Cardiovascular Responses to Epinephrine During Acute Hypercapnia in Dogs: Effects of Autonomic Blocking Drugs

By Emmett Steadman Manley, Jr., Ph.D., Robert Arthur Woodbury, Ph.D., M.D., and Clinton B. Nash, Ph.D.

As early as 1921 Collip showed that the pressor response to epinephrine could be reduced by increasing the hydrogen ion concentration of the blood. Page and Olmsted in 1951 were the first to investigate this point by giving animals high concentrations of carbon dioxide to induce acidosis, and they also observed a marked attenuation of the pressor response to administered catecholamines. Subsequent reports have been concerned principally with the reduction of the pressor response elicited by catecholamines. However, Guzman et al. in 1959 reported that during hypercapnia there was a reduction of the positive chronotropic response to catecholamines which they correlated in a linear fashion with the decrease in blood pH. More recently, however, Bendixen et al. were unable to relate chronotropic response with degrees of acidosis. Agreement is also lacking concerning the effect of hypercapnia upon inotropic responses to catecholamines. Ventilation with 15% CO₂ was found by Darby et al. to produce no decrease in percentage inotropic response to norepinephrine. On the other hand, Bendixen et al. reported that a marked increase in the rate of epinephrine infusion was required to elicit the control increase in myocardial contractile force when the animals were being given high concentrations of carbon dioxide.

The response of the autonomic nervous system to carbon dioxide administration may provide an explanation for the attenuation, during hypercapnia, of the cardiovascular stimulatory effects of epinephrine. Tenney has presented evidence which suggests that the reduction of the pressor response to exogenous epinephrine is more apparent than real and results from a masking of the cardiovascular response due to the activity of endogenous catecholamines released by carbon dioxide inhalation. An increase of plasma catecholamines during hypercapnia has been confirmed, by chemical methods, by Richardson and Woods.7

Page and Olmsted have reported that hypercapnia stimulates certain autonomic ganglia possessing inhibitory functions, the activation of which are believed responsible for the reduction of the cardiovascular effects of epinephrine. Other workers have shown that hypercapnia potentiates the influence of vagal stimulation upon the heart; therefore, increased parasympathetic effects could conceivably diminish the response to catecholamines during carbon dioxide inhalation.

It was an objective of the present study to investigate in a quantitative fashion the modification, by hypercapnia, of the pressor, chronotropic, and inotropic responses to epinephrine, with emphasis on determining their relative sensitivity. Also, previous work by Wood et al. in our laboratory had indicated that phentolamine pretreatment would render...
hypercapnia effective in reducing the inotropic response to epinephrine, and it was felt that this observation should be investigated in greater detail. The influence of the autonomic nervous system was examined by investigating the effect of hypercapnia upon cardiovascular responses to epinephrine in animals subjected to various other pretreatments and procedures designed to interrupt selectively or to reduce various aspects of autonomic function.

**Methods**

The results reported in this paper were obtained from sixty-four healthy mongrel dogs weighing between 7.4 and 15.3 kilograms. Carotid blood pressure was determined under pentobarbital anesthesia with the aid of a Statham pressure transducer and was recorded by a Grass polygraph. Cardiac electrical activity and heart rate were evaluated from lead II of the electrocardiogram. Myocardial contractile force was measured by means of a Walton-Brodie strain gauge arch sutured to the right ventricle. The use of open-chest preparations required artificial ventilation for which a Harvard laboratory pump was used. Acute respiratory acidosis was produced in these experiments by administering through the Harvard pump either 15% CO₂: 85% O₂ or 30% CO₂: 70% O₂.

Blood samples were withdrawn from the femoral artery just before each epinephrine injection and pH was determined immediately with a Beckman model 76 expanded scale pH meter equipped with blood electrodes. All doses of epinephrine were administered intravenously through an indwelling femoral catheter. The control responses to epinephrine were reproducible as determined by three successive epinephrine administrations to each animal before CO₂ ventilation. The dose of epinephrine bitartrate employed was equivalent to 2 μg/kg of the free base except in those animals exhibiting sensitivity to epinephrine (reserpine or chlorisondamine pretreated); in these animals 0.5 μg/kg base equivalent was used.

The responses to epinephrine administrations, expressed as per cent of the preinjection control value, were evaluated statistically by t-test. Other methods of comparing responses were considered, i.e. absolute change, failure to reach a maximal value, but it was decided that a percentage evaluation would provide the most meaningful comparison. This type of analysis is especially applicable in this study because the control parameters are invariably lowered by carbon dioxide and any reduction of response to epinephrine is consequently estimated conservatively.

