Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation

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Intravascular volume expansion has been successfully employed to promote blood flow in ischemic brain regions. This effect has been attributed to both decreased blood viscosity and increased cardiac output resulting from volume expansion. The physiological mechanism by which changes in cardiac output would affect cerebral blood flow (CBF), independent of blood pressure variations, is unclear, but impaired cerebral autoregulation is believed to play a role. In order to evaluate the relationship between cardiac output and CBF when autoregulation is either intact or defective, 135 simultaneous measurements of cardiac output (thermodilution method) and CBF (by the $^{133}$Xe inhalation or intravenous injection method) were performed in 35 severely head-injured patients. In 81 instances, these measurements were performed after manipulation of blood pressure with phenylephrine or Arfonad (trimethaphan camsylate), or manipulation of blood viscosity with mannitol. Autoregulation was found to be intact in 55 of these cases and defective in 26. A wide range of changes in cardiac output occurred after administration of each drug. No correlation existed between the changes in cardiac output and the changes in CBF, regardless of the status of blood pressure autoregulation. A significant (40%) increase in CBF was found after administration of mannitol when autoregulation was defective. These data support the hypothesis that, within broad limits, CBF is not related to cardiac output, even when autoregulation is impaired. Thus, the effect of intravascular volume expansion appears to be mediated by decreased blood viscosity rather than cardiac output augmentation.

Key Words • cardiac output • cerebral blood flow • autoregulation • mannitol

Intravascular volume expansion, alone or in combination with induced hypertension, has been proposed to be useful in the prevention and treatment of focal cerebral ischemia caused by arterial occlusive disorders or by vasospasm after subarachnoid hemorrhage. The beneficial effect of this treatment on regional cerebral blood flow (rCBF), neuroelectrical activity, and clinical symptoms has been demonstrated both in laboratory investigations and in clinical situations and has been related to impaired autoregulation in ischemic brain.

The passive relationship between cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) in regions with impaired autoregulation has been well documented. While this justifies induced hypertension as a possible treatment of decreased perfusion, the physiological mechanism by which intravascular volume expansion results in increased blood flow in ischemic brain remains controversial. Some investigators have argued that the decrease in blood viscosity occurring after intravascular volume expansion accounts completely for the improved rCBF. Others have suggested that cardiac output augmentation, resulting from increased vascular filling pressure after intravascular volume expansion, mediates the effect. They have speculated that, in regions with decreased autoregulation, changes in cardiac output may in some way be transmitted to the vascular bed, even when perfusion pressure is unchanged. A valid explanation for such a mechanism is lacking since, according to Poiseuille's law, flow is the quotient of perfusion pressure and vascular resistance. It is unclear where cardiac output would fit in this equation.

Whatever the relationship between cardiac output and CBF, the status of autoregulation seems to be the keystone, and this parameter should be taken into consideration in any attempt to clarify the subject. In the present study, changes in cardiac output and CBF were measured simultaneously in comatose head-injured patients during tests of blood pressure autoregulation, and before and after manipulating blood viscosity by mannitol. This study was undertaken to analyze
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the relationship between cardiac output and CBF in two groups of patients: one with intact and the other with defective autoregulation.

Clinical Material and Methods

Patient Management

All measurements were performed in comatose patients with severe head injury (Glasgow Coma Scale scores < 8 for at least 6 hours), who were admitted to the Neuroscience Intensive Care Unit of the Medical College of Virginia Hospital in Richmond. Characteristics of the patient population have been described earlier, as have the details of therapeutic management. None of the patients had a history of cardiac disease. All patients were intubated and ventilated artificially. In most patients, pancuronium was used to induce skeletal muscle paralysis during the studies in order to provide optimal respiratory care, maintain a constant PaCO₂, and prevent movement artifacts. A Swan-Ganz catheter was inserted routinely in all patients for optimal hemodynamic monitoring and measurement of cardiac output. Intracranial pressure (ICP) was measured with an intraventricular catheter or a Richmond subarachnoid bolt. Arterial blood pressure (ABP) was monitored from an intra-arterial catheter, and digitally displayed as mean ABP (MABP = □9 systolic ABP + □3 diastolic ABP). End-expiratory pCO₂ was monitored with a capnometer,* and maintained at a constant level during the studies by adjusting the respirator if necessary. Additional PaCO₂ measurements were obtained during each CBF measurement.

