Dynamic autoregulatory response after severe head injury

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Object. The purpose of this study was to evaluate the extent and timing of impairment of cerebral pressure autoregulation after severe head injury.

Methods. In a prospective study of 122 patients with severe head trauma (median Glasgow Coma Scale Score 6), dynamic tests of pressure autoregulation were performed every 12 hours during the first 5 days postinjury and daily during the next 5 days. The autoregulatory index ([ARI] normal value 5 ± 1.1) was calculated for each test. The changes in the ARI over time were examined and compared with other physiological variables.

The ARI averaged 2.8 ± 1.9 during the first 12 hours postinjury, and continued to decrease to a nadir of 1.7 ± 1.1 at 36 to 48 hours postinjury. At this nadir, in 87% of the patients the value was less than 2.8. This continued deterioration in the ARI during the first 36 to 48 hours postinjury occurred despite an increase in cerebral blood flow ([CBF], p < 0.05) and in middle cerebral artery blood flow velocity ([BFV], p < 0.001), and could not be explained by changes in cerebral perfusion pressure, end-tidal CO₂, or cerebral metabolic rate of O₂. A marked decrease in cerebrovascular resistance ([CVR], p < 0.001) accompanied this deterioration in the ARI. Patients with a relatively higher BFV on Day 1 had a lower CVR (p < 0.05) and more impaired pressure autoregulation than those with a lower BFV.

Conclusions. The inability of cerebral vessels to regulate CBF normally may play a role in the vulnerability of the injured brain to secondary ischemic insults. These studies indicate that this vulnerability continues and even increases beyond the first 24 hours postinjury. Local factors affecting cerebrovascular tone may be responsible for these findings.

Key Words • head injury • autoregulation • cerebral blood flow • cerebrovascular resistance • transcranial Doppler ultrasonography

Cerebrovascular abnormalities induced by TBI range from ischemia to hyperemia.³,¹⁵ The severity of the reduction in CBF posttrauma, especially in the first few hours after injury, is associated with outcome,³,⁴,¹¹,¹²,²²,²³ and these vascular changes contribute to some of the clinical problems encountered during the initial recovery period from trauma, especially the vulnerability to secondary ischemic insults⁹ and intracranial hypertension.¹⁵,²¹ The mechanisms that the brain normally uses to regulate CBF have been examined in an attempt to understand the pathological processes responsible for these trauma-induced cerebrovascular changes.

Cerebral pressure autoregulation is the intrinsic ability of the brain to maintain a constant CBF under conditions of changing CPP. Mechanisms for cerebral pressure autoregulation include myogenic, neurogenic, and/or metabolic processes. These processes continuously adjust CVR for changes in CPP so that the CBF normally remains relatively constant. The upper and lower limits of autoregulation reflect the points at which vasomotor adjustments are exhausted and CVR can neither increase nor decrease to maintain CBF.

Impairment of the pressure autoregulatory response has been reported in patients with both minor and severe TBI and may contribute to their vulnerability to secondary brain injury.⁵,⁷,¹¹,¹⁷,¹⁹,²⁶ Secondary ischemic insults such as hypotension and hypoxia after TBI have been observed to double the mortality rate, presumably because the injured brain is unable to maintain an adequate CBF during these events.⁵,⁸,¹⁶ These observations about impaired pressure autoregulation form the basis for much of the current treatment strategy for severe TBI, especially with regard to management of CPP.²⁴

In most of the previous studies in which impaired cerebral autoregulation was demonstrated in humans after TBI, static methods were used; these compared steady-state CBF at two levels of CPP. Dynamic procedures for assessing cerebral autoregulation, which are more practical in critically ill patients, have been described recently.³,¹¹,¹³,¹⁸,²⁰,²⁸ These
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methods have in common the use of transcranial Doppler ultrasonography to measure continuously the BFV in the MCA during transient perturbations in the CPP. In one dynamic procedure, rapid deflation of thigh cuffs is used to induce a transient drop in BP. The rate of recovery of the MCA BFV after this rapid decrease in BP gives an index of dynamic autoregulation. Impairments in dynamic cerebral autoregulation found with this method have been closely correlated with impaired autoregulation measured using static BP changes.25

The purpose of this study was to use this new procedure for measuring dynamic autoregulation to evaluate the extent and timing of disturbances in cerebral pressure autoregulation in severely head injured patients.

