Age, intracranial pressure, autoregulation, and outcome after brain trauma

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Object. The object of this study was to investigate whether a failure of cerebrovascular autoregulation contributes to the relationship between age and outcome in patients following head injury.

Methods. Data obtained from continuous bedside monitoring of intracranial pressure (ICP), arterial blood pressure (ABP), and cerebral perfusion pressure (CPP = ABP - ICP) in 358 patients with head injuries and intermittent monitoring of transcranial Doppler blood flow velocity (FV) in the middle cerebral artery in 237 patients were analyzed retrospectively. Indices used to describe cerebral autoregulation and pressure reactivity were calculated as correlation coefficients between slow waves of systolic FV and CPP (autoregulation index [ARI]) and between ABP and ICP (pressure reactivity index [PRI]).

Older patients had worse outcomes after brain trauma than younger patients (p = 0.00001), despite the fact that the older patients had higher initial Glasgow Coma Scale scores (p = 0.006). When age was considered as an independent variable, it appeared that ICP decreased with age (p = 0.005), resulting in an increasing mean CPP (p = 0.0005). Blood FV was not dependent on age (p = 0.58). Indices of autoregulation and pressure reactivity demonstrated a deterioration in cerebrovascular control with advancing age (PRI: p = 0.003; ARI: p = 0.007).

Conclusions. An age-related decline in cerebrovascular autoregulation was associated with a relative deterioration in outcome in elderly patients following head trauma.

KEY WORDS • age • brain trauma • outcome • autoregulation • intracranial pressure

Traditionally almost all models used for outcome prediction after brain trauma list severity of injury and patient age as two important factors.1,19,23,30 The prognostic potential of the GCS score assigned at hospital admission, although well established in the past, has been challenged recently—it no longer appears to be correlated to outcome when data from recent years are taken into account, possibly due to changes in emergency procedures.3,27 Nevertheless, the worsening of outcome with increasing patient age remains unchanged. Does this reflect a general fragility of elderly patients following head injury or are there particular pathophysiological factors that are responsible for this relationship?

Many factors apart from age have been reported to be useful in determining outcome.3,17,18,21 Various measurements used to describe the initial injury may depend on the patient’s age. More generally, multiple epidemiological factors that influence outcome may also be age dependent. Variables used to describe the pathophysiology of secondary brain damage are rarely investigated as age-related factors that contribute to outcome.26,29 Intracranial pressure and CPP are obvious factors that are frequently highlighted as influencing outcome.12,23 But are they dependent on age? There are probably more data on the differences among infants, children, and adults than on changes in elderly persons in whom pathophysiological links seem to be less recognized. There is a well-known similarity between Alzheimer disease and poor cognitive recovery after brain trauma.11 Certain biochemical markers have been identified that develop similar age profiles in both diseases.31 More generally, multiple markers that have been shown to be associated with worse outcome after head injury6,24,28 may have a specific age dependency.

We sought to investigate a selected subset of brain monitoring variables, focusing on the relationship between brain pressures and blood flow, which possibly contribute to the high incidence of unfavorable outcomes in elderly patients after head trauma. The age dependence of ICP, CPP, blood FV through basal cerebral arteries, and various indices used to describe pressure autoregulation and cerebrovascular reactivity were analyzed in a large group of patients during the acute stage following head injury.

Clinical Material and Methods

Patient Population

Three hundred fifty-eight patients with head injuries who...
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were at least 16 years of age at the time of injury were mon-
itored as a part of their routine medical care at Addenbrooke’s Hospital between 1992 and 2001. Only patients who underwent invasive monitoring of ICP and ABP for longer than 12 hours and in whom monitoring was performed using a bedside computerized system were includ-
ed in our study.

The patients received a sedative agent, mechanical venti-
lation, and a paralytic agent to maintain ICP at a level lower than 25 mm Hg. Systemic hypotension was controlled with fluids and vasodilating drugs so that we could keep CPP higher than a target level of 70 mm Hg to reduce the inci-
dence of a secondary ischemic insult. Episodes of intracra-
nial hypertension were treated with mild hyperventilation (PaCO2 4–4.5 kPa) and moderate hypothermia (35˚C) ther-
apies and mannitol and thiopentone. External ventricular drainage was performed if feasible, depending on the size of the patient’s ventricles. There is no direct evidence that any of the specific medications we used affected autoregulation of CBF; however, CPP- and PaCO2-related changes in auto-
regulation have been previously described. After the pa-
tient had been resuscitated the GCS was used for analysis.

Not all patients in our group could be classified as hav-
ing severe head injury. Twenty percent of the patients had a GCS score greater than 8, but their clinical conditions and abnormalities found on CT scans of the head indicated the need for a full NCCU protocol with ventilation for at least 24 hours.

