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Cerebral Blood Flow in Experimental and Clinical Neurotrauma: Quantitative Assessment

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1. Introduction

In a modern world the traumatic brain injury (TBI) becomes one of major health problems, with annually 500.000 cases in the US alone (Narayan et al., 2002), it poses the largest threat and considerably the most common cause of both the morbidity and mortality of the human young and pediatric population, and it is one of the major cases of disability and long capability in all ages (Langfitt et al., 1977; Levin et al., 1982; Fife & Jagger, 1984; Luerssen et al., 1988; Kraus et al., 1990). Moreover, TBI to children younger than 4 years of age has been shown to cause significantly more severe neurological, cognitive and motor deficits than in older children (Khoshyomn & Tranmer 2004). Thus TBI is a serious social, medical and scientific problem as well. New data, available to improve both efficacy of treatment and life quality after TBI would benefit each patient with TBI.

Despite many successful clinical and laboratory investigations on TBI, many questions of pathophysiology of development and an effective treatment remain open and demand further investigation and understanding (Potts et al., 2006). There is experimental evidence that the inflammatory response may differ in the developing brain as compared to the adult (Fan et al., 2003; Claus et al., 2010; Yoneyama-Sarnecky et al., 2010), another possible factor could be age-dependent differences in posttraumatic cerebral blood circulation (Bayir et al., 2003).

2. Cerebral blood flow in TBI

The comprehensive understanding of pathophysiological processes developing in an injured brain always demands proper understanding of the cerebral blood flow (CBF) alterations as one of the most important factors, which plays an influential role both in disease development and prognosis prediction. In many cases of clinical and animal research, it has proved the importance of monitoring blood flow violations and interesting data were found involving CBF disturbances following the injury. Vascular events after TBI involve hemorrhage, breakdown or increased permeability of the blood brain barrier and edema, and certain changes in cerebral blood flow and local perfusion to the injured area. The exact role of each of these events after trauma is complex and has yet to be fully elucidated.

Post mortem studies of patients who died of severe TBI (90% of these patients had histologic evidence of ischemia) a few decades years ago (Graham & Adams, 1971; Graham et al., 1978; Graham et al., 1989), partly stimulated the interest of CBF; whether

the ischemia was a factor of mortality or a reflection of the severity of injuries is still unknown. Ever since that time, despite many investigations, there is no universally accepted model of CBF changes in TBI. Therefore, the role of cerebral perfusion, both local and general, as well as vasoreactivity in development of a cascade of biochemical reactions after the injury, could be paramount.

Significant changes, perturbations and impairment in CBF and brain metabolism are very common following severe TBI, and the severity of impaired CBF correlates with the severity of TBI and poor outcome (Adelson et al., 1997; Muizelaar et al., 1989). The main peculiarities of cerebral circulation are the ability to autoregulation and high vulnerability to ischemia. Due to unique biological organization, as an extremely high metabolic activity and absence of metabolic stores, the brain requires a constant its supply of blood. Ischemia is poorly tolerated by a non injured brain, and TBI can lead to devastating impairment of autoregulation and profound ischemia (Bayir et al, 2003).

Historically, investigations of CBF were done mostly in adults and mainly without including of the important factor of the timeline. Clinical studies have reported inconsistent and sometimes confusing, findings as decreased blood flow-hypoperfusion, increased flow-hyperemia, and even cerebral vasospasm (Meixensberger, 1993). It was considered that in children with TBI hyperemia is the cause of increased intracranial pressure and cerebral swelling (Bruce et al., 1981), those studies were completed using the intravenous Xenon 133 technique and external probes, in only six people. Animal studies in immature rats as the model of child TBI supported that point of view (Biagas et al., 1996). The authors demonstrated prominent increase of pericontusional CBF 24 hrs after injury, however, the increase was not observed immediately after.

