The Circulatory Effects of Acute Hypervolemia and Hemodilution in Conscious Rabbits

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SUMMARY Our goal was to distinguish the circulatory changes due to acute hypervolemia caused by whole blood and colloid solution from those due to acute hemodilution caused by colloid solution in the conscious rabbit. In six rabbits, homologous whole blood, dextran solution, or modified gelatin solution, equal to 32% of blood volume, was infused over 22 minutes. In six rabbits, 42% of blood volume was exchanged with dextran solution over 34 minutes, at constant left atrial pressure. A similar exchange was performed over 28 minutes in a further six arterial baroreceptor-denervated rabbits. Withdrawn blood later was infused over 10-12 minutes. In all rabbits, the baroreceptor-heart rate reflex was characterized by infusion of phenylephrine and sodium nitroprusside. Whole blood hypervolemia caused stroke volume and blood pressure to rise, without a rise in heart rate. Colloid-solution hypervolemia caused stroke volume and heart rate to rise, with little change in blood pressure. The effects of hemodilution were the same as those of dextran-solution hypervolemia, and the fall in hematocrit was similar, but baroreceptor denervation eliminated the rise in heart rate. We conclude that in the conscious rabbit: (1) acute rise in central venous pressure causes tachycardia only when there is concomitant hemodilution; (2) the tachycardia of hemodilution with unchanged central venous pressure is largely baroreceptor-dependent; (3) the effects of hemodilution on systemic vascular conductance appear to be due to reduction in oxygen-carriage rather than in viscosity; (4) the rabbit can closely match increase in conductance by increase in output, which is largely baroreceptor-independent. Circ Res 48: 825-834, 1981

THERE appear to be differences among animal species with respect to the effects of acute increase in blood volume on cardiovascular functions. There are also inconsistencies among the explanations given for these effects.

In conscious upright humans, Robinson et al. (1966) found that the infusion of 1.0-1.2 liters of isologous whole blood caused a modest rise in cardiac output, a small rise in mean blood pressure, and a fall of heart rate by 9 beats/min. These are the changes to be expected from an increase in ventricular filling, offset by the arterial baroreceptor reflex.

In conscious dogs, on the other hand, Bishop and Peterson (1976) found that the rapid infusion of 0.3-0.8 liters of electrolyte solution also resulted in an increase of cardiac output and blood pressure, but the heart rate, instead of falling, increased by 38 beats/min. These are the changes to be expected from an increase in ventricular filling, offset by the arterial baroreceptor reflex.

In conscious dogs, on the other hand, Bishop and Peterson (1976) found that the rapid infusion of 0.3-0.8 liters of electrolyte solution also resulted in an increase of cardiac output and blood pressure, but the heart rate, instead of falling, increased by 38 beats/min. Again, in conscious dogs, Vatner et al. (1975) found that the infusion of somewhat larger volumes of saline caused an even greater increase in blood pressure and a correspondingly greater tachycardia. Bishop and Peterson (1976) explained this anomalous tachycardia as being due to a reflex that is dependent on vagal afferents, but excluded those which originate from aortic baroreceptors. Vatner et al. (1975) suggested instead that arterial baroreflex sensitivity is reduced progressively as atrial pressure rises, thus permitting tachycardia to occur despite a rise in blood pressure.

In anesthetized rabbits, Stinnett et al. (1976) reported that the rapid infusion of up to 70 ml of dextran solution did not consistently alter either blood pressure or heart rate, but did result in attenuation of the bradycardia and hypotension caused by aortic nerve stimulation. They suggested that the attenuation of the reflex was caused by alteration of the afferent input from the carotid arterial baroreceptors, which sensed some consequence of increased blood volume.

Some of these apparent effects of acute hypervolemia in dogs and rabbits, and some of the differences from the effects in humans, may stem from the fact that the infusion of crystalloid or colloid solutions not only increases blood volume but also reduces the oxygen-carrying capacity and viscosity of the blood, because of hemodilution. For instance, Glick et al. (1964) showed that acute hemodilution will cause a marked increase in heart rate and cardiac output in the dog when there has been little change in blood volume, right atrial pressure, or blood pressure.

Rabbits have the advantage of not possessing natural plasma isoagglutinins to red cells (Cohen and Tissot, 1974). We have therefore used conscious...
rabbits to distinguish the circulatory changes due to hypervolemia from those due to hemodilution.