Clinical Material and Methods

Patient Characteristics

One hundred twenty-two patients who had a GCS27 score of 8 or less on admission or whose GCS score deteriorated to 8 or less within 48 hours of admission were studied between March 1998 and October 2000. The research protocol was approved by the Baylor Institutional Review Board for Human Subject Research, and informed consent for participation in the study was obtained from each patient's nearest relative. When relatives were unavailable to give informed consent, the patients were enrolled in the study according to an approved emergency consent procedure. The demographic characteristics of the patients are summarized in Table 1.

General Management Protocol for TBI

All patients in the study were treated according to a standard protocol that emphasized prompt evacuation of intracranial mass lesions and prevention of secondary insults to the brain. The ICP was monitored using a ventriculostomy catheter, and ICP values greater than 20 mm Hg were treated according to standard protocols. The SjvO2 was monitored in the dominant jugular vein by using a fiberoptic O2 saturation catheter. Systemic factors that exacerbate intracranial hypertension, including hypoxia, hypercapnia, fever, and hypotension, were corrected. Adequate volume resuscitation, proper sedation, and selective use of vasoressors were used to maintain BP. An MABP of at least 80 mm Hg and a CPP of at least 60 mm Hg were maintained, unless a low SjvO2 indicated that a higher CPP was required. The same standard protocol was used throughout the study.

Experimental Measurements

Dynamic Testing of Cerebral Pressure Autoregulation. The MCA BFV was monitored bilaterally with a transcranial Doppler ultrasonography system equipped with dual 2-MHz transducers (DWL Multi Flow, Sipplingen, Germany). The BP was monitored through a radial artery catheter. To decrease BP transiently, large BP cuffs were wrapped around each upper thigh, then the cuffs were inflated to 20 to 40 mm Hg above systolic BP for 3 minutes. Rapid deflation of the cuffs resulted in an abrupt transient drop in MABP. The dynamic cerebral autoregulatory response was analyzed by observing the relative changes in the MCA BFV immediately after the BP drop, as shown in Fig. 1. The result was expressed as the ARI, as described by Aaslid, et al.,1 and Tiecks, et al.28 The ARI is a 10-step scale ranging from 0 (absent autoregulation) to 9 (best autoregulation). The ARI in healthy individuals averages 5 ± 1.1 (mean ± SD). For the purposes of this study, values of the ARI lower than 2.8 (mean − 2 SDs) were considered clearly abnormal.

Dynamic tests of autoregulation were performed every 12 hours during the first 5 days and once per day during the next 5 days after TBI. A minimum of three cuff deflation tests was performed; all test results were averaged. An abrupt decrease in MABP of at least 20 mm Hg was required for a test to be included in the data analysis. No adverse events were recorded arising from the dynamic testing of autoregulation.

Measurement of Global CBF

Eighty-three measurements of CBF were performed using stable Xe-CT scanning (Diversified Diagnostics Products, Houston, TX) in the patients studied. Fifty-four examinations were performed during the first 24 hours and 29 were performed between 24 and 48 hours after TBI. For each examination, the CBFs in all cortical regions of interest were averaged to estimate a global value for CBF. This value was used for calculation of CVR by the equation CVR = CPP/CBF. The normal value of CVR is 1.6 ± 0.4 mm Hg/ml/100 g/min.11 The CMRO2 was calculated by the formula CMRO2 = AVDO2 × CBF. The normal value of CMRO2 is 3.3 ± 0.4 ml/100 g/min.11 For territorial measurements of CBF, cortical regions corresponding to the area supplied by the MCA were averaged.

Measurement of Cortical CBF

Forty-six of the 122 patients also underwent intracere-
tive placement of a thermal-diffusion CBF probe (Flowtronics, Inc., Phoenix, AZ). The probe was placed on the cortex, and care was taken to avoid large cortical vessels. Attention was paid to be sure that the two gold discs were in contact with the cortex. The dura was closed over the CBF sensor, and the bone flap was replaced. The probe was connected to the CBF monitor and calibrated, and the thermal-diffusion CBF values were collected at 30-second intervals along with the other physiological data.

