Sympathoadrenal System and Response of Heart to Acute Exchange Anemia

By T. D. LOVEGROVE, M.D., C. W. GOWDEY, D.Phil. and J. A. F. STEVENSON, M.D.

This report deals with a study of the relative roles that the sympathetic nervous system and adrenal medulla play in the cardiac responses to experimental anemia.

The study by Nahas1 and preliminary reports from this and other laboratories suggested that the cardiovascular responses to both acute anemia and acute hypoxia are reduced by adrenalectomy, sympathectomy or autonomic blockade. The following experiments were done to re-evaluate the relative importance of the sympathetic nerves and the adrenal medulla in the cardiac responses of the dog to acute anemia produced by exchanging dog plasma or dextran for equal volumes of whole blood.

METHODS

Mongrel dogs weighing between 7.7 and 23.6 Kg. were used. Some of these were adrenalectomized several weeks before experiment and maintained on daily intramuscular injections of 8 mg. of cortisone acetate in saline suspension (Cortone) and 1.5 mg. of deoxycorticosterone trimethylacetate (Percorten trimethylacetate). The diet consisted of meat and fox chow with 0.6 per cent saline for drinking water.

For the experiment all animals were maintained under light sodium pentobarbital anesthesia. The adrenalectomized dogs received a slow intravenous infusion of 50 mg. of hydrocortisone sodium hemisuccinate (Solu-Cortef) in 100 ml. of normal saline, and the intact dogs the same volume of saline during the 2.5-hour period that elapsed between the induction of anesthesia and the beginning of the experiment. The mean arterial pressure was recorded on a kymograph by a mercury manometer attached to a cannula in the right femoral artery and the mean pulmonary pressure (PAP) from a saline manometer attached to the catheter in the pulmonary artery. All pressure readings were expressed from the estimated level of the heart, which was arbitrarily chosen as 5 cm. above table level. Cardiac output was determined by the direct Fick method. Oxygen consumption was measured with a Sanborn Metabolator connected to an endotracheal tube. Samples of arterial and pulmonary arterial blood were taken over a 1 to 2 min. period after the animal had been breathing oxygen for 5 min. Blood-gas analyses were done immediately according to Peters and Van Slyke.

Arterial hematocrits were measured in Wintrobe tubes. During the exchange the course of the anemia was immediately checked by a rapid hemoglobin method2 which showed good correlation with the measured hematocrit.

Plasma volume was determined with radioactive iodinated human serum albumin by a method similar to that described by Krieger, Storaasli, Friedell, and Holden.3 The hematocrit reading was corrected4 to estimate the total body hematocrit and thus the blood volume could be calculated. The control blood volume was determined 2 hours after the anesthetic was injected; the blood volume during anemia was measured 30 min. after the end of the exchange.

When the blocking agent, pentolinium bitartrate (Ansolysen) was used, 5 mg./Kg. were injected intravenously after a control cardiac output had been measured. Fifteen minutes later a second cardiac output, which was used as the reference pre-anemic control in these animals, was determined.

The anemia was produced by exchange through the arterial catheter of 50 ml. of dextran in saline (Intradex) or 50 ml. of plasma for 50 ml. of blood: this was continued until the hematocrit had fallen to between 15 and 20 per cent. The cardiac output was determined 15 min. later. The exchange was then continued until the hematocrit reached 7 per cent and the cardiac output was measured 15 and 45 min. later.

In some experiments the response of the cardiac output to an intravenous infusion of epinephrine (1 ìg./Kg./min.) was measured during the control period and 1 hour after the completion of the exchange. In other experiments, after the postanemic measurements had been made, an infusion of anemic blood (hematocrit 8 to 10 per cent) was given to produce hypervolemia, and the cardiac output determined 15 min. later.

Plasma was collected from anesthetized, heparinized, donor dogs; penicillin and streptomycin were added and it was refrigerated until it was used.
RESULTS

Table 1 compares some of the important cardiovascular indices before and after the production with plasma or dextran of an acute exchange anemia in intact, adrenalectomized and adrenalectomized-blocked dogs. There was, as usual, individual variation in the control cardiac outputs. Nash, Davis, and Woodbury have shown in dogs during pentobarbital anesthesia that the cardiac output, after an initial fall, remains fairly constant from the third to the fifth hour. Accordingly, in the present experiments the control output taken 3 hours after the induction of anesthesia was used as the basis for calculating the relative effects of anemia in each individual. Pentolinium caused a significant fall of some 70 ml./Kg./min. in cardiac output, and the effects of anemia in these series have been referred to the postpentolinium control level.

The control cardiac outputs, arterial pressures and arterial oxygen contents of the adrenalectomized animals were not different from those of the intact groups. Anemia appeared to increase the cardiac output in all situations, the results were variable, and the increase was statistically significant (.05) only in the dextran series. In this series the intact and adrenalectomized-blocked groups, and all but 1 animal of the adrenalectomized group, showed significant increases; in the exception, a later infusion of only 7.1 ml./Kg. of low-hematocrit (8 per cent) blood did result in a prompt rise of cardiac output. There is certainly no indication that adrenalectomy alone or combined with sympathetic blockade reduced the response of the cardiac output to either plasma or dextran exchange anemia.