Ten animals were given 15% CO₂ for approximately twelve or thirteen minutes and epinephrine was administered after exactly two minutes of carbon dioxide exposure, and again after ten minutes of exposure. These periods were chosen for epinephrine injections because cardiovascular depression was consistently greatest at the two-minute point and compensation to this depression had reached a relatively stable level at the ten-minute point as determined by a thirty-minute exposure period in ten preliminary experiments. The animals were allowed approximately a thirty-minute recovery interval after which phentolamine, 0.25 mg/kg, was administered and new control responses to epinephrine were obtained. Fifteen per cent carbon dioxide was again administered, epinephrine injected, and data collected as previously described.

A second group of ten dogs was studied in exactly the same manner except that thirty per cent carbon dioxide was used.

A third group of 34 dogs was used to investigate the effects of other modifications of autonomic nervous system function upon cardiovascular responsiveness to epinephrine during hypercapnia. These animals had been exposed previously to ten minutes of 15% CO₂ and to ten minutes of 30% CO₂ as a portion of another study. In this phase of the present study only 30% CO₂ was employed and epinephrine was administered only at the ten-minute point following initiation of hypercapnia. Results obtained from these animals were then compared with results obtained from ten animals previously exposed to CO₂ in a manner identical with that described above, except that these dogs were not subjected to drugs or procedures designed to modify normal autonomic function.

Autonomic modifications included the administration of atropine, 1 mg/kg, to six animals in order to eliminate the influence of the vagi on the heart. These atropine-treated animals were used to study refractoriness to administered epinephrine and endogenously released catecholamines. Ganglionic stimulatory responses were elicited in these animals by the rapid intravenous injection of acetylcholine, 500 μg/kg; this dose having been shown, by preliminary experiments, to produce cardiovascular responses quantitatively similar to those elicited by 2 μg/kg epinephrine. Ganglionic blockade was produced in seven dogs by the administration of chlorisondamine, 3 mg/kg. The establishment of ganglionic blockade was determined, and periodically checked, by the effect of electrical stimulation of the right vagus on cardiac rate.

Reserpine was administered subcutaneously to six animals on a two-day pretreatment schedule with 0.1 mg/kg given forty-eight hours and 0.5
mg/kg given twenty-four hours prior to the experimental period. The free alkaloid was administered in a 20% aqueous solution of ascorbic acid. Animals treated with this dosage schedule were found to be in good physical condition on the experimental day, although the dose chosen was larger than that shown by other investigators to produce almost complete depletion of myocardial catecholamines. Pitman-Moore compound P-286 was administered to ten dogs with an initial dosage of 5 mg/kg followed by two supplemental doses of 2.5 mg/kg given at approximately one-hour intervals. According to De Schaepdryver and Gardier et al., this compound blocks the adrenal release of catecholamines elicited by either chemical or electrical stimulation. Acute bilateral adrenalectomies were performed in five animals through a midline abdominal incision.

Results

EFFECT OF FIFTEEN PER CENT CARBON DIOXIDE UPON CARDIOVASCULAR RESPONSE TO EPINEPHRINE

As demonstrated in figure 1, administration of epinephrine increased mean arterial blood pressure from an average of 121 to 197 mm Hg, representing a level 163% that of control (100% being, in all cases, the value of the parameter before drug administration). Exactly two minutes following initiation of carbon dioxide inhalation, epinephrine elicited a response from an average of 77 to 173 mm Hg, a value 225% of control. This change was significantly greater than the control response. The arterial blood pH at this point of apparent hypersensitivity to epinephrine was 6.95, the control pH being 7.38. Although the blood pH was further depressed to 6.86 after ten minutes of hypercapnia, the epinephrinepressor responses obtained at this time did not differ significantly from the control responses. The contractile force responses were not significantly modified at either the two or ten minute point following initiation of 15% CO₂ inhalation, whereas the positive chronotropic responses seen after ten minutes of hypercapnia were significantly reduced. For clarity of presentation only the percentage values

![Figure 1](http://circres.ahajournals.org/)

Influence of 15% CO₂ upon cardiovascular responses to epinephrine (2 μg/kg, iv). Epinephrine was administered both 2 and 10 minutes following initiation of carbon dioxide inhalation. BF: blood pressure; HR: heart rate; MCF: inotropic response. All responses are reported as per cent of preinjection control values, and in addition, actual control values and changes of blood pressure and heart rate can be observed. Myocardial contractile force is plotted to show the effect of hypercapnia with respect to original control values. An asterisk indicates a significant difference at the 5% level from the control response. Note the augmented pressor response to epinephrine at the two minute point and attenuation of the chronotropic response with no reduction of the other responses after 10 minutes of hypercapnia (10 experiments).
for subsequent results are presented in the text; actual values as well as percentage changes are presented in the figures.