**Methods**

Three separate sets of experiments were performed, each on six New Zealand White rabbits of similar ages (19.0 ± 0.7, 19.0 ± 0.9, and 18.0 ± 0.8 weeks) and weights (2.9 ± 0.2, 2.9 ± 0.1, and 2.7 ± 0.1 kg) to test the effects of hypervolemia, hemodilution, and hemodilution after arterial baroreceptor denervation, respectively. In all rabbits, an initial left thoracotomy was performed in order to implant an electromagnetic flow probe around the ascending aorta; the probe and adjacent aorta were wrapped in nylon fabric to promote fibrous fixation. The connecting plug was fixed to the spinous processes through the skin. In the rabbits of the two hemodilution groups we also implanted a left atrial catheter, following the technique of Warren and Led-ingham (1972). The observations of cardiovascular functions were not made until 10-14 days later, when the animals had regained their preoperative weights. The further vascular cannulations were made under local analgesia with 1% lidocaine HC1.

The rabbits were studied while they sat in a restraining box under conditions that we have described previously (Faris et al., 1980a). On completion of the experiments, autopsies were performed on all rabbits to establish that the flow probe and atrial catheter were placed correctly, and that the lungs and kidneys were macroscopically normal.

The sine-wave electromagnetic flow probes (Biotronix 5000) were 4.5 or 5.0 mm in diameter. In vivo, end-diastolic flow was taken as zero and was monitored on an oscilloscope so that baseline adjustments could be made. The probes were calibrated in vitro by using a roller pump to perfuse a cellophane tube, immersed in saline, with human blood at flow rates of 300-900 ml/min (Case et al., 1966). The effect of altering hematocrit from 38% to 16% by progressive dilution with gelatin or dextran solution was tested at a fixed flow rate of 500 ml/min on four occasions for each solution. There was an approximately linear relation between hematocrit and the deviation of apparent from actual flow. Changes of hematocrit from 32 to 27% by gelatin solution caused an over-reading of flow of 1.5 ± 0.1%, and from 32 to 23% by dextran solution of 1.8 ± 0.1%. In the in vivo experiments, no correction was made for this small source of error.

The blood volume of each rabbit was measured on the day before the first of each series of experiments, by injecting 51 Cr-labeled isologous red cells prepared from a 0.5-ml blood sample (Veall and Vetter, 1958) and counting a saponin-treated 0.5-ml blood sample taken 10 minutes later, when equilibration was complete. The percentage change in blood volume resulting from each infusion or hemodilution procedure was estimated by counting 0.5-ml saponin-treated arterial blood samples taken before, at the end of, and 60 minutes after, each procedure. At the same time, arterial hematocrit was measured by a capillary-tube micromethod (Hawkeley). In all cases of infusion of gelatin or dextran solutions, and of blood-dextran solution exchange, estimates of change in blood volume by the radioisotope method and by hematocrit were well correlated (r = 0.828-0.961) and did not differ systematically in magnitude (t = 1.52-2.03). At the same times, duplicate estimates of Po2, Pco2, pH, (H+) and (HCO3-) were made on 0.5-ml arterial and right atrial blood samples (Corning 165).

Arterial blood pressure was measured by inserting a catheter into a central ear artery, advancing it to the root of the ear, and connecting it to a strain gauge (Statham P23DC). Left and right atrial pressures also were measured by strain gauge, the latter by way of a catheter inserted through the external jugular vein and advanced approximately 7 cm until a central venous pulse and free backflow were evident (Korner and Smith, 1954). The zero level for all pressure measurements was 50 mm above the floor of the restraining box. Heart rate was measured by a tachometer actuated by the signal from the aortic flowmeter. The frequency and relative amplitude of respiratory excursions was recorded by placing a mercury-in-silastic strain gauge around the chest. Mean values of blood pressure, ascending aortic flow, heart rate, and respiratory rate were obtained every 60 seconds by integrating the corresponding signals. Mean stroke index was calculated as (mean aortic flow/kg body weight) + (heart rate), and mean systemic vascular conductance as (mean aortic flow/kg body weight) + (mean arterial pressure). All signals were recorded on paper through the appropriate channels of a Grass polygraph, and also on magnetic tape (Hewlett-Packard 3968A). Infusions were made by a constant-speed syringe, via a catheter advanced through an ear vein. A heat exchanger ensured that the infusate entered the rabbit at 38°C. In none of the protocols did body temperature, measured by a rectal thermometer probe (Yellow Springs 402), change significantly. The infusion system and all catheters were sterile and pyrogen-free.

In the hypervolemia protocol, three different fluids were used to expand blood volume: gelatin solution, dextran solution, and whole blood. Each liter of gelatin solution (Haemaccel, Behring) contained degraded gelatin (mol wt 35,000) 35 g; NaCl, 8.5 g; KCl, 0.38 g; and CaCl2, 0.7 g (319 mOsmol/liter). Each liter of dextran solution (Rheomacrodex, Pharmacia) contained dextran (mol wt 40,000) 100 g, and NaCl, 9.0 g (326 mOsmol/liter). The blood for infusion was taken from a live, heparinized donor rabbit whose blood had been previously cross matched with that of the recipient (Albrey and Simmons, 1960), and was used within 60 minutes. No positive cross matches were encountered. The hematocrit of the donor blood was 35 ± 1%. Following the experiment, 80% of the blood infused was withdrawn. Gelatin solution, dextran
solution, or whole blood was infused at experiments not less than 2 days apart, between the 10th and 16th postoperative days, in random order. The cardiovascular functions were measured over a 30-minute control period preceding each infusion. The volume of each infusate was 32 ± 1% of the rabbit’s estimated blood volume, and was delivered over 22 ± 1 min. The cardiovascular functions then were measured for a further 60 minutes.

