Cerebral autoregulation is a complex intrinsic control mechanism that maintains a constant cerebral blood flow by constantly changing in the cerebral vascular resistance in response to changing arterial BP or CPP. This mechanism was found to be impaired after brain injury; even minor impaired AR has been suggested to be associated with variety of cerebrovascular abnormalities found after injury. Impaired AR may increase the vulnerability of the brain to secondary ischemic insult resulting from reduction in the BP or elevated ICP. Several investigators have found impaired AR response after TBI to be associated with poor outcome and an increased mortality rate, suggesting that impaired AR might reduce the ability of the injured brain to preserve an adequate blood flow in the presence of hypotensive episodes. This increased vulnerability of injured brain to secondary hemodynamic impairments has increased awareness of the importance of maintaining a perfusion pressure in TBI, and a targeted perfusion pressure therapy has progressively gained wide acceptance. Some authors have recommended evaluating AR in the hemodynamic management of severe TBI. The length of AR impairment, however, has not yet been determined, and most studies that have focused on AR response after TBI evaluated cerebral hemodynamic during the first days after the injury. There is little information about the time course for AR recovery after severe TBI.

The aim of the present study was to determine the time course for AR recovery after severe TBI and to evaluate the relationship among type of injury, injury severity, ICP, and outcome in light of the time course for AR recovery.
Methods

Patient Population and Clinical Data

The study cohort consisted of 36 patients (27 males, 9 females) with TBI, all of whom had been treated at Harborview Medical Center in Seattle, Washington, between April 2003 and January 2004. The patients’ mean age was 33 ± 15.1 years (± SEM; range 16–77 years). Clinical and demographic data are presented at Table 1. Clinical data were collected prospectively, and patients included in the study represent a consecutive series in which we enrolled the first patient admitted in each week who met the study inclusion criteria. The study was approved by the human subjects committee and informed assent was given by patients’ next of kin.

The severity of neurological impairment on admission was assessed using the GCS at the end of the resuscitation and initial surgeries. The type of brain injury on admission was assessed on CT scans according to Marshall classification system. For statistical purposes, diffuse axonal injury expressed by either diffuse subarachnoid hemorrhage and/or punctuate intraparenchymal hemorrhages was classified as diffuse injury, whereas acute epidural hematoma, subdural hematoma, intracerebral hematoma, and focal brain contusions were classified as focal injury.

Neurological outcome was assessed using the GOS in all patients at discharge and at 6-month follow-up; for statistical purposes, GOS scores of 1–3 were defined as unfavorable outcome and scores of 4–5 were defined as favorable outcome. Follow-up data were acquired during office visits and by contacting patients or primary care physicians by telephone or letter.

Inclusion criteria were severe TBI that justified mechanical ventilation and ICP monitoring with a GCS score of ≤ 8 at the time of admission. Exclusion criteria included bilateral fixed dilated pupils on admission, brain death declared within 5 days of injury, known cardiovascular or peripheral vascular disease, and carotid artery or intracranial stenosis. Patients with lower-limb long-bone fracture and significant leg injuries were also excluded because these injuries interfered with AR testing with the leg cuff method.

Management Protocol

All patients were admitted to the neurosurgical intensive care unit after initial stabilization and diagnostic measures, either from the emergency department or from the operating room for those who required craniotomy for decompression or mass lesion evacuation. Standard clinical monitoring was performed in all patients, including ICP, systemic arterial BP, central venous BP, and CPP. The management protocol included mechanical ventilation, head elevation and sedation (continuous intravenous administration of propofol), analgesia (continuous intravenous administration of fentanyl), and muscle relaxation (vecuronium) as needed. Elevated ICP was treated by moderate hyperventilation, boluses of mannitol 20%, continuous intravenous administration of 3% saline, and ventricular drainage according to the clinical situation. In all patients ICP was monitored as indicated using a Camino fiberoptic catheter. For statistical analysis, patients were divided into 2 groups: 1) controlled ICP, in which ICP was maintained ≤ 20 mm Hg by sedation, head elevation, and administration of mannitol; and 2) elevated ICP, in which ICP was > 20 mm Hg despite these measures. A fluid regimen and selective use of vasopressor were used to maintain the mean arterial BP ≥ 80 mm Hg and CPP of at least 60 mm Hg.

