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Brain Stem Blood Flow, Pupillary Response, and Outcome in Patients with Severe Head Injuries

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Outline

Abstract

OBJECTIVE: Acute pupillary dilation in a head-injured patient is a neurological emergency. Pupil dilation is thought to be the result of uncal herniation causing mechanical compression of the IIIrd cranial nerve and subsequent brain stem compromise. However, not all patients with herniation have fixed and dilated pupils, and not all patients with nonreactive, enlarged pupils have uncal herniation. Therefore, we have tested an alternative hypothesis that a decrease in brain stem blood flow (BBF) is a more frequent cause of mydriasis and brain stem symptomatology after severe head injury. We determined the relation of BBF to outcome and pupillary response in patients with severe head injuries.

One hundred sixty-two patients with a Glasgow Coma Scale score of 8 or less underwent stable xenon computed tomographic blood flow determination at the level of the superior colliculus, and this blood flow was correlated with pupillary features, intracranial pressure, computed tomographic scan pathology,

and outcome.

A BBF of less than 40 ml/100 g/min was significantly associated with poor outcome (P P P = 0.062) and inversely related to pupillary responsiveness (P = 0.0006), pupil size (P = 0.005), and BBF of less than 40 ml/100 g/min (P = 0.009).

CONCLUSION: These findings suggest that pupillary dilation is associated with decreased BBF and that ischemia, rather than mechanical compression of the IIIrd cranial nerve, is an important causal factor. More important, pupil dilation may be an indicator of ischemia of the brain stem. If cerebral blood flow and cerebral perfusion pressure can be rapidly restored in the patient with severe head injury who has dilated pupils, the prognosis may be good.

Acute pupillary dilation in patients with an intracranial mass lesion was one of the earliest clinical manifestations of a neurosurgical emergency to be described in the literature (2,4,6,15,22,25,28,32,36,40,42). The most widely accepted theory for the cause of the pupillary dilation is that an intracranial mass lesion traps the IIIrd cranial nerve at the tentorial edge as the uncus is herniated downward and medially (18,25,28,36,42,45,47). Continued compression of the medial temporal lobe into the brain stem results in loss of consciousness, decerebrate posturing, and cardiovascular collapse (25,36,40,42,47). An alternative view holds that compromise of brain stem circulation is a major contributing factor to pupillary dilation. This could be the result of either a supratentorial mass causing downward shift of the brain stem, with consequent deformation of the perforating brain stem arteries arising from the basilar artery, or global reduction in whole-brain cerebral blood flow (CBF) that occurs because of raised intracranial pressure (ICP) in the head-injured patient (8,11,12,21,23,33,50). In accordance with this blood flow hypothesis, central brain stem ischemia, and not direct peripheral third nerve compression, would be responsible for pupil dilation. However, regional brain stem blood flow (BBF) has never been fully evaluated in the human head-injured population, because adequate tomographic methods for assessing BBF were not available.

In an earlier study, our group described regional blood flow including BBF in 35 patients. Five had unilaterally unresponsive pupils, and six had bilaterally nonresponsive pupils (5). This earlier study suggested that pupillary responsiveness might be related to BBF. Because pupillary dilation is frequently associated with poor outcome, it seems likely that a decrease in BBF would also correlate with pupillary dilation and an unfavorable outcome. This study was constructed

to test the hypothesis that BBF is a major determinant of the pupillary response and outcome in the patient with severe head injury.

PATIENTS AND METHODS

BBF determination

One hundred sixty-two patients with Glasgow Coma Scale scores of 8 or less admitted to the Medical College of Virginia from 1989 to 1994 underwent determination of CBF, using the stable xenon computed tomography method for measurement of CBF, which is based on the Kety-Schmidt principle that the rate of uptake and the rate of clearance of an inert substance are proportional to the blood flow in the tissue. Two baseline computed tomographic (CT) images were taken at the level of the superior colliculus. Stable, nonradioactive, radiodense xenon gas was delivered through the ventilator circuit of a paralyzed and sedated patient until a gas mixture of 30% xenon in oxygen was reached. Subsequent CT scans through this region were taken at 1-minute intervals for a total of seven xenon-enhanced scan cuts (Fig. 1). The arterial blood xenon was derived from the expired end tidal xenon concentration and converted to Hounsfield units with the use of hematocrit. The area of interest delineating the entire cross section at the level of the superior colliculus was traced on the baseline scans. The amount of tracer in the region of interest on each xenon scan taken at 1-minute intervals was subtracted from the initial baseline scan to derive a curve of enhancement over time. The flow was calculated from the arterial and tissue xenon time curves by using the Kety-Schmidt equation (19,43,51). The primary author who performed correlations with pupil status and outcome was blinded to the results of this BBF data collection. Characteristics of patients with a BBF of less than 20 ml/100 g/min, which is an established ischemic threshold for cerebral cortex, were also evaluated (1,35,41).