The two hemodilution protocols were virtually identical, except that in the first group of six rabbits the arterial baroreceptors were intact, whereas in the second group of six baroreceptor-denervated rabbits the aortic nerves had been divided in the neck, and both carotid sinuses denervated (Faris et al., 1980b) 26 ± 2 days prior to the implantation of the aortic flowmeter. In each protocol, cardiovascular functions were measured during a 30-minute control period, during a period of blood-dextran solution exchange, and for 60 minutes afterward. During the period of blood-dextran solution exchange, blood was withdrawn from the right atrium at a constant rate, and dextran solution was infused during this and the following 60 minutes so as to maintain left atrial pressure constant at the mean control value. In these protocols, the dextran solution described in the hypervolemia protocol was diluted by 20% with aqueous NaCl (9.0 g/liter) to render it less hyperoncotic (308 mOsmol/liter). For the baroreceptor-intact and baroreceptor-denervated protocols, respectively, the blood withdrawn was equivalent to 42 ± 2 and 43 ± 1% of the rabbit’s blood volume, and the periods of blood-dextran solution exchange were 34 ± 2 and 28 ± 1 min. The volumes of dextran solution infused during the period of blood withdrawal were equivalent to 32 ± 5 and 27 ± 1% of blood volume, and during the succeeding 60 minutes were equivalent to 19 ± 2 and 16 ± 2% of blood volume. At the end of the experiments, the withdrawn blood was reinfused over periods of 10 ± 1 and 12 ± 1 min respectively.

Two to 3 days after the completion of each protocol, an estimate was made of the sensitivity of the baroreceptor-heart rate reflex (Faris et al., 1980b), on a time scale commensurate with that of the infusions, by infusing aqueous solutions of phenylephrine or sodium nitroprusside at rates that were increased stepwise from 0.08–0.90 ml/min so as to cause changes in blood pressure and heart rate which were sustained for 2–3 minutes at each rate. The phenylephrine solution consisted of phenylephrine HCl, 0.2 g/liter; NaCl, 9.0 g/liter; and ascorbic acid, 0.05 g/liter. The sodium nitroprusside solution consisted of sodium nitroprusside, 0.1 g/liter, and NaCl, 9.0 g/liter. With changes in blood pressure over the range +28.7 ± 2.1 to −21.0 ± 2.1 mm Hg, the regression of heart rate on blood pressure was approximately linear (r always > 0.90). The mean regression coefficients for the hypervolemia and baroreceptor-intact hemodilution groups of rabbits were −2.49 ± 0.06 and −2.27 ± 0.10 beats/min per mm Hg, respectively. The coefficient for each individual rabbit was applied to the control values of its blood pressure and heart rate in order to estimate the changes in heart rate that would have occurred as a result of changes of blood pressure, had the baroreceptor-heart rate reflex been acting normally and unopposed. In the case of the baroreceptor-denervated group of rabbits, the vasodepressor drug infusions were used to confirm that denervation was complete.

The 60-second mean values for each of the cardiovascular variables were calculated every 5 minutes during the 30-minute control period, every 1 minute during the period of infusion or hemodilution, and every 5 minutes during the subsequent 60-minute period. The absolute values of the cardiovascular variables for each rabbit later were converted into a percentage of the mean control values, or in the case of atrial pressure into a difference from the mean control value. Mean values for each set of six rabbits usually are accompanied by the standard error, indicated as ±. Comparison of means within or between the sets of rabbits has been made by the paired or unpaired t-test, and in some instances analysis of variance has been used to calculate the F statistic.

The procedures followed in these experiments were in accordance with the National Health and Medical Research Council of Australia’s “Statement on Animal Experimentation.”

Results

The Effects of Hypervolemia

The control values of the cardiovascular variables are shown in Table 1. Analysis of variance showed that they were independent of whether blood, gelatin solution, or dextran solution was to be infused subsequently (F always < 3.25).

Following the infusions the actual increases in blood volume were very different from the 32% predicted by the volumes infused (Table 2). By the end of the infusion period, the increases in blood volume resulting from the infusion of whole blood and gelatin solution were much less than predicted, whereas that from the infusion of dextran solution was much greater. During the succeeding 60 minutes, the increase in blood volume from blood infusion was well sustained, but it fell off steeply in the case of the two colloid solutions. With each of the infusion fluids, right atrial pressure rose during the infusion in linear proportion to the increase in blood volume, but 60 minutes later had fallen by an average of 2.2 mm Hg more than predicted by the decline in blood volume. The changes in the cardiovascular variables which occurred during the infusion and the succeeding 60 minutes are shown in Figure 1A.

