In patients with acute liver failure (ALF) and uncontrolled intracranial hypertension, moderate hypothermia (32°C) reduces intracranial pressure (ICP) and cerebral blood flow (CBF), and can be used as a bridge to liver transplantation. The purpose of this study was to test the hypothesis that moderate hypothermia reduced ICP by restoring CBF autoregulation. Nine patients with uncontrolled intracranial hypertension and ALF who fulfilled the criteria for poor prognosis were studied. CBF autoregulation and reactivity to carbon dioxide were evaluated before and 4 hours after cooling (32°C). Significant reductions were observed in the ICP (median, 46 [range, 27-54] mm Hg to 19 [15-22] mm Hg; P < .01) and CBF (median, 111 [69-134] to 56 [38-67] ml/100 g/min; P < .05). The defective CBF autoregulation and the absence of reactivity to carbon dioxide that was observed in all patients was restored with cooling. The results of our study suggest that the improvement in ICP observed with hypothermia may be the result of its effects on CBF autoregulation and provides a tool to explore the mechanisms associated with the deranged CBF autoregulation in ALF. (HEPATOLOGY 2001;34:50-54.)

Encephalopathy in acute liver failure (ALF) is characterized by rapid deterioration in the level of consciousness, increased intracranial pressure (ICP), reduced cerebral perfusion pressure (CPP), and a mortality rate of about 90% in patients who fulfill the criteria for poor prognosis. Over 90% of the patients die from the effects of increased ICP within 12 hours if this is not controlled by repeated mannitol treatments and ultrafiltration. We have recently shown that moderate hypothermia (32°C) as a treatment for uncontrolled increase in ICP is safe and easy to institute; reduces ICP, cardiac index, and noradrenaline requirements; increases CPP and can be used as a bridge to liver transplantation. Although we showed that arterial concentrations of ammonia and its uptake by the brain were reduced, the mechanism by which hypothermia reduces ICP is not clear. Within the range of mean arterial pressure (MAP) of 60 to 160 mm Hg or a CPP of 50 to 150 mm Hg, there is little variation in cerebral blood flow (CBF). This homeostatic mechanism is termed “autoregulation.” This is maintained by direct variation of cerebrovascular resistance with the perfusion pressure. In addition, the Pco2 closely regulates CBF, and within a range of 25 to 55 mm Hg, CBF varies linearly with PaCO2, changing at about 3% per millimeter of mercury. Studies in both patient and animal models of ALF suggest that the CBF is increased in patients with ALF and increased ICP. The mechanism of this increase in CBF has been suggested to result from events that follow glutamine accumulation in the brain, and increased activity of neuronal nitric oxide synthase has been suggested as a possible cause. Studies have also shown that CBF autoregulation is lost in patients with ALF, and this may be the result of cerebral hyperemia that is characteristic of this condition, because the disturbed autoregulation is corrected by hyperventilation that induces arteriolar vasoconstriction. However, the relationship between the increase in CBF following an increase in MAP and its effects on ICP are unknown. The purpose of this study was to test the hypothesis that moderate hypothermia reduced ICP by restoring CBF autoregulation.

PATIENTS AND METHODS

Studies were undertaken with the approval of the local research ethics committee, written informed consent from each patient’s next of kin, and in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The patients’ next of kin were informed of the potential dangers associated with the invasive monitoring, particularly insertion of the intracranial pressure monitors. All the invasive monitoring described in the ensuing methods section, apart from the measurement of CBF, is routine in the management of patients with ALF and severe hepatic encephalopathy who require mechanical ventilation.

Patients. Nine patients (median age, 32 years [range, 22-46 years]; 2 males, 7 females) with uncontrolled intracranial hypertension (see further) and ALF (caused by paracetamol overdose, 7; drug induced, 1; non-A, non-B hepatitis, 1) who fulfilled the criteria for poor prognosis were studied (highest median prothrombin time, 123 [101-172] sec; creatinine, 331 [221-435] µmol/L). Two of these patients formed a part of our previous report. All the patients were mechanically ventilated following sedation with propofol and paralysis with atracurium besylate (300-600 µg/kg/h). ICP and cardiovascular hemodynamics were continuously recorded using a subdural fiberoptic system (Camino, Camino Laboratories, San Diego, CA), pulmonary artery catheter, a right atrial catheter, and an arterial catheter. CBF was calculated as the difference between the MAP and the ICP. Patients were managed according to a standardized protocol as described previously. Noradrenaline was used to keep the CPP above 50 mm Hg and/or a MAP of greater than 90 mm Hg. Patients with raised ICP (>20 mm Hg for 10 minutes) were initially treated with 2 boluses of
mannitol (1 g/kg body weight over 20 minutes) and removal of 500 mL of fluid. If this regime failed to keep the ICP < 25 mm Hg, the patients were defined as having uncontrolled intracranial hypertension, and moderate hypothermia was instituted using a cooling blanket (Blanketrol II, Cincinnati Sub-Zero, Cincinnati, OH). CBF autoregulation was measured in 6 patients, and reactivity to carbon dioxide was measured in 5 patients. Although we would have liked to perform both sets of experiments in the same patients, this was difficult because a single measurement of CBF takes a minimum of 20 minutes. Therefore, simultaneous measurements of CBF autoregulation and reactivity to carbon dioxide could only be performed in 2 patients.

