Effect of Hydrocortisone on Acidotic Failure of the Isolated Heart

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Acute myocardial failure observed when the denervated heart-lung preparation is rendered acidotic is mitigated if 5 to 10 mg. of hydrocortisone are administered to the preparation 12 to 15 min. before the onset of ventilation with high CO₂.

The tolerance of the dog heart to the inhalation of 20 to 30 per cent CO₂ in O₂ in the intact animal, contrasts with the rapid failure produced in the heart-lung preparation when the lungs are ventilated with similar gas mixtures. The reversal of this acidotic failure by adrenalin or noradrenalin has been described elsewhere. Several authors have indicated that high CO₂ produced in the intact animal stimulates the sympathoadrenal system, and it was inferred that the epinephrine and/or norepinephrine released under these circumstances may offset the depressant effect of hypercapnia which is observed in the isolated heart. Furthermore, it was also reported that 17-hydroxycorticosteroid secretion was significantly increased in dogs exposed to 10 to 20 per cent CO₂ mixtures for 2 to 4 hours. The present series of experiments was undertaken in order to investigate the effect of hydrocortisone in the isolated acidotic-failing heart, following ventilation of the heart-lung preparation with a mixture of 15 to 20 per cent CO₂ in O₂. It was hoped that such an investigation might clarify the role of this hormone in the compensatory mechanisms which prevent the occurrence of heart failure in the intact animal during respiratory acidosis.

Methods

The same preparation described by Starling and associates was used. The blood reservoir was made of a plastic sheet and had a 1 L. capacity. Temperature of the blood was maintained constant by a thermostatically controlled heating plate placed under the water bath. Ventilation of the lungs was performed by a constant pressure electronic respirator. Mixtures from 5 to 20 per cent CO₂ in O₂ were connected through a manifold of stopcocks which permitted an instantaneous change from one mixture to the other.

The pressure in the venous reservoir was maintained throughout the experiment at 5 mm. Hg, and the outflow pressure was set at the same level as that of the mean blood pressure of the animal which was measured before establishing the heart-lung preparation.

The experimental procedure was carried out as follows: One and a half liters of blood was collected from one or several dogs. The blood was withdrawn from a carotid artery of the dog under local anesthesia (100 mg. of procaine) after the dog had been paralyzed with succinyl choline chloride (0.1 mg./Kg. body weight), and ventilated mechanically. The heart-lung preparation was performed on a dog anesthetized with Nembutal (25 mg./Kg.). The lungs were ventilated with air until the last ties were placed on the inferior vena cava and the thoracic aorta. When the heart-lung preparation was complete, a mixture of 5 per cent CO₂ in 95 per cent O₂ was used to establish the control level of cardiac output and heart rate, all other variables remaining constant (inflow and outflow pressure, temperature). After 5 min. of equilibration with 5 per cent CO₂ in O₂, the gas mixture was shifted to a mixture containing from 10 to 20 per cent CO₂ in oxygen. The length of exposure to these different mixtures varied according to the rapidity of the onset of failure, but it never exceeded 10 min. After this period of ventilation with a mixture of high CO₂, a mixture of 5 per cent CO₂ was used again.

Pressures in the right and left atria, and in the brachiocephalic artery were recorded continuously by strain gages and direct pen recordings along with the electrocardiogram. Output of the heart was measured volumetrically at regular intervals. Arterial samples were also withdrawn for pH determination.

Following this control period, a single dose of 5 to 10 mg. of hydrocortisone sodium succinate was administered to the preparation 12 to 15 min. before the onset of ventilation with high CO₂.
added to the preparation. As the total volume of the heart-lung preparation contained 2 L of fluid, the concentration of hydrocortisone in the system was 250 to 500 \( \mu g \) per cent. Ten minutes after this addition, the lungs were ventilated again with 15 per cent \( \text{CO}_2 \) in \( \text{O}_2 \) for periods of 20 to 40 min. In several instances 20 per cent \( \text{CO}_2 \) in \( \text{O}_2 \) were also used.

All experiments were terminated within 2 hours following completion of the heart-lung preparation. Beyond this time period the spontaneous deterioration of the preparation obscures results.