Measurement of Brain Tissue PO₂

The brain tissue PO₂ was continuously measured using a miniaturized Clark electrode-Licox probe (GMS, Kiel-Mielkendorf, Germany) in 86 of the 122 patients. An area of brain in the frontotemporal region that appeared to be injured but was not clearly necrotic was targeted for the probe placement. Alongside the brain tissue PO₂ probe, a temperature probe was placed in the cortex, and both were connected to the monitor for automatic temperature-corrected brain tissue PO₂ readings. The position of the brain tissue PO₂ probe was examined on follow-up CT scans. The brain tissue PO₂ values were continuously collected and stored at 30-second intervals in a computer. At the end of the monitoring period, the probes were removed, and calibration drift was determined by measuring a stable PO₂ in a zero O₂ solution, in a Level I arterial blood gas control solution (Ciba Corning Blood Gas Control, Medfield, MA), and in room air.

Statistical Analysis

All summary data are expressed as the mean ± SD or as the median (interquartile range). For the summary data, the mean of variables from the entire period of monitoring was calculated for each patient. The mean values were compared using the Student t-test. Comparison of the time course between groups was performed using two-way repeated-measures ANOVA, followed by the Tukey test when multiple comparisons were made.

Results

Dynamic Testing of Cerebral Pressure Autoregulation

During the first 10 days postinjury, 5430 cuff deflation tests were performed in the 122 patients. A total of 4280 of
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these tests (35/patient) met the inclusion criterion of inducing an abrupt drop in MABP of at least 20 mm Hg. The mean drop in MABP induced by cuff deflation was 23.4 ± 2.9 mm Hg. The mean duration of testing was 5.8 ± 2.5 days. For each patient, the mean values for the ARI during each time interval were used in analyses of the time course.

**Time Course of Cerebral Pressure Autoregulation After Severe TBI**

Compared with the range for the ARI of 2.8 to 7.2 (mean 5) observed in healthy volunteers, values of the ARI were abnormally low in most of the patients with TBI throughout the entire monitoring period. In addition, there was a characteristic evolution of the ARI over time in the individual patients with TBI. This typical pattern consisted of a low ARI on admission that continued to decrease throughout the remainder of the study, the ARI gradually returned toward normal. ARI on Day 2, and peaked at 72 hours after injury (83 ± 1.9, and in only 62 (51%) of the patients the ARI was normal throughout the study period, averaging 34 ± 6 mm Hg during the first 12 hours postinjury, and 36 ± 5 mm Hg on Day 10 (time effect, p < 0.001). The mean values for ICP were slightly higher on Days 2 to 10 than on Day 1, but these differences were not significant (time effect, p = 0.26). The ETCO₂ was nearly constant throughout the study period, averaging 34 ± 6 mm Hg during the first 12 hours and 36 ± 5 mm Hg on Day 10 (time effect, p = 0.46).

**Changes During the First 48 Hours Postinjury**

In these studies of time course, the dynamic pressure autoregulation consistently deteriorated during the first 36 to 48 hours postinjury. This worsening of the ARI occurred in the setting of a constant MABP and CPP, and an apparent improvement in baseline CBF as estimated using the MCA BFV. To examine this phenomenon more closely, the changes in all physiological parameters that were available in this set of patients were examined. Because some of the physiological parameters, such as CBF and brain tissue PO₂, were not available in all patients, the average values for Days 1 and 2 were compared to maximize the number of values available for analysis.

The mean value for the ARI decreased from 2.8 ± 1.9 on Day 1 to 1.7 ± 1.1 on Day 2 (p < 0.001, paired t-test). The ARI on Day 2 was less than that on Day 1 in 92% of patients; the ARI was normal on Day 1 in 53 patients (43%) but remained normal in only 16 patients (13%) on Day 2. As shown in Fig. 3, these changes in the ARI were associated primarily with changes in physiological variables that indicated an increase in baseline CBF and a decrease in baseline CVR between Days 1 and 2 postinjury. The changes in the ARI could not be explained by changes in baseline CPP or ETCO₂.

The BFV in the left MCA increased from 54 ± 24 cm/second on Day 1 to 72 ± 31 cm/second on Day 2 (p < 0.001). The BFV in the right MCA increased from 50 ± 20 cm/second on Day 1 to 69 ± 30 cm/second on Day 2 (p < 0.001). The mean values for MABP, ICP, CPP, and ETCO₂ were not significantly different on Days 1 and 2 (Table 2).