A GOS score was assigned to each patient based on an analysis of the patient records following an outpatient consultation or a telephone-administered questionnaire 6 months after the injury.

Statistical Analysis

Routine clinical and brain monitoring data, which was prospectively collected and approved by the multidisci-
plinary local Neuro Critical Care Users Group, were retrospec-
tively analyzed. No data were included that would make it possible to identify any individuals. At the time of data collection no approval from the local ethical committee was re-
quired.

Bedside Monitoring

Each patient’s ICP was monitored with the aid of an intraparenchymal probe (Camino ICP transducer in 12 pa-
tients and Codman ICP MicroSensors in 346 patients). The patient’s ABP was monitored invasively. Continuous data were analyzed online and stored on the hard disks of bed-
side computers.

The MCA was insonated daily on the side of the ICP bolt for a period of 20 minutes to 2 hours starting from the day of hospital admission until discharge or Day 8 after head injury by using one of three ultrasonography systems (PC-
Dop 842 Doppler Ultrasound Unit; Scimed, Bristol, UK; Neuroguard; Medasonics, Fremont, CA; or Multidop X4; DWL Elektronische Systeme GmbH, Sipplingen, Ger-
many). The depth of the insonation was chosen to be between 4 and 6 cm and was adjusted to insonate segments of the MCA that were not affected by vasospasm (the PCDop 842 unit is not able to detect an FV higher than 200 cm/sec-
ond). This was achieved by insonation of the more distal portion of the MCA or, if necessary, by taking measure-
ments from the other side. Signals were monitored during periods of stable respiratory parameters, free from physio-
therapy, tracheal suction, and other disturbances. Seven hundred eighty-two recordings were obtained in 237 pa-
tients and stored. Transcranial Doppler, ICP, and ABP mea-
surements are conducted routinely for patients with head in-
juries; therefore this monitoring did not expose the patients to any unnecessary interventions.

Signals were sampled from the analog output of the mon-
itors at 30 Hz, digitized (12-bit analog-to-digital converter), and subsequently analyzed as 8-second averages. Mean ICP, ABP, and CPP values were calculated in 1-minute in-
tervals. Time trends were analyzed and global time-aver-
egaged ICP, ABP, and CPP values were recorded for each patient. Indices used to describe cerebral autoregulation and pressure reactivity were calculated as correlation coefficients between slow waves (bandwidth 0.05–0.003 Hz) of the systolic FV and CPP (ARI) and the ABP and ICP (PRI). Both indices have been described in detail previously. An increase in the value of both correlation coefficients toward positive values indicates an increase in the passive behavior of the vascular bed, which leads to disturbed pressure reac-
tivity and, as a consequence, failure of autoregulation.

Apart from these secondary indices, variables derived from the blood FV waveform, such as the pulsatility index and critical closing pressure, were analyzed as being potentially age related.

Results

There were 348 patients ranging in age from 16 to 87 years; 60 patients were female and 288 were male. The ini-
tial GCS scores ranged from 3 to 15; 20% of the patients had a GCS score greater than 8, although a later deteriora-
tion in these patients’ conditions required full NCCU sup-
port with ventilation for longer than 24 hours.

Our analysis indicated that elderly people had a worse outcome after brain trauma. The relationship between the GOS score and age was significant and negative (r = -0.301, p < 0.0001; Fig. 1).

The initial GCS assessment correlated with the patient’s age (r = 0.14, p < 0.01), indicating that there was a tendency for elderly patients to receive a better score.

Continuously monitored variables appeared to be associated with age (Fig. 2): the mean ICP had a weak tendency to decrease with age (r = -0.14, p < 0.01); the ABP tended to increase with age, although insignificantly (p = 0.18); and the CPP increased with age (r = 0.19, p = 0.0004).
Indices of autoregulation and pressure reactivity indicated worsening of cerebrovascular control with age (ARI: r = 0.26, p = 0.002; PRI: r = 0.24, p = 0.003; Fig. 3).

Blood flow velocity was not dependent on age (p = 0.58; Fig. 4), even when all patients who presented with potential vasospasm and hyperemia (FV > 120 cm/second) were excluded. Similarly, the critical closing pressure was independent of age. The pulsatility index indicated only a weak and insignificant tendency to increase with age, but this can be explained by the significant increase in the pulse amplitude of the arterial pressure waveform that occurred with age (r = 0.24, p < 0.00001).

When a multiple regression model of outcome was analyzed, the GCS score, patient age, mean ICP, and PRI appeared to be independent correlates (r² = 0.22, p < 0.00001). Neither TCD-derived autoregulation nor CPP was included as an independent variable in the model at a significance level less than 0.05.