Muizelaar et al. performed 72 measurements of CBF in 32 children with TBI (Muizelaar et al., 1989). CBF is lowest after injury and correlates with the Glasgow Coma score, but founded increase of CBF at some point in their course leads authors to statement the prevalence of hyperemia. Obrist et al. performed serial CBF studies of 75 head-injured adults using Xe133 technique (Obrist et al., 1984). They found that 55% of patients had hyperemia at some point after their injury, and 45% had consistently low CBF, accordingly, hyperemia was associated with elevated intracranial pressure. Kelly et al (Kelly et al., 1996; Kelly et al., 1997), evaluated the role of hyperemia and CBF in outcome and intracranial hypertension, and observed the highest CBF on post injury days 1 to 5, when the lowest blood flows were documented on the day of injury. Significant decrease of posttraumatic CBF has been demonstrated both in human and laboratory investigations (Adelson et al., 1997; McQuire et al., 1998; Chan et al., 1992; Marion et al., 1991; Yamakami & McIntosh, 1991; Bryan et al., 1995; Cherian et al., 1999; Armstead, 1996). In the G. Bouma study of 186 adults after severe TBI, using Xe133 radioactive labeling was shown relatively low CBF in the first 6 hours after injury (Bouma et al., 1991). The average CBF in this study at 4 to 6 hours after injury was 22 mL/100 g/min, and about one third of patients had CBF low enough to be considered ischemic (<18 mL/100 g/min) (Diringer et al., 2002; Astrup et al., 1981), when normal CBF in adults ranges from 33 to 55 mL/100 g/min (Obrist et al., 1984; Chiron et al., 1992). There was a strong correlation between low CBF and poor outcome, with a higher mortality rate for those with ischemia than those without. Thus, ischemia after TBI seems to occur early after injury. These findings were confirmed in a subsequent study using the inhaled stable Xe133 enhanced CT scan CBF technique (Bouma et al., 1995). Another study of 32 adults shows the significant changes of CBF from 27 cc/100 g/min at admission to 44 cc/100 g/min by 24 hrs (Marion et al., 1991).

Infants during the first 6 months of life also have a CBF of about 40 mL/100 g/min, which steadily increases during childhood to reach a peak of about 108 mL/100 g/min between the ages of 3 and 4 years, then goes down to 71 mL/100 g/min after the age of 9 years (Suzuki, 1990), and decreases to adult levels in the late teen age (Chiron et al., 1992). Therefore, it seems that CBF rises through early childhood, then decreases to reach adult levels by late adolescence (Chiron et al., 1992; Mansfield, 1997). Considering that large range of age depending variations, comparisons of CBF data in children could be valid only in small, well-defined age selected ranges, and some investigators of CBF revisited their opinion on prevalence of hyperemia in pediatric TBI (Zwienenberg & Muizelaar, 1999). In the largest report of CBF in 30 children with TBI (Adelson et al., 1997) it is observed, that hypoperfusion was common in admission (about 25 mL/100 g/min) and increased by 24 hrs up to 55 mL/100 g/min. Young age (<24 months) and low CBF in the early period after TBI were associated with poor outcomes. In the most recent publication of the same group of authors it was proven that a younger age, early or later low CBF are correlated with poorer outcomes in children, a relationship of low CBF and an unfavorable outcome (Adelson et al., 2011).

3. CBF Doppler studies in humans

The application of investigative methods based on Doppler Effect allows the performance of continuous monitoring of cerebral blood flow. Due to non-invasiveness and simplicity of application they become one of the first choice investigative methods in clinical and animal research, as Transcranial Doppler, Laser Doppler, etc.

Investigations of CBF with Transcranial Doppler (TCD) techniques allowed the performance of noninvasive and more frequent studies, and as it was shown in study of 57 patients with severe TBI (GCS = <8), that decreased flow was most pronounced during first eight hrs after injury, and significantly increased after that time period (van Santbrink et al., 2002). Correlation between impaired flow and GCS and outcome on admission, was founded in another study in 121 patients with TBI (Chan et al., 1992). Experimental TBI investigations show reduced response of CBF to endogenous vasodilators as nitric oxide (NO) (Cherian et al., 2004; Hlatky et al., 2003).

There are several investigations on Cerebral Blood Flow (CBF) in TBI. It is well established that CBF decreases significantly following TBI in clinical patients (Golding et al., 1999; Robertson et al., 1992) and in experimental animal models (Cherian et al., 1999). Moderate to severe TBI leads to severe reduction of CBF, causing secondary ischemia to already injured brain tissue with increased metabolic demands (Bayir et al., 2003; Potts et al., 2006; Manvelyan, 2006). Clinical research proves the dependence of TBI mortality to primary or secondary ischemia during autopsy (Adams et al., 1983).

