Influence of Respiratory Acidosis on ECG and Pressor Responses to Epinephrine, Norepinephrine and Metaraminol.* (23012)

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Mines(1), reported that perfusion of an isolated frog heart with acid lengthened the A-V interval and led to heart block and that "perfusion with an alkaline solution quickly removed the block and then steadily reduces the A-V interval." Andrus and Carter(2) found that rhythm and conduction time in isolated dog's and terrapin's hearts could be correlated with pH of the perfusate. When an acid perfusate was used, rate slowed and conduction time lengthened. Opposite effects were observed when an alkaline perfusate was used. Andrus(3) noted that the stimulating effect of adrenalin and tyramine upon isolated auricles of the rabbit was enhanced by pH of 7.8 and diminished by pH of 7.0. Burget and Visscher(4) reported the relationship between adrenalin effect and blood pH in pithed cats. They found progressively greater adrenalin effects with increasing blood pH up to 8.0.

Methods. Dogs were anesthetized with intravenous 5% sodium pentobarbital (30 mg/kg). Gas mixtures were administered through a cuffed endotracheal tube. Blood pressures were recorded through an indwelling femoral artery catheter connected to a pressure transducer and thence to a 2 channel direct writing oscillograph. Mean arterial blood pressures were recorded by use of an electrical integrating circuit in the oscillograph. In the first phase of this investigation electrocardiograms were recorded on the second channel of the oscillograph. Arterial blood samples were drawn through the femoral artery cannula and blood pH determinations were made on these samples. Blood pH was determined at 38°C with a specially constructed glass electrode pH meter(5). Five animals were subjected to respiratory acidosis by inhalation of 30% CO_2-70% O_2 gas mixtures. Sympathomimetic agents were administered intravenously by a femoral vein catheter. Doses and agents used were: epinephrine 2.7 γ/kg, norepinephrine 2 γ/kg, and metaraminol 73 γ/kg. These doses were calculated to produce approximately the same moderate elevation of mean arterial pressure in the intact dog with each of the drugs. Ten dogs were subjected to complete cardiac bypass using a pump homologous lung oxygenator in the extra corporeal circuit(6). The roots of the aorta and pulmonary artery were clamped and the animals were maintained on total by-pass as long as 2 hours. The homologous lung was ventilated with 30% CO_2-70% O_2 for 15 minutes at 18-22 respirations per minute and at a pressure of 16-18 cm of water. Blood flow was regulated to maintain a mean systemic arterial pressure of 75 to 100 mm Hg. Following 15 minutes of equilibration on CO_2, the responses to intra-arterial epinephrine, norepinephrine and metaraminol were recorded. Doses used were: epinephrine 1.3 γ/kg, norepinephrine 1.0 γ/kg, and metaraminol 22 γ/kg. As soon as the animal's response to the 3 pressor agents was completed, an arterial blood pH was determined. The ventilating gas was then changed to 100% oxygen and the homologous lung ventilated with this gas for 15 minutes to lower the CO_2 content of blood and return the pH to a normal range. Following this period of equilibration, the same drugs at the same dosages were again administered and the pressor responses recorded. After the response to the last of the drugs was complete, the arterial blood pH was again determined.

Results. In the 5 intact dogs subjected to respiratory acidosis, average blood pH was 6.76 as compared with the average control pH of 7.34 while breathing room air. All sympathomimetic agents given in amounts indicated above produced cardiac irregularities in dogs at control pH. These arrhythmias

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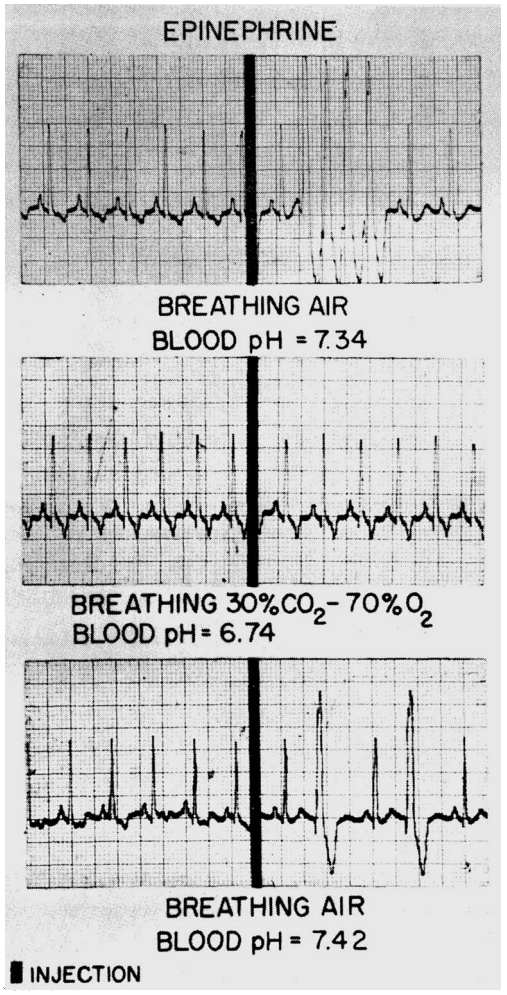

