The Circulatory Adjustments to Posthemorrhagic Anemia in Dogs

By J. D. Hatcher, M.D., Ph.D., F. A. Sunahara, Ph.D., O. G. Edholm, M.B., B.Sc., and J. M. Woolner, M.D.

Several measures of cardiovascular function were made in nine dogs before, during, and after the production of anemia by daily venesections. Stress is laid on the time sequence of the various changes in the circulation and their relation to each other. From the results obtained it was concluded that the elevated cardiac output observed in anemia was not the result of an increase in right atrial pressure or a decrease in tissue oxygen tension, per se. It is suggested that the increased cardiac output may be due to a slowly elaborated or slow-acting humoral agent produced as a result of tissue anoxia.

The various cardiovascular adjustments which occur in anemia are well described. Less is known about the time relationships of these changes during the development of the anemia and during treatment. Further, the mechanism responsible for the compensatory elevation in cardiac output has not been clarified.

This paper is concerned with an investigation of these points in dogs made anemic by daily bleedings.

METHOD

The following cardiovascular measurements and calculations were made in nine dogs before, during and after the production of anemia by venesections of approximately 100 to 200 cc. per day for six to eight days. All observations were made with the dogs anesthetized with sodium pentobarbital. An initial dose of 30 mg. per kilogram was given intravenously followed by 60 to 120 mg. intramuscularly every one to two hours, as necessary.

The cardiac output was determined by the direct Fick technic. The oxygen content of arterial and mixed venous blood (right ventricle) was determined by the method of Peters and Van Slyke. Oxygen consumption was measured with a Benedict-Roth type of spirometer. Mean pressures from the right atrium were measured with a cardiac catheter connected to a saline manometer and from a peripheral artery through an inlying needle connected to a mercury manometer. The heart rate was counted from the arterial pressure tracing. The hemoglobin was determined by the method of King and Gilchrist. The plasma volume was measured by the method of Harrington and associates, and the hematocrit was measured in Wintrobe tubes. The peripheral blood flow in the calf (muscle) and paw (skin) was determined by an adaptation of the technic described by Barcroft and Edholm. The total blood volume, total systemic resistance and per cent utilization of arterial oxygen were calculated. The details of these technics have been previously described.

Three control studies were carried out on different days prior to the period of daily venesections. When the cardiac output began to rise the daily bleedings were stopped and the responses of the animal observed. In three instances (dogs 7, 8, and 9) the daily venesections were stopped when the cardiac output reached very low levels. Observations were made at arbitrary intervals during and after the venesection phase. During the bleeding period, experiments were carried out 18 hours after the preceding venesection and prior to the venesection of the day of study. Venesections were carried out under light sodium pentobarbital anesthesia on days when observations were not made.

The above measurements were also made in five dogs before, during, and after the daily administration of an anesthetizing dose of sodium pentobarbital on six to eight consecutive days.

The effects on the cardiovascular system of four to five hours of sodium pentobarbital anesthesia were measured in five dogs. These results have been presented elsewhere.

RESULTS

Control Experiments

A statistical analysis of the effects of the daily administration of an anesthetizing dose of sodium pentobarbital is shown in table 1.
No significant change ($P > 0.05$) was noted in any variable except hemoglobin which showed a progressive decrease due to repeated blood sampling.

**Anemia Experiments**

Determinations were made of hemoglobin, cardiac output, oxygen consumption, and the oxygen content of arterial and mixed venous blood.

**Hypodynamic Phase.** The cardiac output decreased to a variable extent during the bleeding period and reached minimum values midway or towards the end of this period (figs. 1 and 2). The decrease in hemoglobin at the time of the minimum cardiac output in all animals except dog 6 in which a parallel rise in the arteriovenous oxygen difference occurred mainly through a rise in venous oxygen content (table 3). These findings considered with the fact that neither the hemoglobin nor the oxygen consumption changed during this period (table 3) indicate that the tissue oxygen tension was increased or at least unchanged during the hypodynamic response over that observed at the end of the venesection period when the cardiac output was either low, normal or beginning to rise.

