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THE CONSEQUENCES OF TRAUMATIC BRAIN INJURY ON CEREBRAL BLOOD FLOW AND AUTOREGULATION: A REVIEW

Elke M. Golding, Ph.D.[1], Claudia S. Robertson, M.D.[1] and Robert M. Bryan, Jr, Ph.D.[2]

Departments of Neurosurgery[1] and Anesthesiology[2], Baylor College of Medicine, 6560 Fannin St, Suite 944, Houston, Texas, 77030, USA

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ABSTRACT

In this decade, the brain argueably stands as one of the most exciting and challenging organs to study. Exciting in as far as that it remains an area of research vastly unknown and challenging due to the very nature of its anatomical design: the skull provides a formidable barrier and direct observations of intraparenchymal function *in vivo* are impractical. Moreover, traumatic brain injury (TBI) brings with it added complexities and nuances. The development of irreversible damage following TBI involves a plethora of biochemical events, including impairment of the cerebral vasculature, which render the brain at risk to secondary insults such as ischemia and intracranial hypertension. The present review will focus on alterations in the cerebrovasculature following TBI, and more specifically on changes in cerebral blood flow (CBF), mediators of CBF including local chemical mediators such as K^+, pH and adenosine, endothelial mediators such as nitric oxide and neurogenic mediators such as catecholamines, as well as pressure autoregulation. It is emphasized that further research into these mechanisms may help attenuate the prevalence of secondary insults and therefore improve outcome following TBI.

1. Epidemiology of Traumatic Brain Injury

Traumatic brain injury (TBI) is currently the leading killer and cause of disability in children and young adults under 44 years of age (1, 2). In the United States, the incidence of TBI has been estimated to be 2 million cases per year (3). Of these patients, approximately 52,000 will die and 80,000 will sustain some loss of function (4). A recent updated report by Sosin and colleagues (5) has established that firearms now account for more TBI-associated deaths (44%) than do motor vehicle accidents (34%) and falls (9%).

The severity of injury is categorized according to a patient's Glasgow Coma Score (GCS). This scale, ranging from 3 to 15 points, was originally developed in order to standardize assessment of impaired consciousness. Mild TBI is defined as a GCS of 13 or greater, moderate TBI between 9 and 12, and severe TBI between 3 and 9. Epidemiology studies have shown that 80% of head injury victims suffer from mild TBI, 10% from moderate and 10% from severe TBI (6, 7). The fact that the most common insult is of a mild severity suggests that a large portion of victims will survive. However, the subsequent financial burden to the community for treatment and rehabilitation of these patients has been estimated at an annual figure of four billion dollars (8). The astonishing reality of these statistics is compounded in the light of knowing that at the present time, clinical treatment following TBI is quite limited. The focus of medical management is reducing the risk of secondary complications and includes ventilation, muscle relaxation, mannitol to reduce brain swelling and narcotic analgesics for sedation and pain relief (9). While research into head trauma has reached unprecedented proportions over the past ten years, there are currently no proven treatments available to prevent the destructive biochemical processes that may be occurring following head trauma.

2. Experimental Models of TBI

The pathophysiology resulting from human head injury is extremely variable and depends on factors such as the age of the patient, preexisting conditions (for example alcohol consumption, diabetes, heart disease), the severity and locus of injury and the specific type of CNS injury (contusion, hemorrhage, ischemia). As such, no single experimental model

can possibly simulate the pathophysiological heterogeneity as seen in the clinical setting. Nevertheless, as scientists we have the opportunity to assess each facet of the sequelae following TBI using animal models with the ultimate objective of extrapolating the findings to the human condition. There are presently six main experimental head injury models available. The authors can recommend two excellent reviews that present detailed synopses on each of these models (10, 11). Briefly, we will describe the two most frequently used TBI models: the ***fluid percussion (FP) model*** and rigid percussion which is more commonly referred to as the *controlled cortical impact (CCI) model*. These are both models of compression concussion produced by distortion of the exposed dura by a brief pulse of fluid or a piston, respectively, while the head is held rigid. Such injuries are distinguished from acceleration concussion which is produced by a blow to the freely moving head (12). In the *FP model*, a small volume of saline is injected into the subdural space. This model of injury replicates many aspects of human TBI including development of cerebral edema (13), CBF alterations (14), diffuse axonal injury, (15) and behavioral suppression (16). However, the FPI model produces histological changes different from that seen in severe clinical TBI, cortical contusion is not a prominent feature and the biomechanics of the injury is difficult to quantify. In the *CCI model*, a piston impacts the exposed dura of the brain. This model produces neurological and cognitive deficits (17), disruption of the BBB (18), cortical contusions and axonal injury (19) which are also features of severe human TBI. While each of these injury models has its limitations, research employing both models is required in order to complete the entire picture of clinical TBI pathophysiology. In the present review, data will therefore be specified according to whether the FPI or CCI model was employed because, as will be seen, in some cases the findings are disparate.