**Measurement of CBE.** A second arterial catheter was inserted into the right femoral artery (115.11, Vygon, Ecouen, France), and a jugular bulb catheter was inserted into the left-inferior jugular vein (4F Opticath, U440, Abbot Laboratories, Queensborough, UK) through a 5F hemostasis introducer (Fast Cath, Daig Corporation, Minnetonka, MN). CBF was calculated using a modification of the Kety-Schmidt method measuring the rate of uptake of nitrous oxide (N2O) by the brain as described previously. Briefly, following baseline blood sampling to determine background concentration, N2O (5%) was administered to the patient, and blood was withdrawn simultaneously from the arterial and jugular bulb catheters into 20-mL syringes using a Harvard parallel withdrawal pump (Harvard Apparatus, Inc., Natick, MA) at a rate of 0.824 mL/min. After 20 minutes, the pump was turned off and 1-mL samples were taken from the arterial and jugular bulb catheters. Five 1-mL aliquots were taken from each syringe, and levels of N2O were measured in the gaseous phase using an infrared N2O analyzer (ADC 7000 gas analyzer calibrated for N2O; range, 0-225 parts per million). CBF was calculated from the formulas:

\[
\text{CBF} = \frac{(S/(V_e/100))}{(A_e - V_i/t)} \times 100 \text{ g/min}
\]

where \( V_e \) = venous end volume sample; \( A_e \) = integrated arterial sample; \( V_i \) = integrated venous sample; \( t \) = time (minutes); and \( S \) = blood/brain partition coefficient (for N2O = 1.0). CBF measurements were only accepted if the sample at time zero was devoid of N2O, and if the end venous and arterial values were within 10% of each other.

**Measurement of CBF Autoregulation and Carbon Dioxide Reactivity.** CBF was only measured for the autoregulation studies with the PaCO2 maintained between 4.0 and 4.5 kPa, and ensuring that the arterial hydrogen ion concentrations were not different between the measurements. In 6 patients, CBF autoregulation was evaluated before and 4 hours after cooling, by measuring the CBF before and after increasing the resting MAP by 20 to 30 mm Hg by infusion of noradrenaline. An elevation in CBF by 10% or more with the change in CPP and MAP was taken as the evidence for lost autoregulation. In 5 subjects, the reactivity of the cerebral vasculature to altered tensions of arterial CO2 was assessed both before and after cooling. CBF was measured with the PaCO2 set between 4.0 and 4.5 kPa, and then after it was increased to between 5.5 and 6.0 kPa, both confirmed by arterial blood gas analysis. A minimum of 30 minutes was allowed between the CBF measurements to allow for the clearance of N2O and to establish the new PaCO2 cerebral blood flow autoregulation was assessed only in those patients who maintained hemodynamic stability for the required period.

**Analysis.** Statistical analysis was performed using the Statistical Package for the Social Sciences, version 9.0 for Windows (SPSS, Chicago, IL). All the data were expressed as median and range. The Wilcoxon signed rank test was used to compare pre- and postcooling (times > 4 hours) observations. Spearman rank correlation was used to test the relationship between variables.

**RESULTS**

All the studies were completed successfully, and no complications were observed related with either the monitoring or with the measurement of CBF autoregulation.

