	28.2
	H	20.0	7.55	4.61	92.5	156	1,613	29.6
Mean and SE	N	38.7 ±0.63	7.33 ±0.01	2.62 ±0.23	121.0 ±3.1	155 ±6.2	4,116 ±367	17.2 ±1.5
	H	18.3 ±1.06	7.57 ±0.01	2.30 ±0.24	115.0 ±3.8	160 ±8.7	4,547 ±432	14.8 ±1.6
Probability*		<0.001	<0.001	<0.05	NS	NS	NS	<0.05

* Statistical evaluation performed by the two-tailed Student's t test for dependent samples.

thetic activity, but lacked the close relationship observed with the Pa_{CO_2}. This serves to acknowledge factors regulating cardiac function apart from autonomic innervation.

The experiment depicted in figure 1 demonstrates the relationship among hypocapnia, cardiac output and postganglionic sympathetic nervous system activity. The first column presents data obtained during the initial normocapnic period. Postganglionic activity appeared as bursts of action potentials with a frequency of about two/sec and a duration of less than 0.5 sec. Maximum single potentials were about 20 μV. The integrated sympathetic activity demonstrated maximum cumulative electrical activity approximating 200 μV, with

TABLE 2. Changes in Cardiac Output and Sympathetic Activity with Hypocapnia (Eight Experiments)

Dog and Experiment	Pa_{CO_2}	Cardiac Output (l/min)	Sympathetic Activity†	Pa_{CO_2}	Cardiac Output (l/min)	Sympathetic Activity†
1A	35.0	2.29	2.55	17.5	1.82	1.70
1B	38.5	1.92	2.65	18.5	1.54	1.54
2A	43.5	2.62	3.65	26.0	1.42	0.80
3A	37.0	4.43	2.70	16.0	3.48	1.70
4A	39.3	1.85	3.00	17.5	1.77	1.80
4B	39.5	1.71	4.30	14.0	1.45	2.60
6A	37.7	2.16	5.45	15.0	1.81	2.40
6B	40.7	2.01	4.70	14.5	1.57	2.00
Mean and SE	38.9 ± 0.90	2.37 ± 0.31	3.63 ± 0.39	17.4 ± 1.35*	1.86 ± 0.24**	1.82 ± 0.20***

† sq cm of pen deflection/50 mm sec.
* $t = 18.70$, $P < 0.001$.
** $t = 3.92$, $P < 0.01$.
*** $t = 5.49$, $P < 0.001$.

the average approximating 100 μV per burst. The changes seen during hypocapnia are shown in column 2, figure 1. Duration and amplitude of the bursts of postganglionic activity were diminished while the frequency of bursts were unchanged. Associated with the decrease in sympathetic activity, cardiac output decreased. Addition of carbon dioxide to the inhaled gas mixture returned the animal to normocapnia. The postganglionic bursts of activity increased in duration and amplitude (fig. 1, column 3) and resembled those obtained during the initial control period. Cardiac output also returned to control level.

In this experiment (fig. 1), the data recorded during the initial control period were obtained when the dog was slightly hypercapnic ($Pa_{CO_2} = 47$ mm Hg). Postganglionic activity was greater during this initial control period than during the second control period when the animal was normocapnic ($Pa_{CO_2} =$ 40 mm Hg). Others have found that hypercapnia is associated with an increase in postganglionic sympathetic nerve activity [10] and circulating catecholamines.[11]

Peak and mean airway pressures were measured intermittently throughout the experiments. Changes were negligible. During each experiment, esophageal temperature did not vary by more than ±0.5 C. Pa_{O_2}, measured at frequent intervals, was 100 ± 18 mm Hg. No significant alterations in Pa_{O_2} occurred with changes in arterial carbon dioxide.

Discussion

The circulatory response to hyperventilation reflects the interaction of a number of parameters. The mechanical effect of intermittent positive-pressure ventilation will cause some reduction of both stroke volume and cardiac output.[12] This was stabilized by maintaining tidal volume and rate constant in the paralyzed animal so that separation of the effect of respiratory alkalosis from the mechanical factors of ventilation was possible.