An increase in MCA BFV may not always indicate an increase in actual CBF; vasoconstriction could also increase MCA BFV with either no change or even a decrease in CBF. To confirm that these changes in MCA BFV indicated a true change in CBF, other direct and indirect measures of CBF were examined. Measurements of global CBF by using Xe-CT scans were available for some of the patients studied. Global CBF increased from 36 ± 15 ml/100 g/min on Day 1 (54 patients) to 47 ± 13 ml/100 g/min on Day 2 (29 patients, p < 0.05; Fig. 3). In addition, measures of

### TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Day 10</th>
<th>Overall Effect</th>
</tr>
</thead>
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<tr>
<td>MABP (mm Hg)</td>
<td>86 ± 16</td>
<td>89 ± 11</td>
<td>92 ± 13</td>
<td>91 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP</td>
<td>70 ± 18</td>
<td>71 ± 13</td>
<td>74 ± 16</td>
<td>83 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP</td>
<td>17 ± 8</td>
<td>20 ± 5</td>
<td>19 ± 8</td>
<td>18 ± 4</td>
<td>0.26</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>36 ± 4</td>
<td>36 ± 4</td>
<td>36 ± 5</td>
<td>37 ± 5</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. Statistical analysis was performed using one-way repeated-measures ANOVA.
† Significantly different from Day 1.

**Changes During the First 48 Hours Postinjury**

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local cortical CBF (thermal-diffusion CBF), and indirect measures, such as SjvO₂, AVDO₂, and brain tissue PO₂, confirmed the MCA BFV findings. As summarized in Table 3, SjvO₂ (122 patients), brain tissue PO₂ (86 patients), and thermal-diffusion CBF (46 patients) significantly increased and AVDO₂ (122 patients) significantly decreased from Day 1 to Day 2. The CMRO₂ values based on Xe-CT CBF values and the corresponding AVDO₂ values were constant during the first 2 days postinjury (p = 0.81).

The CVR was calculated by the formula CVR = CPP/CBF, and estimated by the formula CVR = CPP/BFV, using MCA BFV to substitute for CBF. The CVR decreased significantly between Day 1 and Day 2 according to both methods of calculation. The CVR values based on MCA BFV decreased from 1.42 ± 0.45 mm Hg/cm/sec on Day 1 to 1.06 ± 0.33 mm Hg/cm/sec on Day 2. The CVR values based on global CBF decreased from 1.92 ± 0.69 mm Hg/ml/100 g/min on Day 1 to 1.34 ± 0.46 mm Hg/ml/100 g/min on Day 2.

The CVR values based on cortical CBF in the MCA territories that was calculated from the Xe-CT CBF findings showed the same trend as values based on the mean global CBF. The MCA territorial CVR decreased from 2.08 ± 1.03 mm Hg/ml/100 g/min for the left MCA and 2.46 ± 1.31 mm Hg/ml/100 g/min for the right MCA on Day 1 to 1.47 ± 0.61 mm Hg/ml/100 g/min for the left and 1.55 ± 0.7 mm Hg/ml/100 g/min for the right MCA territory (both sides, p < 0.01; Fig. 4). The ARI for the left and right MCA had the same trend as territorial CVR. The ARI for the left MCA decreased from 2.8 ± 1.6 on Day 1 to 1.9 ± 1.1 on Day 2, whereas the ARI for the right MCA changed from 2.9 ± 1.4 to 1.8 ± 1.2 (both sides, p < 0.001).

Comparison of Physiological Variables Based on Initial MCA BFV

These comparisons of changes in the ARI with those in other physiological variables indicated that cerebral pressure autoregulation was dependent on the baseline CBF or cerebrovascular tone. To study this hypothesis, patients were divided into two groups based on their MCA BFV (mean of left and right sides) during the first 12 hours postinjury. Patients with an initial MCA BFV greater than the median value of 50 cm/second were included in the high BFV group (44 patients), and those with an initial MCA BFV less than 50 cm/second were considered to belong to the low BFV group (47 patients). As shown in Fig. 5, sim-