Measurements of CBF and tests of autoregulation were performed only after written informed consent was obtained from the patient’s next of kin. The protocol was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia. All 33Xe CBF measurements were performed in the Neuroscience Intensive Care Unit in agreement with the radiation safety regulations of the Office of Environmental Health and Safety of the Virginia Commonwealth University.

CBF Measurements

Measurement of CBF was performed by the 33Xe inhalation or intravenous technique as described by Obrist, et al. Details of the procedures used are described elsewhere. With the inhalation method, patients breathed a gas mixture containing 5 to 8 mCi 33Xe/liter for 1 minute. With the intravenous injection method, 33Xe dissolved in saline (0.3 mCi/kg body weight) was injected, after which ventilation was halted for 20 seconds, in order to prevent the xenon from being expired in large part during the first passage through the lungs before reaching the systemic circulation. Washout of radioactivity from the hemispheres and expired air was monitored over a 15-minute period. In most studies, a system with 16 probes, concentrically arrayed in a Plexiglas helmet, was used. More recent measurements were made with a portable system containing 10 probes.‡

From the obtained curves, CBF infinity (CBF₀) was calculated. Mathematically, CBF₀ is equivalent to the height-over-area method and is relatively insensitive to compartmental “slippage,” which is likely to occur with CBF measurements in brain trauma. Since no large regional differences in flow were found in this study, only the average results of all detectors were used and were considered to represent “global” hemispheric flow. All CBF data were corrected to a standard PaCO₂ of 34 mm Hg by assuming a 3 % change in CBF/torr PaCO₂ to facilitate comparison with baseline values and data from other studies. The methodological considerations regarding these methods have been discussed previously.

Measurement of Cardiac Output

Cardiac output was measured by the thermodilution method of Ganz, et al.* Ice-cold normal saline (10 cc) was injected into the central venous port of the Swan-Ganz catheter. The temperature change in the pulmonary artery was registered by a thermistor, and cardiac output was calculated by a microcomputer.§ During each CBF study, cardiac output measurements were obtained in triplicate. The average value was calculated and used for further analysis. If there was a gross discrepancy between the three readings, only the two closest determinations were used.

Autoregulation Tests

After a baseline CBF measurement was obtained, the patient’s blood pressure was slowly raised with intravenous administration of phenylephrine in normal saline (80 mg/500 ml) to a value 30% higher than baseline MABP. This usually took 20 minutes and, after stabilization of blood pressure at the higher level for a few minutes, a second CBF measurement was obtained. On some occasions, when baseline CBF and/or MABP was high, autoregulation was tested by slowly decreasing blood pressure and Arfonad (trimethaphan camsylate, 500 mg/500 ml dextrose 5%) to a value of 30% lower than baseline MABP. These tests were always performed under simultaneous monitoring of evoked potentials, to ensure patient safety.

In keeping with earlier studies, autoregulation was defined as being intact if the percentage change in CPP divided by the percentage change in cerebrovascular

* Capnometer, Model HP 47210 A, manufactured by Hewlett-Packard, Waltham, Massachusetts.

† Tasc-5 CBF measurement system manufactured by the Harshaw Chemical Company, Solomon, Ohio.

‡ Novo-10a CBF machine, manufactured by Novo Diagnostics, Hartford, Connecticut.

§ Mennen cardiac output computer manufactured by MedSearch Systems, Inc., Bethesda, Maryland.
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TABLE 1
Effect of phenylephrine, Arfonad, and mannitol on physiological data

<table>
<thead>
<tr>
<th>Blood Pressure Autoregulation</th>
<th>Phenylinephrine</th>
<th>Arfonad</th>
<th>Mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Study</td>
<td>Intact</td>
<td>Defective</td>
<td>Intact</td>
</tr>
<tr>
<td>no. of cases</td>
<td>26</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predrug</td>
<td>96 ± 12</td>
<td>92 ± 10</td>
<td>111 ± 10</td>
</tr>
<tr>
<td>postdrug</td>
<td>127 ± 14</td>
<td>123 ± 8</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predrug</td>
<td>18 ± 10</td>
<td>18 ± 5</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>postdrug</td>
<td>20 ± 15</td>
<td>16 ± 6§</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>cardiac output (% change)</td>
<td>+7 ± 31</td>
<td>+15 ± 21§</td>
<td>-10 ± 13</td>
</tr>
<tr>
<td>CBF (ml/100 gm/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>predrug</td>
<td>36 ± 11</td>
<td>21 ± 6</td>
<td>41 ± 8</td>
</tr>
<tr>
<td>postdrug</td>
<td>35 ± 10</td>
<td>32 ± 8</td>
<td>40 ± 8</td>
</tr>
<tr>
<td>CBF % change</td>
<td>-1 ± 12</td>
<td>+53 ± 20§</td>
<td>-2 ± 8</td>
</tr>
</tbody>
</table>