During the infusion of gelatin solution and of blood, the rates of increase in right atrial pressure were similar, corresponding to the similar increases in blood volume. When the other cardiovascular changes are compared in these two cases, only in
TABLE 1  Control Values of Cardiovascular Variables for the 30-Minute Period Preceding Hypervolemia from Infusion of the Fluids Indicated, and Preceding Hemodilution by Blood-Dextran Solution Exchange with Arterial Baroreceptors Intact or Denervated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypervolemia</th>
<th>Hemodilution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole blood</td>
<td>Gelatin</td>
</tr>
<tr>
<td>Mean R atrial pressure</td>
<td>0.1 ± 0.7</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean L atrial pressure</td>
<td>2.1 ± 0.5</td>
<td>0.72 ± 0.05</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stroke volume</td>
<td>74.6 ± 3.4</td>
<td>73.6 ± 1.2</td>
</tr>
<tr>
<td>(ml/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean heart rate</td>
<td>261 ± 9</td>
<td>260 ± 9</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aortic flow</td>
<td>192 ± 12</td>
<td>186 ± 9</td>
</tr>
<tr>
<td>(ml/kg per min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systemic conductance</td>
<td>2.48 ± 0.24</td>
<td>2.49 ± 0.12</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>74.6 ± 3.4</td>
<td>73.6 ± 1.4</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are grand means ± SE for all six rabbits in each protocol. Mean systemic conductance was calculated as (mean aortic flow/kg) + (mean arterial pressure).

the case of gelatin solution was there a small, but consistent, rise in heart rate. In each case, stroke volume and cardiac output increased, the increases being greater in the case of gelatin solution, but matched by a rise in systemic vascular conductance so that blood pressure did not change. During the infusion of blood, the systemic vascular conductance remained virtually unaltered, so that blood pressure rose. After the infusion period, in each case right atrial pressure fell rapidly toward the pre-infusion control level. During the 60 minutes after the infusion of blood, stroke volume, cardiac output, and systemic vascular conductance remained high despite the rapid fall in blood volume and central venous pressure.

During and following the infusion of dextran solution the cardiovascular changes were quantitatively greater than those that attended the infusion of gelatin solution. During the infusion there was a greater rise in central venous pressure, corresponding to the greater rise in blood volume, and a greater increase in heart rate, stroke volume, cardiac output, and systemic vascular conductance. Midway through the infusion period, stroke volume and systemic vascular conductance appeared to approach upper limits, but heart rate, cardiac output, and blood pressure continued to rise.

When the effects of the baroreceptor-heart rate reflex due to change in blood pressure were allowed for (Fig. 2), heart rate still rose during, and remained elevated after, the infusions of gelatin and dextran solutions, although not in the case of blood infusion.

No consistent changes were evident in the measures of respiratory exchange (Table 3), except that right atrial PO₂ rose during the infusion of gelatin solution (t = 3.32, P < 0.05).

The Effects of Hemodilution with Intact Baroreceptors

The control values of the cardiovascular variables were similar in this group of rabbits to those in the hypervolemia group (Table 1). The only differences were that hematocrit and blood pressure

TABLE 2  Changes in Blood Volume and Hematocrit during the Hypervolemia and Hemodilution Protocols

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypervolemia</th>
<th>Hemodilution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole blood</td>
<td>Gelatin</td>
</tr>
<tr>
<td>Control blood volume</td>
<td>42.0 ± 2.6</td>
<td>42.0 ± 2.6</td>
</tr>
<tr>
<td>(ml/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change in blood volume</td>
<td>20.3 ± 1.9</td>
<td>20.0 ± 2.5</td>
</tr>
<tr>
<td>at end of infusion/dilution</td>
<td>17.2 ± 1.6</td>
<td>12.1 ± 1.2</td>
</tr>
<tr>
<td>% change in blood volume</td>
<td>31.7 ± 1.0</td>
<td>31.6 ± 1.2</td>
</tr>
<tr>
<td>60 min later</td>
<td>33.5 ± 1.0</td>
<td>26.8 ± 1.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.9 ± 1.0</td>
<td>28.8 ± 1.0</td>
</tr>
</tbody>
</table>

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FIGURE 1 The changes in cardiovascular variables for a control period of 30 minutes before, during (stippled areas), and for 60 minutes after infusions which produced hypervolemia, or blood-dextran exchange which produced hemodilution. Change in right (RAP) and left (LAP) atrial pressure is expressed as the difference in mm Hg from, and change in the remaining variables as % of, grand mean control values (see Table 1). Bars represent ± 1 SE for the grand mean of the 30-minute control values and otherwise for the mean values at the times indicated. A: Data from experiments in the same six rabbits in which the equivalent of 32% of blood volume was infused as homologous blood, modified gelatin solution, and dextran solution, B: Data from experiments in two separate groups of six rabbits, with arterial baroreceptors intact or denervated, in which 42% of blood volume was withdrawn while dextran solution was infused so as to maintain LAP constant. At the end of the experiment, the withdrawn blood was reinfused (cross-hatched areas).

were somewhat higher, and systemic conductance lower. Left atrial pressure was consistently 1 mm Hg higher than right atrial pressure, and this difference was not altered by hemodilution.