### TABLE 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SjvO₂ (%)</td>
<td>67 ± 8</td>
<td>70 ± 9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>brain tissue PO₂ (mm Hg)</td>
<td>27 ± 19</td>
<td>36 ± 20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>rTD-CBF (ml/100 g/min)</td>
<td>26 ± 17</td>
<td>39 ± 21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AVDO₂ (ml/dl)</td>
<td>4.3 ± 1.5</td>
<td>3.4 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMRO₂ (ml/100 g/min)</td>
<td>1.68 ± 0.79</td>
<td>1.73 ± 0.91</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* Statistical analysis was performed using paired t-tests. Abbreviation: rTD-CBF = regional thermal diffusion CBF.
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Fig. 5. Graphs showing comparisons of patients with initial MCA BFV above and below the median. The group with initial MCA BFV's below the median was significantly different from the group with initial MCA BFV's above the median value (p < 0.05). The + means that the change in the group with an initial MCA BFV below the median is significantly different from that in the group with an initial MCA BFV above the median value (p < 0.05). Statistical analysis was performed using two-way repeated-measures ANOVA.

TABLE 4
Values for physiological variables in patients with initial MCA BFV above or below median*

<table>
<thead>
<tr>
<th>Parameter (mm Hg)</th>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Group × Time Interaction</th>
<th>Group Effect</th>
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<tr>
<td>MABP</td>
<td>high</td>
<td>85 ± 12</td>
<td>89 ± 11</td>
<td>0.37</td>
<td>0.45</td>
</tr>
<tr>
<td>low</td>
<td>87 ± 15</td>
<td>90 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPP</td>
<td>high</td>
<td>71 ± 10</td>
<td>73 ± 12</td>
<td>0.62</td>
<td>0.97</td>
</tr>
<tr>
<td>low</td>
<td>70 ± 18</td>
<td>73 ± 16</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>high</td>
<td>16 ± 5</td>
<td>16 ± 5</td>
<td>0.42</td>
<td>0.33</td>
</tr>
<tr>
<td>low</td>
<td>15 ± 4</td>
<td>18 ± 6</td>
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</tr>
<tr>
<td>ETCO₂</td>
<td>high</td>
<td>36 ± 4</td>
<td>36 ± 4</td>
<td>0.69</td>
<td>0.82</td>
</tr>
<tr>
<td>low</td>
<td>36 ± 3</td>
<td>35 ± 4</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Statistical analysis was performed using two-way repeated-measures ANOVA. High denotes above median and low denotes below median.

icular differences in global CBF were observed between the two groups. The MCA BFV in the high BFV group averaged 67 ± 14 cm/second during the first 12 hours postinjury and 74 ± 13 cm/second on Day 2. In the low BFV group, MCA BFV was initially 38 ± 11 cm/second and increased to 63 ± 23 cm/second on Day 2 (time effect, p < 0.001; group × time interaction, p = 0.011; two-way repeated-measures ANOVA). As shown in Fig. 5, similar findings were observed with CBF values obtained using Xe-CT scanning.

The changes in the ARI mirrored the MCA BFV findings in these two groups of patients. The ARI was significantly increased in the low BFV group on Day 1: 3.3 ± 1.2 compared with 2.4 ± 1.1 in the high BFV group. In addition, the decrease in the ARI between Days 1 and 2 was greater in the low BFV than in the high BFV group. Table 4 demonstrates no differences between the high and low BFV groups in physiological variables such as MABP, CPP, ICP, and ETCO₂, which might confound these relationships.

**Discussion**

The results of this study indicate that many patients (49% on Day 1 and 87% on Day 2) experience impaired dynamic cerebral pressure autoregulation after severe head injury. This finding is consistent with previous studies in which static testing of autoregulation was used; a similar incidence of abnormalities, ranging from 41 to 83% of patients, was reported in these studies.4,6,17,22 Muizelaar, et al.,17 demonstrated disturbed autoregulation in 15 of 37 measurements in pediatric patients, whereas Cold and Jensen6 observed regional loss of autoregulation, indicated by a 20% flow increase, in 29 of 35 studies. Impaired autoregulation has even been reported after mild TBI.28 Junger, et al.,11 demonstrated the use of dynamic testing for poorly functioning or absent cerebral autoregulation in 28% of 29 patients.