Median temperature before cooling was 36.4°C (range, 35.5-37.3°C), and this was successfully reduced to 33.1°C (range, 31.8-33.5°C) within 1 hour of starting cooling (\( P < .01 \)). Significant reductions were observed in the ICP (median, 46 [range, 27-54] mm Hg to 19 [range, 15-22] mm Hg; \( P < .01 \)) and heart rate (median, 119 [range, 88-128] to 86 [range, 64-106]; \( P < .01 \)). Cardiac index (median, 10.8 [range, 8.5-12.1] to 5.6 [range, 4.9-6.2] L/min/m²; \( P < .01 \)) and CPP (median, 111 [range, 69-134] to 56 [range, 38-67] mmHg/ml/100 g/min; \( P < .05 \)). MAP was unchanged, but the noradrenaline requirement was significantly reduced (median, 0.9 [range, 0.6-1.4] to 0.4 [range, 0.1-0.6] \( \mu g/kg/min; \ P < .05 \)). Significant increases were observed in the CPP (median, 48 [range, 35-61] to 66 [range, 53-74] mm Hg; \( P < .05 \)), systemic vascular resistance (median, 765 [range, 538-939] to 1,246 [range, 1,032-1,431] dyn · s · cm/m²; \( P < .05 \)), and cerebral vascular resistance (median, 0.3 [range, 0.2-1.6] Wood units to 1.4 [range, 0.7-2.2] Wood units; \( P < .05 \)). There was no significant change in the hydrogen ion concentration (median, 38 [32-56] mmol/L to 44 [31-52] mmol/L, \( P = ns \); PaCO2 (median, 13.4 [9.9-16.4] kPa to 14.1 [10.3-15.2] kPa; \( P = ns \); or in PaCO2 with cooling (3.9 [range, 3.8-4.1] kPa to 4 [range, 3.9-4.2] kPa; \( P = ns \)).

All 6 patients showed evidence of defective CBF autoregulation before institution of hypothermia, evidenced by an increase in CBF following increased MAP (Fig. 1). Following cooling, CBF autoregulation was restored in all 6 patients (Fig. 2). The percentage change in CBF with the increase in MAP was significantly less following cooling (precooling; median, 21.8% [range 10.8%-60.8%]; postcooling; median, 5% [range, −7.0%-8.0%]; \( P < .04 \)). In addition, the increase in CBF induced by the increased MAP was associated with an increase in ICP before cooling (median, 32 [range, 27-54] to 40 [range, 34-59] mm Hg; \( P < .04 \) (Fig. 3). No significant changes in ICP were observed during increased MAP following cooling (median, 18 [range, 15-22] to 20 [range, 15-22] mm Hg; \( P = .7 \)).

The amount of noradrenaline required to produce this increase in blood pressure was significantly lower in the cooled patients (precooling; median, 0.6 [range, 0.4-1.8] mg/kg/min; postcooling; median, 0.2 [range, 0.1-0.5] \( \mu g/kg/min; \ P < .05 \)). No significant correlation was detected between the change in MAP with the change in ICP either before or after cooling. Similarly, there was no significant correlation between the change in systemic vascular resistance and the change in cerebral vascular resistance.

There was no significant change in CBF with the increase in PaCO2 in all 5 patients before cooling, but significant increase in CBF was noted after cooling (precooling; median CBF, 69 [range, 74-78] ml/100 g/min at a median PaCO2 of 3.9 [range, 3.8-4.1], and 70 [range, 69-80] ml/100 g/min at a median PaCO2 of 6.3 kPa [range, 5.9-6.4]; \( P = 4 \); postcooling; median CBF, 46 [range, 38-57] ml/100 g/min at a median PaCO2 of 4 kPa [range, 3.9-4.2], and 56 kPa [range, 57-63] ml/100 g/min at a median PaCO2 of 6.1 kPa [range, 5.8-6.2]; \( P < .05 \)). Before cooling, the increase in carbon dioxide concentration was associated with a small increase in the ICP (median ICP, 46 mm Hg [range, 31-54] at a median PaCO2 of 3.9 kPa [range, 3.8-4.1]) to, median ICP, 49 mm Hg [range, 33-55] at a median PaCO2 of 6.3 kPa [range, 5.9-6.4]; \( P = .3 \). After cooling, the ICP did not change significantly with the increase in PaCO2 (median ICP, 19 mm Hg [range, 17-22] at a median PaCO2 of 4 kPa [range, 3.9-4.2] to, median ICP, 21 mm Hg [range, 14-22] at a median PaCO2 of 6.1 kPa [range, 5.8-6.2]; \( P = .3 \). The percentage
change in CBF with the increase in PaCO2 was significantly greater following cooling (precooling: median, 2.5% [range, −0.2%–7.8%]; postcooling: 19% [range, 10.5%–23.6%]; P < .04). Individual patient data are presented in Table 1.

DISCUSSION

The results of this study confirm our previous observation that hypothermia successfully reduces intracranial hypertension and has beneficial effects on the cardiovascular factors such as heart rate, cardiac output, and noradrenaline requirements. Although we have previously shown that hypothermia reduces arterial ammonia concentration and its uptake by the brain, the mechanisms by which it reduces ICP are not clear.4 This study clearly shows that hypothermia successfully reduced CBF, and restored CBF autoregulation and reactivity to carbon dioxide.