**Hyperdynamic Phase.** The cardiac output rose slowly to a maximum one to seven days after the final venesection (figs. 1 and 2). The average hemoglobin level at the time was not statistically different from the average value observed at the end of the venesection period (table 3). In dog 9 the cardiac output rose 13 days after the final venesection at which time a marked increase in oxygen consumption and partial recovery of the hemoglobin level was noted.

The gradual rise in cardiac output was accompanied by a parallel decrease in arteriovenous oxygen difference. This decrease in arteriovenous oxygen difference occurred during the venesection phase and was greatest when the cardiac output was minimal (table 2).
The results, considered from the aspect of per cent utilization of arterial oxygen and cardiac output during the hyperdynamic phase, can be divided into two groups. In one group of five dogs the essential adjustment was an elevated cardiac output. The per cent utilization was within or below control limits. In the other group of four dogs, the increase in cardiac output was less marked, and the per cent utilization of arterial oxygen was increased.

**Recovery Phase.** Following the peak response, the cardiac output fell gradually to control levels when the hemoglobin was, in most instances, only partially recovered. As shown in figure 1, the cardiac output was usually still elevated at hemoglobin levels which, during the venesection period, were associated with a low or normal cardiac output.

**Mean Right Atrial Pressure.** In most cases there was a transient fall in right atrial pressure during the early part of the venesection phase (figs. 1 and 2); subsequently the right atrial pressure increased to control levels or above. During the last half of the venesection phase this elevation was very striking and coincided with the minimum cardiac output in some instances (fig. 2).

During the hyperdynamic phase the right atrial pressure was at or above control levels; on the average a significant increase was observed. No correlation was obtained between right atrial pressure and other indexes.

**Mean Arterial Blood Pressure and Total Peripheral Resistance.** No consistent response in mean arterial blood pressure was found during or after the venesection period. The calculated total peripheral resistance increased during the bleeding period and reached a maximum at the time of the lowest cardiac output. Following the final venesection, minimal resistance values were observed coincident with the maximum cardiac output.

**Heart Rate and Stroke Output.** The heart rate was increased and the stroke output decreased at the time of the minimum cardiac output. When the cardiac output was at a maximum the stroke output was increased and the average heart rate was above control levels, but
TABLE 2.—Cardiovascular Effects in Nine Dogs Following Daily Venesections of 100 to 200 cc. per Day for Six to Eight Days

<table>
<thead>
<tr>
<th>Period</th>
<th>Hemoglobin gm./100 cc</th>
<th>A-V O₂ difference cc./100 cc.</th>
<th>O₂ Consumption cc./min.</th>
<th>Cardiac Output L/min.</th>
<th>Heart Rate beats/min.</th>
<th>% Utilization Arterial O₂</th>
<th>Pressures</th>
<th>Total Systemic Resistance Dyne. sec. cm.</th>
<th>Peripheral Blood Flow cc./100 cc tissues/min.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Right Atrial mm Hg</td>
<td>Arterial Pressure mm Hg</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>13.94</td>
<td>4.49</td>
<td>115.5</td>
<td>2.72</td>
<td>109</td>
<td>29.5</td>
<td>-42</td>
<td>123.6</td>
<td>3742</td>
</tr>
<tr>
<td>S.D.</td>
<td>±1.39</td>
<td>±1.66</td>
<td>±36.5</td>
<td>±0.67</td>
<td>±20.5</td>
<td>±11.7</td>
<td>±27.5</td>
<td>±19.3</td>
<td>±712</td>
</tr>
<tr>
<td>S.E.M.</td>
<td>±0.46</td>
<td>±0.55</td>
<td>±12.2</td>
<td>±0.22</td>
<td>±6.8</td>
<td>±5.9</td>
<td>±9.7</td>
<td>±6.4</td>
<td>±237</td>
</tr>
<tr>
<td>N*</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Minimum cardiac output values