Clinical features

ICP, pupillary size, and pupillary response to light at the time of BBF measurement were documented by the neurosurgical intensive care nursing staff. Pupillary size was arbitrarily classified as less than 5 mm or greater than or equal to 5 mm, and pupils of 5 mm or more were considered dilated. The largest pupil size for each patient was also evaluated in the logistic regression. Dilation of one pupil, both pupils, or neither pupil was also recorded. Pupillary response was categorized as bilaterally nonreactive (BNR), unilaterally nonreactive (UNR), sluggish, or normally reactive (R). In addition, the presence of a lesion at the brain stem or uncal herniation on the CT scan was documented at the time of the BBF calculation by an independent radiologist.

Outcome was determined at 12 months according to a dichotomized Glasgow Outcome Score; outcome was favorable if the patient was well or moderately disabled and

unfavorable if the patient was severely disabled, vegetative, or dead. These data were collected by research nurses, and all authors were blinded to the patient's score.

All patients were managed in accordance with our established Medical College of Virginia severe head injury protocol. ICP was monitored by intraventricular catheters. ICP was managed in a stepwise manner, using ventricular drainage, sedation (morphine, 2-10 mg/h) and paralysis (vecuronium, 4-10 mg/h), ventilation to a PaCO2 of 33 +/- 2 mm Hg, administration of mannitol, moderate hypothermia (34 +/- 2[degrees]C), decompressive craniotomy, and administration of barbiturates, as needed.

Statistics

The data were managed and analyzed with the Statistical Analysis System (SAS) software package (39). Descriptive statistics, including frequency counts, mean +/- standard deviation, range, and confidence limits of percentage, were used to describe the age, sex distribution, ICP, BBF, and outcome of the entire sample and the BBF distributions of the BNR and normally reactive subgroups. Cross-classification tables, [chi]2 tests, or Fisher's exact test (when the counts were small) was used to examine the possible relation between pairs of variables. We used Wilcoxon's rank-sum test to compare the BBF distributions of BNR and normally reactive subgroups. Spearman correlation indices evaluated the relation between continuous variables (maximum pupillary size and BBF). Logistic regression was used to determine the effect of each prognostic factor on the 12-month dichotomized outcome, independent of the other factors (13).

RESULTS

Of the 162 patients with xenon data, 124 were male and 38 were female. The mean age was 33.7 +/- 17.9 years (range, 6-90 yr).

BBF and outcome

The mean BBF for all patients was 41.6 ml/100 g/min (range, 0-167 ml/100 g/min). Approximately 80% of the BBF values were in the range of 20 to 59 ml/100 g/min. Although there were two extremely high values (136 and 167 ml/100 g/min), the overall BBF was normally distributed and symmetric. A BBF of less than 40 ml/100 g/min was significantly associated with poor outcome (P = 0.009) (Fig. 2). The distribution of BBF and outcome is presented in Table 1.

Figure 3 describes the overall outcome for patients with a BBF of less than 40 ml/100 g/min or greater than or equal to 40 ml/100 g/min. A good outcome was achieved by 7 of 40 patients with a BBF of less than 40 ml/100 g/min and 44 of 74 patients with a BBF of 40 ml/100 g/min or more. An unfavorable outcome

occurred in 33 of 40 patients with a BBF of less than 40 ml/100 g/min and in 30 of 74 patients with a BBF of 40 ml/100 g/min or more. At 1 year, eight of nine patients with a BBF of less than 20 ml/100 g/min were dead, and the other was severely disabled.

