Influence of Respiratory Acidosis on Circulatory Effect of Epinephrine in Dogs

By Henrik H. Bendixen, M.D., Myron B. Laver, M.D., and Werner E. Flacke, M.D.

In 1880 Gaskell showed that the tone of isolated frog hearts was depressed by exposure to weak acids, and restored by subsequent application of alkaline solutions. The cardiac depressant effect of lowered pH was later confirmed by Jerusalem, working with cat heart-lung preparations; by Price in dog heart-lung preparations; by Williams in isolated rabbit auricles; and by McElroy in isolated guinea-pig hearts.

The circulatory effects of epinephrine were subsequently found to vary with changes in acid-base balance. In 1920 Snyder reported the vascular reaction to epinephrine in frogs to be dependent on hydrogen ion concentration. Similar findings were published by McCarrison and Salant, both working with frogs. Burget studied the influence of pH on circulatory response to epinephrine in pithed cats and found a progressive increase in epinephrine effect as the pH increased from 6.9 to 8.0 units; respiratory acidosis was more effective in decreasing epinephrine response than was metabolic acidosis at the same pH. The antagonism between acidosis and epinephrine pressor response was studied in dogs by Page and by Houle. Similar antagonism between acidosis and epinephrine response was reported for the nictitating membrane of the cat by Tenney.

The studies cited do not include investigations in the intact organism of the effects of epinephrine on both heart and peripheral circulation. New methods and techniques in surgery and anesthesia contribute to the need for further study of vasopressor effects.

Methods

Fourteen healthy mongrel dogs with an average weight of 17.2 kg were studied. No premedication was given; induction and maintenance of light, general anesthesia was with thiopental sodium. In each case a tracheostomy was performed, a large-bore endotracheal tube inserted, and the trachea tied around it for airtight fit. Ventilation with pure oxygen was controlled by a Harvard Apparatus Company respiration pump. Both femoral arteries were cannulated with polyethylene catheters, one for continuous monitoring of arterial blood pressure, the other for sampling arterial blood; the tips of both catheters were placed in the lower part of the abdominal aorta. A femoral vein was also cannulated with a polyethylene catheter for injection or infusion of drugs; the tip of this catheter was placed in the lower part of the inferior vena cava. A lumbar laminectomy was performed as described by Brewster, and two polyethylene catheters placed at different levels in the thoracic epidural space (approximately T6 and T10) in preparation for sympathetic block. A Walton-Brodie 120 Ohm strain gauge arch was sewn to the upper part of the left cardiac ventricle as described by Boniface and by Cotten.

Blood pressure was measured by a Sanborn transducer (Model no. 267B). The electrocardiogram (standard limb lead II), arterial blood pressure, and contractile force of the left ventricle were recorded on a Sanborn Polyviso (Model no. 150). A separate one-channel Sanborn amplifier-recorder was used to allow simultaneous recording of electrocardiogram at different paper speeds. Mean arterial pressure was derived by electrical

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damping. Arterial blood was collected in syringes, wet with heparin solution and capped with stopcocks. Determinations of pH were made with a Beckman glass electrode, pCO₂ by the Severinghaus electrode* (both at 37°C). Duplicate analyses agreed within 0.01 pH units and 2 mm Hg CO₂ pressure.

Following preparation of the dog a 30-minute rest period was allowed. At the beginning of each experiment atropine sulfate, 1 mg/kg, was injected intravenously in two or three divided doses. Lidocaine hydrochloride (Xylocaine) 0.5% (9 to 16 ml in three to five divided doses) was subsequently injected over a 15-minute period into the thoracic epidural space for sympathetic block.

In ten dogs the influence of pH changes was studied during a single period of epinephrine infusion; in the remaining four dogs, repeated infusions were made. An even distribution of the first ten experiments over a pH range from 7.00 to 7.60 units was desired. Accordingly, in each of six dogs, carbon dioxide (3% to 20%) was added to inspired oxygen in sufficient concentration to produce the required degree of respiratory acidosis. In the remainder of the ten experiments ventilation was adjusted to produce the desired degree of respiratory alkalosis. As soon as a steady state (as indicated by repeated blood gas measurements) had been reached, usually after five minutes, infusion of epinephrine in normal saline (6 to 12 μg/ml) was started. The rate of infusion was at first sufficiently slow to cause no circulatory effect, and subsequently the rate was increased in steps. Each infusion rate was maintained long enough for the circulatory variables to become steady. In each case the rate of infusion was increased until no further rise in contractile force or mean arterial pressure could be obtained, or persistent conduction irregularities (ventricular ectopic beats) appeared. Arterial blood samples were drawn at frequent intervals for determination of pH and blood gases.

In four dogs, two to seven successive dose-response curves were obtained, allowing ten minutes for recovery between assay periods. A fall in pH, greater than 0.1 unit, was (arbitrarily) not accepted. In two dogs this criterion necessitated an increase in ventilation in order to counteract the decreasing pH.

Results

In all experiments parasympathetic and sympathetic reflex activity was prevented by injecting atropine and blocking sympathetic

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*Supplied by the National Welding Equipment Co., San Francisco, California.

