Hemodynamic Effects of Anemia with and without Plasma Volume Expansion

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With the collaboration of John A. Ward, M.D.

Hypervolemic anemia and normovolemic anemia were produced in dogs. Cardiac outputs increased comparably with similar degrees of anemia in the hypervolemic and normovolemic animals. No significant association between right atrial mean pressure and cardiac output was found. Right atrial and pulmonary arterial pressures increased in a degree comparable to blood volume increase. Systemic mean pressures did not change significantly; there was a significant decrease in total peripheral resistance. The results are consistent with the concept that the increase in cardiac output occurring with hypervolemic anemia is related primarily to the anemia and not to the increase in blood volume.

STUDIES by Witham, Fleming and Bloom1 have shown that the infusion of 500 ml. of 6 per cent isoncotic dextran in man at a rate of 25 ml./min. produces an average increase of cardiac output of 38 per cent. The result of such an infusion is to increase blood volume and to produce an anemia by dilution of hemoglobin. Since either mechanism could account for the increase in cardiac output, the present study is designed to evaluate the respective roles of anemia and plasma volume expansion in the increase of cardiac output occurring with dextran infusion.

The essential features of the experimental design were as follows. One group of dogs were made progressively anemic by bleeding and replacing the volume of blood removed with an equal volume of isoncotic dextran. In a second group of dogs, comparable degrees of anemia were produced by successive infusions of isoncotic dextran without preliminary bleedings. Thus the bled and dextran-infused dogs would tend to have normovolemic anemia; the unbled, dextran-infused dogs would tend to have hypervolemic anemia.

METHODS

The studies were performed upon 21 fasted dogs, whose weights were from 10.9 to 29 Kg. The animals were anesthetized with Nembutal, 25 mg./Kg. i.v. Supplemental Nembutal in amounts of 25 to 50 mg. was given at intervals of 30 minutes to one hour, in order to keep the level of anesthesia constant. Number 9 cardiac catheters were inserted into the pulmonary artery and right atrium by fluoroscopic visualization. A no. 12 cannula was inserted into the femoral artery or common carotid artery. A no. 32 endotracheal tube was placed in the trachea for the collection of expired air. Right atrial, pulmonary arterial, and systemic arterial pressures were recorded upon the Sanborn Poly-Viso Electrocardiograph, using Sanborn Electromanometers. Mean pressures were determined by electrical integration. Five centimeters above the animal board was taken as zero in pressure measurements. Plasma volumes were determined with T-1524 dye, the dye concentrations being read upon the Coleman Jr. Spectrophotometer. Whole blood volumes were calculated from plasma volume and hematocrit. Cardiac outputs were measured by the Fick principle. Three minute samples of expired air were collected in Douglas bags, measured in a wet-test meter and analyzed in the Scholander 0.5 ml. gas analyzer. Duplicates were required to check within 0.04 per cent for both carbon dioxide and oxygen. Midway during the collection of expired air, heparinized blood samples were collected from the pulmonary artery and femoral artery over a period of one minute. These blood samples were stored in ice over mercury, and were analyzed for oxygen in the Van Slyke manometric apparatus. Duplicate samples were required to check within 0.2 ml./100 ml.

PROCEDURE

After insertion of endotracheal tube, arterial cannula, and pulmonary arterial and right
atrial catheters, control measurements of blood volume, cardiac output and pressures were made in twenty-one dogs. Eleven dogs were then given, at approximately forty minute intervals, three separate infusions over a five minute period of 6 per cent isoncotic dextran solution equal to 2 per cent, 3 per cent and 3 per cent of body weight respectively (unbled dogs). The measurements of blood volume, cardiac output, and pressures were repeated twenty to thirty minutes after each infusion. Ten other dogs were bled from the femoral artery on three separate occasions of 1 per cent, 2 per cent and 3 per cent of body weight respectively (bled dogs). After each bleeding, the volume of blood removed was replaced with an equal volume of 6 per cent isoncotic dextran. Measurements of blood volume, pressures and cardiac output were repeated twenty to thirty minutes after bleeding and twenty to thirty minutes after each dextran infusion.

**Results**

The results are summarized in tables 1 and 2. There was no significant change in whole blood volume of the bled dogs. In the unbled dogs, blood volume increase was significant. The mean increase in blood volume in this group was $88 \pm 10$ per cent; $p \leq 0.001$.

As shown in tables 1 and 2, cardiac output increased significantly after infusion in both the bled and unbled dogs. In the bled dogs, control hemoglobins were 9.4 to 14.1 Gm./100 ml. of blood. After production of moderate anemia by bleeding and dextran replacement, the hemoglobin then being 7.7 to 10 Gm., a significant increase in cardiac output was observed. In the unbled dogs, the first dextran infusion produced a more severe degree of anemia than this in the majority of animals, so that no comparable observation could be made in this group. After production of severe anemia, with a hemoglobin level of 4 to 6.2 Gm., a significant increase in cardiac output was observed in both the bled and unbled groups of dogs. Cardiac outputs of normovolemic and hypervolemic dogs during severe anemia were not significantly different; mean difference $33 \pm 27$ ml./Kg./min.; $p \geq 0.2$.