FIG. 1.

were ventricular extrasystoles originating from different foci, with frequent runs of ventricular tachycardia. In some tracings, changes in atrial conduction, with changing atrial pacemaker or nodal rhythm, were also observed. The ECG abnormalities were minimal or absent when identical amounts of these pressor agents were administered to acidotic animals (Fig. 1, 2, 3). As a rule, pressor responses in the presence of respiratory acidosis were reduced when compared with those responses obtained in the control state, although in some instances the differences were small (Table I).

In the 10 dogs subjected to total cardiac by-pass, mean arterial blood pH was 6.67 while the homologous lung was being ventilated with 30% CO_2-70% O_2. Blood pH rose to 7.41 after 15 minutes of ventilation of the homologous lung with 100% O_2. Average increases in mean arterial blood pressure to epinephrine, norepinephrine, and metaraminol during respiratory acidosis were 14, 16 and 23 mmHg respectively; at normal blood pH, mean pressor responses to these agents were 36, 26, and 38 mmHg respectively; (Table II). Statistical analysis of differences in pressor responses during acidosis and at normal blood pH reveals a P value of less than 0.001 for all 3 agents. For dosages employed, epinephrine and norepinephrine gave responses which

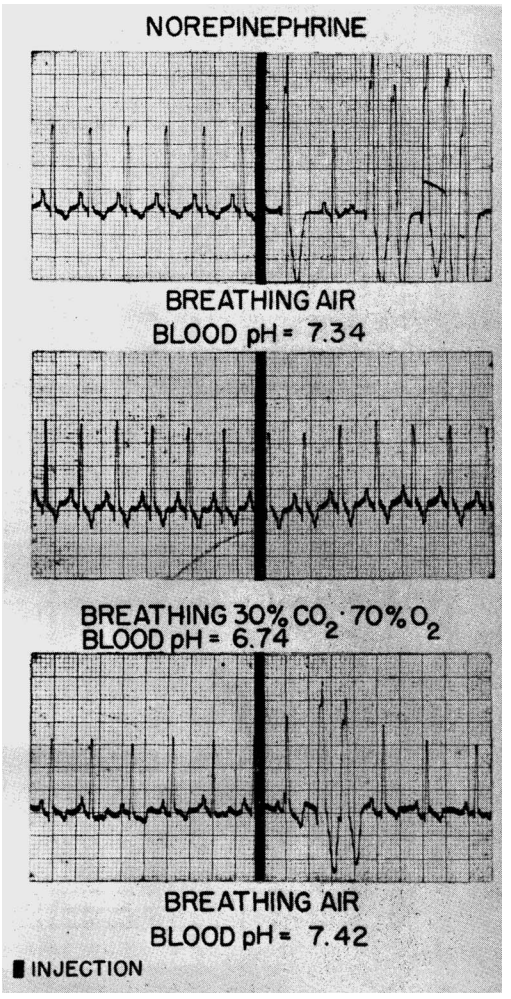

FIG. 2.

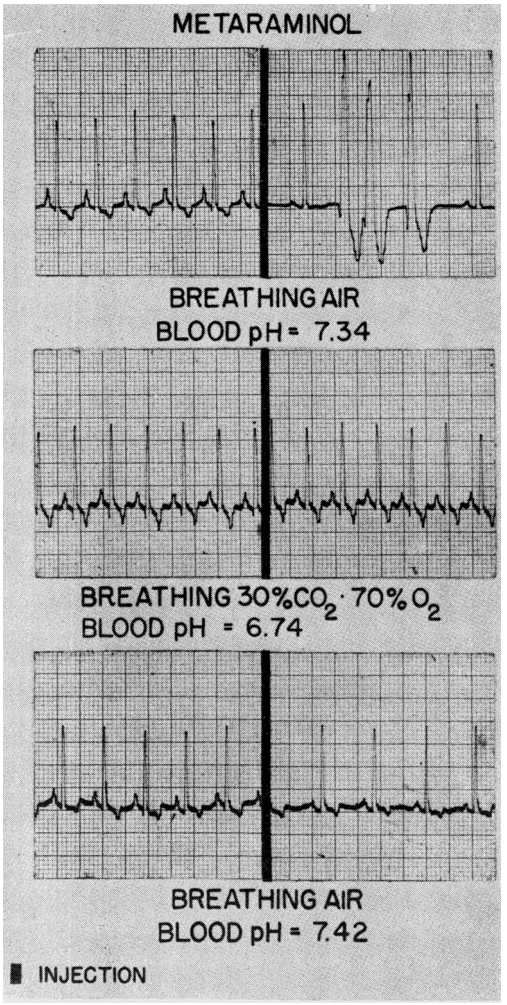

FIG. 3.

were comparable as to intensity and duration. Metaraminol gave a greater response than did the other agents and the duration of the pressor effect was more prolonged.