3. The Nature and Pathophysiology of TBI

The pathophysiology of traumatic brain injury can be divided into two separate stages, namely the primary and secondary injury. The *primary injury* occurs at the moment of impact and includes contusions and lacerations of the brain, fractures of the skull, and intracranial hemorrhage. Due to the time at which it occurs, the primary injury cannot be

prevented by the clinician. *Secondary injury*, on the other hand, is due to the subsequent complications (raised intracranial pressure, ischemia, swelling, and infection) that are presented clinically over a period of hours to days after the initial insult (20). Fortunately, the delayed nature of these events provides an opportunity for therapeutic intervention and the possibility of alleviating the ensuing functional deficits.

Various factors have been implicated in the injury biochemical cascade including excitatory amino acids (21, 22, 23, 24), calcium (25, 26), magnesium (27), potassium (13, 22), sodium (13), catecholamines (28), opioid peptides (29), arachidonic acid metabolites (30, 31), oxygen free radicals (32) and cytokines (33, 34). Although there is a plethora of experimental studies examining each of these factors as well as therapeutic strategies (see 35 for review), to date no Phase III clinical trials have been clearly successful (36). One of the main problems could be the fact that most investigators have concentrated on blocking isolated factors, in the hope of finding the "magic bullet" for TBI therapy. However there is most likely a complex interplay between secondary injury factors in producing the huge cascade of events observed following the insult. Perhaps greater understanding of how these mechanisms interact and the factors that render the brain more vulnerable and susceptible to further damage, may pave the way for future preventative and therapeutic regimens.

4. Susceptibility of the Injured Brain to Secondary Insults

The injured brain is highly susceptible to secondary insults as shown both clinically (37) and experimentally (38, 39, 40). Moreover, the development and extent of secondary injury to the brain accounts for a major component of the morbidity and mortality of TBI (41). Immediately following brain trauma, specific cells are rendered dysfunctional although not mechanically destroyed. If the subsequent milieu is favorable, many of these cells may have the opportunity for repair. However, as is too often the case, episodes of hypoxia or ischemia may facilitate the brain into a spiralling cascade of irreversible damage. The present review will focus on the perturbations of the cerebral circulation accompanying TBI, including changes in cerebral blood flow (CBF), cerebrovascular reactivity and cerebral autoregulation, with respect to increasing the susceptibility of the brain to secondary insults.

5. General Concepts of Cerebral Blood Flow

5.1. Relationship between pressure and flow

Maintenance of CBF is imperative as exemplified in the fact that complete stoppage of blood flow to the brain for only 4-5 minutes results in death of brain tissue. The control of blood flow in the brain is accomplished by alterations in cerebral perfusion pressure (CPP) and cerebral vascular resistance. CBF is proportional to CPP divided by the vascular resistance (R) as shown in Equation 1:

$$CBF \cong CPP/R. \quad (1)$$

CPP is defined as the pressure gradient in the brain; that is the difference between the pressure in the incoming arteries (supplying blood to the brain) and the pressure in the outgoing veins (draining blood from the brain) as shown in Equation 2:

$$CPP = \text{mean arterial pressure} - \text{venous pressure}. \quad (2)$$

Since venous pressure is essentially equal to the intracranial pressure (ICP), CPP can be expressed in terms of ICP and the mean arterial pressure (MABP):

$$CPP = MABP - ICP. \quad (3)$$

CBF is largely independent of CPP within the range of MABP between 50 and 150 mmHg, due to the phenomenon known as cerebral autoregulation. This will be discussed in further detail later.

Vascular resistance essentially reflects changes in diameter of the vasculature: vasoconstriction causes an increase in resistance, while vasodilation causes a decrease in vascular resistance. Under physiological conditions, CBF is mainly regulated by changes in the resistance of cerebral arteries. Unlike in many peripheral tissues where the microvasculature plays a dominant role, the larger cerebral arteries, such as the middle cerebral artery, provide approximately 45-50% of the overall resistance of the cerebral

circulation (42). A number of factors contribute towards changes in cerebrovascular resistance including local chemical factors, endothelial factors and neurogenic factors. These will be briefly discussed below.

5.2. Local Chemical Mediators of CBF

Changes in vascular resistance can be mediated by chemical factors, released by the brain parenchyma, which act locally on cerebral vascular smooth muscle (VSM) cells, to produce either constriction or dilation of the cerebral vessels. A variety of chemical factors have been proposed including K^+, Ca^{2+}, H^+, osmolarity, and adenosine (see 43 for review). The effect of each of these factors on the cerebrovasculature is shown schematically in Figure 1.

5.3. Endothelial Mediators of CBF

The endothelium releases several vasoconstricting and vasodilating factors, which then act on the VSM, thereby contributing to maintenance of cerebral blood flow (44 for review). Vasoconstricting factors include endothelin and thromboxane A_2. Vasodilating factors include nitric oxide (NO), prostacyclin (PGI_2), and the endothelium-derived hyperpolarizing factor (EDHF). These endothelial factors can be released by different stimuli such as neurotransmitters (including acetylcholine (ACh) and norepinephrine (NE)), autacoids (such as bradykinin (BK)) and shear stress.