**EFFECT OF FIFTEEN PER CENT CARBON DIOXIDE UPON CARDIOVASCULAR RESPONSE TO EPINEPHRINE IN PHENTOLAMINE-TREATED DOGS**

Control injection of epinephrine in these animals decreased the mean arterial blood pressure to an average level 61% of the control pressure (fig. 2). This depressor response was rapidly eliminated during hypercapnia as indicated by the absence of significant change of blood pressure after the two-minute epinephrine injection. Neither the positive inotropic nor the positive chronotropic response was reduced at the two-minute point, but after ten minutes of hypercapnia the inotropic response was reduced and the positive chronotropic response was absent. Arterial blood pH at the time of these injections was, respectively, 6.88 and 6.81.

**EFFECT OF THIRTY PER CENT CARBON DIOXIDE UPON CARDIOVASCULAR RESPONSE TO EPINEPHRINE**

The two-minute hypercapnic pressure response did not differ from the control response, but ten minutes of hypercapnia did reduce the pressor response (fig. 3). Refractoriness to the positive chronotropic response developed rapidly when the higher concentration of carbon dioxide was employed, as this response was significantly reduced at the two-minute injection point and essentially eliminated at the ten-minute point. Myocardial contractile force response to epinephrine was reduced significantly after ten minutes of carbon dioxide ventilation but not after two minutes. As would be expected, arterial blood pH was depressed to a greater degree by the higher concentration of carbon dioxide; the control pH of 7.42 was reduced to 6.70 after two minutes of CO₂ inhalation and was further depressed to 6.55 after ten minutes.

Figure 4 illustrates the control cardiovascular effects of a typical animal to epinephrine and also the responses observed to epinephrine after this animal was ventilated with 30% CO₂ for ten minutes. Inspection of this record reveals that the pressor, positive chronotropic, and positive inotropic effects were markedly attenuated both in amplitude and duration.

**EFFECT OF THIRTY PER CENT CARBON DIOXIDE UPON CARDIOVASCULAR RESPONSE TO EPINEPHRINE IN PHENTOLAMINE-TREATED DOGS**

The control depressor response to 542 of the preinjection blood pressure was rapidly and
Influence of 30% CO₂ upon cardiovascular responses to epinephrine. (2 μg/kg, iv). See figure 1 for details. Note the early reduction of chronotropic response. With this higher concentration of CO₂ it was possible to reduce the response of all parameters after 10 minutes of ventilation (10 experiments).

Effect of administration of epinephrine (2 μg/kg, iv) to a dog both before (left) and during hypercapnia (right) caused by ten-minute exposure to 30% CO₂. Epinephrine was administered ten minutes after initiation of hypercapnia with continuation of hypercapnia during the response. BP: arterial blood pressure; CF: myocardial contractile force; EKG: electrocardiogram. Note that the pressor, positive chronotropic, and positive inotropic responses to epinephrine were attenuated both in amplitude and duration.

completely eliminated when 30% CO₂ was administered to the phentolamine-treated dogs (fig. 5). The chronotropic effects were also eliminated quickly by the combination of phentolamine and the higher concentration of carbon dioxide. This combination produced a significant attenuation of the inotropic response at the two-minute epinephrine injection and almost complete elimination of this response when tested after ten minutes of hypercapnia.

The record obtained from one of the animals...
Influence of 30% CO₂ upon cardiovascular responses to epinephrine (2 µg/kg, iv) in phentolamine-treated (6.25 mg/kg, iv) dogs. See figure 1 for details. Note that the control blood pressure is represented by the top of the bar in those instances where blood pressure was reduced (indicated by arrow) by epinephrine. Note also the rapid onset and degree of refractoriness in these animals. After ten minutes of hypercapnia all responses are essentially absent (8 experiments).

Effect of administration of epinephrine (2 µg/kg, iv) to a phentolamine-treated (6.25 mg/kg, iv) dog both before (left) and during hypercapnia (right) caused by ten minutes ventilation with 30% CO₂. See figure 4 for details. Note that the depressor, positive chronotropic, and positive inotropic responses to epinephrine are eliminated completely.