It is suggested that trauma roughly disturbs the brain autoregulation, the fine relations between vasoconstrictor and vasodilator production, and accordingly with increased cerebral metabolic demands, makes the brain more vulnerable to ischemia. But, it is very speculative to suggest that the hypoperfusion is connected with vasodilator activity, following hyperemia with vasoconstrictors. Blood flow in the brain is influenced by a wide variety of vasodilators as arachidonic acid metabolites, prostacyclin (Bayir et al., 2003), acetylcholine, calcitonin gene-related peptide, adenosine, and many others (Golding et al., 1999; Bayir et al., 2003), and vasoconstrictors as serotonin, thromboxane, endothelin, and others (Golding, 2002).

The reductions in CBF and further hyperemia after TBI may have been due to the production or reduction of one or more of these cerebral vasoconstrictors or vasodilators. TBI increases the synthesis of cerebral vasoconstrictors including thromboxane (DeWitt et al., 1988) and endothelin (Armstead, 1996) and decreases the release or impairs the vasodilator action of prostacyclin (Al-Turki & Armstead, 1998). Greater TBI-induced release of endothelin-1 in newborn pigs vs. juvenile as age dependent differences in cerebral autoregulation response was shown in Armstead study (Armstead, 1999).

So, insufficient and sometimes controversial data on CBF, demands further investigation, and proper understanding of the role of regional vascular changes beyond vasoactive mediators, as a result of local inflammatory and angiogenesis. This will be appreciated in understanding mechanisms of cerebral autoregulation impairment and CBF disturbances in TBI and then CBF effective regulation will become a therapeutic real target.

We started our own investigations of CBF changes in 69 patients with severe TBI using Ultrasound Transcranial Doppler measurements by strictly considering the timeline. The measurements were started immediately after patient admission to the hospital, in initial hours of TBI onset, and then monitored during the subsequent two week period. Thus, letting us perform the monitoring of the CBF changes in the injured brain. We recorded the mean blood flow velocity in Median Cerebral Artery (MCA), as the biggest artery of the Willis Circle, providing the main blood volume of anterior circulation. The selection of patients was done according to their severity of injury; patients with intracranial hematomas due to possible vascular external compressions were excluded from the study.

The most interesting finding was the total drop in the blood flow during initial hours after injury onset. If it is considered that the mean velocity in MCA, measured in healthy volunteers, is equal to 62 ± 12 cm/s, in patients with acute TBI it was notably reduced down to 36 ± 14 cm/s, which is on the border for development of cerebral primary ischemia. This condition is described as hypovolemia, which means reduced blood flow to the brain.

The following next two days (post-injury 2-3) were marked with notable increase of the CBF velocity in MCA, reaching and overcoming the mean numbers, up to 87 ± 14 cm/s, and continuously growing during a week after injury, up to 120 cm/s, which is Doppler sign of hypervolemia. Some exceptional cases recorded blood flow velocity of 174 cm/s, which exceeds the mean flow velocity three times (!), and develops exclusively as the vasospasm, on postinjury days 6-8. Later on, by the end of two week monitoring period, the CBF velocity drops to mean levels, 66 ± 8 cm/s.

Two patients did not survive the injury; one with the lowest flows recorded, passed on Day 1, and another with the severe cerebral vasospasm, passed on Day 8 post-injury.

Clinical data suggests that during severe neurotrauma cerebral blood flow goes through succeeding processes of hypovolemia, hypervolemia and in most uncontrolled and/or severe cases, vasospasm. Hypovolemia develops immediately after injury and lasts one-two days, and could lead to primary brain ischemia, then cerebral perfusion trends to recover and increasing intensity, reaching hypervolemia also. Development of the arterial spasm (on days 7-8) leads to secondary ischemia.

4. Laser Doppler animal experimental studies

Clinical investigations proved the key role of CBF in primary (due to hypoperfusion) and secondary (mostly due to vasospasm) ischemia in TBI. The animal studies show the correlation between trauma severity and reduction of CBF. The pathological pathways of

CBF reductions are impairments of cerebral autoregulation and cerebral perfusion pressure, and release endogenous vasoconstrictors, responsible also for inflammatory response, serotonin, endothelin, alteration in brain tissue metabolism and ions transport, etc. These experiments demonstrate that TBI leads to significant reduction in cortical CBF of mature and immature experimental animals.

Reduced CBF has been shown in many models of TBI. Moderate fluid percussion injury caused up to 50% reduction in CBF within 15-30 min after injury (Yamakami & McIntosh, 1989). Controlled cortical impact reduced cortical CBF by about 35% (Cherian et al., 1994) to 50% (Bryan et al., 1995).