|         |                       |                             |                      |                     |                      |                        |                       |                    |                                |                                |
| X       | 8.27                 | 5.82                        | 94.0                 | 1.72                | 134                  | 50.5                   | -39.4                 | 116.5               | 7404                           | 6.8                            |
| S.D.    | ±1.48               | ±1.67                       | ±14.1               | ±0.86               | ±14.8                | ±10.5                 | ±20.3                 | ±28.5               | ±3018                           | ±2.5                            |
| S.E.M.  | ±0.52               | ±0.66                       | ±14.6               | ±0.30               | ±5.2                 | ±8.7                  | ±9.3                  | ±10.6               | ±136                            | ±0.8                            |
| N*      | 8                   | 8                           | 8                   | 8                   | 8                     | 8                     | 8                     | 7                   | 7                               | 7                               |
| P†      | <0.01               | 0.05                        | 0.37                | <0.01               | 0.06                 | <0.01                 | >0.5                  | >0.5                | 0.04                            | 0.13                            |

Maximum cardiac output values

|         |                       |                             |                      |                     |                      |                        |                       |                    |                                |                                |
| X       | 6.82                 | 2.18                        | 127.0               | 6.07                | 122                  | 24.8                   | -26.3                 | 121.3               | 1644                           | 9.2                            |
| S.D.    | ±1.03               | ±0.59                       | ±29.3               | ±1.68               | ±20.6                | ±6.8                  | ±21.0                 | ±34.6               | ±178                            | ±3.6                            |
| S.E.M.  | ±0.34               | ±0.19                       | ±9.7                | ±0.56               | ±6.9                 | ±2.2                  | ±7.4                  | ±2.2                | ±109                            | ±1.3                            |
| N*      | 9                   | 9                           | 9                   | 9                   | 9                     | 9                     | 9                     | 9                   | 9                               | 9                               |
| P†      | <0.01               | 0.28                        | 0.01                | 0.2                 | 0.35                 | 0.05                  | >0.5                  | >0.5                | <0.01                           | 0.03                            |

Average values are shown for the control period (before venesection phase), at the times of minimum cardiac output (during venesection phase) and maximum cardiac output (after venesection phase). Minimum and maximum cardiac output responses are considered two extremes of physiologic change to repeated venesection. The minimum cardiac output occurred one to three days before the final venesection with three exceptions where it coincided with the final venesection. The maximum cardiac output occurred one to seven days after the final venesection with one exception where the peak output occurred 13 days after the final venesection.

* Excluding dog 6 (see text) mean = 88.1, S.D. = ±40.5, S.E.M. = 15.3, P = 0.02.
† N = number of measurements.

TABLE 3.—Comparison of Results Obtained at the Time of the Final Venesection with those Obtained at the Time of the Maximum Cardiac Output

<table>
<thead>
<tr>
<th>Period</th>
<th>Hemoglobin gm./100 cc.</th>
<th>Arterial O₂ Content cc./100 cc.</th>
<th>Venous O₂ Content cc./100 cc.</th>
<th>O₂ Consumption cc./min.</th>
<th>Total Systemic Resistance, Dynes. sec. cm.</th>
<th>Plasma and Total Blood Volume cc./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>1065</td>
<td>9.50</td>
<td>6.68</td>
<td>7.44</td>
<td>200</td>
<td>180</td>
</tr>
<tr>
<td>S.D.</td>
<td>±0.95</td>
<td>±1.2</td>
<td>±1.1</td>
<td>±0.9</td>
<td>±1.1</td>
<td>±1.7</td>
</tr>
<tr>
<td>S.E.M.</td>
<td>±0.04</td>
<td>±0.1</td>
<td>±0.07</td>
<td>±0.1</td>
<td>±0.1</td>
<td>±0.1</td>
</tr>
<tr>
<td>N*</td>
<td>1065</td>
<td>9.50</td>
<td>6.68</td>
<td>7.44</td>
<td>200</td>
<td>180</td>
</tr>
</tbody>
</table>

* Each final venesection value is an average of the measurement made on the day of (and thus prior to) the final venesection and the day after the final venesection.
† Significance of difference between final venesection and maximum cardiac output values.
‡ Significance of change compared to control values.

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Peripheral Blood Flow in Calf and Paw. The calf blood flow was elevated both at the time of the minimum and at the time of the maximum response in cardiac output, although in the former instance the elevation was not statistically significant (table 2). The paw blood flow fell below control levels at the time of the minimum cardiac output in most instances. Coincident with the maximum cardiac output an increase in paw blood flow was usually observed. However, in both phases the paw flow changes were transient, lasting only one to two days as compared with the longer lasting calf blood flow changes (figs. 1 and 2).