Discussion

Age and Vascular Factors

The initial GCS score in elderly patients admitted to Adenbrooke’s NCCU indicates that the primary injury was usually slightly less severe than for younger patients. Also the postinjury course seems to be more favorable in elderly patients from the point of view of brain protection against secondary insults: the ICP seems to be lower and the CPP higher in elderly patients. What then makes outcome worse if these factors traditionally linked with outcome are more favorable? It may be that critical thresholds may become less favorable in elderly patients; however, such an analysis would be impossible using our material. The only variables shown to deteriorate with age in our data were vascular pressure reactivity and autoregulation. This association may indicate that worsening of the indices of blood-flow regulation with age is responsible for the worse outcomes. Indeed, in all our previous studies, when these indices were considered they were strong and independent predictors of outcome after traumatic brain injury.⁷⁴,⁷⁵ This finding obviously does not exclude other possible factors;⁶ in fact, it does not even indicate that failure of autoregulation is a direct cause of worse outcome in elderly patients. In some age-related cerebral degenerative disorders, such as Alzheimer disease, vascular function has been reported to deteriorate,⁵⁰,⁶⁰ although opinions about this are still divided. Dynamic autoregulation seems to be independent of age as well as CO₂ reactivity, although only in men; it has been reported to deteriorate in women.⁶⁴,⁶⁵ Therefore, worsening of vascular pressure reactivity with age seems to be a unique feature of head injury. It is possible that there is an unknown variable that constitutes an independent cause of this worsening. It may be reflected by the altered brain biochemical profiles reported in so many studies, although in none of them has age been shown to be a factor responsible for gradual worsening so far.
Pressure reactivity correlates with age, but in the multiregression model it remains a factor correlating with an outcome independent on age. This emphasizes a special role for pressure reactivity and autoregulation in optimizing the treatment of head-injured patients. It is interesting that blood FV, which, after exclusion of cerebral vasospasm, generally correlates with global CBF, does not depend on age. Conventional knowledge indicates that CBF decreases with age as metabolic needs and overall brain functionality seem to decrease. Although new magnetic resonance imaging–based studies in which a partial blood volume correction has been applied have posed a challenge to this belief. Again, as in the case of cerebrovascular reactivity, results from acute traumatic brain injury are different from the studies in healthy volunteers.

In this study we focused on continuous rather than threshold-like changes with age and collected our data in scatterplots (Figs. 1–4), instead of performing other forms of analysis. From the formal point of view, the age threshold (which maximizes the F ratio between expected values of outcome distribution) of 49 years may be revealed in our group of patients: the mortality rate increases past this threshold twofold from 22 to 44% (p < 0.00004, Kruskal–Wallis test). Intracranial pressure decreases from 19 ± 12 mm Hg to 15 ± 6 mm Hg (p < 0.004), CPP increases from 72 ± 14 mm Hg to 79 ± 12 mm Hg (p < 0.001), and the PRI deteriorates from 0.01 ± 0.13 to only 0.05 ± 0.12 (p < 0.03). Therefore, the threshold analysis does not indicate that cerebrovascular deterioration may be a prime suspect.

Limitations of the Study

There are obviously many aspects that remain to be investigated regarding age-related phenomena in traumatic brain injury. Our study is strictly correlative rather than a direct test of the hypothesis. Only thanks to the large number of patients and data points were we able to find a correlation, which in itself is relatively weak. It is well known that head-injured patients usually form a very heterogeneous group. Averaging across a large number of patients allows us to minimize the white noise resulting from this heterogeneity. The final correlation, however, does not provide a quantitative relationship with age, which remains unknown; therefore, a prospective study on well-selected subgroups of patients that takes into account comorbidities such as diabetes and vascular diseases should be of greater clinical importance.

We also did not analyze the patients’ CT scans in detail. A new study that focused on this aspect showed that in a subgroup of 126 patients treated between 2000 and 2002, a correlation between the CT scanning Marshall score and age was not significant (Hiler, et al., manuscript in preparation).

Another limitation is derived from the fact that, although ICP, ABP, and CPP were monitored continuously, TCD blood FVs were only monitored intermittently. This is a technical limitation of the TCD technique, which cannot be easily improved, unless new methods of probe holding are developed.

Conclusions

An age-related deterioration in cerebrovascular reactivity may be a factor responsible for the worse outcome seen in elderly patients following head trauma. Autoregulation may be disturbed due to the trauma itself, but it also deteriorates with advancing age. Cumulative vascular comorbidity may be a factor that slowly but steadily contributes to this process.

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FIG. 3. Graphs demonstrating the relationships between age and the PRI (158 patients; upper) and ARI based on ultrasonographic recordings (237 patients; lower). Both indices indicate a gradual worsening of cerebrovascular control with age.

FIG. 4. Graph showing the relationship between blood FV and age.
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References


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