* Measurements of mean arterial blood pressure (MABP), mean intracranial pressure (ICP), cardiac output (percent change), and cerebral blood flow (CBF) are given before and after drug administration. Values are means ± standard deviations. Arfonad = trimethaphan camsylate.
† Significant change from baseline value (p < 0.01).
‡ Significant change from baseline value (p < 0.05).
§ Significantly different compared to intact autoregulation (p < 0.05).

resistance (CVR = CPP/CBF) was positive and equal to or less than 2.16,18

Administration of Mannitol

Mannitol was given only to patients who had not received this drug during the previous 4 hours and who were not likely to need it in the next 8 hours (ICP < 20 mm Hg and stable), in order not to jeopardize their blood osmolality. After blood pressure was allowed to return to baseline values following the autoregulation test, an intravenous bolus of 0.66 gm/kg mannitol as a 20% solution in water was administered over a period of 3 minutes. Twenty-five minutes later, CBF and cardiac output measurements were repeated.

Statistical Analysis

The obtained values for MABP, ICP, cardiac output, and CBF before and after administration of each applied drug were compared using Wilcoxon's signed-rank test. The relationship between the changes in cardiac output and CBF was analyzed with the Spearman rank correlation test.

Results

A total of 135 combined measurements (MABP, ICP, cardiac output, and CBF) were obtained in 35 patients. All measurements were performed between 5 and 127 hours after injury (mean 39.6 hours). Fifty-four of these measurements were baseline studies and the remaining 81 were performed within 1 to 4 hours after one of these baseline studies, following manipulation of blood pressure or blood viscosity. Thus, in 81 instances the relative change of cardiac output and CBF could be compared.

Blood pressure was raised with phenylephrine in 44 instances. Autoregulation was found intact in 26 (59%) of these cases and defective in 18 (41%). Blood pressure was lowered with Arfonad in nine cases, of which autoregulation was determined to be intact in seven (78%) and defective in two (22%). In 28 instances, cardiac output and CBF were measured after administration of mannitol. Autoregulation was found intact in 22 of these cases and impaired in six.

The effects of phenylephrine, Arfonad, and mannitol on MABP, ICP, cardiac output, and CBF are summarized in Table 1. Since the average of the absolute values of cardiac output (which ranged between 2.0 and 16.4 liters/min in this study) would be of limited significance, only the mean and the standard deviation of the relative (percentage) change of cardiac output in each patient are reflected.

There was a wide variation in the changes observed in cardiac output. The relative change in cardiac output ranged between −39% and +96% after phenylephrine administration, between −24% and +33% after Arfonad, and between −25% and +131% after mannitol. With the exception of phenylephrine in defective autoregulation, no statistically significant changes in cardiac output were found after any of the applied pharmacological manipulations. The data presented in Table 1 show a direct correlation between MABP and CBF and an inverse correlation between blood viscosity and CBF when autoregulation was impaired (assuming that mannitol decreases viscosity, a fact that has been well established6,26). No correlation between CBF and any other parameter existed when autoregulation was intact. In particular, no correlation between cardiac output and CBF was found, regardless of the autoregulatory status.

In one patient (Case 43), who was hypotensive and probably suffering from volume depletion, cardiac output and CBF were measured 5 hours after injury. After restoration of intravascular volume, measurements were repeated 3 hours later: MABP had risen from 87 to 96 mm Hg, cardiac output had increased 18% from 5.4 to 6.3 liters/min, while CBF did not change significantly (from 19.2 to 18.2 ml/100 gm/min). (Because
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these data do not represent a pharmacological manipulation, they are not included in Table 1.) Then, in the same patient, MABP was increased a further 20% with administration of phenylephrine from 96 to 115 mm Hg, after which cardiac output fell by 40% to 3.8 liters/min and CBF increased by 74% to 31.6 ml/100 gm/min, thus showing an impaired upper level of autoregulation. This case illustrates the lack of any relationship between cardiac output and CBF after head injury, even when autoregulatory mechanisms do not function properly.