The recent data of different investigators shows the one-time only continuous monitoring of CBF in animals with TBI model during a few minutes and up to hours. Due to technical difficulties there was no data on the subsequent days and weeks, whenever clinical data shows significant importance of CBF monitoring and repeated investigation during at least a two week period after TBI onset.

For our investigation of cerebral circulation in TBI a rodent model of cortical impact injury was used including adult mice and 21 day immature mice as a model of adult and baby brain injury (a total of 50 animals). For the CBF investigations we used the laser Doppler device LASERFLO BPM2 (Vasamedics, US). Laser Doppler flowmeter (LDF) measures relative perfusion continuously, using a transmitter/receiver probe that emits monochromatic laser light which is reflected by moving RBC according Doppler effect (Stern et al., 1977; Wardel et al., 1993). The power and frequency of the reflected are proportional to the blood volume and blood velocity. Perfusion is calculated as a product of blood volume and velocity in 1mm³ tissue volume under the probe (Haberl et al., 1989). The blood flow in the scanned area is presented in absolute or relative numbers. The power and CBF was monitored using a LDF with the fiber optic needle probe mounted on a stereotactic manipulator and placed approximately 0.5 mm above the dura mater or the pial surface, carefully positioned away from the visible large vessels. Once a suitable placement was obtained, the probe was left at that point for the duration of the experiment, and removed and replaced on the same position after cortical injury.

Measurements were recorded and compared between mice based on a percentage change from baseline values (intact cortex) after experimental procedures. LDF monitored the cortical blood flow in different time points: from the intact skull, intact cortex right after craniotomy, from injured cortex after TBI, and prior to scarification of the animal on 5 different groups (five animals in each) on Day 1, Day 3, Day 7, Day 14 and Day 28. Prior to euthanasia all animals under surgical dosage of anesthesia were placed on a warming pad (to keep the animal under the same condition as during initial investigation) and after a skin incision right above the craniotomy site, the Doppler probe was maintained above the cortex. The measurements show the sufficient drop of flow right after the injury in both groups of animals, CBF falls down about 31% in adults and 33% in babies (*t-test*: $P < 0.05$, the difference between two groups is not significant). The next investigation was performed on the next day, and it is more likely the tendency to restoration of the CBF, when the Flow in adults were reduced about 15% of the Pre-Injury level, and increased about 15 % in babies (*t-test*: $P < 0.05$, the difference is not significant). On the Day 3 blood flow continues the tendency to restoration and the differences were less prominent in adults (decreased about 5% of the Pre Injury level) and babies (increased about 8%), there was no statistically significant difference between that values again (*t-test*: $P < 0.05$, the difference is not significant).

The most significant changes of CBF were recorded on Day 7, when in both groups the Flow reached the highest values during all investigation time points, 43% in adults and 56% in babies comparing the Pre-Injury level of the flow. On days 14 and 28 we saw the restoration of the Flow in both groups. The mean values of the flow presented by those numbers: the flow in the intact cortex is about 25 $\text{mLLD}/\text{min}/100\text{gTissue}$ \pm 8 (in adults) and \pm 5 (in immature) (*t-test*: $P < 0.05$, the difference is not significant). When tissue perfusion was less than 10-12 $\text{mLLD}/\text{min}/100\text{gTissue}$ right after injury, it is an indication of severe cortical ischemia, leading to death of the animal.

Performing 35-day long monitoring of cortical local perfusion gives the following data. Cortical perfusion in an intact brain is similar in both mature and immature CNS. The mean absolute values of the perfusion in the intact cortex are 25 \pm 8 $\text{mLLD}/\text{min}/100\text{gTissue}$ (in adults) and 25 \pm 5 $\text{mLLD}/\text{min}/100\text{gTissue}$ (in immature) (*t-test*: $P < 0.05$, the difference is not significant). The consequent measurements show the sufficient drop of perfusion immediately after the injury in both groups of animals, falls down about 31% in adults and 33% in immature (*t-test*: $P < 0.05$, the difference between two groups is not significant). During the following posttraumatic days one and three local cortical perfusion in both groups had tendency toward the restoration of flow in pre-injury level, as it was measured from the intact brain, then significant change in perfusion was recorded in both groups on day seven, when perfusion reached its highest values during all investigative time points. On following days 14 and 28 the restoration of the perfusion in the both groups were recorded.