At the end of the period of blood-dextran solution exchange, blood volume had been expanded by 7%, and 60 minutes later by 16%, in order to maintain left atrial pressure constant. At this time the changes in the cardiovascular functions were similar to those that had occurred in the case of dextran hypervolemia, and there had been a similar fall in hematocrit (Fig. 1B; Table 2). The only consistent difference was that, in this case, blood pressure fell slightly, whereas it had risen after dextran infusion ($t = 2.69$, $P < 0.05$). Sixty minutes later, hematocrit and blood pressure had fallen a little further, while the values of the other cardiovascular functions had continued to rise (Fig. 1B; Table 2), although the
lower blood pressure remained the only consistent difference from the case of dextran infusion (t = 2.57, P < 0.05). When heart rate was corrected for change in blood pressure, so that the effects of the baroreceptor-heart rate reflex were subtracted, a tachycardia still was evident during and after the period of blood-dextran solution exchange (Fig. 2).

At the end of the experiment, in four rabbits the blood that had been withdrawn was reinfused over 10 ± 1 minute. The withdrawn blood was equivalent to 43.5 ± 0.6% of the control blood volume, and its infusion produced an increase in blood volume from 114 ± 5% to 147 ± 7% of the control value. The hematocrit of the withdrawn blood was 26.3 ± 0.8%, and during its reinfusion the arterial hematocrit of the rabbit rose from 22.4 ± 0.4% to 25.0 ± 0.7%. The pattern of change of the cardiovascular functions was qualitatively similar to those which occurred in the first group of rabbits when donor whole-blood was infused, although there were greater increases in atrial pressure, stroke volume, cardiac output, and blood pressure (Fig. 1B) consistent with the greater volume and rate of infusion.

The Effects of Hemodilution after Arterial Baroreceptor Denervation

The control values of certain of the cardiovascular variables in this group were different from those of the baroreceptor-intact group of rabbits that were subjected to hemodilution (Tables 1 and 2). Blood pressure and heart rate were higher, and blood volume, stroke volume, and systemic vascular conductance were less (t always > 2.34; P always < 0.05). However, the changes in blood volume and hematocrit which took place during the hemodilution protocol were very similar (Table 2). There were no significant changes in the respiratory variables (Table 3).

The changes that took place in the cardiovascular variables during and after blood-dextran solution exchange were indistinguishable from those that

| Table 3 | Arterial and Venous (Right Atrial) Blood Gas Tensions, Arterial pH, and Respiratory Rate, before (B) and after (A) Hypervolemia by Infusion of Whole Blood, Gelatin Solution, and Dextran Solution; or Hemodilution at Constant Left Atrial Pressure by Blood-Dextran Solution Exchange, with Arterial Baroreceptors Intact or Denervated |
|------------------------|------------------------|------------------------|------------------------|------------------------|
|                        | Whole blood            | Gelatin solution       | Dextran solution       | Baroreceptor-intact    | Baroreceptor-denervated |
|                        | B A                    | B A                    | B A                    | B A                    | B A                    |
| P.O2 (mm Hg)           | 77.0 ± 2.8             | 75.8 ± 3.2             | 81.0 ± 4.5             | 73.7 ± 5.5             | 78.3 ± 5.5             | 86.7 ± 5.5             | 93.8 ± 5.7             | 97.0 ± 5.7             |
| P.O2 (mm Hg)           | 36.0 ± 2.9             | 37.7 ± 3.2             | 39.2 ± 4.5             | 44.5 ± 5.5             | 40.0 ± 6.5             | 38.0 ± 6.5             | 44.2 ± 6.5             | 36.2 ± 6.5             | 33.7 ± 6.5             | 32.8 ± 6.5             |
| P.CO2 (mm Hg)          | 29.0 ± 1.5             | 26.5 ± 2.2             | 31.7 ± 2.2             | 30.5 ± 3.2             | 31.7 ± 2.2             | 30.5 ± 3.2             | 31.7 ± 2.2             | 30.5 ± 3.2             | 37.3 ± 3.2             | 37.7 ± 3.2             |
| pH                     | 7.45 ± 0.02            | 7.49 ± 0.02            | 7.44 ± 0.05            | 7.40 ± 0.02            | 7.43 ± 0.05            | 7.46 ± 0.02            | 7.39 ± 0.02            | 7.42 ± 0.02            | 7.46 ± 0.02            | 7.47 ± 0.02            |
| Respiratory rate        | 109 ± 0.01             | 97 ± 0.02              | 100 ± 0.05             | 96 ± 0.05              | 108 ± 0.01             | 102 ± 0.01             | 118 ± 0.01             | 101 ± 0.01             | 112 ± 0.01             | 110 ± 0.02             |
| (beats/min)            | ±8 ± 7                 | ±17 ± 17               | ±10 ± 8                | ±19 ± 17               | ±12 ± 17               | ±21 ± 17               | ±19 ± 17               | ±12 ± 17               | ±19 ± 17               | ±19 ± 17               |