There was no significant decrease in cardiac output after the first bleeding of 1 per cent of body weight without dextran replacement. Control cardiac outputs were from 94 to 284 ml./Kg./min.; mean, $180 \pm 18$ ml. After bleed-
TABLE 2.—Hemodynamic Effects of Anemia with Hypervolemia
(Umbled Dogs)

<table>
<thead>
<tr>
<th>Determination</th>
<th>Control</th>
<th>After final infusion</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Range</td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>Whole Blood Volume ml.</td>
<td>1043–2448</td>
<td>1851–5917</td>
<td>+1519 ± 270</td>
</tr>
<tr>
<td>Cardiac Output, ml./Kg./min.</td>
<td>51–321</td>
<td>160–439</td>
<td>+130 ± 33</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>51–321</td>
<td>160–439</td>
<td>+132 ± 32</td>
</tr>
<tr>
<td>Systemic Pulse Pressure, mm. Hg</td>
<td>22–62</td>
<td>40–75</td>
<td>−22.7 ± 2.2</td>
</tr>
<tr>
<td>Systemic Mean Pressure, mm. Hg</td>
<td>60–165</td>
<td>90–160</td>
<td>+13 ± 5.5</td>
</tr>
<tr>
<td>Total Peripheral Resistance, Dynes/sec./cm.²</td>
<td>1825–4995</td>
<td>1212–4320</td>
<td>−1589 ± 430</td>
</tr>
<tr>
<td>Right Atrial Mean Pressure, mm. Hg</td>
<td>0–7</td>
<td>3–16</td>
<td>+6.3 ± 1.6</td>
</tr>
<tr>
<td>Pulmonary Arterial Mean Pressures</td>
<td>8–19</td>
<td>16–35</td>
<td>+11.2 ± 2.3</td>
</tr>
</tbody>
</table>

-ing, cardiac outputs were from 81 to 201 ml./Kg./min.; mean, 166 ± 13 ml./Kg./min. The mean decrease of 14 ± 16 ml./Kg./min. is not significant; p ≥ 0.4.

Significant decrease in hematocrit was observed in both groups of dogs following dextran infusion (tables 1 and 2). A regression curve was plotted showing the relationship between the per cent change from control cardiac output and the per cent change from control hematocrit, (fig. 1). Eliminated from this figure and calculation were dogs no. 18 and no. 21, both in the unbled group. These dogs were in anesthetic shock initially, and showed great increases in cardiac output of 510 per cent and 210 per cent following the first dextran infusion. A significant negative regression of cardiac output on hematocrit was found; b = −1.3819; t = 4.31; p ≤ 0.001.

Systemic pulse pressure showed no significant increase in the normovolemic anemic animals, but did show a significant increase in the hypervolemic anemic animals, (tables 1 and 2). A regression curve was plotted to show the relationship between the per cent change in cardiac output and the product of pulse pressure and heart rate. A highly significant association was found; b = 2.0344; t = 7.756; p ≤ 0.001. Systemic mean pressures showed no significant change in either group of dogs, and total peripheral resistance showed a significant decline in both groups (tables 1 and 2). Regression of per cent change in total peripheral resistance on per cent change in hematocrit showed no significant association; b = 0.308; t = 1.94; p ≥ 0.05.

Right atrial mean pressure showed no significant increase in the bled dogs, but did show a significant increase in the unbled dogs. In the unbled dogs, a regression curve of change in cardiac output on right atrial mean pressure showed no significant association; b = −0.121; t = 0.02; p ≥ 0.9. In the entire group, a regression curve was plotted to show the association between whole blood volume and right atrial mean pressure (fig. 2). The regression of right atrial mean pressure (mm. Hg change from control) on whole blood volume (ml. change from control) is significant; b = 0.0027; t = 4.91; p ≤ 0.001. In the entire group of dogs, a regression curve (fig. 3) was plotted to show the association between pulmonary arterial pressure and whole blood volume. There was a significant association statistically; b = 0.0042; t = 2.77; p ≤ 0.01. Regression of per cent increase in cardiac output on per cent increase in whole blood volume showed no significant association; b = 0.253; t = 0.10; p ≥ 0.9.
Both groups of dogs showed a significant increase in pulmonary arterial pressure (tables 1 and 2). The mean increase in pressure was $7.2 \pm 2.6$ mm Hg greater in the hypervolemic dogs. This difference was significant; $p = 0.02$. In unbled dogs, the mean increase in pulmonary arterial pressure was $5.9 \pm 2$ mm Hg greater than the mean increase in right atrial pressure. This difference was significant; $p \leq 0.02$.