The ability serially to monitor and grade the autoregulatory response over time is unique to dynamic autoregulation methods, and the contribution of this study is the unexpected evolution of autoregulation that was observed over time. Although the lowest BFV and CBF values occurred during the initial 12 hours postinjury, the ability to autoregulate continued to worsen during the first 36 to 48 hours. The clinical implications of these findings are important. It is likely that most secondary insults occur in the first few hours postinjury, because this is when most hemodynamic instability occurs.12,15 These studies indicate that the inability of the injured brain to compensate normally for hypotensive insults persists well beyond the initial 6 to 12 hours, and that vigilance should continue throughout the first few days after injury.

The underlying cause of impaired autoregulation after TBI is not known. Even the mechanism of normal autoregulation is poorly understood, and is probably complex. There are four general theories about the mechanism of normal autoregulation. 1) The myogenic theory hypothesizes that vascular smooth-muscle cells have an intrinsic ability to detect and respond to varying perfusion pressures. The underlying mechanisms are thought to be an activation of stretch-sensitive channels in smooth-muscle cells that causes an intracellular calcium increase and therefore constriction. 2) The metabolic theory proposes that local metabolic factors control autoregulation. 3) The neurogenic theory hypothesizes that perivascular nerves play a role in CBF regulation. 4) The fourth theory supposes that endothelial factors may also play a role in autoregulation; in some experimental models, an intact endothelium is necessary for pressure autoregulation.
Trauma could potentially alter any or all of these factors. A myogenic response to intravascular pressures can be demonstrated in isolated cerebral vessels, and an analogous evolution of impairment in the myogenic response over time has been observed in one experimental TBI model. The dilation of cerebral (pial) arterioles in response to increased venous pressures and the reversal of this response by local hyperoxia lend further support to the hypothesis that a metabolic component of cerebral autoregulation involves an O₂-sensitive mechanism.

The other physiological parameters that were analyzed in this study revealed no confounding factors that might be responsible for the impaired autoregulatory response. A reduction in CPP could reduce the ability to autoregulate; however, CPP was well maintained in these patients with TBI and did not change significantly as the autoregulatory response deteriorated over the first 2 days postinjury. The PaCO₂ has an important effect on the autoregulatory response, with hyperventilation improving and hyperventilation impairing autoregulation. All patients received mechanical ventilation throughout the first few days of the study, however, and ETCO₂ levels were kept constant. The possibility cannot be entirely excluded that at least some of the observed changes in autoregulation are induced by medications that are given to critically ill patients with TBI for anesthesia, sedation, analgesia, or control of ICP. Nevertheless, the same management protocol was used for all patients, and no single medication appeared to be responsible for the changes in the ARI that were observed during the first 48 hours.

The only consistent association with the changes in the autoregulatory response was in measures of CBF and CVR. When CBF was low (and CVR was high) on admission, the dynamic autoregulatory response was better preserved. When CBF increased (and CVR decreased) over the first 48 hours postinjury, the autoregulatory response became more impaired. The dependence of autoregulation on baseline cerebrovascular tone may explain these findings.

Some limitations of the dynamic autoregulatory response should be acknowledged. This procedure is more convenient for testing autoregulation in critically ill patients because it requires only a small and very brief perturbation in BP and because it can be easily done in the intensive care unit. This method, however, uses BFV in the large arteries supplying the brain to estimate CBF. Although BFV can be altered by both changes in vessel flow and in vessel diameter, this method has been well validated in healthy volunteers. Under the limited circumstance of a transient drop in BP, changes in BFV closely predict changes in flow measured by more standard methods. Another concern with this testing procedure is that dynamic changes might not predict the ability of the brain to maintain a constant CBF over longer periods of time. Nonetheless, the dynamic ARI has been shown to correlate closely with the findings of static autoregulation testing.

Conclusions

The ability to autoregulate pressure is commonly impaired in patients with severe TBI, and this vulnerability persists and even increases after the 1st day postinjury. Additional studies are needed to determine if impaired autoregulation leads to an increased risk for secondary ischemic insults, but this seems to be a reasonable hypothesis. If so, dynamic autoregulation testing, which can be performed serially in the intensive care unit, could be a method for targeting preventive treatment in patients who are at greatest risk, or for determining in individual patients how long treatment should be continued.

References


R. Hlatky, et al.
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