Anemia-induced Changes in Cardiac Output in Dogs Treated with Dichloroisoproterenol

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With the collaboration of James G. Boyd

In 1957, it was reported from this laboratory that the production of acute severe anemia in dogs by the exchange of dextran solution for whole blood led to marked and rapid increases in the cardiac output. The mechanisms involved in this response are not yet clear, but the increased cardiac output was not diminished by previous adrenalectomy or adrenalectomy combined with ganglionic blockade by pentolinium bitartrate. With the availability of a new compound, dichloroisoproterenol (DCI), which blocks the increases in both the rate and force of contraction of the heart induced by electrical stimulation of cardiac postganglionic sympathetic nerves, or by intravenous injections of small doses of epinephrine or norepinephrine, it was of interest to ascertain whether this substance would modify the cardiac responses to experimental anemia.

Methods

Adult mongrel dogs, weighing between 10 and 20 Kg., were anesthetized with pentobarbital sodium (30 mg./Kg., I.V.). The mean arterial pressure was recorded on a kymograph by a mercury manometer attached to a polythene catheter in the right femoral artery; heart rate was determined from the electrocardiogram using a Grass polygraph. Cardiac output was determined by the direct Fick method. Oxygen consumption was measured with a Benedict-Roth spirometer connected to an endotracheal tube. Samples of arterial and mixed-venous blood (obtained from a catheter placed in the pulmonary artery with the aid of fluoroscopy) were drawn over 1-minute periods after the dog had been breathing oxygen for five minutes. Blood-gas analyses were done immediately, according to the method of Van Slyke and Neill. Arterial hematocrit levels were measured in Wintrobe tubes.

Two and one-half hours after the beginning of anesthesia, the first control cardiac output was measured. Three groups of experiments were performed. Two groups of dogs received dichloroisoproterenol (10 mg./Kg.) dissolved in 200 ml. saline and infused intravenously over a 20-minute period, and the other group (controls) received a similar infusion of saline. Thirty minutes after the infusion, another cardiac output measurement was made. One group of the DCI-treated dogs was followed for a period of 2.5 hours to determine the cardiovascular effects of dichloroisoproterenol per se. The other DCI-treated group and the untreated group were then made anemic.

Anemia was produced by exchange through the arterial catheter of 50 ml. of dextran (6 per cent) in saline for 50 ml. of blood; this was continued until the hematocrit level had fallen to less than 15 per cent. Cardiac output and other cardiovascular indices were measured 15, 30, and 95 minutes after completion of the exchange, which usually required 20 minutes.

Five dogs of the DCI-group were injected intravenously with epinephrine (2 /µg./Kg.) before, and at 150 minutes after, the administration of the dichloroisoproterenol, and their heart rates were followed for several minutes after each injection. The 150-minute post-DCI period was chosen to test the epinephrine-blocking activity, because this period corresponded to the end of the experiments in the anemia series.

To investigate the DCI-blocking action further and the possible effect of subsequent anemia on the blockade, four dogs were prepared as before. During the control period, the heart rate and arterial pressure were followed closely during occlusion of both carotid arteries, below the sinus, for 45 seconds and during tilting of the dog (head up) to 45 degrees from the horizontal for 60 seconds. These tests were repeated, and then DCI was injected, as before, in a dose of 10 mg./Kg., and the carotid occlusion and tilting tests were repeated again 15 minutes later. Thirty minutes after the DCI infusion, anemia was produced, as described above, by exchange of dextran for blood. During the anemic period at a time 45 minutes after completion of the exchange, the carotid occlusion and...
ANEMIA ON CARDIAC OUTPUT

Effects of Dichloroisoproterenol

TABLE 1

A. Cardiovascular effects

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Heart rate (beats/min.)</th>
<th>Cardiac output (ml./Kg./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control period</td>
<td>136.5 ± 3.95</td>
<td>172.6 ± 11.83</td>
<td>251.0 ± 35.95</td>
</tr>
<tr>
<td>30 minutes after DCI</td>
<td>122.5 ± 6.29</td>
<td>163.0 ± 5.22</td>
<td>233.0 ± 33.16</td>
</tr>
<tr>
<td>70° minutes after DCI</td>
<td>123.8 ± 6.25</td>
<td>160.0 ± 13.97</td>
<td>201.8 ± 25.08</td>
</tr>
<tr>
<td>100° minutes after DCI</td>
<td>128.0 ± 6.94</td>
<td>188.0 ± 12.44</td>
<td>178.4 ± 27.82</td>
</tr>
<tr>
<td>150° minutes after DCI</td>
<td>131.2 ± 6.88</td>
<td>191.0 ± 13.69</td>
<td>191.0 ± 24.25</td>
</tr>
</tbody>
</table>

B. Blocking effect on heart

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Change in heart rate in beats/min.; mean and 95 per cent confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>-20.8 (-6.3 to 18.4)</td>
</tr>
<tr>
<td>2 mg./Kg.</td>
<td>(21.5 to 42.5)</td>
</tr>
<tr>
<td>Carotid occlusion</td>
<td>0.7 (-0.8 to 2.2)</td>
</tr>
<tr>
<td>(45 seconds)</td>
<td>(11.7 to 24.5)</td>
</tr>
<tr>
<td>Head-up tilt</td>
<td>-4.7 (-6.7 to -2.7)</td>
</tr>
<tr>
<td>(90 seconds)</td>
<td>(22.7 to 28.7)</td>
</tr>
</tbody>
</table>

These times correspond to the 15-, 45-, and 95-minute postexchange measurements in the anemia series.

tilting tests were repeated. Following this, at 95 minutes after the exchange, hypoxemia was produced by having the dog breathe 5 per cent oxygen in nitrogen for 75 seconds.