Next we examined brain slices stained for vascular proliferation with *Esculentum Lectin*. Enormously large dilated blood vessels appeared at the 7 days post injury in both groups, coinciding with the maximal perfusion, registered by Doppler monitoring. Moreover, on the same day activated microglia/macrophages were prominent within the ipsi-lateral cortex and hippocampus of both age groups (figure 1).

The fact of decreasing blood flow immediately after injury still demands further understanding. Recent papers show the connection between the CBF decreases and NO level reduction after moderate TBI, increase of the cytokines expression (Ahn et al., 2004). One of the probable ways of understanding it is cerebral circulation. Cerebral microcirculation depends on very delicate interaction of vasoconstrictors and vasodilators. TBI is roughly interacting with that system, which leads to the release of cerebral vasoconstrictors (DeWitt et al., 2000) and decreases the production or affect of the activity of vasodilators (Al-Turki & Armstead, 1998). The other findings associated with CBF reduction on early time points after TBI, is the increased cytokine expression and production. However, the role of their changes in activity is not clear yet (Ahn et al., 2004).

So, the reduction of CBF immediately after severe TBI onset could be explained by the changing histochemistry of the brain and vessels, but the symmetric changes in CBF in immature and mature brain on day 7 demands further investigation and understanding. One of the most probable reasons of it could be prevalence of vasodilatation effect due to impairment of cerebral autoregulation. Clinical studies shows the presence of vasospasm on days 7-9, and it shows increased blood flow in main arteries of the brain, Willis circle, whenever the microcirculation in cerebral cortex could be altered due to local conditions. It remains speculative since simultaneous measurement of cerebral hemodynamics and vasoactive agents *in vivo* studies is limited.