The close relation in these experiments between the increasing coefficient of oxygen utilization and the decreasing arterial oxygen content during the production of anemia is shown clearly in figure 1. The graph also shows that with moderate anemia (arterial oxygen around 10 volumes per cent) the cardiac output fell below control levels, whereas with severe anemia (arterial oxygen below 5 volumes per cent) it rose. This inverse correlation in severe anemia was significant (r = —0.8; p < .001) in the intact and adrenalectomized dogs made anemic with dextran, but not in those given plasma. Total peripheral resistance fell in all groups. The mean pressure in the pulmonary artery usually increased with severe anemia.

In the intact groups it was found that 23 per cent more (p < .001) blood per kilogram body weight had to be removed from the dogs exchanged with plasma than from those exchanged with dextran to produce a comparable degree of anemia; the mean control hematocrit

| Table 1.—Summary of Important Cardiovascular Indices in Acute Anemia |
|--------------------------|---------------------|---------------------|---------------------|---------------------|
| Group | No. of exp. | Cardiac output (ml/Kg/min.) | Art. P. (mm. Hg) | T.P.R. (mm. Hg/ml/min./Kg.) | O\textsubscript{2} Util. (%) |
|      |           | Control | Control | Anemia $|$ | Control | Control | Anemia $|$ | Control | Control | Anemia $|$ |
| Plasma | Intact | 0 | 139 ± 17* | 161 ± 12 | 118 ± 7 | 88 ± | 80.93 ± 300.54 ± 1321.9 ± 1167.9 ± 2.4 |
|        | Adrx. $+$ | 9 | 113 ± 25 | 161 ± 27 | 109 ± 8 | 77 ± | 101.24 ± 210.49 ± 0.4257.3 ± 3.355.9 ± 4.0 |
|        | Pento $+$ | 6 | 125 ± 47 | 161 ± 18 | 82 ± 8 | 77 ± | 210.68 ± 0.47 ± 0.6287.3 ± 3.465.25 ± 3.2 |
| Dextran | Intact | 5 | 127 ± 22 | 208 ± 8 | 124 ± 10 | 121 ± | 61.10 ± 180.59 ± 0.0522.4 ± 5.354.8 ± 5.7 |
|        | Adrx. $+$ | 4 | 152 ± 18 | 224 ± 30 | 121 ± 7 | 127 ± | 130.85 ± 210.68 ± 14.183.1 ± 1.550.9 ± 2.9 |
|        | Pento $+$ | 4 | 80 ± 15 | 266 ± 30 | 75 ± 13 | 107 ± | 90.92 ± 220.41 ± 0.0432.6 ± 8.334.4 ± 3.5 |

* Mean ± S.E.M.
$+$ Adrx.—adrenalectomized.
Pento.—pentolinium bitartrate, 5 mg./Kg.
$*$ The values shown under anemia are of the maximum response whether obtained at 15 or 45 min.
Fig. 1. Relation of coefficient of oxygen utilization and of cardiac output to arterial oxygen content in acute exchange anemia.

levels of 44.6 and 45.0 per cent were eventually reduced to 8.1 and 8.0 per cent respectively.

The response of the arterial pressure also differed between the plasma and dextran intact groups. The exchange of plasma, which had been taken from healthy dogs and stored in the refrigerator for only 1 or 2 days, produced a moderate but significant rise in arterial pressure that was transient. At the end of the exchange the arterial pressure was significantly lower than the pre-anemic level. On the other hand, the dextran exchange produced no appreciable change in blood pressure.

Table 2 shows, in the 4 groups, the mean blood volumes and cardiac outputs measured during the control period and 45 min. after the production of anemia; and in 3 groups, the effect of a postexchange infusion of anemic blood (hematocrit 8 per cent). In the adrenalectomized group later given dextran the control blood volume was less than in the other groups, but this was not associated with a reduced cardiac output. In the adrenalectomized, pentolinium-blocked group the control blood volume was normal, perhaps because of the lowered capillary hydrostatic pressure, since the cardiac output was reduced by the ganglionic blockade. The blood volume was reduced by the exchange of plasma for whole blood in the intact group, and, in the face of this, the cardiac output failed to increase significantly with the anemia; in these animals restoration of the volume to normal, or slightly above, by infusion of anemic blood resulted in an abrupt and marked increase in cardiac output. No significant changes in blood volume were found in the anemic period in any of the dextran groups, and large increases in cardiac output consistently accompanied the anemia. The postexchange infusion of a solution of dextran with erythrocytes added to produce a hematocrit level of 8 per cent had very little effect on the cardiac output compared with that produced by the infusion of low-hematocrit blood in the plasma-exchanged animals. The arterial oxygen content was reduced equally in all groups by the exchange procedure, and it was not increased by the postexchange infusion of anemic blood. The total peripheral resistance and the venous oxygen content fell in all groups. The pulmonary artery pressure rose in the 3 dextran groups but not in the plasma group until the coincident hypovolemia had been corrected.