REFRACTORINESS TO ENDOGENOUSLY RELEASED CATECHOLAMINES

The six animals that had received atropine were used to investigate the effect of hypercapnia upon the response to endogenously released catecholamines. After determination of the control response to acetylcholine, the animals were given 30% CO₂ for ten minutes at which time the injection of acetylcholine was repeated. The pressor responses were reduced significantly at this time, but there...
EPINEPHRINE RESPONSIVENESS DURING HYPERCAPNIA

Cardiovascular responses to large doses (500 μg/kg, iv) of acetylcholine, in atropinized (1 mg/kg, iv) dogs, both before and during hypercapnia caused by ten minutes ventilation with 30% CO₂. See figure 1 for details. Note that there is no observable difference in the chronotropic and inotropic responses (6 experiments).

was no modification of the positive chronotropic or positive inotropic effects (fig. 7).

INFLUENCE OF MODIFICATIONS OF THE AUTONOMIC NERVOUS SYSTEM UPON HYPERCAPNIA-INDUCED REFRACTORINESS TO EPINEPHRINE

The pressor response to epinephrine was significantly reduced following ten minutes exposure of the nontreated animals to 30% CO₂ (table 1). A similar reduction of this response was observed in those animals subjected to ganglionic blockade by prior administration of chlorisondamine, and in those animals pretreated with atropine. No significant reduction of the pressor response was found in animals pretreated with reserpine, P-286, or adrenalectomy. The positive chronotropic response to epinephrine was reduced by ten minutes of hypercapnia in all groups with the possible exception of those animals pretreated with chlorisondamine. In contrast to the ease with which the positive chronotropic response was attenuated, the positive inotropic response was difficult to reduce under the conditions employed in this study. As seen in table 1 there was no reduction of the inotropic response in the adrenalectomized animals, in the animals not treated with autonomic blocking agents (serving as controls), or in the animals treated with either atropine or reserpine. The inotropic response was reduced, however, in those animals pretreated with chlorisondamine or P-286.

INFLUENCE OF AUTONOMIC MODIFICATIONS UPON BLOOD pH REDUCTION BY HYPERCAPNIA

The reduction of blood pH by ventilation with carbon dioxide was found to be very consistent and reproducible within all groups, treated or nontreated, and no significant differences between groups were found.

REDUCTION OF REFRACTORINESS BY PRIOR EXPOSURE TO CARBON DIOXIDE

It became apparent during the course of the study that a difference existed between the degrees of refractoriness developing in animals which had been previously exposed to high concentrations of carbon dioxide and the degrees of refractoriness seen in animals not previously exposed. Figure 8 compares the cardiovascular effects of epinephrine on ten dogs which had, within the previous two hours, been exposed to ten minutes of 15% CO₂ and ten minutes of 30% CO₂, with the cardiovascular effects of epinephrine on ten dogs
that had never been exposed to high concentrations of carbon dioxide. The pre-exposed group had a slightly lower initial blood pH than the animals not previously exposed, but the control responses to epinephrine were similar in both groups (fig. 8). The animals previously exposed to high concentrations of carbon dioxide demonstrated a reduction of the pressure responses from 158% of control to 134% of control following ten minutes exposure to 30% CO₂, whereas those that had not previously been exposed demonstrated a reduction of the average pressor response from 155 to 119% of the control pressure. Both of these reductions were statistically significant, but the degree of refractoriness was possibly greater in those animals never previously exposed to carbon dioxide. The positive chronotropic response appeared to have been reduced less in those animals previously exposed, but again the reduction of this response was significant in both groups.

Those animals that had been exposed previously to CO₂ did not exhibit a significant reduction of the positive inotropic response to epinephrine when exposed again to 30% CO₂ for ten minutes, but those animals never pre-exposed to high concentrations of CO₂ did exhibit a significant reduction of this response.