**DISCUSSION**

Increase in cardiac output was observed to follow bleeding with dextran replacement by Wilson and associates in man and by Sunahara and Beck in dogs. Our observations in the bled dogs are in agreement with the observations of these writers. However, we found significant increase in cardiac output at a higher hemoglobin level than did Sunahara and Beck.
in dogs or Brannon, Merrill, Warren and Stead in studies of chronic anemia in man. Sunahara and Beck found no consistent increase in cardiac output with normovolemic anemia until the hematocrit fell below 14. The studies of Sunahara and Beck were made during continuous bleeding and infusion, without allowing an interval for adjustment as we did in our observations. Therefore it is possible that in their studies, the degree of anemia was changing too rapidly to determine the true hemoglobin level at which cardiac output is affected. Brannon and coworkers found, in their studies of chronic anemia in man, no consistent change in the circulation when the hemoglobin was above 7 Gm./100 ml. or about 50 per cent. Since we did not make repeated observations of cardiac output at a given degree of anemia, it would not be justified to conclude that permanent elevation of cardiac output would be found at a hemoglobin level of 7.7 to 10 Gm./100 ml. of blood. The fact that dogs with and without expansion of whole blood volume showed no significant difference in increase of cardiac output at comparable degrees of anemia suggests that anemia and not increase in whole blood volume is primarily responsible for the increase in cardiac output. Ferguson, Shadle and Gregg, however, found increase in cardiac output of dogs whose blood volume was expanded by transfusion of whole blood. These authors measured cardiac outputs during rather than after rapid infusion of blood which may explain their observation of an increase in cardiac output. During moderate rate of blood infusions in the closed chest dog, these workers observed no impressive increase in cardiac output.

The increase in right atrial and pulmonary arterial pressures in the unbled dogs is probably related to the increase in whole blood volume. A significant association was shown between right atrial mean pressure increase and whole blood volume increase, and between pulmonary arterial pressure rise and increase in whole blood volume. Similar pressure increases following infusion of saline, acacia, and dextran have been observed. The greater increase in pulmonary arterial than in right atrial pressure is of interest. Observations in two dogs have shown that the elevation in pulmonary arterial pressures are accompanied by equal or greater elevations in left ventricular diastolic pressure.

Similar increases in left ventricular diastolic pressure following hypervolemia produced by blood transfusion were observed by Gregg and Wiggers and by Ferguson and associates. Gowdey, Hatcher and Sunahara have suggested that the higher filling pressure of the left ventricle is responsible for the greater elevation of pulmonary arterial than of right atrial pressure accompanying hypervolemia.

The lack of positive association between right atrial mean pressure and cardiac output is in keeping with the concept that the cardiac output in these anemic dogs is increased primarily by anemia and not by increase in ventricular filling pressure, which is related to the degree of hypervolemia. Similar lack of relation between ventricular filling pressure and cardiac output has been found in man by Stead and Warren and by Fleming and Bloom, and, in the dog, by Ferguson and associates. Other studies have shown that hypervolemia without anemia does not lower the total peripheral resistance. The fact that our anemic dogs with and without hypervolemia showed comparable degrees of diminution in total peripheral resistance suggests the possibility that anemia increases the cardiac output at least in part by lowering the total peripheral resistance; however, our failure to find significant association between change in total peripheral resistance and change in degree of anemia suggests that other factors are involved. This is in keeping with the concept that in the intact animal, the heart's output is regulated to keep the systemic arterial blood pressure constant.

**SUMMARY**

Hypervolemic anemia and normovolemic anemia were produced in dogs. Cardiac outputs increased comparably with similar degrees of anemia in the hypervolemic and normovolemic animals. No significant association between right atrial mean pressure and cardiac output was found. The hypervolemic dogs showed an increase in right atrial pressure which was correlated with the increase in whole blood volume. Pulmonary arterial pressures increased
in both groups of dogs, more so in the hypervolemic group. Both groups of dogs showed no significant change in systemic mean pressure and a significant decrease in total peripheral resistance. The results are consistent with the concept that the increase in cardiac output occurring with hypervolemic anemia is related primarily to the anemia and not to the increase in blood volume.

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SUMMARY IN INTERLINGUA

Anemias hyper- e normovolemic esseva producite in canes. Le rendimentos cardiac se augmentava comparabilemente con simile grados de anemia in le animales hyper- e normovolemic. Nulle association significative inter le valores median del pression dextero-atrial e le rendimento cardiac esseva trovate. Le canes hypervolemic monstrava un augmento del pression dextero-atrial que esseva correlazione con le augmento del volumine total de sanguine. Pressiones pulmo-arterial esseva augmentate in ambe gruppos de canes. In le gruppo hypovolemic iste augmento esseva plus que in le gruppo normovolemic. Ni le un ni le altero gruppo de canes mostrava ulle significative alteration in le pression systemic median; ambes mostrava un significative reduction del total resistentia peripheric. Le resultatos es de accordo con le concepto que le augmento del rendimento cardiac occurrente con anemia hypervolemic es relateate primarimente al anemia e non al augmento del volumine de sanguine.

REFERENCES

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