Cerebral Circulatory Effects of Acutely Induced Hypervolemia in Human Subjects

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Hemodynamic alterations incident to acute changes in intravascular volume have been extensively investigated in man as well as in animals. From these studies have emerged well-defined concepts of the responses elicited by acute reductions in blood volume. On the other hand, studies of the effects of expansion of the intravascular volume have yielded no clear hemodynamic sequence whereby the cardiovascular system reacts or adjusts to its expanded contents. Thus, many observers have noted an increase in right atrial pressure and cardiac output; others have noted the pressure increase but have found no consistent change in cardiac output. Fowler, Bloom, and Ward have adduced evidence indicating that selective expansion of the plasma volume (dextran) induces a consistent increase in cardiac output, whereas expansion of the intravascular contents with whole blood fails to elicit this response. In addition, several groups have investigated the effects of plasma volume expansion on renal blood flow and have largely agreed that renal perfusion is substantially increased under these circumstances.

There is no evidence that blood flow to the brain is influenced by expansion of the intravascular volume. Cerebral vascular resistance is largely governed by alterations in the CO\textsubscript{2} tension of the blood. There is evidence, however, which would suggest that cerebral blood flow may vary with alterations in perfusion pressure, as with acute hypotension, or with changes in viscosity and/or O\textsubscript{2} capacity, as with anemia or polycythemia.

The present study was undertaken to investigate the effects of acute expansion of the blood volume on the cerebral circulation. Selective expansion of the plasma space was achieved with 5 per cent albumin\* solution. Whole blood expansion was effected by the rapid intravenous infusion of 500 cc. of whole blood which had been withdrawn from the same subject six to seven days prior to the experiment. The results indicate that the response of the cerebral circulation is largely dependent upon the type of expansion employed.

Methods

Fifteen subjects without evidence of significant cardiovascular disease were studied. Several of the subjects had degenerative disorders of the nervous system, none of which supposedly affects cerebral blood flow or the reactivity of the vasculature. Selection of the patients for either the "albumin" or "whole blood" group was made without regard for the clinical diagnosis; persons of small stature were more apt to be placed in the "whole blood" group for technical reasons. In each subject, an initial determination of the cerebral blood flow was made, following which the blood volume was acutely expanded. In nine instances, 5 per cent albumin was infused, and in six subjects, whole blood was given. The amount of infusate was varied according to the size of the individual subject so that each received approximately 9 to 11 ml./Kg. Fifteen minutes following the completion of the infusion, a second cerebral blood flow measurement was made. In none of the experiments (except for A.S.) were the patients agitated or excited nor were respiratory irregularities detected.

Cerebral blood flow (CBF) was measured by the nitrous oxide method of Kety and Schmidt, as modified by Scheinberg and Stead. The analytical methods employed were described in a previous publication from this laboratory. Mean arterial blood pressure (MABP) was measured.

\*"Albumisol" employed in this study was kindly provided by Dr. J. C. Richards of Merck Sharpe and Dohme.
TABLE 1
Effects of Blood Volume Expansion on Cerebral Circulatory Function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis*</th>
<th>Infusate (ml./min./100 Gm.)</th>
<th>Cerebral blood flow (ml./min.)</th>
<th>Cerebral vascular resistance (mm. Hg./ml./min./100 Gm.)</th>
<th>Mean arterial blood pressure (mm. Hg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.D.</td>
<td>25</td>
<td>N.</td>
<td>750</td>
<td>65</td>
<td>95</td>
<td>1.25</td>
</tr>
<tr>
<td>T.R.</td>
<td>45</td>
<td>Ep.</td>
<td>500</td>
<td>47</td>
<td>57</td>
<td>2.30</td>
</tr>
<tr>
<td>W.M.</td>
<td>33</td>
<td>Ep.</td>
<td>1000</td>
<td>54</td>
<td>61</td>
<td>1.76</td>
</tr>
<tr>
<td>L.J.</td>
<td>34</td>
<td>C.A.</td>
<td>750</td>
<td>42</td>
<td>54</td>
<td>1.86</td>
</tr>
<tr>
<td>L.K.</td>
<td>36</td>
<td>Ale.</td>
<td>750</td>
<td>67</td>
<td>84</td>
<td>1.19</td>
</tr>
<tr>
<td>R.M.</td>
<td>43</td>
<td>Ale.</td>
<td>750</td>
<td>48</td>
<td>65</td>
<td>1.67</td>
</tr>
<tr>
<td>J.D.</td>
<td>36</td>
<td>N.</td>
<td>500</td>
<td>65</td>
<td>79</td>
<td>1.29</td>
</tr>
<tr>
<td>F.S.</td>
<td>38</td>
<td>N.</td>
<td>750</td>
<td>53</td>
<td>100</td>
<td>1.94</td>
</tr>
<tr>
<td>J.C.</td>
<td>37</td>
<td>Ale.</td>
<td>750</td>
<td>35</td>
<td>37</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Mean difference
Standard error
Probability