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<table>
<thead>
<tr>
<th>Atropine sulfate</th>
<th>Sympathetic block</th>
<th>Carbon dioxide in inspired oxygen</th>
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<tr>
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<td>124</td>
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<tr>
<td>Heart rate (T)</td>
<td>X</td>
<td>132</td>
<td>140</td>
</tr>
</tbody>
</table>

**Table 1**

Atropine was always given first, followed by epinephrine injection of lidocaine approximately 5 minutes later. Carbon dioxide inhalation took place last.

\[ r = \frac{1}{n} \sum r_i \]

where \( r \) represents the difference in rank.

\[ s = \text{not significant.} \]
A representative epinephrine dose-response curve for contractile force of left ventricle, mean arterial pressure, and cardiac rate per minute. The control values prior to the start of infusion are plotted as 100%.

To quantify the influence of arterial pH or pCO₂ on the circulatory effect of epinephrine, the correlation graphs shown in figure 2 were constructed. The rate of epinephrine infusion needed to double contractile force and mean arterial pressure, and to increase cardiac rate by 50%, is correlated with the arterial pH or pCO₂ at the time. The linear correlation of epinephrine effect on contractile force with pH or carbon dioxide is high; for epinephrine effect on mean arterial pressure and on cardiac rate the correlation is not significant.*

In figure 3 the effects of epinephrine on contractile force were further examined by arranging the ten experiments in three groups, according to the mean pH during the period of infusion and a mean curve was constructed for each. Figure 3 shows that pH has little influence on the minimal and maximal effects of epinephrine. The most striking influence of pH on epinephrine effect appears to be on the steepness of the dose-response curve; at infusion rates of 0.75, 1.0, and 2.0 µg/kg per minute, the difference between the top curve and the bottom curve is significant.

The circulatory effects of repeated periods of epinephrine infusion were similar in the four experiments. Figure 4 presents the results of seven successive periods of epinephrine infusion to the same dog. Arterial pH was maintained between 7.35 and 7.45 only by increasing the ventilation to compensate for developing metabolic acidosis. The per cent change in contractile force, mean arterial pressure, and cardiac rate is plotted against the rate of epinephrine infusion for each of seven successive periods of infusion in the

*The correlation coefficients (r) are given below the individual graphs in figure 2. The coefficients were obtained by using Spearman's formula:

\[ r = 1 - \frac{6 \sum D^2}{N(N^2 - 1)} \]

where D represents the difference in rank. The coefficients for epinephrine effect on contractile force were significant (P < 0.01, using the two-tailed T test), whereas the coefficients for epinephrine effect on mean blood pressure and on cardiac rate were not significant (P > 0.05).

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same dog. For each circulatory variable the baseline (100%) represents the steady value recorded prior to the first period of infusion. Each period of infusion was continued, with increasing rates of infusion, until a rise in mean arterial pressure to twice the baseline level was obtained. Figure 4 shows little change, for the first five infusion periods, in the rate of epinephrine infusion required to double mean arterial pressure. In the sixth and seventh periods more epinephrine is needed to double the pressure, but in all seven infusion periods the end point of 200% is readily reached. During intervals between infusions, the mean arterial pressure tended to remain above its initial control value, whereas the contractile force diminished to values below the control. Following successive infusions the increase in contractile force, above the baseline, gradually diminished. The most striking changes in cardiac rate involve the smaller slope of the dose-response curve and the failure to return to baseline levels in the intervals.

In seven of the ten experiments correlating pH values with circulatory response during a single period of epinephrine infusion, a level was reached at which no further increase in contractile force could be obtained with increasing rates of epinephrine infusion. At this point mean arterial pressure continued to rise in response to epinephrine infusion. In these seven experiments a descending limb was evident on the dose-response curve for contractile force. The same phenomenon was apparent in the last three periods of successive epinephrine infusions. It was noted that, at the time of differential response, the cardiac rate remained constant. In one of the three experiments, which did not show differential response, the infusion was stopped as the plateau of maximal response was being reached, owing to the appearance of persistent ventricular ectopic beats in the electrocardiogram. In the other two experiments, not showing differential response, the arterial pH was normal or above normal.

Discussion

These experiments were designed to quan-
The circulatory depressant effects of respiratory acidosis and the relation between acidosis and the circulatory effects of epinephrine were studied in anesthetized intact dogs after sympathetic and parasympathetic block. Respiratory acidosis invariably depressed myocardial contractile force, cardiac rate, and mean arterial pressure, but only the fall in contractile force showed a relation with the degree of acidosis.

The effect of epinephrine on myocardial contractile force decreased with decreasing arterial pH, but no correlation was found between pH and the effect of epinephrine on arterial blood pressure and on cardiac rate. During continuous infusion of epinephrine, arterial pressure continued to rise after the contractile force had reached its maximum. With repeated periods of epinephrine infusion in the same animal, the response of the myocardial contractile force declined, while the response of the arterial blood pressure was unchanged. Such "differential tachyphylaxis" may occur under clinical conditions with prolonged infusions of vasopressor agents.
Seven successive dose-response curves obtained in one dog show a response of mean arterial pressure to epinephrine, which changes very little from the first to the seventh period of infusion. The response of contractile force, and of cardiac rate, diminishes progressively with each period of infusion.

References


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