Dynamic Cerebral AR Measurements

The methodology used for calculating the dynamic AR has been described by Tiecks et al. Briefly, this method has a more practical utility in the critical ill patients than the static AR method. It uses bilateral MCA mean blood flow velocity measurements obtained using transcranial Doppler ultrasound with rapid deflation of bilateral thigh cuffs, which produces a rapid short decrease in the BP whereas the rate of MCA mean blood flow velocities recovery gives an index of AR. The changes in
BP and mean blood flow velocity values in the proximal MCAs immediately before and after the cuff release are used to calculate the AR index (an average of at least 3 repeated measurements are used to define the AR index for each test). Previously, studies in healthy volunteers have shown the median AR index to be 5; 80% of individuals have AR index > 4, and 100% have an AR index > 2.5. For statistical purposes, an AR index < 1 was regarded as a poor AR response and an AR index ≥ 1 and < 2.8 was redefined as a moderately impaired AR response.

In each patient, both MCAs were identified by transcranial Doppler ultrasonography according to standard criteria. The transducers were then fixed in place by head band, and blood flow velocities were continuously monitored and recorded (MultidopX, DWL Corp.). The mean arterial BP was measured continuously using a radial artery arterial line.

Dynamic cerebral AR was assessed in several defined time periods during the clinical course (Period I: within 48 hours; Period II: Days 3–5 after injury; Period III: Days 6–8; Period IV: Days 9–11; Period V: Days 12–14; Period VI: Days 15–18; and Period VII: Days 19–23. In each patient AR was measured up to Period IV and each patient in whom the AR index did not recover to a normal range by Period IV was further evaluated in Periods V–VII until recovery was measured.

### Statistical Methods

For statistical analysis, the Fisher exact and Student t-tests and multivariate ANOVA were used. Regression analysis was used to compare AR values from each brain side. Mean data are presented ± the SEM.

### Results

A total of 198 dynamic AR tests were conducted in 36 patients during the study period. Regression analysis indicated close correlations between the AR index of both brain sides (r = 0.98, p < 0.0001). We therefore assigned 1 AR index for each individual for each period by averaging the AR index values for both MCA territories.

The average AR index was impaired (2.2 ± 0.19, 1.36 ± 0.24, 2.14 ± 0.32, 2.4 ± 0.37) for Periods I, II, III and, IV, respectively (p < 0.0001). In general, 64% (23 of 36), 83% (30 of 36), 55% (20 of 36), 33% (12 of 36), and 8% (3 of 36) of patients had an impaired AR index in Periods I, II, III, IV, V, and VI, respectively (Fig. 1). Poor autoregulation response was found in 20% (7 of 36), 36% (13 of 36), 33% (12 of 36), 42% (15 of 36), 25% (9 of 36), 3% (1 of 36), and 0% (0 of 36) of the patients in Periods I, II, III, IV, V, and VI, respectively (Fig. 1).

### Autoregulation Recovery and Injury Severity Related to GCS Scores

Twelve (33%) of 36 patients had a GCS score of 3–5 on admission, and 9 patients experienced impaired AR. These patients exhibited a tendency for late AR recovery, and 65, 67, and 58% of them had impaired AR in Periods III, IV, and V, respectively, compared with 45, 45, and 21% of the patients with GCS scores ≥ 6 (Table 2). Furthermore, patients with a GCS of 3–5 had a significantly lower AR index in Period IV (1.29 ± 0.4 vs 3.08 ± 0.44, p = 0.0137) than patients with a GCS score of ≥ 6, and their AR recovery pattern, marked by a recovery in Period III, was significantly different from that in patients with a GCS score of 3–5 (p = 0.0303, Fig. 2A).

### Autoregulation Recovery and Brain Injury (Focal or Diffuse) Type

Eleven of 36 patients had focal injuries, and 25 suffered diffuse injuries. Patients with the diffuse-type TBI exhibited a tendency for late AR recovery as 64, 60, and 18% of them had impaired AR in Periods III, IV, and V, respectively, compared with 36, 36, and 18% of the patients with focal injuries (Table 2). Furthermore, patients with diffuse injury had a significantly lower AR index in Period III (1.7 ± 0.3 vs 3.15 ± 0.72, p = 0.035) compared with patients with focal injury, and the intergroup AR recovery pattern was significantly different (p = 0.001, Fig. 2B).