* Indicates t > 2.57, P < 0.05 for difference between before and after values.
occurred in the baroreceptor-intact group (Fig. 1B), with two notable exceptions. After baroreceptor denervation, there was no significant elevation of heart rate, and blood pressure fell and remained low throughout the 60-minute post-exchange period.

At the end of the experiment, the withdrawn blood was reinfused in all six rabbits over 12 ± 1 min. The withdrawn blood was equivalent to 43 ± 1% of the control blood volume, and its infusion caused blood volume to rise from 113 ± 4% to 139 ± 3% of the control value. The hematocrit of the withdrawn blood was 26.8 ± 1.3%, and during its infusion the arterial hematocrit rose from 21.4 ± 0.8% to 24.7 ± 1.1%. The pattern of change of the cardiovascular variables was very similar to that which occurred in the baroreceptor-intact group (Fig. 1B). In particular, left atrial pressure rose by 6.0 ± 0.6 mm Hg, but heart rate fell slightly.

In the final experiment in this group, the blood pressure changes produced by infusing phenylephrine and sodium nitroprusside were not associated with significant changes in heart rate, suggesting that arterial baroreceptor denervation was complete.

The Effect of Hematocrit on Heart Rate and Conductance

When the data from the three hypervolemia protocols and the baroreceptor-intact hemodilution protocol were examined, there was a linear relation between change in hematocrit and, on the one hand, change in heart rate (Fig. 3) and, on the other hand, change in systemic vascular conductance (Fig. 4).

Discussion

The several changes in cardiovascular functions that were associated with acute hypervolemia and acute hemodilution were not individually unexpected. However, they have not, previously, been comprehensively recorded and compared in conscious animals, and have seldom been described in the rabbit. In particular, in none of the previous studies in conscious dogs of acute hypervolemia (Vatner et al., 1975; Bishop and Peterson, 1976; Vatner and Boettcher, 1978; Barnes et al., 1979) and acute hemodilution (Glick et al., 1964; Chamorro et al., 1973) have all the relevant cardiovascular variables been controlled, especially blood volume.

It is clear that in experiments such as these the magnitude of an acute increase in blood volume cannot be predicted accurately from the volume of fluid infused, but must be measured directly. The increase in blood volume caused by infusing whole blood or gelatin solution was less than that predicted and, in the case of the more hypertonic dextran solution, was greater. These phenomena have been described (Davies et al., 1963; Deavers et al., 1963; Schwartzkopff et al., 1968), but neither they nor the rapid loss of infusate from the circulation (Table 2) are appreciated generally. The advantage of using rabbits to study the effects of acute isohemetic hypervolemia is that they do not possess natural plasma isoagglutinins (Cohen and Tissot, 1974), so that there is not the confounding variable of transfusion reaction which has deterred the use of homologous blood in dogs and in humans.
In the hypervolemia experiments, by the end of the infusion period, right atrial pressure had risen in the same proportion to the increase in blood volume, whether blood, gelatin, or dextran had been used (Fig. 1; Table 2). Sixty minutes later there was evidence of the stress-relaxation effect described by Prather et al. (1969) in dogs, in that atrial pressure was less than that expected from the residual increase in blood volume. The same phenomenon was evident in the hemodilution experiments in baroreceptor-intact rabbits (Fig. 1; Table 2). Our data suggest that by the end of the experiments vascular capacity had increased by 10-15%, and that this increase occurred whether or not there had been hemodilution.

It is noteworthy that the baroreceptor-denervated rabbits had a lower initial blood volume than those with intact baroreceptors, and showed evidence of less rapid stress relaxation during hemodilution (Table 2). In view of their normal central venous pressure, this suggests that baroreceptor denervation caused a contraction of vascular capacity. This may be a phenomenon related to that reported by Tarazi et al. (1968) in men with essential hypertension.