**Discussion**

Of the three cardiovascular responses to epinephrine evaluated, it was found that the relative sensitivity to attenuation by carbon dioxide was as follows: (from the most to the least susceptible); positive chronotropic, pressor, and positive inotropic. As revealed by figure 1, the positive chronotropic response was attenuated at a time when there was no appreciable modification of the pressor or positive inotropic responses. In addition, figure 3 indicates that 30% CO₂ will almost eliminate the chronotropic response before there is a significant reduction of the other two responses. Carbon dioxide, in high concentration, should be added to veratramine as another agent possessing the unusual ability to block selectively the chronotropic response

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**Table 1**

<table>
<thead>
<tr>
<th>Modification</th>
<th>Dose of epinephrine</th>
<th>Drug</th>
<th>Chronicotropic response</th>
<th>Pressor response</th>
<th>Inotropic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated</td>
<td>10</td>
<td>2.0</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.2</td>
<td>1.4</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
</tr>
<tr>
<td>Reserpine</td>
<td>0.2</td>
<td>1.4</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
</tr>
<tr>
<td>Chloralhydrin</td>
<td>0.5</td>
<td>3.1</td>
<td>209 ± 5.15</td>
<td>209 ± 5.15</td>
<td>209 ± 5.15</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>0.5</td>
<td>3.1</td>
<td>209 ± 5.15</td>
<td>209 ± 5.15</td>
<td>209 ± 5.15</td>
</tr>
<tr>
<td>P-235</td>
<td>2.0</td>
<td>1.2</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
<td>158 ± 4.12</td>
</tr>
</tbody>
</table>
| *Produced by inhalation of 20% carbon dioxide for ten minutes.*
| †Statistically different from the control response at the 2% level.
| ‡All responses are expressed as per cent of the preinjection value.
| ‡Standard error of the mean.
EPINEPHRINE RESPONSIVENESS DURING HYPERCAPNIA

Cardiovascular responses to epinephrine (2 μg/kg, iv) both before (A) and during (B) hypercapnia caused by ten minutes ventilation with 30% CO₂ in animals previously exposed to high concentrations of CO₂ and in animals never previously exposed to high concentrations of CO₂. Epinephrine was administered after 10 minutes of 30% CO₂ inhalation in both groups; however, the animals represented by dark bars had, within the previous two hours, been exposed to ten minutes of both 15 and 30% CO₂. The animals represented by lighter bars had never been previously exposed to high concentrations of CO₂. All responses are reported as per cent of preinjection control values. BP: pressor response; HR: chronotropic response; MCF: inotropic response. Note that the animals previously exposed develop refractoriness to a lesser degree than do those animals exposed for the first time, this being particularly evident with the inotropic response in which case the animals previously exposed demonstrate no significant reduction of response (20 experiments, 10 in each group).

Blood pH values have been used previously as an index of cardiovascular responsiveness to epinephrine. However, the discovery of an early period of apparent hypersensitivity to epinephrine (fig. 1) when the blood pH was 6.95 emphasizes the observation that blood pH determinations are of value in this respect only when they reflect conditions present within the cellular sites which respond to epinephrine. A more reliable index of responsiveness would appear to be the duration of exposure to the agent employed to produce the change in blood pH. Because carbon dioxide is highly diffusible and has been shown by Hartree and Hill to penetrate cellular membranes rapidly, it can be expected that the latent period for the development of tissue acidosis would be much less when produced by CO₂ inhalation than when produced by administration of fixed acids. Page and Olmsted and Wood et al. demonstrated that a comparable blood pH produced by infusions of large quantities of dilute HCl did not markedly reduce pressor responses to epinephrine until the animals approached a state of irreversible shock. In contrast, a pH of 7.14 initiated with low concentrations of CO₂ did not immediately produce a reduction of epinephrine responsiveness but attenuation of the pressor response developed following maintenance of this relatively small reduction in pH. The present study shows clearly that reduction of responsiveness to epinephrine is well established in less than ten minutes when high concentrations (30%) of CO₂ are employed. The apparent hypersensitivity (percentage response) seen in figure 1 following two minutes of 15% CO₂ inhalation is composed of a slightly increased response (in mm

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Hg rise) seen on a background of blood pressure reduced by the abrupt change in blood pH. This augmented response indicates that two minutes ventilation with this concentration of CO₂ is inadequate to depress responsiveness to epinephrine appreciably although blood pressure was reduced by the direct depressant effects of CO₂.

