Hemodynamic Effects of Hypervolemia with and without Anemia

By NOBLE O. FOWLER, M.D., WALTER L. BLOOM, M.D., AND JOHN A. WARD, M.D.

With the collaboration of Robert H. Franch, M.D.

Hypervolemia was produced in dogs by infusion of matched whole blood or of red cells suspended in dextran. In the dogs which had received matched whole blood, bleeding with simultaneous volume replacement with dextran produced acute hypervolemic anemia. This was associated with increased cardiac output, whereas no increase of cardiac output was seen in the same animals with a comparable amount of hypervolemia without anemia. The results suggest that anemia rather than hypervolemia was the important factor in causing an increase of cardiac output in these experiments.

Previous studies by Witham, Fleming and Bloom, and by Fowler, Franch, and Bloom have demonstrated that the infusion of 6 per cent isoncotic dextran produced hemodilution anemia by virtue of increased plasma volume in both man and the dog. Increase in cardiac output was also found following dextran infusion in man and in the dog. Gowdey, Hatcher and Sunahara observed hypervolemia, hemodilution anemia, and increased cardiac output following acacia infusion in dogs.

Thus, the infusion of 6 per cent isoncotic dextran and of other plasma volume expanders has been observed to produce two important hemodynamic effects, an expansion of intravascular volume and hemodilution anemia, and an increase in cardiac output. It seemed desirable to determine whether the increase in cardiac output is related to the expansion of intravascular volume or to the concomitant anemia. In our previous study, acute anemia with hypervolemia was produced in one group of dogs, anemia without hypervolemia in another. Significant increase in cardiac output was seen in both groups of animals, suggesting that the increase in cardiac output was related to anemia rather than to expansion of blood volume. This paper presents a further study of the mechanism of increased cardiac output associated with dextran infusion.

Methods

Hypervolemia was produced in two groups of dogs. One group received matched whole blood infusion in stages. A second group received red cells suspended in dextran in stages. In the first group, anemia was then produced by bleeding with simultaneous volume replacement with dextran. Thus a comparison of the hemodynamic effects of hypervolemia without anemia and with anemia could be made in the same animals. The differences in hemodynamic effects of hypervolemia without anemia and of hypervolemia with anemia indicated that anemia was the important factor in the observed increase in cardiac output.

The procedures used were similar to those employed in our previous study: plasma volumes were determined by means of T-1824 dye, cardiac output by the direct Fick principle, and the pressures were recorded upon the Sanborn Polysino using Sanborn electromanometers and Statham transducers.

The studies were performed upon 21 dogs weighing from 7.3 to 11.8 Kg. The animals were anesthetized with pentobarbital sodium 25 mg./Kg. intravenously. Supplemental pentobarbital sodium in amounts of 23 to 50 mg. was given at intervals of 30 minutes to 1 hour in order to keep the level of anesthesia constant. The tachycardia produced by the anesthesia used in these experi-
ments may interfere with an evaluation of the effect of acute anemia upon the heart rate. Intrapleural pressures were recorded by means of a no. 12 cannula inserted in the fourth right intercostal space without admitting air to the pleural space. Right atrial and intrapleural pressures were recorded with a sensitivity of 4 cm. deflection for 10 mm. Hg, thus allowing pressures to be read to the nearest 0.1 mm. Hg.

The red cells suspended in dextran were prepared as follows. Red cells of the donor dogs were checked with the plasma of the recipient dogs for agglutination microscopically. Approximately 40 hours prior to the time of study, the donor dogs were bled aseptically into Erlenmeyer flasks. The flasks were sealed aseptically and the blood was allowed to settle for 40 hours, at which time the supernatant plasma was decanted. The volume of plasma decanted was replaced with 6 per cent isoncotic dextran.* For infusions of fresh whole blood, cross-matched heparinized blood was obtained from donor dogs and used within 3 hours. Ten animals received fresh whole blood and 11 were given red cells suspended in dextran. The volumes of the 3 infusions were equal to 2, 3, and 3 per cent of body weight respectively. Infusions were given at intervals of approximately 30 min. In addition to measurements after each infusion, measurements of cardiac output and pressures were made during the second half of the first or second infusion. In the animals receiving whole blood only, when observations were completed following the third infusion, 700 to 1000 ml. of blood were removed at a rate of 50 ml./min. with simultaneous replacement of the volume removed with 6 per cent isoncotic dextran. In this way sudden anemia was produced without

* The dextran used in this study was kindly supplied by the Laros Manufacturing Company, Bethlehem, Pa.
Results

Results are shown in figures 1–3. All pressures are measured relative to atmospheric pressure.

