Loss of cerebral regulation during cardiac output variations in focal cerebral ischemia

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Focal cerebral ischemia was induced in anesthetized macaque monkeys by unilateral middle cerebral artery occlusion. The effect of blood volume expansion by a colloid agent and subsequent exsanguination to baseline cardiac output (CO) on local cerebral blood flow (CBF) was measured by the hydrogen clearance technique in both ischemic and nonischemic brain regions. Cardiac output was increased to maximum levels (159% ± 92%, mean ± standard error of the mean) by blood volume expansion with the colloid agent hetastarch, and was then reduced a similar amount (166% ± 82%) by exsanguination during the ischemic period. Local CBF in ischemic brain regions varied directly with CO, with a correlation coefficient of 0.89 (% change CBF/% change CO), while CBF in nonischemic brain was not affected by upward or downward manipulations of CO. The difference in these responses between ischemic and nonischemic brain was highly significant (p < 0.001).

The results of this study show a profound loss of regulatory control in ischemic brain in response to alterations in CO, thereby suggesting that blood volume variations may cause significant changes in the intensity of ischemia. It is proposed that CO monitoring and manipulation may be vital for optimum care of patients with acute cerebral ischemia.

Key Words • ischemia • autoregulation • cardiac output • cerebral blood flow • macaque monkey

The ability of the cerebral circulation to maintain a constant blood flow in the face of alterations in perfusion pressure (autoregulation) has been a long-accepted physiological tenet. It is also known that autoregulatory capacity is lost to varying degrees when brain tissue becomes damaged or ischemic such that blood flow in an ischemic circulatory bed may become pressure-passive. Blood volume variations can cause marked alterations in cardiac output (CO), even in the absence of arterial blood pressure changes, and multiple clinical observations support the importance of blood volume maintenance in treating patients with clinical cerebral ischemia due to vasospasm after subarachnoid hemorrhage.

Laboratory investigations have confirmed that cerebral blood flow (CBF) to ischemic brain regions may be augmented when blood volume is expanded. However, some investigators have asserted that this effect is due to blood viscosity reduction and hemodilution, and have largely ignored the relative contribution of CO alterations to the responses of ischemic brain when blood volume is expanded. Keller and coworkers first proposed that CO rather than hemodilution might be the most important determinant of blood flow responses in ischemic brain tissue, since their focally ischemic monkeys undergoing isovolemic hemodilution did not exhibit changes in either CO or CBF despite marked reduction in hematocrit. Further investigation using the primate stroke model has substantiated this initial work.

The present study was designed to test and quantify the regulatory capacity of ischemic and nonischemic brain tissue in a primate stroke model, with upward and downward manipulation of CO caused by adjusting blood volume independent of changes in perfusion pressure.

Materials and Methods

Experimental Protocol

This experimental protocol was fully approved by the University of Colorado Animal Care Committee.
Eight adult macaque monkeys (*Macaca nemestrina*) of both sexes, each weighing 5 to 10 kg, were sedated with intramuscular ketamine (10 mg/kg), then anesthetized with intravenous pentobarbital (20 mg/kg) after endotracheal intubation. Controlled ventilation with a volume respirator was begun, and the animals were immobilized with pancuronium (0.1 mg/kg). Bilateral femoral cutdowns were performed for insertion of an aortic catheter, pulmonary artery catheter, and central venous pressure line. Arterial blood was sampled for gas measurement, and ventilatory parameters were adjusted to maintain arterial pCO$_2$ at between 35 and 40 mm Hg. Cardiac output was determined by the dye-dilution method, and hematocrit was measured throughout all studies. Burr holes were then placed in the following four areas: Region A, the frontal convexity, left hemisphere; Region B, the frontal convexity, right hemisphere; Region C, the parietal convexity, right hemisphere; and Region D, the frontal operculum, right hemisphere. Next, 90% platinum/10% iridium electrodes were placed transdurally in these burr holes for measurement of local CBF by the hydrogen clearance technique.$^{30}$ A subdural intracranial pressure (ICP) monitor was placed in the left parietal region.