In the hypervolemia experiments, the circulatory changes caused by infusion of gelatin and dextran solutions were qualitatively similar (Fig. 1), the quantitative differences being attributable to the differences in the magnitude of blood volume expansion or hemodilution (Table 2). The changes produced by blood infusion were quantitatively less than those that resulted from infusion of gelatin solution, even though the increases in blood volume and right atrial pressure were similar and persisted longer. There was also a qualitative difference, in that heart rate did not rise with blood infusion. Comparison of the circulatory changes produced by dextran hemodilution in the baroreceptor-intact group, in which left and right atrial pressures were unchanged, with those of dextran hypervolemia, reveal a remarkable similarity (Fig. 1). Indeed, the only consistent difference was that, with hemodilution, blood pressure fell slightly whereas, with hypervolemia, it rose. In all cases the circulatory changes were complex and interdependent. They will be discussed under three main headings: heart rate, systemic conductance, and stroke volume.

Heart Rate

The rapid increase in atrial pressure caused by gelatin or dextran infusion was associated with a parallel but modest rise in heart rate (Fig. 1). In the dog, this would be ascribed to the Bainbridge (1915) reflex, and would be attributed to engagement of cardiopulmonary or, more specifically, atrial (Linden, 1976) receptors. This mechanism does not serve as a satisfactory explanation for our findings in the conscious rabbit for several reasons. Following the infusion of solutions of gelatin or dextran, atrial pressure declined rapidly, yet the tachycardia persisted. Moreover, the elevation of atrial pressure by homologous blood infusion, and the even greater elevation caused by the rapid reinfusion of isologous blood, were not accompanied by tachycardia. It is clear that the Bainbridge reflex is not in evidence in the conscious or anesthetized (Stinnett et al., 1976) rabbit in the sense in which it can so readily be demonstrated in anesthetized (Bainbridge, 1915) and conscious (Vatner et al., 1975, Bishop and Peterson, 1976) dogs in response to acute volume-loading. Neither is it likely that a tachycardia induced by volume-loading with blood was concealed by the effect of the modest rise in blood pressure on the baroreceptor-heart rate reflex, because when the effects of the small blood pressure changes were corrected for by means of the data acquired from phenylephrine and sodium nitroprusside infusion, no net tachycardia was revealed (Fig. 2). However, a tachycardia still was apparent in association with the infusion of the colloid solutions when a similar correction for blood pressure change was applied, and though the sensitivity of the baroreceptor-heart rate reflex is reported to be depressed by volume-loading with aqueous solutions in conscious dogs (Vatner et al., 1975) and anesthetized rabbits (Stinnett et al., 1976), we had overcorrected for the effects of blood pressure change, a net tachycardia still would be in evidence. It is conceivable that pulmonary J receptors (Paintal, 1973) were engaged as a result of pulmonary congestion and increase in interstitial fluid so that a countervailing reflex barorecardia prevented full expression of the Bainbridge reflex, but the absence of change in blood gases or respiratory rate (Table 3) makes this unlikely.

If the tachycardia resulting from the infusion of colloid solutions was correlated imperfectly with change in atrial pressure, it did occur consistently when there was hemodilution (Fig. 3). We therefore turned our attention to the effects of hemodilution per se, and to explaining the tachycardia that occurred when right and left atrial pressures and blood pressure did not alter (Fig. 1B). The absence of change in arterial Po2 (Table 3) seems to exclude engagement of the carotid chemoreceptors as the cause. It is possible that the combination of hemodilution and increased cardiac output activated cardiac chemoreceptors (Coleridge and Coleridge, 1980). Those that are sympathetically innervated produce reflex tachycardia, but they are located chiefly in the epicardium and are therefore unlikely to predominate over the depressor effects of activating the vagally innervated myocardial chemoreceptors. A direct effect of hemodilution on the heart seems unlikely, because perfusion of the sinus node with electrolyte solution does not cause tachycardia (James and Nadeau, 1963), and Glick et al. (1964) observed that cardiac denervation markedly reduced the tachycardia associated with acute hemodilution. The matter seems to have been re-
solved, at least in part, by the experiments of our final protocol, in which arterial baroreceptor denervation virtually abolished the tachycardic response to hemodilution. The other notable effect of baroreceptor denervation was to uncover a fall in blood pressure, so that the simplest explanation of the heart rate changes in hemodilution is that the rise in systemic vascular conductance is offset not only by the increase in cardiac output but also by engagement of the arterial baroreceptor reflex, which helps sustain blood pressure and is responsible for the tachycardia. A further, or even an alternative, contributing factor is that if the rise in systemic vascular conductance is indeed due to reduced tone in vascular smooth muscle, then the arterial baroreceptors that are in series with smooth muscle (Kirchheim, 1976) may be unloaded. This would accord with the suggestion by Stinnett et al. (1976) that, in dextran-infused rabbits, the carotid sinus pressor response to change in blood volume.