Following the injection of red cells suspended in dextran, there was no significant change in mean arterial blood pressure, right atrial, pulmonary arterial, or intrapleural pressure from one time interval to the next. However, when the results following the final infusion are compared with the control, significant increase was found in right atrial and pulmonary arterial pressures (fig. 1). Cardiac output increased over the control during the time of infusion only (85 ± 12 ml/Kg./min., p < 0.001). In the ensuing studies performed 20 min. following each infusion, there were no significant increases in cardiac output.

The infusion of fresh whole blood resulted in no significant increase in mean arterial blood pressure or intrapleural pressure. Right atrial pressure increase was significant after the third infusion only. Pulmonary arterial mean pressure increased following each infusion; the changes were not significant from one period to the next. However, after the final infusion, as well as after bleeding and dextran replacement, pulmonary arterial mean pressure had increased significantly over the control (fig. 2). During the infusion of whole blood, the mean of cardiac outputs increased and 20 min. after completion of the transfusion, the mean of cardiac outputs fell significantly from the elevated output during infusion, but remained unchanged from control mean output. When cardiac output was measured 20 min. following each transfusion, no significant increase was noted from period to period or when compared to the control output. The mean cardiac output increased significantly after volume for volume bleeding and dextran replacement.

The mean hemoglobin concentration of animals transfused with whole blood did not change from the control of 11.5 Gm./100 ml. The mean hemoglobin dropped to 3.8 Gm./100 ml. after bleeding and dextran replacement. The mean hemoglobin of animals receiving transfusions of red cells suspended in dextran was 14.2 Gm./100 ml. before infusion and was 13.2 Gm./100 ml. blood after the final infusion.

Figure 3 is a scatter diagram showing the relationship between changes in stroke volume and in effective right heart filling pressure 20 min. after each infusion. The relationship between the two variables, as determined by regression coefficient, was significant at p < 0.001 level. It may be seen that in two instances there was increase in stroke volume following dextran infusion without rise in right heart filling pressure. A similar analysis relating the change in stroke volume to change in right heart filling pressure from control indicated a significant association, p < 0.02. In each of 7 instances of bleeding and dextran infusion, there was an increase in stroke volume of 6 ml. or more above control; however, in 3 of the 7 animals, there was no increase in right heart filling pressure.
In the dogs receiving matched whole blood infusions, followed by bleeding and simultaneous dextran volume replacement, heart rates following the third blood infusion were from 112 to 168/min., with a mean of 138. Following the production of anemia by bleeding and dextran replacement, heart rates were 116 to 168/min., the mean being 139. Four animals showed an increase during anemia of 4 to 24 beats/min., 3 showed a decrease of 6 to 20, and one showed no change.

**DISCUSSION**

Although Gregg and Wiggers found increased cardiac stroke volume with red cell infusion in dogs, their experiment differed from ours in several respects. In their study, dogs were made polycythemic, whereas ours were not; their infusions were given over a much longer time interval and at a much slower rate than ours; most important, however, is that some observations were made during the period of infusion.

Increase in cardiac output following dextran infusion may be due to anemia, to expanded intravascular volume, or to increased right heart filling pressure. The observations in our present series of animals indicate that it is possible to expand blood volume to a considerable degree without increasing cardiac output if there is no anemia, since cardiac output was increased significantly by whole blood or red cells suspended in dextran during the infusion only.