Discussion. In intact animals the differences in response during respiratory acidosis and under normal pH conditions were not uniformly large. This is particularly evident when acidotic and post acidotic responses in the intact dog are compared. The marked cardiac irregularities produced by these agents under normal blood pH probably masked the pressor response. It is also possible that the degree of bradycardia produced, via the parasympathetic pressoreceptor pathways, during acidosis may have affected the response in intact dogs.

In those experiments in which the heart was excluded from the circulation of the animals, and therefore did not play a role in the responses obtained, the agents were perfused only through the extra cardiac vascular system and a more accurate measurement of their effect on peripheral vascular resistance could be recorded. Obviously, these peripheral vascular resistance changes could be mediated through the central nervous system or through direct action on peripheral vessels. The experiments reported here do not separate these two possible sites of action of these drugs. The method of total cardiac bypass employed (the pump homologous lung oxygenator) serves as a useful experimental tool in separating cardiac and extracardiac effects of pharmacologic agents. Purposefully the control portion of the experiment, in which the animal's pH was near normal, was performed after the animal had been subjected to a period of respiratory acidosis, and consequently deterioration in the preparation would decrease the responses at normal pH rather than the responses obtained under conditions of lowered blood pH.

At the present time we are unable to interpret the mechanism by which severe respiratory acidosis decreases response to pressor

TABLE I. Pressor Responses before, during and after Respiratory Acidosis in Dogs.

	Pre-acidosis		Respiratory acidosis		Post-acidosis	
	Pre-inj. B.P. (mm Hg)	Post-inj. B.P. incr. (%)	Pre-inj. B.P. (mm Hg)	Post-inj. B.P. incr. (%)	Pre-inj. B.P. (mm Hg)	Post-inj. B.P. incr. (%)
Epinephrine	139	36	133	18	117	38
Norepinephrine	131	57	133	29	122	34
Aramine	122	59	142	21	128	28
	pH = 7.34*		pH = 6.76*		pH = 7.27*	

* Avg values for 5 dogs.

TABLE II. Pressor Responses during and after Respiratory Acidosis in Dogs during Total By-Pass.

	Respiratory acidosis		Post-acidosis	
	Pre-inj. B.P. (mm Hg)	Post-inj. B.P. incr. (mm Hg)	Pre-inj. B.P. (mm Hg)	Post-inj. B.P. incr. (mm Hg)
Epinephrine	78 ± 3.5*	14 ± 3.4	89 ± 5.6	36 ± 6.6
Norepinephrine	80 ± 2.3	16 ± 2.5	88 ± 6.8	26 ± 3.4
Aramine	84 ± 2.7	23 ± 2.7	92 ± 6.5	38 ± 4.7
	pH = 6.67†		pH = 7.41†	

* ± stand. error of the mean. † Avg values for 10 dogs.

drugs. It is possible that changes in some component of plasma other than H^+, CO_2, or HCO_3^- are responsible. It seems unlikely that changes in plasma potassium are responsible for the observed effects since plasma potassium changes very little in 15 minutes with 30% CO_2 breathing in the dog(7).

Page and Olmsted(8) reported that dogs subjected to respiratory acidosis (30% CO_2) were refractory to pressor drugs, whereas metabolic acidosis (0.1 normal hydrochloric acid intravenously) in dogs did not produce a depressed response to pressor agents. Studies are now in progress comparing pressor responses in dogs subjected to total cardiac by-pass at normal blood pH levels and during metabolic acidosis.

Summary and conclusions. 1. Sympathomimetic agents were administered to intact dogs under conditions of respiratory acidosis and at normal blood pH. Arterial pressure responses and electrocardiograms were obtained. In the presence of respiratory acidosis, the pressor responses were somewhat diminished and ECG abnormalities were absent or minimal as compared to the control state. 2. The same agents were administered to dogs subjected to total cardiac by-pass. Pressor responses under conditions of respiratory acidosis were uniformly much less in these animals than responses subsequently obtained in the same animals in which the arterial blood pH was at or near normal values.

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