The proximal right middle cerebral artery (MCA) was exposed by transorbital dissection$^{12}$ and, following collection of baseline circulatory parameters, the MCA was occluded at its origin with an aneurysm clip. After repeated data collections, blood volume was expanded incrementally with intravenous boluses of 6% hetastarch warmed to 37°C. Local CBF, CO, and hematocrit determinations were performed after administration of each bolus until maximum CO had been achieved. At that point, incremental exsanguination was begun, taking care not to lower mean arterial blood pressure (MABP) by excessively rapid withdrawal of blood. Local CBF, CO, and hematocrit were determined following each withdrawal until CO values were returned to near those recorded prior to blood volume expansion. Following each study, the animal was sacrificed with a barbiturate overdose.

Cerebral blood flow values were determined from hydrogen clearance curves using the reaction time (t$_2$) method and the initial slope index. Brain regions were considered ischemic if CBF fell to less than 40% of control values after MCA occlusion.

### Statistical Analysis

Regulatory capacity responses to changes in CO were determined for ischemic and nonischemic regions by the correlation coefficient ratio: % change in CBF/% change in CO. Data were examined statistically using a two-tailed t-test.

### Results

#### Hemodynamic Effects of Blood Volume Variations

Incremental bolus injections of 6% hetastarch produced stepwise increases in CO until a maximum level was reached, thereby demonstrating an intact Frank-Starling effect$^{29}$ in these animals (Table 1). The volume of hetastarch required to bring CO to maximum values was 33 ± 5 ml/kg (mean ± standard error of the mean). Cardiac output was elevated from 0.9 ± 0.2 to 2.6 ± 1.0 liters/min, an increase of 159% ± 92% over control values. The MAPB was not altered significantly by blood volume expansion, nor was pulse pressure, heart rate, or ICP. Stroke volume was increased from 7 ± 3 to 18 ± 9 ml (p < 0.01). Hematocrit was reduced from 44% ± 5% to 28% ± 4% by hetastarch infusions, a decrease of 36% ± 8% (p < 0.001).

Progressive exsanguination of 24 ± 10 ml/kg of whole blood led to reduction of CO to 1.2 ± 0.3 liters/min. This brought about a reduction from the maximum CO of 166% ± 82% (p < 0.01), apparently mediated by a reduction in stroke volume to 8 ± 3 ml (p < 0.05). Once again, no significant alterations in MAPB, pulse pressure, heart rate, or ICP were observed. Hematocrit was reduced to 23% ± 5% by exsanguination, a further reduction of 19% ± 13% below that achieved by blood volume expansion with hetastarch (p < 0.05).

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Value</th>
<th>Significance</th>
<th>Volume Expansion to Max CO</th>
<th>Significance†</th>
<th>Exsanguination to Baseline CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>volume of 6% hetastarch infusion (ml/kg)</td>
<td>33 ± 5</td>
<td></td>
<td>24 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>volume of blood removed (ml/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean arterial blood pressure (mm Hg)</td>
<td>114 ± 11</td>
<td>n.s.</td>
<td>116 ± 18</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>pulse pressure (mm Hg)</td>
<td>74 ± 7</td>
<td>n.s.</td>
<td>85 ± 20</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>173 ± 50</td>
<td>n.s.</td>
<td>155 ± 43</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>stroke volume (ml)</td>
<td>7 ± 3</td>
<td>p &lt; 0.01</td>
<td>18 ± 9</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>pulmonary artery wedge pressure (mm Hg)</td>
<td>4 ± 2</td>
<td>p &lt; 0.001</td>
<td>11 ± 4</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>cardiac output (liters/min)</td>
<td>0.9 ± 0.2</td>
<td>p &lt; 0.01</td>
<td>2.6 ± 1.0</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>intracranial pressure (mm Hg)</td>
<td>5 ± 4</td>
<td>n.s.</td>
<td>4 ± 3</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>44 ± 5</td>
<td>p &lt; 0.001</td>
<td>28 ± 4</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± standard error of the mean. Max CO = maximum cardiac output; baseline CO = control cardiac output.† P values represent statistical significance of difference between adjacent values; n.s. = not significant.
Cardiac output and focal ischemia