In Fig. 1, all individually recorded changes in cardiac output are plotted against the corresponding changes in CBF, itemized for the status of autoregulation. As can be readily observed from these plots, no relationship seems to exist between cardiac output and CBF. Statistical testing indeed confirms this observation (correlation coefficient $R_s = +0.05$ for intact, and $R_s = -0.05$ for defective autoregulation, Spearman's rank correlation test).

Discussion

One of the most striking observations in this study is the wide range of cardiac output changes occurring after the administration of phenylephrine, Arfonad, or mannitol. This made it impossible to attribute a statistically significant effect to any of these drugs on cardiac output. To explain this finding, one needs to take a closer look at the physiological regulation of cardiac output.

Cardiac output is normally regulated by the interaction of venous return (preload), resistance to outflow (afterload), and myocardial contractility. Under normal circumstances, cardiac reserve is high and the amount of venous return is the determining factor of cardiac output, the heart being able to pump out any amount of blood that enters the right atrium (Frank-Starling law of the heart), within broad limits independent of outflow resistance. Venous return is determined by systemic filling pressure and blood flow through the tissues, which is in turn dependent on the rate of metabolism. Thus, under physiological conditions, cardiac output is regulated by the metabolic demands of the tissues rather than by the heart action itself.9

It is not always clear where iatrogenic action will intervene in this mechanism and what the eventual effect on cardiac output will be. The response of cardiac output to any particular drug will depend not only on the drug's intrinsic pharmacological action, but also on the status of hemodynamic parameters such as circulating blood volume, myocardial contractility, and vascular reactivity at the time of administration.

Effect of Phenylephrine

The $\alpha$-adrenergic agonist phenylephrine causes vasoconstriction in most organs including the skin, thus increasing peripheral resistance. Arterial blood pressure rises but due to increased resistance, this does not lead to increased flow through these organs. Thus, venous return remains unaltered, leaving cardiac output more or less unchanged, which is in agreement with our observations. Since cerebral blood vessels have few $\alpha$-adrenergic receptors, administration of phenylephrine will not lead to pharmacological cerebral vasoconstriction. However, with intact autoregulation cerebral vasoconstriction will occur (due to increased blood pressure), maintaining a stable CBF such that venous return from the brain to the heart will also remain unchanged. With defective autoregulation, administration of phenylephrine was accompanied by a modest but statistically significant increase (+15%) of cardiac output. Under those circumstances, the increased CBF leads to increased venous return from the
brain to the right atrium, resulting in elevated cardiac output.

Effect of Arfonad

The effect of Arfonad on cardiac output is twofold. First, by blocking impulse transmission in the autonomic ganglia, it causes massive peripheral vasodilation, thus reducing afterload, which may increase cardiac output especially when early cardiac failure is present. However, Arfonad also decreases postcapillary venous tone, which may reduce venous return to the right atrium and consequently may diminish cardiac output. Thus, the resulting change of cardiac output from Arfonad will depend on the patient's hemodynamic status at the time of its administration. In the present study, cardiac output could indeed go either way after administration of Arfonad.

Effect of Mannitol

In previous studies, mannitol has been shown to increase cardiac output. This effect has been attributed to a possible positive inotropic activity of mannitol, a reduction of peripheral resistance due to lower blood viscosity, or (especially in head injury) an improvement of blood flow in the brain stem. Mannitol may also cause an increase in circulating blood volume by osmotic absorption of water from the extravascular into the intravascular compartment. However, Brown, et al., did not find an increase in serum blood volume after administration of mannitol, while it caused a significant increase of cardiac output. In the present study, however, an increase of cardiac output after mannitol administration was not always seen. A possible explanation for the discrepancy between the present data and those of Brown, et al., might be that, in the latter experiment, mannitol was administered in the very early stage after experimental head injury (15 minutes after injury), when cardiac output was still reduced as a result of the head injury, while in the present study baseline cardiac output varied widely.