We used a modification of the Kety-Schmidt method, employing an integrated blood-sampling technique.3,17–19 This technique measures global CBF (mL/100 g perfused brain/min) without providing any information on regional perfusion. Although a previous study showed reduced CBF in ALF,12 others have shown increased CBF as was observed in this study.8,9,11 In portacaval-shunted rats, ammonia infusion produces an increase in CBF and which precedes cerebral edema.13 In agreement with our observation, hypothermia in this animal model prevents cerebral hyperemia and reduces brain edema.13

Most studies that have demonstrated dysregulation of CBF in patients with ALF have used transcranial Doppler to determine the mean velocity in the middle cerebral artery.7,8,16 Recently published data suggest that this dysregulation of CBF may extend to involve the area of the brain subserved by the anterior cerebral artery.20 Our results are consistent with these previous studies that suggest a loss of CBF autoregulation in patients with ALF. The rapidity of restoration of CBF with cooling is unique to ALF, because re-establishment of CBF autoregulation in other conditions such as head trauma and inflammatory conditions of the brain and meninges may take days.21,22 Similar rapid restoration of CBF autoregulation has been shown with liver transplantation.7 Even before cooling, all the 6 patients had a MAP of >60 mm Hg, which is above the normal lower limit of CBF autoregulation. In this study, CPP was also measured that was >50 mm Hg in 5 of the

![Fig. 1](image1.png)

Fig. 1. Relationship between CBF and (A) MAP and (B) CPP in patients with ALF before cooling. The figures show that CBF autoregulation is lost as evidenced by increase in blood flow with the increase in MAP and CPP. Median temperature before cooling was 36.4°C (range, 35.5–37.3°C) and 33.1°C (range, 31.8–33.5°C) after cooling.

![Fig. 2](image2.png)

Fig. 2. Relationship between CBF and (A) MAP and (B) CPP in patients with ALF 4 hours after cooling (32°C). The figures show that CBF autoregulation is restored as evidenced by no significant changes in CBF with the increase in MAP CPP. Median temperature before cooling was 36.4°C (range, 35.5–37.3°C) and 33.1°C (range, 31.8–33.5°C) after cooling.
6 patients, indicating that they were within the range of CBF autoregulation, confirming that CBF autoregulation was truly lost before cooling and restored subsequently.\textsuperscript{5,6}

Before cooling, the patients showed a lack of CBF reactivity to CO\textsubscript{2}, which was restored after cooling. It is possible that the lack of response to CO\textsubscript{2} before cooling may be the result of the limited further capacity for cerebral vasodilation at the upper end of the response curve, and that cooling induces cerebral vasoconstriction, thereby restoring the response curve.\textsuperscript{5,6}

The correction of both CBF autoregulation and reactivity to CO\textsubscript{2} with hypothermia suggests that a common mechanism must underlie the dysregulated CBF that is characteristic of ALF. The mechanisms of derangement in CBF autoregulation are not clear, but are possibly mediated by some unknown toxic factor that is produced by the necrotic liver, because hepatectomy in patients with ALF is followed by rapid improvement both in intracranial pressure and in CBF autoregulation.\textsuperscript{23,24} It is possible that moderate hypothermia may restore CBF autoregulation by reducing the production of this presumed toxic substance through reduction in the metabolic rate as evidenced by its effects on the resting energy expenditure.\textsuperscript{3} Studies in portacaval-shunted rats undergoing ammonia infusion have shown that administration of a glutamine synthase inhibitor reduces cerebral hyperemia and an increase in brain water.\textsuperscript{15} Experiments in healthy rats undergoing ammonia infusion showed that the responsiveness to CO\textsubscript{2} was restored if glutamine synthase was inhibited before ammonia infusion.\textsuperscript{25,26} These experiments suggest that dysregulation of CBF and its responsiveness to CO\textsubscript{2} follow the accumulation of glutamine. We have previously shown that hypothermia reduces both the arterial concentrations of ammonia and its uptake by the brain, suggesting that it may modulate the improvement in autoregulation and reactivity to carbon dioxide through the reduction of glutamine synthesis.\textsuperscript{4} Alternatively, or in addition, hypothermia may produce the beneficial effects on cerebral circulation through a reduction in the excitatory neurotransmitter glutamate or nitric oxide production.\textsuperscript{14,15,27,28} Our study does not allow any firm conclusion on this point.