### TABLE 2

Local CBF responses in ischemic and nonischemic brain tissue to blood volume variations*

<table>
<thead>
<tr>
<th>Region</th>
<th>Preocclusion CBF</th>
<th>Post-MCA Occlusion CBF</th>
<th>Volume Expansion at Max CO</th>
<th>Exsanguination To Baseline CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonischemic brain (Region A)</td>
<td>65 ± 28</td>
<td>65 ± 30</td>
<td>66 ± 32</td>
<td>61 ± 31</td>
</tr>
<tr>
<td>ischemic brain (Regions B, C, &amp; D)</td>
<td>78 ± 29</td>
<td>20 ± 11†</td>
<td>34 ± 15‡</td>
<td>18 ± 4§</td>
</tr>
</tbody>
</table>

* Values represent local cerebral blood flow (CBF) in ml/100 gm/min; MCA = middle cerebral artery; max CO = maximum cardiac output; baseline CO = control cardiac output. For a description of regions studied, see text.
† Significantly different from preocclusion CBF (p < 0.001).
‡ Significantly different from post-MCA occlusion CBF (p < 0.01).
§ Significantly different from max CO CBF (p < 0.02).

### Effects of MCA Occlusion on Local CBF

Ischemic brain regions were defined as those areas registering local CBF values less than 40% of preocclusion values. These ischemic regions in the right hemisphere recorded a fall in local CBF from 78 ± 29 to 20 ± 11 ml/100 gm/min following MCA occlusion, a reduction to 26% ± 10% of control values (Table 2). There were no significant differences in intensity of ischemia recorded between any of these areas in the right cerebral hemisphere, with the frontal convexity (Region B), the parietal convexity (Region C), and the frontal operculum (Region D) measuring 26% ± 14%, 29% ± 8%, and 22% ± 8% of control CBF values, respectively, following MCA occlusion. Nonischemic regions (Region A, frontal convexity contralateral to the MCA occlusion) registered CBF values of 65 ± 28 ml/100 gm/min before occlusion and 65 ± 30 ml/100 gm/min after.

### Effects of Blood Volume and CO Variations on Local CBF

Incremental increases in CO brought about by bolus injections of 6% hetastarch resulted in incremental increases in local CBF in ischemic brain regions, while no significant effects were observed in nonischemic brain tissue. The increases in local CBF to ischemic brain regions were also invariably maximum at the highest CO. Incremental decreases in CO brought about by progressive exsanguination likewise led to progressive decreases in CBF to ischemic brain regions. The maximum lowering of CBF also invariably occurred at the lowest CO achieved. We intentionally exsanguinated the animals only until the final CO was similar to the pre-volume-expansion value. Local CBF in nonischemic brain regions was not altered by exsanguination.

When local CBF values following MCA occlusion were compared to those observed after maximum CO had been achieved by blood volume expansion and after CO had been returned to control values by exsanguination, we observed a selective vulnerability of ischemic regions to these upward and downward deflections of CO (Table 2). After analyzing the responses of all ischemic regions taken together, we observed that local CBF was increased from 20 ± 11 to 34 ± 15 ml/100 gm/min, an increase of 70% (p < 0.01). Exsanguination caused local CBF in ischemic regions to fall to 18 ± 4 ml/100 gm/min, a lowering of local CBF to 27% ± 15% of preocclusion values (p < 0.05). Local CBF to nonischemic regions following MCA occlusion was not significantly altered either by increases in CO or by a return to baseline CO.

### Regulatory Responses to Variations in Cardiac Output

The regulatory capacity of ischemic and nonischemic brain regions was assessed by comparing the percentage changes in local CBF to percentage changes in CO (%ΔCBF/%ΔCO). This ratio in normally regulating tissue would theoretically be zero since changes in local CBF would not occur. However, a positive correlation coefficient should exist if regulation were partially or completely abolished.

When %ΔCBF and %ΔCO values were analyzed after maximum CO was reached (Table 3), we found that ischemic brain regions showed increases of 100% ± 101% in local CBF, whereas nonischemic regions took a different pattern.