### RESULTS

The results of this study are reported in table 1 and figure 1. Figure 1 is a representative record showing the hemodynamic changes occurring in 1 of 8 heart-lung preparations. During the first control period of ventilation with 15 per cent \( \text{CO}_2 \), the most striking change was the increase in left atrial pressure which rose above 30 mm. Hg within 2 min. Voltage of the R wave of the electrocardiogram was

#### Table 1.—Changes Before (1) and After (2) Hydrocortisone Administration

<table>
<thead>
<tr>
<th>pH range</th>
<th>Mean pH</th>
<th>Group</th>
<th>No. of heart-lung preparations</th>
<th>Heart rate (beats/min.)</th>
<th>Cardiac output (ml./min.)</th>
<th>Stroke volume (ml./beat)</th>
<th>Stroke work (Gm.-cm./beat)</th>
<th>Left atrial pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.83-7.62</td>
<td>7.76</td>
<td>1</td>
<td>6</td>
<td>157 ± 20</td>
<td>581 ± 85</td>
<td>3.71 ± 32</td>
<td>595 ± 95</td>
<td>4.9 ± 1.3</td>
</tr>
<tr>
<td>7.46-7.41</td>
<td>7.42</td>
<td>1</td>
<td>4</td>
<td>135 ± 10</td>
<td>672 ± 73</td>
<td>5.09 ± 94</td>
<td>687 ± 70</td>
<td>5.6 ± 1.8</td>
</tr>
<tr>
<td>7.45-7.35</td>
<td>7.39</td>
<td>2</td>
<td>4</td>
<td>117 ± 11</td>
<td>587 ± 54</td>
<td>5.06 ± 37</td>
<td>800 ± 72</td>
<td>7.0 ± 1.8</td>
</tr>
<tr>
<td>7.34-7.25</td>
<td>7.31</td>
<td>1</td>
<td>5</td>
<td>111 ± 16</td>
<td>496 ± 102</td>
<td>4.60 ± 31</td>
<td>664 ± 181</td>
<td>16.5 ± 9.5</td>
</tr>
<tr>
<td>7.33-7.24</td>
<td>7.30</td>
<td>2</td>
<td>4</td>
<td>113 ± 16</td>
<td>592 ± 131</td>
<td>5.38 ± 14</td>
<td>687 ± 104</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>7.14-6.91</td>
<td>7.04</td>
<td>1</td>
<td>5</td>
<td>110 ± 16</td>
<td>186 ± 197</td>
<td>1.65 ± 1.48</td>
<td>231 ± 218</td>
<td>40.3 ± 11.9</td>
</tr>
<tr>
<td>7.09-6.96</td>
<td>7.03</td>
<td>1</td>
<td>8</td>
<td>102 ± 11</td>
<td>567 ± 94</td>
<td>5.77 ± 1.08</td>
<td>817 ± 105</td>
<td>11.4 ± 4.5</td>
</tr>
</tbody>
</table>

**FIG. 1.** Selected records showing the effect of 15 per cent \( \text{CO}_2 \) in \( \text{O}_2 \) on the heart-lung preparation before and after administration of 5 mg. of hydrocortisone.
reduced and the heart rate was slower, but no arrhythmia was present. Arterial blood pH fell to 7.15 and the heart was extremely dilated. Cardiac output dropped to less than half its control value. Three minutes after the gas mixture ventilating the lungs was switched back to 5 per cent CO₂, the values of all these variables came back to their control level.

In the following control period, while the preparation was ventilated with 5 per cent CO₂, 5 mg. of hydrocortisone were added to the system. Twelve to 15 min. later, ventilation with 15 per cent CO₂ was resumed, and signs of heart failure were observed—mainly cardiac dilatation and an increase in left atrial pressure above 10 mm. Hg. But, this episode was transient as cardiac dilatation receded and, except for left atrial pressure, all the variables measured stabilized close to their control values on 5 per cent CO₂ for periods of up to 40 min. of ventilation with 15 per cent CO₂ with corresponding pH of 7.18 to 7.05.

Left atrial pressure was 2 to 5 mm. Hg higher than during the control period and bradycardia was also present, indicating that the depressant effects of high CO₂ were not completely reversed. Central venous pressure, systemic pressure, and cardiac output were the same or greater than on 5 per cent CO₂. The preparation could be shifted back and forth from 5 to 15 per cent CO₂, without further change in the physiologic variables, for periods of 30 to 40 min.

When the preparation was ventilated with 20 per cent CO₂ with a resulting arterial pH depressed below 7.0, 10 mg. of hydrocortisone were required to offset acidic failure, and the transient episode of failure was more pronounced. It would appear that within the range of pH studied (7.40 to 6.90), a concentration of 100 μg. per cent per 0.1 pH unit drop, is required to prevent acute acidic heart failure.