5 per cent albumin

| L.J.    | 38  | N.         | 500                         | 78                            | 63                                            | 1.08                            | 1.49                            | 85                              | 94                              |
| R.A.    | 34  | M.S.       | 500                         | 105                           | 103                                           | 0.73                            | 0.81                            | 77                              | 83                              |
| G.S.    | 44  | Park.      | 500                         | 64                            | 75                                            | 1.19                            | 1.00                            | 76                              | 75                              |
| A.S.    | 37  | Ep.        | 500                         | 65                            | 76                                            | 1.40                            | 1.24                            | 91                              | 94                              |
| E.B.    | 30  | N.         | 500                         | 73                            | 53                                            | 1.38                            | 1.94                            | 101                             | 103                             |
| P.R.    | 39  | M.S.       | 500                         | 59                            | 82                                            | 1.32                            | 1.02                            | 78                              | 84                              |

Mean difference
Standard error
Probability

Whole blood

* Abbreviations: N. = Normal; Ep. = Epilepsy; C.A. = Cortical atrophy; Ale. = Alcoholism; M.S. = Multiple sclerosis; Park. = Parkinsonism.

Results

The results of these studies are presented in tables 1 and 2. The data were analyzed by the method of paired observations; only significant values of P are included.

Expansion of the intravascular volume with 5 per cent albumin induced the anticipated hemodilution, which was manifested by a significant decrease in both packed cell volume (P < 0.001) and arterial oxygen content (P < 0.001). This was associated with a 32 per cent increase in CBF, which was highly significant (P < 0.01); since MABP was essentially unchanged, calculated CVR decreased significantly (P < 0.01). The increase in cerebral perfusion was further reflected in the significant decline (P < 0.05) in arteriovenous oxygen difference, CMRO₂ remaining unchanged. There was no change in pH or pCO₂ to account for these hemodynamic alterations. The presence of a mild anemia in some of the subjects was reflected in the rather low preinfusion values for packed cell volume and O₂ content.

Expansion of the blood volume with whole blood was accompanied by changes in cerebral perfusion, but these alterations were neither consistent nor significant. In two ex-
HYPEROVolemIA EFFECTS ON BRAIN CIRCULATION

Effects of Blood Volume Expansion on Arterial and Cerebral Venous Blood Constituents

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arterial O2 Content (volume per cent)</th>
<th>A-VO2 (volume per cent)</th>
<th>Arterial CO2 Content (volume per cent)</th>
<th>CMRO2 (ml/min/100 gm.)</th>
<th>Hematocrit</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C*</td>
<td>E*</td>
<td>C</td>
<td>E</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>D.D.</td>
<td>15.11</td>
<td>13.26</td>
<td>6.15</td>
<td>5.42</td>
<td>41.94</td>
<td>42.85</td>
</tr>
<tr>
<td>T.R.</td>
<td>18.13</td>
<td>16.07</td>
<td>6.76</td>
<td>6.73</td>
<td>42.21</td>
<td>42.59</td>
</tr>
<tr>
<td>W.M.</td>
<td>17.18</td>
<td>14.51</td>
<td>6.54</td>
<td>5.17</td>
<td>50.15</td>
<td>50.02</td>
</tr>
<tr>
<td>L.J.</td>
<td>16.06</td>
<td>13.53</td>
<td>6.12</td>
<td>4.8</td>
<td>48.40</td>
<td>48.01</td>
</tr>
<tr>
<td>L.K.</td>
<td>16.28</td>
<td>14.82</td>
<td>5.67</td>
<td>6.36</td>
<td>47.93</td>
<td>48.22</td>
</tr>
<tr>
<td>R.M.</td>
<td>14.99</td>
<td>13.43</td>
<td>8.52</td>
<td>5.90</td>
<td>46.41</td>
<td>50.81</td>
</tr>
<tr>
<td>J.D.</td>
<td>18.76</td>
<td>16.43</td>
<td>8.05</td>
<td>4.64</td>
<td>42.11</td>
<td>46.33</td>
</tr>
<tr>
<td>F.S.</td>
<td>18.22</td>
<td>15.40</td>
<td>6.35</td>
<td>4.93</td>
<td>43.62</td>
<td>44.19</td>
</tr>
<tr>
<td>J.C.</td>
<td>18.01</td>
<td>16.96</td>
<td>9.68</td>
<td>5.50</td>
<td>42.80</td>
<td>42.62</td>
</tr>
</tbody>
</table>

Mean difference: -2.15, -1.15, -1.05, -0.316, -3.78
Standard error: 0.169, 0.25, 0.15, 0.4, 0.45
Probability: <0.001, <0.001, <0.05, <0.001, <0.001

*C = Control
+E = Following blood volume expansion.