This study revealed a marked potentiation by phentolamine of the cardiac blocking effects of carbon dioxide (figs. 2 and 5). Thirty per cent carbon dioxide used in conjunction with phentolamine induces almost complete refractoriness to the cardiovascular effects of epinephrine within a ten-minute hypercapnic period (figs. 5 and 6). In earlier reports from this laboratory by Wood et al., the depressor response to epinephrine has been shown to be attenuated by hypercapnia. The present study indicates that loss of the depressor response requires ventilation for only two minutes with the lower concentration (15%) of carbon dioxide. A possible explanation for this rapid loss is that carbon dioxide increases plasma catecholamines by release from endogenous stores, as shown by Richardson and Woods, and that these catecholamines then exert the typical depressor effect in the phentolamine-treated dog, thus masking effectively the response usually elicited by exogenous epinephrine administration. Another possible explanation is based on the theory that carbon dioxide is released from skeletal muscle cells when intracellular acidity is increased by accumulation of lactic acid secondary to epinephrine-induced glycolysis. The released carbon dioxide would then dilate the blood vessels in skeletal muscle and would be responsible for the vasodilator action of low doses of epinephrine. Carbon dioxide was strikingly ineffective in reducing the cardiac stimulatory responses observed in atropinized dogs receiving large intravenous doses of acetylcholine. Increases in heart rate to exogenous epinephrine were reduced readily under similar conditions in both nontreated and atropinized dogs. The inotropic responses elicited by acetylcholine were not reduced to the slightest degree by hypercapnia. These findings may indicate some interference by carbon dioxide on the entrance of catecholamines into the responsive sites, because the heart apparently is able to respond to sympathetic mediators during hypercapnia if the stimulus is appropriate. It is probable that the cardiac responses elicited during hypercapnia in these animals are due to the sympathetic ganglion-stimulating property of acetylcholine which results in a release of the sympathetic mediators in proximity to the site of action.

The reduction of the epinephrine pressor response seen in the nontreated animals following ten minutes exposure to 30% CO₂ was also observed in the animals pretreated with chlorisondamine or atropine (table 1). There was no significant reduction of the response in the animals pretreated with drugs or procedures reported to reduce available catecholamine stores (reserpine, P-286, or adrenalectomy). This latter finding offers support for the contention of Temney that pressor refractoriness to administered epinephrine is secondary to high titers of circulating catecholamines released by carbon dioxide, and consequently, it is then difficult to elicit an additional response on this background. Page and Olmsted have reported that ganglionic blockade restores epinephrine pressor responsiveness in hypercapnic dogs; however, in the present investigation there was no difference between the control (nontreated) animals and those animals pretreated with chlorisondamine. The chlorisondamine-treated dogs did appear to have less reduction of the positive chronotropic response to epinephrine during hypercapnia (table 1), but this difference was of borderline statistical significance and may not be of biological importance. The animals pretreated with chlorisondamine demonstrated a reduction of the positive inotropic response to epinephrine, whereas the control animals did not. In this respect ganglionic blockade increased the refractoriness observed. In addition to the chlorisondamine animals, the P-286 pretreated group also demonstrated a significant reduction of the inotropic response.
These are interesting observations, but ones for which plausible explanations are not apparent. The finding that prior exposure to carbon dioxide rendered the animals less susceptible to subsequent development of cardiovascular refractoriness was an interesting observation. Perhaps this finding can be explained best by an acclimatization or adaptation process, the prior exposure changing the receptor sites in some manner, so that compensatory mechanisms were mobilized and available when subsequent exposures to carbon dioxide were initiated. Considerable work has been reported concerning acclimatization of the respiratory centers to hypercapnia by Kellogg, and Seevers has shown that rats which had first been exposed to low concentrations of carbon dioxide survived concentrations of carbon dioxide which were lethal to rats not previously exposed to carbon dioxide.

Summary

The reduction of cardiovascular responsiveness to epinephrine which develops during hypercapnia has been investigated in the pentobarbital-anesthetized dog. Parameters evaluated include arterial blood pH and pressor, chronotropic, and inotropic responses to epinephrine. Hypercapnia was induced by ventilation with either 15 or 30% carbon dioxide for a constant interval (either 2 or 10 minutes) before administration of epinephrine.

In this species and under the conditions employed, it was shown that the chronotropic, pressor, and inotropic responses to epinephrine were reduced in that order by hypercapnia. These responses were found to be reduced both in amplitude and duration. Phenolamine enhances the cardiac blocking activity of carbon dioxide. The depressor response to epinephrine, following phenolamine, was found to be exquisitely sensitive to elimination by hypercapnia. Cardiac stimulatory responses elicited by acetylcholine in atropinized dogs were not reduced by the intensity of hypercapnia employed in this study. The degree of refractoriness to epinephrine produced by high concentrations of CO₂ was less in those animals that had been exposed previously to high concentrations of carbon dioxide. Arterial blood pH determinations were found to be misleading when employed as an index of epinephrine responsiveness.

Reduction of available catecholamine stores by reserpine, adrenalectomy, or P-286 reduced the pressor refractoriness. Ganglionic blockade was largely ineffective in this respect as was parasympathetic blockade with atropine.

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References


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