### TABLE 3

Regulatory responses of ischemic and nonischemic brain tissue to cardiac output variations*

<table>
<thead>
<tr>
<th>Factor</th>
<th>%ΔCBF</th>
<th>%ΔCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonischemic brain blood volume expansion</td>
<td>+1 ± 18†</td>
<td>+159 ± 92§</td>
</tr>
<tr>
<td>exsanguination</td>
<td>+9 ± 40‡</td>
<td>-166 ± 82</td>
</tr>
<tr>
<td>ischemic brain blood volume expansion</td>
<td>+100 ± 101</td>
<td>+159 ± 92</td>
</tr>
<tr>
<td>exsanguination</td>
<td>-87 ± 64</td>
<td>-166 ± 82</td>
</tr>
</tbody>
</table>

* %ΔCBF = percentage change in cerebral blood flow; %ΔCO = percentage change in cardiac output.
† Significantly different from ischemic brain value (p < 0.001).
‡ Significantly different from ischemic brain value (p < 0.01).
§ Significantly different from nonischemic brain exsanguination value (p < 0.001).
Discussion

Although it has long been known that ischemic brain tissue loses its autoregulation capacity in response to alterations in perfusion pressure, it has not been widely appreciated that a similar loss of regulation may occur due to alterations of CO brought about by blood volume variations. Davis and Sundt observed that nonischemic brain tissue maintained its regulation in response to increases in CO caused by hypervolemia. However, they also noted that blood volume decreases could result in depression of CBF, even in normal brain tissue. The present study has demonstrated that quite significant changes in local CBF may occur in ischemic brain tissue in response to changes in CO in both positive and negative directions. This finding may prove to be vital in the clinical management of the ischemic stroke patient.

**Hypervolemic Hemodilution**

Numerous clinical studies have shown that intravascular blood volume expansion with colloid agents may be a vital adjunct to management of cerebral ischemia due to vasospasm and carotid occlusive disease. Vander Ark and Pomerantz proposed in 1973 that CO augmentation may reverse ischemic stroke deficits. Pritz, et al., were the first group to

**TABLE 4**

<table>
<thead>
<tr>
<th>Region</th>
<th>%ΔCBF/%ΔCO</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonischemic brain</td>
<td>0.01 ± 0.21</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>ischemic brain</td>
<td>1.02 ± 1.11</td>
<td></td>
</tr>
</tbody>
</table>

* Values represent percentage change in cerebral blood flow (%ΔCBF)/percentage change in cardiac output (%ΔCO).
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report improved neurological function occurring with an increased intravascular blood volume independent of any change in blood pressure. However, a number of large clinical trials have not demonstrated favorable results in patients with ischemic stroke treated with hemodilution. The majority of investigators who have reported success with intravascular blood volume therapy in ischemic stroke syndromes have attributed these results to its theoretical effects of blood viscosity reduction and hemodilution brought about by infusion of colloid agents.

The term “hypervolemic hemodilution” coined by Wood and Fleischer has subsequently become the main treatment rationale. Wood, et al., demonstrated increases in local CBF to ischemic regions in their canine stroke model when blood volume was expanded with autologous plasma or with low-molecular-weight dextran. They attributed these blood flow increases to hemodilutional effects. Cardiac output was increased by their infusions, but they ignored any contribution of CO to their results since whole-blood infusions did not significantly increase CBF to ischemic regions. However, the blood transfusions in their dogs increased CO, on the average, by only 42% and 59%, whereas plasma and dextran increased CO an average of 100% and 114%, respectively.

Cardiac Output Versus Hemodilution

Keller and coworkers showed that dextran infusions in a primate stroke model selectively increased CBF to ischemic regions, but they attributed these results to hypervolemic CO augmentation rather than to hemodilution since isovolemic hemodilution with exchange transfusions of dextran and blood did not affect CBF to ischemic regions. Tranmer, et al., also demonstrated that infusions with hetastarch in the primate stroke model resulted in increases in CO and associated increases in CBF in ischemic brain tissue. The present study supports the contention that CO elevation rather than hemodilution is responsible for the increases in CBF to ischemic tissue that occur during colloidal hypervolemia, since percentage changes in CBF were directly proportional to percentage changes in CO in a positive or a negative direction. Interestingly, these percentage increases or decreases in CBF correlated almost one-to-one with percentage changes in CO. If hemodilution were to explain the results, then increasing hemodilution brought about by exsanguination should have resulted in further increases rather than the observed “paradoxical” decreases in local CBF to ischemic tissue.