Plasma and Total Blood Volume. The plasma and total blood volumes reached minimal values at the end of the venesection period. Between the time of the final venesection and maximum cardiac output the plasma volume and the total blood volume on the average remained unchanged (table 3). No correlation was noted between these blood volume changes and any other variable.

DISCUSSION

It is generally stated that the anemic organism compensates for the reduced oxygen carrying power of the blood and maintains adequate oxygenation of the tissues by two mechanisms which may act singly or together. These mechanisms are (1) an increased per cent utilization of arterial oxygen, and (2) an increased cardiac output.

During the venesection period and prior to an elevation in cardiac output, tissue oxygenation was maintained by a greater per cent utilization of arterial oxygen. After the final venesection the percent utilization of arterial oxygen decreased towards normal, and in over half of the animals studied the per cent utilization of arterial oxygen was within or below normal limits when the cardiac output was at a maximum. In these instances the maximum cardiac output might be viewed as an overcompensation, for less marked elevations in cardiac output would be required if the per cent utilization of arterial oxygen were increased more.

The fact that a fairly critical degree of anemia was necessary (approximately 7 Gm. per 100 cc. blood) before the high cardiac output phase was initiated is in agreement with other similar investigations. This is emphasized by the fact that during the venesection phase no rise in cardiac output was observed despite a progressive decline in hemoglobin, except in dog 6 which initially was moderately anemic.

Decrease in cardiac output during the venesection phase was probably determined by reduction in blood volume. Once the rise in cardiac output was initiated, however, it continued to rise to a maximum independent of further change in the hemoglobin and total blood volume.

The low blood volume and elevated right atrial pressure observed at the time of the elevated cardiac output would indicate, as Sharpey-Schafer pointed out, a reduction in the capacity of the vascular bed. This reduction would appear to be largely venous in view of the significant increase in calf blood flow and, in some instances, paw blood flow. The elevations in right atrial pressure were moderate and might have been missed if measurements had not been made serially throughout the whole study. This may be responsible for the failure of others to demonstrate this finding.

The concept advanced by Sharpey-Schafer that the right atrial pressure brings about the elevation in cardiac output, in keeping with Wiggers' modification of Starling's law, may be disputed for various reasons. The over-all correlation between right atrial pressure and cardiac output in the present experiments was quite insignificant (R = 0.08). In half of the animals studied an increase in right atrial pressure was encountered several days before the cardiac output rose. Indeed, in some cases the maximum right atrial pressure was observed at the time of the minimum cardiac output. If the elevated right atrial pressure acted as the stimulus for the increased cardiac output, one would have expected a coincident elevation in both. The finding of a low cardiac output and high right atrial pressure in some animals towards the end of the venesection period might suggest the presence of cardiac failure. However, the essentially normal blood pressure, the ensuing hyperdynamic response of the heart and the absence of "clinical" signs negate this possibility.
The elevation in right atrial pressure observed following daily venesection could be due to an increase in venomotor tone and a shift of blood to the central veins and heart as suggested by Sharpey-Schafer, but there is no other evidence to support this. Such an adjustment would maintain cardiac filling at the best level possible during the period of chronic reduction of blood volume.

At the time of the minimum cardiac output the total peripheral resistance was at a maximum in spite of the diminished viscosity of the blood. The observed decrease in paw blood flow, although not statistically conclusive, suggests that the skin was involved in the vasoconstriction. The calf blood flow, with two exceptions, was within or above control levels at this time, indicating the absence of constriction.

During the hyperdynamic phase the calf blood flow was significantly elevated, which agrees with the observations made by Abramson and colleagues on the forearm blood flow in anemic subjects. The paw blood flow during the high cardiac output phase was variable, possibly reflecting the adverse effects of sodium pentobarbital anesthesia on temperature regulation.

Some investigators have concluded that the increased cardiac output during anemia was the result of the decrease in total peripheral resistance which in turn resulted from the direct effects of anoxia on the peripheral blood vessels. This would imply a direct relationship between the degree of tissue anoxia and the degree of elevation in cardiac output.