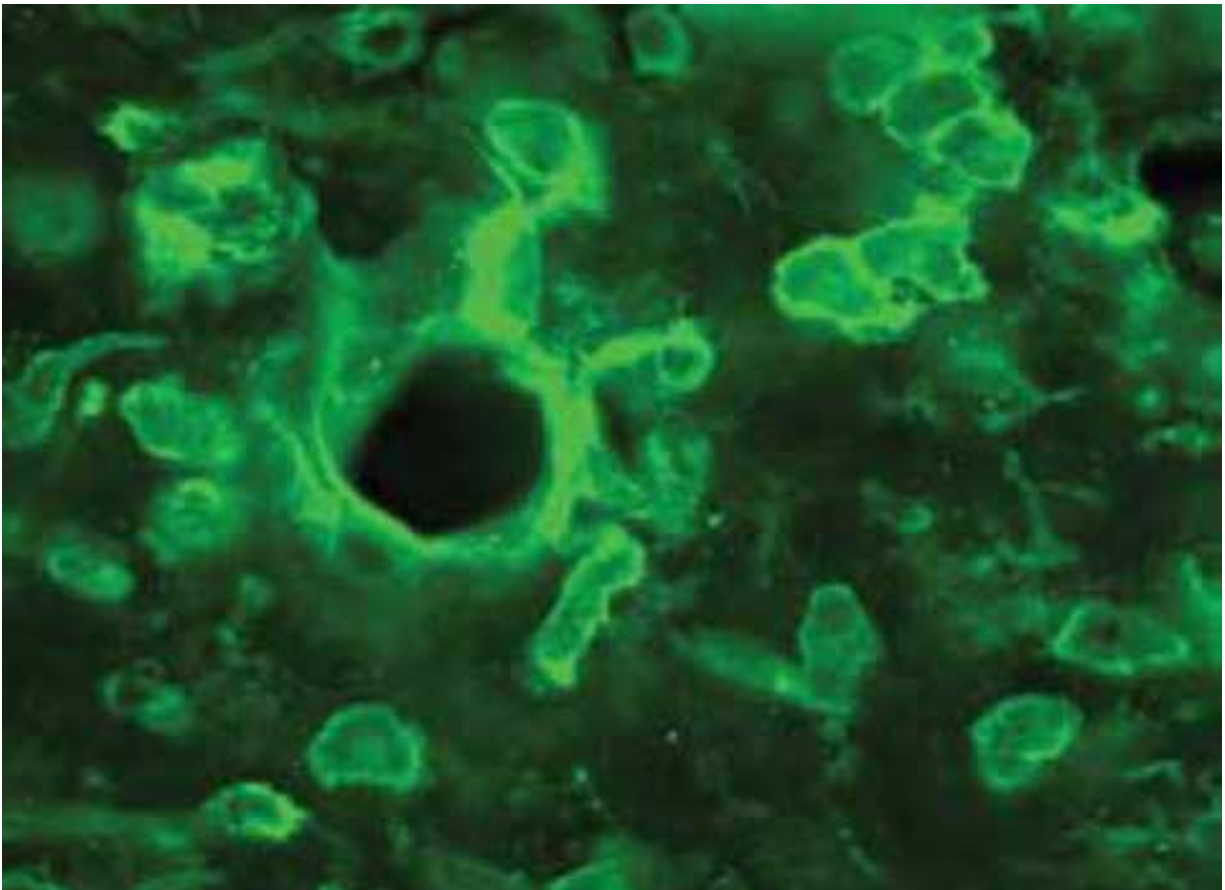


Fig. 1. Enormously enlarged vessel with activated microglial cells.

5. Conclusion

Cerebral Blood Flow is an important chain in the development of cascade of multiple biochemical and vascular events in TBI, contributing to both severity and prognosis. Despite the lack of complete data and existing controversies, and the level of brain maturity, CBF changes in brain injury in both human and experimental research are similar: immediate drop after injury onset (hypovolemia), recovery up to initial levels on following days, and further development of hyperperfusion and vasospasm.

In normal condition the cerebral circulation has the ability to maintain a stable CBF over a wide range of cerebral perfusion pressures (CPP); this phenomenon is designated as cerebral autoregulation and mainly represents the capacity of the brain's resistance vessels to dilate in response to a decrease in CPP or to constrict in response to an increase in CPP. The caliber changes of the autoregulatory vessels are mediated by myogenic, metabolic, or neurogenic mechanisms (Brownlee & Langille, 1991; Bryan et al., 1995; Busto et al., 1997). The smaller arterioles dilate proportionately more than larger arterioles at a mean arterial blood pressure below physiological levels (Ellis et al., 1979; Engelborghs et al., 2000). However, larger arterioles tend to be more responsive than smaller arterioles at normal and increased levels of arterial pressure (Engelborghs et al., 2000). The other findings associated with CBF reduction at early time points after TBI is the increased cytokine expression and production, however the role of their activity changes is not clear yet (Ahn et al., 2004). Destruction of cortical regions could effectively produce deafferentation in subcortical and

cortical target regions resulting in reduced energy requirement and metabolic rates. The blood vessel can participate in the regulation of blood flow by changing its own structure, a process known as vascular remodeling (Langfitt et al., 1977; Langille et al., 1989; Brownlee & Langille, 1991). It is characterized by changes in vessel wall thickness and organization, which allows the vasculature to cope with physiological or pathological conditions. The processes involved in vascular remodeling include cellular hypertrophy and hyperplasia, as well as enhanced protein synthesis (Golding et al., 1999; Golding, 2002). So, the reduction of regional CBF immediately after severe TBI onset could be explained by the changing histochemistry of the brain and caliber of the vessels, but the symmetric changes in CBF in immature and mature brain on day 7 demand further investigations and understanding. The most probable reason for it could be the reverse effect of changed levels of vasoactive agents due to impairment of cerebral autoregulation, or expressed production of vasoconstrictors. Clinical studies show the presence of vasospasm on days 7-9 (Hlatky et al., Robertson, 2003; Voulgaris et al., 2005) and it shows increased blood flow in the main arteries of the brain, Willis circle, whenever the microcirculation in cerebral cortex could be different and altered due to local conditions.

Being an influent factor in outcomes of TBI, cortical perfusion is not the determinant of increased vulnerability of immature to neurotrauma.

CBF must be monitored in TBI, as an important participating factor in pathophysiology, strong predictor of prognosis and a tool to prevention of primary and secondary ischemia.

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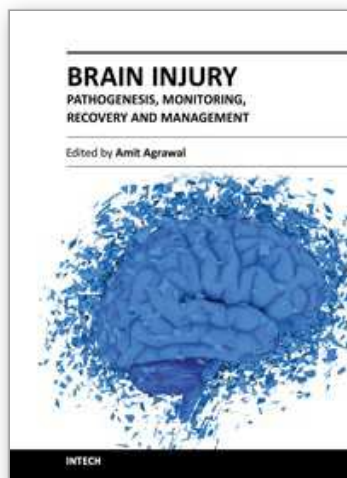
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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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