Our findings agree with the observations of both Little and Smith [2] and Morgan *et al.*[3] who reported that hypocapnia produced decreases in stroke volume and cardiac output in anesthetized dogs. Similarly, in man, other investigators [4, 5] have found that hypocapnia during anesthesia results in decreased cardiac output. Theye *et al.*[4] suggested that alteration in sympathetic activity was the responsible mechanism. At variance with these findings are those of Kontos *et al.*[6] and Linde and Goldberg,[7] who did not observe significant changes in cardiac output during hypocapnia in dogs. Two factors which might account for the variation in observations are: 1) lack of control of body temperature and 2) the cardiovascular effects of the anesthetics. In many of the

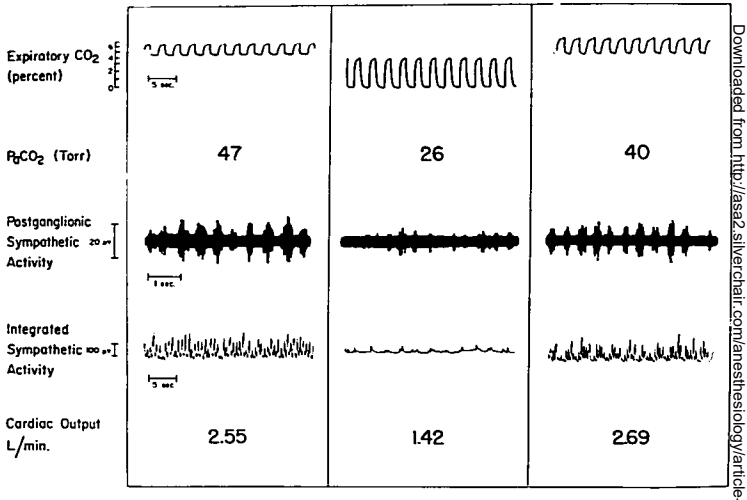

FIG. 1. Summary of data obtained during experiment 2A. The data in each column were obtained at 20-minute intervals. The data in the first and third column served as the control for the experiment depicted in column 2.

previous experiments,[2, 6, 7] body temperature was not monitored or controlled. Body temperature, in part, determines metabolic rate and cardiac output. Failure to control body temperature rigorously, in a study in which cardiac output is measured, can lead to erroneous conclusions. The anesthetic also is likely to influence the effect of respiratory alkalosis on cardiac output, and might account for the different results mentioned. Peiss and Manning[12] have shown that small doses of barbiturates (5 mg/kg pentobarbital) will reduce hypothalamically-induced cardiovascular responses markedly. Little and Smith,[2] Theye *et al.*,[4] and the present authors did not use barbiturates as the principal anesthetic, and observed a significant reduction in cardiac output associated with hypocapnia. Conversely, Kontos *et al.*[6] and Linde and Goldberg[7] found that dogs anesthetized with barbiturates did not demonstrate reductions in cardiac output during hypocapnia.

Whether a decrease in cardiac output during hypocapnia is the result of a direct effect on the myocardium or an indirect effect through sympathetic nerve control of cardiac or extracardiac functions has not been determined. In the present study, the spontaneous activity of a postganglionic sympathetic nerve was measured. Hypocapnia reduced spontaneous activity in the postganglionic nerve, apparently by decreasing the number of active nerve fibers. The decreased activity was readily reversible by returning the animal to normocapnia. Furthermore, the changes in spontaneous sympathetic activity could not be attributed to changes in arterial blood pressure or oxygen tension, since these parameters did not change significantly when arterial carbon dioxide tension was varied.