Although previous studies in patients with ALF have demonstrated that CBF changes in parallel with arterial pressure,\textsuperscript{7,16} the direct effect of increased CBF on ICP has been unclear, because concomitant measurement of CBF, ICP, and MAP in the same patients has been lacking. Our study demonstrates that the in-

![TABLE 1. Changes in Reactivity to Carbon Dioxide With Cooling](image)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Time</th>
<th>PacO\textsubscript{2} (kPa)</th>
<th>CBF (mL/100 g/min)</th>
<th>ICP (mm Hg)</th>
<th>PacO\textsubscript{2} (kPa)</th>
<th>CBF (mL/100 g/min)</th>
<th>ICP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 3</td>
<td>a</td>
<td>3.9</td>
<td>69</td>
<td>46</td>
<td>4</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>6.3</td>
<td>74</td>
<td>48</td>
<td>6.1</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Patient 6</td>
<td>a</td>
<td>4.1</td>
<td>78</td>
<td>54</td>
<td>4.2</td>
<td>57</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>6.4</td>
<td>80</td>
<td>55</td>
<td>6.2</td>
<td>63</td>
<td>22</td>
</tr>
<tr>
<td>Patient 7</td>
<td>a</td>
<td>3.8</td>
<td>64</td>
<td>31</td>
<td>3.9</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>5.9</td>
<td>69</td>
<td>33</td>
<td>5.8</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Patient 8</td>
<td>a</td>
<td>3.9</td>
<td>69</td>
<td>46</td>
<td>4</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>6</td>
<td>70</td>
<td>49</td>
<td>5.8</td>
<td>51</td>
<td>21</td>
</tr>
<tr>
<td>Patient 9</td>
<td>a</td>
<td>4</td>
<td>76</td>
<td>49</td>
<td>4.2</td>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>6.3</td>
<td>74</td>
<td>51</td>
<td>6.1</td>
<td>58</td>
<td>21</td>
</tr>
</tbody>
</table>

Mean (SE)

| a | 3.9 (0.05) | 70.2 (2.3) | 45.2 (3.8) | 4.1 (0.06) | 47 (3.0) | 19.6 (1) |
| b | 6 (0.09)*  | 73.4 (1.9) | 47.4 (3.7) | 6.1 (0.08)* | 56 (2.6)* | 19.8 (1.5) |

\textsuperscript{NOTE.} a, before increase in the partial pressure of carbon dioxide; b, after increase in the partial pressure of carbon dioxide.

\textsuperscript{*}P < .04, comparison between values at a and b. Wilcoxon signed rank test.
crease in MAP increases CBF, which results in an increase in ICP and suggests a critical pathogenic role for the increased CBF in the causation of intracranial hypertension in ALF. This lack of autoregulation and the increase in ICP produced by an increase in MAP and CPP suggests the need to exercise caution when treating ALF patients with increasing doses of vasopressors without monitoring the ICP. This relationship supports the hypothesis that increased ICP in patients with ALF is a 2-stage process.8 The first stage refers to brain swelling as a result of increased glutamine synthesis caused by the effects of ammonia. This produces alterations in the compliance of the brain, and acute changes in ICP that are characteristic of ALF may be the result of increases in CBF.8

In this study, we also showed that patients require significantly less inotropic support following cooling. The pathogenesis of circulatory disturbances in ALF is not clear, but is manifested by a markedly dilated peripheral and splanchnic circulation.30 In addition to restoring CBF to normal values and correcting its autoregulation, cooling reduced the cardiac index and increased systemic vascular resistance. It is also interesting to note that the hypothermic patients required significantly fewer amounts of nor-adrenaline to achieve the same increase in MAP, suggesting that hypothermia may have profound effects on correcting the vascular hyporesponsiveness that is characteristic of patients with liver failure.31 Although cooling increased both the systemic vascular resistance and cerebral vascular resistance, no direct correlation between these have been found, suggesting that the mechanisms of cerebral vasodilatation are different from the mechanism of systemic vasodilatation. Alternatively, the lack of a demonstrable relationship may be a result of the relatively small sample size.

It is important to state that although there were no complications related directly to the invasive monitoring that was used in the patients in this study, questions about the level of monitoring that patients with ALF should undergo remains a point of discussion. Intensive studies of the sort described in this article are difficult to perform without an adequate team of people; 3 experienced medical doctors and 2 nurses were directly involved in performing each study.

In conclusion, the results of our study suggest that the improvement in ICP observed with hypothermia may be the result of its effects on CBF autoregulation and provides a tool to explore the mechanisms associated with the deranged autoregulation that is important in the pathogenesis of intracranial hypertension in ALF.

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REFERENCES