In summary, whereas we can offer an explanation of the tachycardia that accompanies pure hemodilution in the rabbit, we cannot yet explain adequately that which is caused by volume-loading with colloid solutions. It is clear, however, that in interpreting experiments that are designed to test the effects of volume-loading, the confounding effects of hemodilution must be taken into account.

**Systemic Vascular Conductance**

No consistent change in conductance was produced by the infusion of whole blood. It manifestly rose when colloid solutions were infused, in both the hypervolemia and the hemodilution experiments, and whether or not the arterial baroreceptors were intact (Fig. 1). This rise was independent of the changes in blood volume, atrial pressure, blood pressure, or arterial PO₂, so cannot be attributed to reflexes arising from atrial or arterial baroreceptors, nor from carotid chemoreceptors. Activation of pulmonary J receptors (Paintal, 1973) or vagally innervated cardiac chemoreceptors (Coleridge and Coleridge, 1980) causes a reflex rise in systemic vascular conductance, but is associated with bradycardia. The only consistent association of the conductance changes was with the degree of hemodilution (Fig. 4). We are not able to state with certainty whether the conductance changes were an effect of lowered blood viscosity or of lowered oxygen carrying capacity of the blood. However, the evidence is slight that changes of blood viscosity as evidenced in vitro have a major effect on blood flow in vivo (Djojosugito et al., 1970), whereas the vasodilator effects of reduced oxygen-carrying capacity of the blood have been demonstrated clearly both by CO inhalation in conscious rabbits (Körner, 1965) and by conversion of hemoglobin into methemoglobin in anesthetized dogs (Gowdey, 1960; Murray and Escobar, 1968). The close relation that we found (Fig. 4) between oxygen-carrying capacity of the blood as estimated by hematocrit, and conductance, favors the latter explanation. The fact that central venous PO₂ did not fall except with the extreme reduction of hematocrit which occurred in the baroreceptor-intact hemodilution experiment (and then only from 44 to 36 mm Hg) suggests that, in the conscious rabbit, cardiac output is remarkably well able to increase in order to maintain oxygen delivery. There is no evidence, from our data, of the superfluous perfusion that would be predicted if reduced blood viscosity were making a major contribution to the change in conductance. This conclusion has an important bearing on the growing clinical practice of employing hemodilution in surgical situations, for although there may be some intrinsic merit in increasing tissue blood flow by hemodilution, we have found no evidence that oxygen delivery to the tissues is enhanced thereby.

This notable increase in systemic vascular conductance associated with hemodilution has a bearing on experiments that have been designed to test for interaction between volume-loading and the control of blood pressure by the arterial baroreceptors. Thus an alteration in the properties of vascular smooth muscle rather than interaction of reflexes within the central nervous system may, at least in part, account for the attenuation of the blood pressure response to aortic nerve stimulation (Stinnett et al., 1976) or to variation of carotid sinus pressure (Chen et al., 1979) which have been reported following dextran infusion in anesthetized rabbits.

**Stroke Volume**

There was a striking increase of stroke volume in all experiments in which there was hemodilution (Fig. 1), and this contributed importantly to the close matching of cardiac output to systemic vascular resistance which was evident in the baroreceptor-intact animals. It is noteworthy that the increase in stroke volume was independent of an increase in ventricular filling pressure, and was not dependent on a reduction in mean blood pressure. This pattern in the conscious rabbit is different from that reported in conscious, reclining dogs (Vater and Boettcher, 1978; Barnes et al., 1979), in which acute volume loading with electrolyte solution did not cause an increase in stroke volume but only in heart rate. In part, the difference may be explained by the rise in blood pressure that was a feature of the dog experiments, but it does appear that there is a genuine species difference, and that the rabbit responds to acute increase in central blood volume by increase in stroke volume rather than by increase in heart rate.

The mechanism that underlies this increase in stroke volume is not altogether clear. The independence from ventricular filling pressure and blood pressure suggested that enhanced ventricular contractility might be the cause, as was reported by Murray et al. (1969) during hemodilution in anesthetized dogs. The tachycardia that occurred in the
baroreceptor-intact rabbits, the possible origins of which were discussed earlier, is consistent with this explanation. However, the increase of stroke volume that accompanied hemodilution in the baroreceptor-denervated animals was independent of heart rate (Fig. 1B), and both Glick et al. (1964) and Chamorro et al. (1973) found that the increase of stroke volume that occurred with hemodilution in the conscious dog was unaffected by β-blockade (although they did not control ventricular filling pressure as we did). Thus it may be that some consequence of hemodilution per se contributes to the phenomenon. The explanation may be no more than that the intrinsic properties of the left ventricle of the rabbit render it peculiarly well adapted to respond to a fall in peripheral resistance by increasing stroke volume and so supporting blood pressure.

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Circ Res. 1981;48:825-834
doi: 10.1161/01.RES.48.6.825

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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