The results of the present study, however, indicate that the tissue oxygen tension was increased, or at least unchanged, at the time of the maximum cardiac output compared with that which obtained at the end of the venesection period when the cardiac output was either low, normal or beginning to increase. Furthermore, the maximum decrease in total systemic resistance occurred, not when the tissue anoxia was marked (at the end of the venesection period), but, rather, at the time of the maximum cardiac output response when anoxia of the tissues was at least less severe. The direct relationship between tissue anoxia and cardiac output described by other investigators would not appear to apply to the period during which the cardiac output was increasing to a maximum value. The severe anoxic stress present at the end of the venesection period may well be the stimulus for the initiation of the elevation in cardiac output, but it would not appear to be a sustaining factor.

Subsequent observations on the effects of concentrated whole blood infusions administered to anemic dogs and man during the high cardiac output response emphasize this point. Following rapid correction of the anemia the cardiac output decreased towards normal, but this took place slowly over several hours. During this time the total systemic resistance remained low and increased only as the cardiac output decreased.

These findings suggest that the decrease in total peripheral resistance which accompanies the rise in cardiac output is not due to the direct effects of anoxia on the peripheral blood vessels. These changes in total peripheral resistance might represent either a homeostatic mechanism which maintained a normal blood pressure during the period of elevation in cardiac output, or the result of some slowly developed indirect mechanism which acts on peripheral vessels, indirectly eliciting a rise in cardiac output.

The slow appearance of the elevated cardiac output in posthemorrhagic anemia has prompted Sharpey-Schafer to suggest that a slow-acting or slowly elaborated humoral mechanism may be involved in this compensation. The slow rise in cardiac output to a maximum over a period of several days following the final venesection as well as its slow disappearance even on rapid correction of the anemia also suggests an indirect mechanism, possibly humoral in nature, which is initiated in some way by the stimulus of the low oxygen-carrying capacity of the blood. As intimated above, such a substance could elicit this response in cardiac output by acting either directly on the heart or by effecting directly or indirectly a decrease in the total systemic resistance.

Summary

Cardiovascular measurements were made in nine dogs before, during, and after the pro-
duction of anemia by daily venesections of 100 to 200 cc. per day for six to ten days.

The cardiac output generally fell at some time during the course of the venesection period, and when the hemoglobin reached approximately 7 Gm. per cent the cardiac output began to rise; at that time the daily bleedings were discontinued. The cardiac output continued to rise slowly to a maximum over the course of one to seven days after the final venesection during which time the hemoglobin and total blood volume remained unchanged. The rise in cardiac output was mainly the result of a decreased arteriovenous oxygen difference.

The right atrial pressure was elevated and the total blood volume was reduced at the time of the maximum cardiac output, but the initial elevation in right atrial pressure usually preceded the initial rise in cardiac output by several days. This lack of correlation indicated that the increased cardiac output was not due to an increased right atrial pressure. The significance of the elevated atrial pressure is discussed.

Tissue anoxia was marked at the end of the venesection period, and as the cardiac output rose to a maximum the degree of tissue anoxia was lessened. A decrease in total peripheral resistance did not occur when tissue anoxia was marked but, rather, when the cardiac output was elevated and when tissue anoxia was at least less severe. These results do not substantiate the concept of a balanced relationship between the degree of tissue anoxia and the degree of cardiac output elevation where tissue anoxia, by directly lowering the total peripheral resistance, elicits a rise in cardiac output. The relationship of total peripheral resistance to other findings is discussed.

It is concluded that existing theories do not adequately explain the mechanism of the cardiac output elevation in anemia. The slow rise in cardiac output to maximum values in response to anemia suggests the possibility that a slow-acting or slowly elaborated humoral mechanism may be involved in this compensation.

Acknowledgments

The authors wish to thank Mr. G. C. Stewart for technical help and Mrs. T. Van Noordwijk for assistance with the blood volume determinations.

REFERENCES

The Circulatory Adjustments to Posthemorrhagic Anemia in Dogs
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Circ Res. 1954;2:499-505
do: 10.1161/01.RES.2.6.499

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