Pupillary response, BBF, and outcome

In patients with BNR pupils, the mean BBF was 30.5 +/- 16.8 ml/100 g/min, and in those with R pupils, it was 43.8 +/- 18.7 ml/100 g/min (P = 0.001). Table 2 presents the frequency distribution of BBF in BNR and R pupils. More than 75% of the BNR patients had a BBF of less than 40 ml/100 g/min, compared with less than 40% of patients with normally reactive pupils. Figure 4 depicts the relation between pupillary response and BBF. Twenty of 38 patients with a BBF of less than 40 ml/100 g/min had BNR pupils, whereas 7 of 79 patients with a BBF of 40 ml/100 g/min or more had BNR pupils (P P

Figure 5 describes the relation between pupillary response and outcome. Twenty-three of 27 patients with BNR pupils and 16 of 24 patients with UNR/sluggish pupils had poor outcomes, compared with 22 of 56 patients with R pupils. Only a small fraction of patients with BNR and UNR/sluggish pupils (4 of 27 patients and 8 of 24 patients, respectively) had good outcomes, compared with 34 of 56 patients with R pupils. None of the patients with a BBF of less than 20 ml/100 g/min had normally reactive pupils; six of nine patients had BNR pupils, two had UNR pupils, and the remaining patient had sluggish pupils.

Pupillary size, BBF, and outcome

The maximum pupillary size of all patients was 4.2 +/- 1.7 mm. The maximum pupillary size of those with BNR pupils was 6.4 +/- 1.6 mm, whereas the maximum pupillary size of those with normally reactive pupils was 3.6 +/- 1.2 mm (P P

Figure 6 graphically depicts the relation of BBF and pupillary size. Seventy of 92 patients with pupils that were 5 mm or less in size had a BBF of at least 40 ml/100 g/min, whereas only 22 of them had a BBF of less than 40 ml/100 g/min. Similarly, only 10 of 26 patients with pupils more than 5 mm in size had a BBF of 40 ml/100 g/min or more, and 16 of these patients had a BBF of less than 40 ml/100 g/min (P

Figure 7 presents pupil size and outcome. The percentages of those with good and poor outcome are similar for patients with pupils less than or equal to 5 mm. However, in patients with pupils greater than 5 mm, 20 of 25 had an unfavorable outcome, compared with only 5 of 25 patients with a good outcome (P

ICP, pupillary parameters, computed tomography results, and BBF

When the relation between ICP and pupillary size was tested, no correlation was found. In patients with a pupillary size of less than 5 mm, the mean ICP was 21.4 +/- 10.0 mm Hg, whereas in those with one or both pupils 5 mm or greater in size, the ICP was 17.9 +/- 7.5 mm Hg (P = 0.148). The ICP was not correlated with pupillary reactivity. Patients with BNR pupils had a mean ICP of 24.3 +/- 13.4 mm Hg, whereas those with normally reactive pupils had a mean ICP of 20.2 +/- 8.8 mm Hg (P = 0.302). The presence of a traumatic hematoma or contusion at the superior colliculus observed on the CT scan was weakly correlated with a high ICP (P = 0.0612). Patients with brain stem abnormalities (n = 9) had an average ICP of 26.4 +/- 10.2 mm Hg, compared with 20.1 +/- 9.4 mm Hg in patients in whom brain stem abnormalities were not found. The maximum ICP at the time of the study was not associated with age (P = 0.250) or minimum BBF for the patient (P = 0.841), but it was weakly associated with the maximum pupillary size for that patient (P = 0.062). The ICP at the time of the xenon study did not correlate with outcome at 12 months (P = 0.680).

The finding of hemorrhage or contusion at the superior colliculus on the CT scan was not associated with BBF (P = 0.6740) or abnormal pupillary reactivity (P = 0.7158). Isolated uncal herniation was not noted on any CT scans; however, diffuse swelling obliterating the subarachnoid spaces was seen on a few CT scans.