Results

The effect of 10 mg./Kg. dichloroisoproterenol in five dogs on the mean arterial pressure, heart rate, and cardiac output are shown in table 1 (A). The effects of DCI on the positive chronotropic effect of injected epinephrine, carotid occlusion, and head-up tilting are given in table 1 (B). There is a tendency for arterial pressure, heart rate, and cardiac output to decrease immediately after the infusion of DCI, but they are not significantly different from the control values at any time up to the end of 150 minutes. It was found that as soon as 15 minutes after the DCI infusion, the effect of epinephrine on heart rate was blocked. Table 1 (B) shows that in the control period several adrenergic stimuli, including epinephrine, carotid occlusion, and tilting always increased the heart rate. Epinephrine given after the third measurement of cardiac output in the postexchange period—150 minutes after the DCI infusion—produced no change in heart rate or an actual decrease. Of even greater importance is the demonstration that DCI also blocked the effects of carotid occlusion and tilting immediately and when tested midway through the anemic period. Even as powerful an adrenergic stimulus as hypoxia was blocked by DCI: 95 minutes after the production of anemia, hypoxia led only to a decrease in heart rate. On the other hand, the arterial pressure was increased by each of the stimuli, although the pressor responses were somewhat less after DCI and less still during the subsequent anemic period. Thus DCI effectively blocked the action of adrenergic stimuli on the heart over the whole period of anemia studied in these experiments.

Figure 1 illustrates the minimal changes in cardiac output following DCI and the very large increases in output when the hematocrit level was acutely decreased by the dextran exchange.

The effects on the mean arterial pressure, hematocrit level, and cardiac output of the dextran-for-blood exchange in 9 untreated and 14 DCI-treated dogs are summarized in table 2. It will readily be seen that in both groups the cardiac output increased markedly with
the severe reduction in hematocrit level. There were minimal changes in heart rate and arterial pressure in both groups over the experimental period.

In figure 2, the changes in cardiac output and arterial oxygen content in the DCI-treated and control groups following the production of acute severe anemia are shown. The postinfusion (DCI or saline) and postexchange outputs are calculated as percentages of the control pre-exchange values taken as 100 per cent. It can readily be seen from the figure that DCI infusion did not affect the marked rise in cardiac output which occurred when the arterial oxygen content was lowered by the acute anemia.

**Discussion**

The results show that dichloroisoproterenol blocks the positive chronotropic effect of injected epinephrine and of several adrenegically mediated stimuli. This is in agreement
with the work of Moran and Perkins, who first demonstrated adrenergic blockade of the mammalian heart by DCI. They showed that the increases in both heart rate and force of contraction—the so-called beta effects—induced by electrical stimulation of cardiac postganglionic sympathetic nerves and by injected catecholamines were abolished by DCI, but the "alpha" effects (e.g., rise in arterial pressure) of the catecholamines were not abolished. In order to assure complete blockade, in the present experiments a dose of 10 mg./Kg. DCI was chosen; this dose was large enough to diminish somewhat the increases in arterial pressure ("alpha" effects) evoked by the various adrenergic stimuli and in three dogs, not included in the paper, led to death during the exchange procedure. Our results indicate that the DCI blockade persisted even after the production of severe anemia; in other words, exchange of dextran for blood did not appear to remove the DCI from the receptor sites in the heart.

The marked rise in cardiac output which regularly accompanies the production of severe acute anemia was not affected by blocking the heart with large doses of DCI. It may be argued that, although DCI can block the cardiac actions of exogenous catecholamines, the adrenergic transmitters are liberated in such close proximity to the receptor sites during anemia that DCI fails to block their effect. This possibility seems most unlikely in view of the evidence that DCI does block the effects of electrical stimulation of cardiac sympathetic nerves and of the reflexes induced by carotid occlusion, tilting, and hypoxia even during acute anemia.

Earlier studies by Nahas and preliminary reports from this and other laboratories suggested that the cardiovascular responses to acute anoxia and anemia were reduced by adrenalectomy, sympathectomy, or autonomic blockade. In 1957, we reported that adrenalectomy or adrenalectomy, plus ganglionic blockade, did not prevent the elevation in cardiac output induced by severe anemia; this led us to agree with Harrison, Blalock, Pilcher, and Wilson, who concluded from their experiments with anoxemia, that in the control of circulatory minute volume, chemical regulation is more important than nervous regulation and that the cardiac nerves play no role in the control of cardiac minute output. The present experiments suggest that whatever chemical regulation there may be it is unlikely, at least in the early stages of acute anemia, to involve the action of the catecholamines on the heart.

In figure 1 and table 2, it can be seen that as times goes on in the period of anemia the very high initial cardiac output decreases back towards the normal level. At least part of this may be due to a diminishing blood volume which is suggested by the tendency towards hemoconcentration; at the same time, there is an osmotic (dextran) diuresis. In earlier experiments in which plasma or...
Dextran was exchanged for blood, we showed that the cardiac output did not increase with erythrocyte depletion if hypovolemia occurred.

**Summary**

The cardiac output of anesthetized dogs was markedly elevated by the production of severe acute anemia by exchanging dextran for blood. Dichloroisoproterenol, in a dose which completely blocked the positive chronotropic effect of epinephrine and several reflexes, usually had minimal effects on the cardiac output. The cardiac responses to acute anemia were not different in the DCI-treated and the control groups. It is concluded that the effect of acute anemia on cardiac output is probably not mediated by the action of adrenergic substances on the heart.

**Acknowledgment**

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**References**


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