Increase in right atrial and pulmonary arterial pressure was more pronounced with dextran infusion than with whole blood infusion; further there was some increase in these pressures after bleeding and dextran replacement in the blood-infused dogs. Thus, one cannot be certain that the failure to increase the cardiac filling pressure following blood infusion to an extent comparable with that seen following hypervolemic anemia was not responsible for the failure of cardiac output to increase significantly. It was shown by Fowler, Bloom, Ward and Franch that comparable degrees of expansion of whole blood volume were produced by infusion of equal volumes of whole blood and of dextran. Therefore, the greater rise in right atrial and pulmonary arterial pressures after dextran cannot be explained by different degree of blood volume increase. It seems more likely that blood contains vasodilator substances, or that the anemia produced by dextran may cause some alteration in pressure-volume relationships in the vascular system.

The mechanism by which the production of acute anemia through expansion of plasma volume causes an increase in cardiac output is not clear. Sunahara and Beck observed increased cardiac output without rise in right atrial pressure in bled dogs given plasma infusion. In some of the animals in the present series, increase in cardiac stroke volume occurred with anemia without increase in right ventricular filling pressure. These observations suggest that the increased cardiac output occurring with acute anemia was not due to increase in cardiac filling pressure. Viscosity studies in a previous presentation indicated that the dextran used in our studies was only slightly less viscous than heparinized dogs whole blood, the differences observed being less than 10 per cent. This makes it unlikely that the cardiac output increase was related to decreased blood viscosity. Justus, Cornett and Hatcher transfused blood from acutely anemic dogs into dogs without producing anemia in the recipient animals. An increase in cardiac output was observed in the recipient dogs, suggesting that a humoral substance may be important in mediating the increase in cardiac output associated with acute anemia. A possible effect of such a humoral agent upon heart rate in our studies may have been masked by the anesthetic agent.

**SUMMARY**

Twenty-one dogs were rendered hypervolemic without anemia, either by the infusion of red cells suspended in dextran or by the infusion of fresh whole blood. Each animal received three infusions amounting to 2, 3, and 3 per cent respectively of body weight. In the dogs which had received fresh whole blood, 700 to 1,000 ml. of blood was removed...
HEMODYNAMIC EFFECTS OF HYPERVOLEMIA

with simultaneous replacement with an equal volume of dextran. In general the nonanemic hypervolemic animals showed no increase in cardiac output and no striking changes in mean arterial blood pressure 20 min. after infusion. Pulmonary arterial pressure rose moderately in both groups of dogs and right atrial pressure rose slightly. After bleeding and dextran infusion, there was a slight rise in both pulmonary arterial and right atrial pressure and striking increase in cardiac output. These studies suggest that the increase in cardiac output following dextran infusion is related to the anemia produced thereby and not to the expansion of whole blood volume or to the increase in cardiac filling pressure.

SUMMARIO IN INTERLINGUA

Viati-un canes esseva rendite hypervolemic sin anemia. Le methodos usate esseva (1) infusion de erythrocytos suspendite in dextrano o (2) infusion de fresc sanguine integre. Omne animal recipiva tres infusiones amontante—respectivemente—a 2, 3, e 3 pro cento del peso corporee. In le casos del canes que habeva recipite fresc sanguine integre, inter 700 e 1000 ml de sanguine esseva extrahite e simultaneemente reimplaciate per le mesme volumine de dextrano. In general, le nonanemic animales hypervolemic monstrava nulle augmento del rendimento cardiac e nulle frappante alterationes del pression medie de sanguine arterial 20 minutes post le infusion. Le pression pulmuno-arterial ascendeva moderatemente in ambe gruppos de canes, e le pression dextero-atrial montava levemente. Post le sanguination e le infusion de dextrano, il occurreva un leve augmento del pressiones pulmuno-arterial e dextero-atrial e un frappante augmento del rendimento cardiac. Iste studies suggere que le augmento rendimento cardiac post infusiones de dextrano es relationate al concomitante anemia e non al expansion del volume total de sanguine o al augmento del pression de replenation cardiac.

REFERENCES


Hemodynamic Effects of Hypervolemia with and without Anemia
NOBLE O. FOWLER, WALTER L. BLOOM and JOHN A. WARD
Robert H. Franch, M.D.

Circ Res. 1958;6:163-167
doi: 10.1161/01.RES.6.2.163
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/6/2/163

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/