Logistic regression of outcome

Three sets of logistic regression were undertaken with the use of different BBF measurements. The first used all of the xenon BBF values for each patient. In this group, unfavorable outcome at 12 months was directly related to age (P = 0.0438) and inversely related to pupillary responsiveness (P = 0.0002) and maximum pupillary size (P = 0.0198). BBF (P = 0.3287), the number of dilated pupils (P = 0.5175), and the presence of an abnormality on the CT scan (P = 0.8749) were not significantly related to outcome. Second, we divided the data into two groups, corresponding to patients with a BBF of less than 40 ml/100 g/min and those with a BBF of 40 ml/100 g/min or more. A BBF of less than 40 ml/100 g/min was significantly related to unfavorable outcome (P = 0.0099), age (P = 0.0342), pupillary responsiveness (P = 0.0069), and maximum pupillary size (P = 0.0197), but not to the CT findings (P = 0.8532) or the number of dilated pupils (P = 0.2524). Third, when using only the minimum BBF for each patient, age (P = 0.0284), maximum pupillary size (P = 0.0302), and pupillary responsiveness (P = 0.0018) were significantly correlated with outcome, but minimum BBF (P = 0.4610), the number of dilated pupils (P = 0.2748), the maximum pupillary size (P = 0.0302), and the presence of an abnormality on the CT scan (P = 0.759) were not significantly related to outcome. Thus, age, pupillary reactivity, and maximum pupillary size are consistently associated with outcome at all BBF

levels. BBF was significantly related to outcome only at levels less than 40 ml/100 g/min.

DISCUSSION

Impairment of brain stem blood supply and oxygenation, as well as compression of the peripheral third nerve, may be the cause of fixed, dilated pupils in the head-injured population. There is observational and experimental evidence that supports these two explanations.

Indirect observational and related experimental data to support brain stem ischemia

Our first argument against mechanical compression is derived from postmortem pathological studies in head injury patients that demonstrate ischemic and hemorrhagic injury in the brain stem without uncal herniation. These findings are associated with damage of the perforating branches of the basilar artery caused by supratentorial mass expansion or brain stem torque (11,12,16,21,23,33,50). Also, temporal lobe herniation is not observed in all postmortem cases of patients with fixed, dilated pupils. Likewise, dilated pupils are not observed in all cases of temporal lobe herniation (7,9,36,40,42).

Second, a sizable herniation of the uncus against the third nerve would be likely to cause a complete peripheral third nerve palsy with ipsilateral eye deviation and ptosis of the eyelid. This is not consistently seen in the neurotrauma patient. In direct relation to this argument is the observation that complete third nerve palsies occur after even trivial traction injury to the peripheral nerve during basilar aneurysm surgery. These third nerve palsies remain apparent for weeks after the surgical trauma. In contrast, the mydriasis in head trauma patients often is reversed immediately with decompression or mannitol therapy (8,10).

Third, the ipsilateral pupil does not always dilate first. Instead, bilateral mydriasis may occur simultaneously, or the contralateral pupil may dilate first. The "crossing fibers of the third nerve" explanation for this is dubious at best (8,52).

Our fourth argument is the rapid reduction in pupil size that may be observed after administration of mannitol (8). For example, a recent patient of ours with a Glasgow Coma Scale score of 4 required mechanical ventilation, sedation, and paralytic agents for ICP control. Despite these measures, both pupils became dilated as the ICP increased. A rapid infusion of mannitol reduced the ICP and returned the pupils to a size of 3 mm and reactivity. It is difficult to believe that mannitol can repeatedly diminish the mass effect of a wedged portion of

uncus at the tentorial edge in such a short period of time. It is more likely that the rapid change in pupillary reactivity in this situation is the result of increasing CBF and thus oxygen delivery to the brain stem (20,26,27).

Finally, the ischemic theory to explain pupillary dilation is strengthened by previous hypoxia studies during cardiac arrest and ischemia in animal models (3,24,29,44). Specifically, Sobotka and Gebert (44) demonstrated pupillary dilation within minutes after complete brain ischemia in dogs. Maximum mydriasis was attained by 5 minutes. Constriction occurred after reperfusion, and the length of time until a return to normal pupillary dilation was directly related to the duration of ischemia. Binnion and McFarland (3) demonstrated that complete cardiac arrest in dogs caused pupillary dilation that could be reversed with cardiac massage.

Data supporting brain stem ischemia

The observations in our retrospective study are strengthened by animal studies that indicate that pupillary dilation is associated with reduced BBF. Sunami et al. (46) in 1983 measured blood flow by the hydrogen clearance technique in the inferior colliculus (IC) after increasing supratentorial pressure by placement of an epidural balloon in 40 cats. At the start of anisocoria, blood flow in the IC dropped rapidly and dramatically from 33.7 to 20.5 ml/100 g/min. Nagao et al. (30) in 1984 showed similar results in 52 cats. Ipsilateral pupillary dilation was observed in 16 of 30 animals when the IC blood flow ranged from 14.8 to 53.3 ml/100 g/min. The average IC blood flow decreased from 33.7 to 19.6 ml/100 g/min.