The relationship between the activity of the sympathetic nervous system and cardiac output is complex and controversial. Some investigators feel that cardiac output is controlled primarily by nervous influence on the heart. In the heart–lung preparation or the isolated heart, sympathetic nerve stimulation increased both heart rate and pumping capa-

bility. Otton and Wilson [14] found that sympathetic denervation of the myocardium by high thoracic epidural block reduced cardiac output both by slowing of rate and by reducing the myocardial response to filling pressure. Sarnoff *et al.*[15] found that by stellate ganglionic stimulation cardiac output could be placed on a higher curve in relation to cardiac filling pressure. On the other hand, denervation of the myocardium hardly affects the ability of an animal to regulate cardiac output.[16, 17] Guyton [18] has suggested that the principal role of the sympathetic nervous system in regulation of cardiac output resides in its effect on the systemic circulation. Thus, the possible pathways for hypocapnia and depressed sympathetic activity resulting in reduced cardiac output are at least two; *i.e.*, decreased stimulation of heart and decreased mean systemic pressure resulting in a decreased venous return.

A great variation in the response of the animals to hypocapnia was observed. Some animals responded to hypocapnia with a marked decrease in cardiac output and sympathetic activity (fig. 1), while in others only slight changes were observed. There was a good correlation between the changes of spontaneous sympathetic activity and cardiac output when hypocapnia was induced. Bronk *et al.*[9] found that hyperventilation decreased cardiac sympathetic discharge. However, it is not clear whether the decrease was due to hypocapnia *per se*.

The question arises whether the postganglionic activity monitored distal to the celiac ganglion reflects the activity of the sympathetic system throughout the body. Other investigators [10, 19] have shown that the responses of abdominal sympathetics and the cardiac sympathetics to such stimuli as hypoxia and hypercapnia are qualitatively similar. The investigations of Weidinger *et al.*[20] support the assumption that changes in activity recorded from the renal nerve are representative of activity in the remainder of the peripheral sympathetic system. This does not settle the question regarding the mechanism by which decreased sympathetic activity is associated with decreased cardiac output. Whether it is the sympathetic decrement on the heart alone or on the systemic circulation alone or a combination of the two is still open to investigation. It is clear that hypocapnia was associated with decreases in both cardiac output and sympathetic activity.

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Drugs

GLUCAGON Intravenous glucagon (2 μg/kg) restored A-V conduction time to normal in dogs following its increase by prior administration of propranolol. This action of glucagon is not one of beta-adrenergic stimulation. Rather, it appears that the cardiac effects of glucagon are mediated through a pathway similar to that which mediates the effects of catecholamines, *i.e.*, the activation of adenyl cyclase and consequent formation of cyclic 3',5'-AMP. Unlike the cardiac effects of catecholamines, those of glucagon are not blocked by beta-adrenergic blockade. Glucagon, therefore, may be able to reverse the cardiodepressant effects of propranolol without reversing its effectiveness in controlling arrhythmias. (*Whitsitt, L. S., and others: Effects of Beta-receptor Blockade and Glucagon on the Atrioventricular Transmission System in the Dog, Circ. Research 23: 585 (Nov.) 1968.*)

ANTI-MOTION-SICKNESS The effectiveness of a drug in reducing susceptibility to acute motion sickness is readily determined in a slow-rotation room where the stressful accelerations are under quantitative control. Fifty subjects were used, each serving as his own control, to evaluate 16 representative anti-motion-sickness drugs. Only drugs with sympathomimetic or parasympatholytic actions and some of the antihistamines were notably effective. The summation effect of dextroamphetamine sulfate and l-scopolamine hydrobromide provided far better protection than any single drug. (*Wood, C. D., and Graybiel, A.: Evaluation of Sixteen Anti-motion Sickness Drugs Under Controlled Laboratory Conditions, Aerospace Med. 39: 1341 (Dec.) 1968.*)

ATROPINE VS. SCOPOLAMINE Central nervous system and peripheral effects of atropine, scopolamine, and eight other drugs were evaluated separately. Scopolamine was less potent than atropine against sarin poisoning in guinea pigs; against the convulsant action of intracerebral carbachol or acceleration of screen climbing in mice; and production of mydriasis in mice and rabbit. Scopolamine was almost twice as potent as atropine in prevention of bradycardia after methacholine. (*Madill, H. D., Stewart, W. C., and Savote, M. L.: Central and Peripheral Anticholinergic Potency of Some Drugs Antagonistic to Anticholinerterase Poisoning, Canad. J. Physiol. Pharmacol. 46: 559 (July) 1968.*)