There was a negative correlation between the change in cardiac output and the change in total peripheral resistance in both the plasma and the dextran series: \( r = -0.76 \) (\( p < .01 \)) and \( r = -0.87 \) (\( p < .01 \)), respectively. In the dextran series there was a negative correlation, \( r = -0.87 \) (\( p < .001 \)), between the change in cardiac output and the change in the coefficient of oxygen utilization. In the plasma but not in the dextran series, the changes in arterial and in pulmonary artery pressures were related to the changes in blood volume: \( r = 0.70 \) (\( p < .02 \)) and \( r = 0.67 \) (\( p < .02 \)), respectively; the changes in pulmonary artery pressure were also correlated with the changes in cardiac output \( (r = 0.77 \ p < .01) \).

The infusion of epinephrine usually led to an increase in arterial pressure and cardiac output in both the control and anemic periods. The cardiac output appeared to increase more in the dogs exchanged with plasma than in those with dextran; smaller increases were produced by epinephrine during anemia in the adre-
SYMPATHOADRENAL SYSTEM IN ACUTE EXCHANGE ANEMIA

Table 2.—Changes in Blood Volume and Cardiac Output in Exchange Anemia

<table>
<thead>
<tr>
<th>No.</th>
<th>Blood volume</th>
<th>Cardiac output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Anemic 45 min.</td>
</tr>
<tr>
<td>1. Intact-Plasma</td>
<td>6</td>
<td>90.5 ± 7.5§</td>
</tr>
<tr>
<td>2. Intact-Dextran</td>
<td>5</td>
<td>81.4 ± 3.7</td>
</tr>
<tr>
<td>3. Aдрx.*-Dextran</td>
<td>3</td>
<td>71.3 ± 8.0</td>
</tr>
<tr>
<td>4. Aдрx.*-Pento.†-Dextran</td>
<td>4</td>
<td>90.2 ± 5.3</td>
</tr>
</tbody>
</table>

* Adrx.—adrenalectomized.
† Pento.—pentolinium bitartrate, 5 mg./Kg.
§ Mean ± S.E.M.

Discussion

The control cardiac outputs shown in table 1 vary widely from animal to animal, but the mean values are in the same range as those obtained by other investigators.6-9 With adequate adrenocortical substitution therapy the control cardiac output, arterial pressure, hematocrit level and arterial oxygen content of our adrenalectomized dogs were not significantly reduced from those of the intact groups. Nor were the cardiovascular responses to acute anemia significantly reduced from those of the control groups by adrenalectomy or by adrenalectomy and ganglionic blockade. It therefore appears that an intact adrenal medulla is not essential to the production of an increased cardiac output by acute anemia; nor does sympathetic blockade in an anesthetized, adrenalectomized animal reduce this response.

Nahas et al.1 found that their non-narcotized, adrenalectomized dogs had low hematocrit values (average 33 per cent) and high resting heart rates (average 188); their animals were given only desoxytocorticosterone acetate, and hypoxia did not cause the usual increases in heart rate and cardiac output. The authors point out, however, that under these circumstances, it is not possible to draw a definite conclusion because any adaptive mechanism might already be operating at close to its maximum. On the other hand, in 1927, Harrison, Blalock, Pilcher, and Wilson9 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 tension of oxygen in the coronary blood—and hence in the heart muscle—is the most fundamental physiologic factor in the regulation of the circulatory minute volume." In their acutely adrenalectomized dogs severe hypoxia produced a moderate or marked increase in cardiac output provided that the pre-anoxemic cardiac output was not too low from shock.

Pentolinium in a dose of 5 mg./Kg. blocks cardiovascular reflexes involving the vagus and sympathetic nerves for at least 6 hours10 and, as in the present experiments, reduces the cardiac output. The marked increases in oxygen utilization with small increases in cardiac output during moderate anemia (hematocrit 30 to 15 per cent) have also been observed in other investigations.6, 11

Blalock and Harrison11 found that when the circulation was not handicapped by a diminished blood volume, chronic experimental anemia caused the cardiac output to increase. In our experiments the exchange of dextran for blood produced anemia without reducing the blood volume and the cardiac output increased markedly, whereas the exchange of plasma for blood produced hypovolemia as well as anemia and the cardiac output did not increase. This hypovolemia may have been due in part to a more rapid removal of plasma proteins by the liver and other pathways, to

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differences in the osmotic pressure of the two solutions, or to some substance in the infused plasma. These observations emphasize that an adequate blood volume is essential whereas the sympathoadrenal system is not essential to the response of the cardiac output to severe anemia.

SUMMARY

An increase of cardiac output after severe, acute, exchange anemia was observed in chronically adrenalectomized dogs on adequate supportive therapy, as well as in intact dogs. Production of anemia by the exchange of plasma for equal volumes of blood led to a decrease in blood volume, and the cardiac output did not increase until this hypovolemia had been corrected. Dextran exchange did not reduce the blood volume and consequently the cardiac output showed an immediate response to the anemia. Ganglionic blockade did not modify the response of the adrenalectomized animals.

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