BBF in the head-injured population

Normal BBF was found to be 42 +/- 8 ml/100 g/min, as determined by the xenon computed tomography technique, in a single study reported in the literature (43). That study was performed when the xenon computed tomography technique was in development. The values were obtained without anesthesia, as in our patients. With improved CT scanning and computer acquisition of data, the normal BBF values may be different. In our head injury study, an average BBF of 30.5 +/- 16.5 ml/100 g/min was associated with BNR pupils and a poor outcome at 1 year. This does not mean that this blood flow level is the ischemic threshold for the brain stem; instead, this is the mean BBF value at which function was lost.

The concept that neurological function is lost at higher levels of CBF (~25 ml/100 g/min) than the threshold level for occurrence of ischemic brain damage (~18 ml/100 g/min) is well established in the literature (17,48). That poor outcome occurs with a BBF of less than 40 ml/100 g/min may also support the vigorous autoregulation of blood flow to the brain stem that has been presented

by other authors. BBF was shown to be rigorously maintained, up to a defined break point, with increasing ICP (38,49,53). In particularly, Zierski et al. (53) in 1983 used an epidural balloon model in cats to show that BBF was well preserved with decreasing cerebral perfusion pressure, achieved by increasing ICP, when compared with blood flow in the caudate, thalamus, hypothalamus, and supratentorial regions. BBF is also well maintained before and during the Cushing reflex and is stable during 4 to 5 minutes of experimental hypoxemia and ischemia in newborn piglets (31,32,38,53). Thus, the brain stem seems to be defended against changes in CBF and oxygen delivery. It is likely that a damaged brain stem may actually require a higher blood flow than noninjured tissue and that once the critical perfusion threshold for the brain stem is reached, a further minimal reduction in flow may have major consequences, including pupillary dilation.

The slight decrease in good outcome in patients with a BBF of more than 60 ml/100 g/min (Figure 2) may be explained in two ways. The most probable reason is the small number of patients in this subgroup. Only 2 of 4 patients with a BBF greater than 81 ml/100 g/min and 9 of 15 with a BBF of 60 to 80 ml/100 g/min had good outcomes. Another reason may be that hyperemia of the brain stem in this head-injured population is also associated with worse outcome. Cerebral hyperemia is well documented after head injury (14,31,34,37,49). Elevated hemispheric blood flow has been associated with increased morbidity and mortality, increased ICP, and "luxury perfusion injury" in the head-injured population (14,34,49). A similar trend may occur with hyperemia of the brain stem.

In the present study, we speculate that BBF was not correlated with ICP because, at the time of the xenon computed tomography studies, ICP was being controlled by mechanical ventilation, sedation, paralytic agents, and mannitol therapy. Therefore, ICP levels at the time of the flow study were artificially lowered and controlled. Also, reduced BBF did not correlate with the finding of a brain stem lesion on CT scans, although the number of patients studied was small. Most patients with low BBF did not demonstrate hyperdensity or hypodensity in the brain stem. As we would expect, magnetic resonance imaging would be a better radiographic tool for evaluation of such brain stem pathology.

Our findings cannot conclusively differentiate between a central or peripheral etiology for the traumatic dilated pupil, but they support pathological and experimental data that suggest an ischemic central etiology. We believe that third nerve palsies after head trauma can exist because of uncal herniation, ischemia of the brain stem, or a combination of the two. The presence of nonreactive pupils remains an excellent indicator of a potential mass lesion and

is also an excellent outward indicator of a more potentially devastating pathophysiological occurrence, inadequate blood flow to the brain stem. Rapid, aggressive restoration of CBF and, equally important, cerebral oxygenation should be of primary concern when the pupil dilates. BBF would be expected to improve with the administration of mannitol, mild hyperventilation, and the maintenance of cerebral perfusion pressure by vasopressors and volume expansion. Arterial and brain oxygenation should be kept well above normal limits. Direct measurements of brain oxygenation may be useful in this regard. If a mass lesion exists, these measures temporize until definitive, decompressive craniotomy can be undertaken. Postoperatively, a similar approach to preservation of flow and oxygenation should be maintained.

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