Blood Viscosity Autoregulation

Muizelaar, et al., performed studies on the effects of the colloid agent mannitol on local CBF in head-injured patients and have shown that mannitol normally causes a reflex cerebrovasoconstriction without causing a change in CBF. They felt that this effect reflected the brain’s normal autoregulatory response. However, if cerebral autoregulation is impaired by trauma or ischemia, then increases in CBF occur because vessels are unable to constrict in response to colloid administration. They believe that this is supportive evidence for “blood viscosity autoregulation.”

Brown, et al., observed increases in CBF to traumatized brain tissue when mannitol was given. They believed that these increases correlated most closely with increases in CO. Our present results favor the contention that “cardiac output regulation” is the most operative factor rather than blood viscosity.

Muizelaar and Muizelaar thought that changes in CBF are not related to alterations in CO in autoregulating and poorly autoregulating brain tissue. They measured CBF and CO in patients with head injuries after administration of phenylephrine, trimethaphan, or mannitol. There was no correlation between the resulting changes in CBF and CO. The discrepancies between this work and the results of others may be attributed to several factors: 1) mannitol did not produce a major increase in CO in patients with poorly autoregulating brain; 2) the complicated properties of mannitol may not have the same effects as a colloid agent (hetastarch) on CBF and CO; and 3) the pathophysiology of injured brain tissue may differ from that of ischemic brain tissue.

Cardiac Output Regulation

The mechanism for the phenomenon of CO regulation is unclear, although Muizelaar, et al., suggested that blood volume expansion may distort cerebral vessels and bring the “Bayliss effect” into play such that a vessel-walls muscle contraction normally occurs, causing a compensatory vasodilation. Vessels in ischemic or traumatized tissue may have lost this Bayliss autoregulation since they are no longer able to contract actively against passive vessel stretch brought about by blood volume expansion, thus causing an increase in blood flow through these collateral vessels. It is known that the increase in CO in our monkeys is caused by an increase in stroke volume and pulse pressure, and perhaps this hyperdynamic effect improves the pulsatile flow of blood in collateral vessels as well. Regardless of the mechanism, it seems clear from these studies that areas of brain with impaired regulatory capacity are unable to resist changes in CO, just as they are unable to respond to alterations in perfusion pressure.

Laboratory Model

The primate model of focal cerebral ischemia seems consistently to be the closest approximation to the human situation for experimental ischemia. Indeed, thresholds for cerebral ischemia in monkeys (15 to 23 ml/100 gm/min) are very similar to those observed in humans (18 ml/100 gm/min) and MCA occlusion in monkeys consistently produces local cortical CBF values near or below this ischemic threshold. The average value for local CBF in ischemic
areas following MCA occlusion in this study was 20 ± 11 ml/100 gm/min, which very closely approximates a truly ischemic brain focus. Blood volume expansion to maximum CO produced an increase in CBF to 34 ± 15 ml/100 gm/min, a value sufficiently above the ischemic threshold to alter favorably the intensity of ischemia in the affected vascular distribution. Allowing CO and blood volume to return to baseline led to a recurrence of local CBF values near or below the threshold for ischemic damage and physiological neuronal dysfunction. Our laboratory has shown that these changes in CBF do produce alterations in the neuroelectric function of the ischemic brain. This therefore implies a definite therapeutic benefit of blood volume expansion and provides experimental support for clinical trials.

Conclusions

Cerebral blood flow and CO measurements during alterations in intravascular blood volume in our primate stroke model have clearly demonstrated a profound loss of regulatory control in response to alterations in CO in ischemic brain regions. This demonstrates that blood volume variations may cause significant changes in the degree of brain ischemia; therefore, CO and blood volume status may be important parameters to observe and, possibly, to manipulate in patients with acute stroke.

References

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