### Autoregulation Recovery and ICP

Thirteen of 36 patients experienced elevated ICP, whereas in 23 patients ICP was controlled. Patients with persistently elevated ICP exhibited a tendency for late AR recovery and in 77, 85, and 54% of them AR was impaired in Periods III, IV, and V, respectively, compared with 39,
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Autoregulation Recovery and Outcome

Twenty of 36 patients had a favorable outcome at 6 months postinjury. In patients with an unfavorable outcome there was a tendency for late AR recovery, as 75, 65, and 50% of them had impaired AR in Periods III, IV, and V, respectively, compared with 31, 37.5, and 12.5% in patients with a favorable outcome (Table 2). Furthermore, 8 (40%) of 20 patients with an unfavorable 6-month outcome had poor AR in Period V compared with 1 (6%) of 16 patients with a favorable outcome (p < 0.05). The AR recovery pattern in the favorable outcome group was significantly different than that in the unfavorable outcome group (p = 0.007, Fig. 2D).

Discussion

To the best of our knowledge, the present study is the first to evaluate the time course for AR recovery in patients with TBI related to injury type. Our findings are consistent with those reported in other studies and show that the majority (64% of 36) of the patients with severe TBI experienced impaired AR within the first 48 hours of injury. Using the same cuff deflation dynamic AR testing, Hlatky et al. found that only 16 of 122 patients with severe TBI had an AR index within normal range on Day 2.
Autoregulation recovery following severe TBI

Our data suggest that factors associated the severity of primary and secondary brain damage measured by type of brain injury, GCS score, and ICP are associated with profound and prolonged AR impairment (AR “paralysis”). Patients with focal brain injury, higher GCS score (≥ 6), or controlled ICP had a tendency toward earlier AR recovery (on Days 5–11) and for overall moderate AR impairment. However, diffuse brain injury, lower GCS score (3–5), or elevated ICP was associated with a late AR recovery pattern, occurring in the end of 2nd week after the injury, and many patients experienced prolonged AR paralysis (poor or absent AR) over that time period. This pattern was found mainly in patients with an unfavorable outcome, who experienced a significant tendency toward prolonged AR paralysis and late recovery, whereas patients with a favorable outcome exhibited a tendency toward earlier AR recovery (on Days 5–11) and less profound AR impairment.

The findings in the present study suggest a correlation between outcome and AR that is consistent with published findings. Paneri et al. have evaluated the correlations among AR, death, and outcome in 32 patients with severe TBI and found the AR index to be significantly lower in nonsurvivors than survivors (p = 0.0004) with a significant correlation between AR index and GOS score (r = 0.464, p = 0.011). Steiger et al. have found a correlation between the rate of dynamic AR and GOS score, and in evaluating 187 patients with severe TBI Czosnyka et al. found that an unfavorable outcome was significantly (p < 0.00002) associated with lower AR values. Also consistent with our findings Czosnyka et al. found that impaired AR was associated with poor outcome, elevated ICP, and lower GCS score.
Whether impaired AR is directly associated with poor outcome depends on other variables not yet defined as profound, prolonged, impaired AR may increases brain vulnerability to BP insults; AR impairment might be aggravated or prolonged by elevated ICP and pressure support therapy. Based on our data, we cannot provide answers to this issue, referred by Czosnyka et al. as a chicken-or-egg issue, and further study should be done to evaluate clinical variables associated with AR impairment.

Conclusions

The time course for AR recovery after severe TBI can be delayed, and a failure to recover during the 2nd week after injury is associated with an unfavorable outcome and is common in patients with a lower GCS score, diffuse brain injury, and elevated ICP. However, in patients with a favorable outcome, AR recovered earlier—that is, by the end of 1st week and beginning of the 2nd week injury. This pattern was dominant in patients with higher GCS scores, focal injury, or controlled ICP. The present findings suggest that AR impairment after severe TBI may last longer than previously believed and that perfusion pressure management and adequate maintenance of BP should be considered in some patients with severe TBI for a period of at least 2 weeks. Further studies should be conducted to evaluate the impact of prolonged AR impairments on outcome and to assess factors associated with profound and prolonged AR impairment.

Disclosure

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