Mannitol caused a statistically significant increase of CBF when autoregulation was defective. From our results, it seems unlikely that this effect was mediated by an increase of cardiac output as Brown, et al., have suggested, but that the reduction of blood viscosity with defective “viscosity autoregulation” was responsible. There is, however, no satisfying explanation for the fact that the increased CBF (and thus, venous return) did not lead to an increase in cardiac output under these circumstances, as was the case with phenylephrine. Possibly, the much smaller number of tests with mannitol than with phenylephrine in patients with impaired autoregulation (six vs. 18 tests) as well as the smaller increase in CBF (40% vs. 53%) account for this difference.

Relationship Between Cardiac Output and CBF

The relationship between cardiac output and CBF has been a matter of controversy for a long time. Vander Ark, et al., were among the first to suggest a possible positive correlation between rCBF and cardiac output in ischemia caused by vasospasm after subarachnoid hemorrhage. They reported a case in which neurological symptoms from focal cerebral ischemia were reversed by increasing heart rate with atropine. Unfortunately, in this case neither cardiac output nor CBF was measured and possible changes in blood viscosity were not considered.

Davis and Sundt showed that a 38% increase in cardiac output from β-stimulation in normal cats was not accompanied by a rise in CBF, although a 32% drop in cardiac output from hypovolemia resulted in a 24% decrease in CBF. Although the authors could not fully explain this finding in animals with normal regulation, which was in disagreement with earlier data, the clinical importance was evident: hypovolemia should be avoided at any cost in patients with jeopardized CBF.

Wood, et al., demonstrated that a 71% increase in cardiac output after hypervolemic hemodilution in dogs was associated with only a small (not statistically significant) increase in CBF. They postulated that the reduction of blood viscosity resulting from volume expansion accounted for both the increase in cardiac output and the smaller increase in CBF. This conclusion was supported by their earlier observation that transfusion of whole blood failed to promote CBF in ischemic brain, despite a 42% increase in cardiac output.

Keller, et al., on the contrary, found that isovolemic hemodilution which left cardiac output constant failed to produce any changes in rCBF in a primate model of cerebral ischemia, while intravascular volume expansion associated with a maximum increase in cardiac output of 187% significantly increased rCBF in ischemic regions. Since hematocrit fell by the same rate in both groups, they concluded that blood viscosity changes play only a minor role in the improvement of CBF after volume expansion. However, these authors did not address the fact that, in their experiment, MAP was in the animals that underwent isovolemic hemodilution was markedly lower than in the hypervolemic group (85 vs. 110 mm Hg), which may have flawed their observations.

Excellent clinical results from emergency treatment with colloidal volume expansion in patients suffering from acute middle cerebral artery stroke were reported by the same group. Although no CBF measurements were performed, the clinical improvement in their patients was obvious. Unfortunately, from this report it is not possible to decide whether the beneficial effect resulted from reduction of blood viscosity or from cardiac output augmentation, although the authors suggested that the latter was probably the most important factor.

The physiological mechanism by which changes in cardiac output would affect CBF remains conjectural. Increased pulse pressure and improved pulsatile flow in collateral vessels after augmentation of cardiac output...
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have been proposed as possible explanations, but no conclusive evidence for this theory has been given. In addition, this explanation stresses the importance of blood pressure changes rather than cardiac output itself.

Although impaired autoregulation is believed to play a major role in the relationship between cardiac output and CBF, no study in humans has thus far been presented in which this factor was actually measured. In the present study, the status of autoregulation was clearly defined and tested, while cardiac output could be measured with a high standard of accuracy without any relevant disturbance of hematocrit due to repeated cold water injections, which may be a problem in animals with a much smaller blood volume.

As the presented data indicate, there is no relationship between cardiac output and CBF, regardless of the status of autoregulation. With defective autoregulation, however, a strong inverse correlation existed between blood viscosity (after administration of mannitol) and CBF. These observations support the hypothesis that the improvement in rCBF in focal ischemia from intravascular volume expansion is mediated by a reduction of blood viscosity rather than by cardiac output augmentation.

We wish to stress the importance of maintaining optimal blood viscosity as well as blood pressure in patients with jeopardized cerebral circulation and defective autoregulation, rather than aiming at increased cardiac output itself. We do not deny the usefulness of monitoring cardiac output in patients with cerebral ischemia. Maintaining a normal or slightly increased cardiac output will probably prevent accidental reductions in blood pressure, which would have a detrimental effect on rCBF, when autoregulation is defective. Monitoring of cardiac output may also be useful in preventing congestive heart failure due to fluid overload, which may also affect neurological function. This is, of course, especially important in older patients with impaired cardiac function.

References


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