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Experiments CBF decreased, and in each instance there was a slight increase in packed cell volume. In three subjects, CBF increased: one subject (A.S.), an epileptic, experienced several minor seizures during the second blood flow determination; in another experiment (P.R.), the possibility of technical error is raised because arteriovenous oxygen difference increased appreciably in the face of a measured increase in CBF. There was a slight increase in MABP of 4 mm. Hg, which proved to be a significant ($P < 0.05$) change. In any event, the cerebral circulation responds in a variable and unpredictable manner to an increase in blood volume which does not alter the concentration of red cells.

Discussion

The results of these studies indicate that the cerebral circulation reacts to, or participates in a reaction to, an abrupt increase in intravascular volume. The response to expansion with whole blood was capricious, and it seems likely from these data that the cerebral circulation is not affected by an increase in whole blood volume which does not alter the relationship of red cells to plasma; on the other hand, when the plasma volume was selectively expanded, there was a consistent and significant increase in cerebral blood flow.

A precise formulation of the hemodynamic events whereby plasma volume expansion increases cerebral perfusion is not possible from these data. The failure of whole blood to alter cerebral blood flow consistently indicates that this effect is probably not mediated via engorgement of the vascular tree. In all experiments, the second measurement of blood flow was delayed in order to minimize the effects of a rapid phleboysis on cardiac output. It seems likely that the increase in CBF is intimately related to the change in hematocrit and that the effects of albumin infusion are largely those of an acutely induced "anemia," or, more precisely, a reduction in the...
red cell/plasma ratio. Fowler, Bloom, and Ward\textsuperscript{7} have compared the effects of these two types of blood volume expansion (whole blood versus dextran) on cardiac output in dogs. As a result of these studies, they have advanced the view that dextran induces a relative anemia which, in turn, and through obscure mechanisms, leads to an increase in cardiac output; these authors considered differences in viscosity insufficient to account for the observed hemodynamic changes.

It has been clearly established that CBF is increased in persons with anemia\textsuperscript{12} although the stimulus for this protective mechanism has not been elucidated. Justus, Cornett, and Hatcher\textsuperscript{17} infused blood from anemic dogs into nonanemic recipients and observed an increase in cardiac output in the absence of anemia in the recipient animals. These studies would suggest the presence of a humoral substance in anemic animals which might be responsible for the increase in cardiac output; the cerebral vasculature could respond directly to such a humoral substance or indirectly by way of the enhanced cardiac output.

Evidence bearing on the effects of hemodilution on CBF has been adduced in previous studies. Shenkin, Spitz, Grant, and Kety\textsuperscript{18} studying the effects of hypertonic glucose on CBF in patients with brain tumors, observed that cerebral perfusion was significantly increased. These authors ascribed the changes to hemodilution and the attendant decrease in viscosity. Schieve and Wilson,\textsuperscript{19} during the course of experiments designed to establish the relative importance of changes in pH and pCO\textsubscript{2} on CBF, observed that hypertonic NaHCO\textsubscript{3} and NaCl infusions were associated with an increase in CBF. Although significant hemodilution was noted with each, these authors believed that the accompanying changes in perfusion were related only to the alterations in pCO\textsubscript{2}.

There emerges from these considerations the concept that increments in intravascular volume of the magnitude herein reported require no appreciable cardiovascular adjustments if the ratio of red cells to plasma remains unaltered. However, if this ratio declines as the result of an increase in the plasma volume alone, the spurious "anemia" thus induced apparently sets into play the compensatory mechanisms of a true anemia, which, in turn, serve to maintain an optimal oxygen supply to vital organs. Within the framework of this concept, the increase in cerebral perfusion, the changes in cardiac output,\textsuperscript{8,14} and the increase in renal blood flow\textsuperscript{8,10} which occur under circumstances of an increase in plasma volume, are in complete consonance.

**Summary**

Expansion of the blood volume with 5 per cent albumin solution was associated with a 32 per cent increase in cerebral blood flow and a commensurate decrease in cerebral vascular resistance. Expansion of the intravascular volume with whole blood was not associated with any consistent cerebral hemodynamic alteration. It is suggested that the response of the cerebral circulation was largely governed by the factitious "anemia" induced by the selective expansion of the plasma volume.

**References**

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