**DISCUSSION**

The positive inotropic effect of hydrocortisone on the acidotic failing heart is characterized by a delayed but sustained action. This effect is only obtained if the hormone is administered to the preparation 12 to 15 min. before ventilation with high CO₂ in O₂; its administration after the installation of severe failure is inoperative. But, once its action is manifest it is sustained for periods as long as 40 min. These properties have some analogy with those of the glycoside compounds. Furthermore, this hormone does not seem to affect any of the parameters of the nonfailing heart which were measured in the present series of experiments, within a pH range of 7.45 to 7.35.

Its action in this respect is quite different from that of epinephrine or norepinephrine which have a profound immediate positive chronotropic and inotropic effect in the nonfailing heart as well as in the acidotic-failing heart-lung preparation ventilated with 15 per cent CO₂ in O₂. Given at the rate of 4 μg./min. either of these sympathomimetic amines will rapidly and completely restore cardiac output, pressures and heart rate, to their exact control values. However, this effect is short acting and a constant infusion of epinephrine or norepinephrine must be maintained during the whole period of exposure to high CO₂ in order to prevent heart failure.

The partial reversal of cardiac acidotic failure by hydrocortisone in the heart-lung preparation would suggest that this hormone may also be operative, along with the sympathomimetic amines, in offsetting the depressant effect of hypercapnia in the intact animal, thus maintaining cardiovascular homeostasis in the course of respiratory acidosis. The mechanism of corticoid release during hypercapnia is not clear. According to Richards and Stein, it is dependent on the integrity of the hypophysis. However, the dose of hydrocortisone used to offset acidic heart failure produced in the preparation a level 25 to 50 times higher than the normal level of adrenals steroids in plasma which ranges from 10 to 20 μg. per cent. Taking the figures of Stein and Richards, this dose would correspond to the total amount secreted by the anesthetized dog breathing 20 per cent CO₂ for a period of 3 to 4 hours. Therefore, it is probable that, in the intact animal, increased corticoid secretion, if involved at all, is not the only factor operative in offsetting the cardiac depressant effect of CO₂. The role of the
HYDROCORTISONE IN THE ACIDOTIC HEART

sympathoadrenal system and of the increased production of circulating sympathomimetic amines has already been mentioned.

The observations reported in this series of experiments, may also indicate that the adrenal corticoids have a cardiotonic activity. In confirmation of this suggestion are the experiments of Emelee who showed that 10 to 25 µg. of compound B, F, and S had a positive inotropic action in the papillary muscle of the cat.

Several clinical reports point toward the possibility of a cardiotonic effect of the corticoids. Fleischbaker claims a similarity in action between cortisone and digitalis. Braun has reported marked improvement in patients with cor pulmonale who were given 3 to 10 mg. of ACTH by intravenous infusion or, as gel, 20 to 40 mg. intramuscularly for 5 to 9 days. Riemer has observed the favorable action of prednisone, 2.5 mg. three times daily over several months, in a series of patients with cardiac decompensation. However, no evidence of a direct cardiac effect of the hormone on the heart was noted.

Summary

Acute myocardial failure is observed when the denervated heart lung preparation is rendered acidic by increasing abruptly from 5 to 15 or 20 per cent the CO₂ concentration in the respiratory mixture of CO₂ and O₂. Such a failure does not occur when hydrocortisone succinate is administered to the preparation 12 to 15 min. before the onset of ventilation with high CO₂. Within the range of pH studied (7.40 to 6.90), a concentration of 100 µg. per cent per 0.1 pH unit drop, is required to prevent acute acidotic heart failure. These results may indicate that in the intact dog, the increased corticoid output of hypercapnia could be one of the factors counteracting the negative inotropic effect of CO₂ on the myocardium.

Acknowledgment

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SUMMARIO IN INTERLINGUA

Acute disfallimento myocardial es observate quando le enervate preparato de corde e pulmon es rendite acidotic per un augmento abrupte, amontante a inter 5 e 15 o 20 pro cento, in le concentration de CO₂ in le mixtura respiratori de CO₂ e O₂. Nulle tal disfallimento occurre, si succinato de hydrocortisone es administrate al preparato 12 a 15 minutas ante le initiation del ventilation a alte contento de CO₂. Intra le limites de pH studiate (i.e. ab 7,40 usque 6,90), un concentration de 100 µg pro cento pro omne reduction del pH per 0,1 unitates es requirite pro prevenir acute disfallimento acidotic del corde. Iste resultatos indica posiblemente que in le can intakte le augmentate rendimento de corticoid in hypercapnia es un del factores que contrabalancla le negative efecto inotropic que CO₂ exerce super le myocardio.

REFERENCES

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