5.4. Neurogenic Mediators of CBF

Cerebral arteries are innervated by several neurogenic systems including the (a) sympathetic-noradrenergic system mediated by norepinephrine (NE) and neuropeptide Y (NPY), (b) parasympathetic cholinergic system mediated by ACh and vasoactive intestinal polypeptide (VIP), (c) central aminergic system mediated by NE and serotonin (5-HT), and (d) trigeminal system mediated by substance P (SP) and calcitonin gene-related peptide (CGRP). These neurogenic mediators are presented in Table 1, along with their vasoactive action on the cerebrovasculature. While neurogenic control of CBF remains under intense investigation, its functional significance is still unclear.

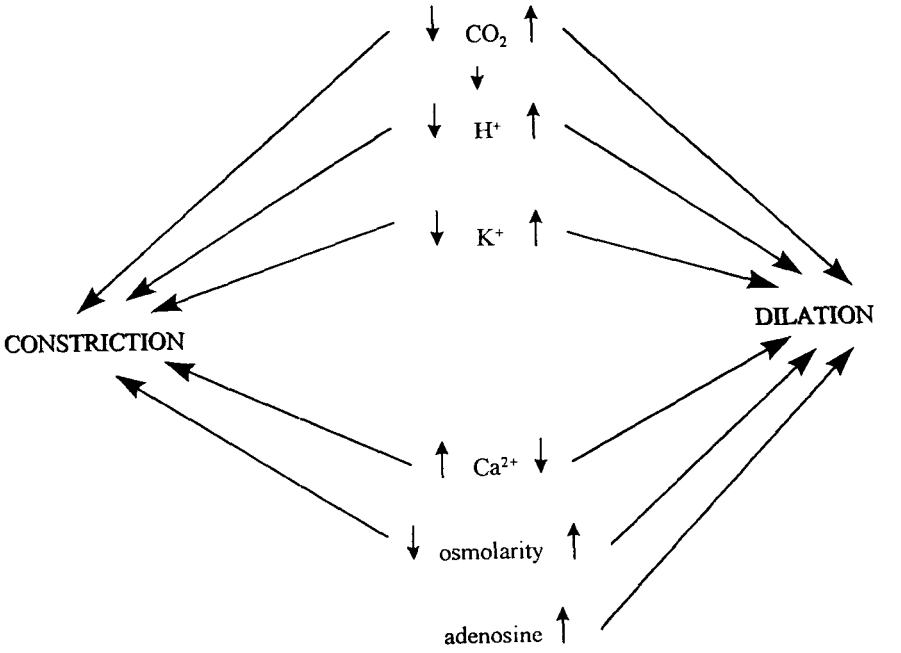

Figure 1: Summary of the effect of local chemical mediators on the cerebrovasculature (adapted from 152).

TABLE 1: The innervation of cerebral vessels by the four systems, the selective mediators and their effect on the vasculature (adapted from 152).

Neurogenic System	Mediators	Vasoactivity
sympathetic-noradrenergic	NE and NPY	constriction
parasympathetic cholinergic	ACh and VIP	dilation
central aminergic	NE and 5-HT	constriction
trigeminal	SP and CGRP	dilation

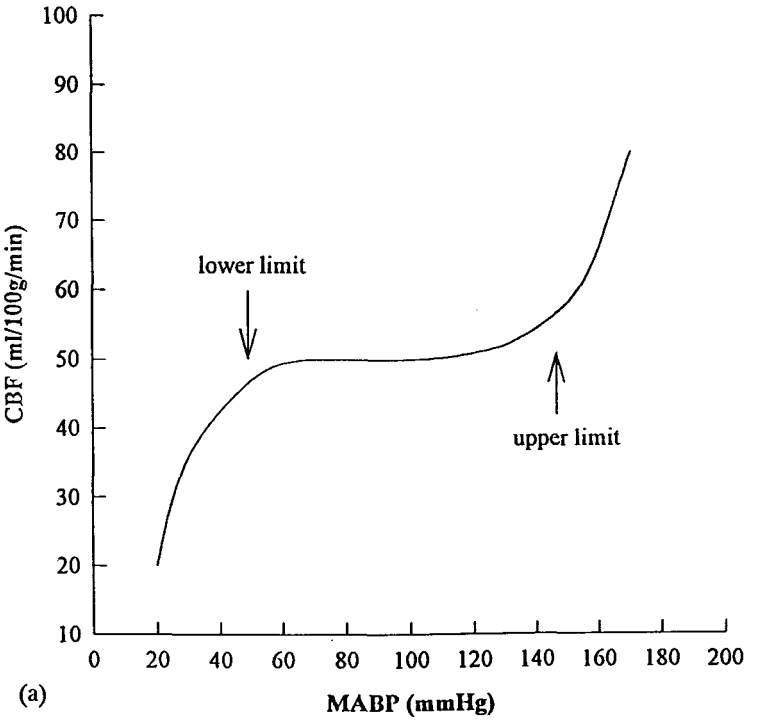

Figure 2 (a) Typical steady state values of CBF as a function of mean arterial blood pressure (MABP) during hypotension and hypertension, demonstrating the lower and upper limits of autoregulation. (b) Dynamic autoregulatory response in the rat showing changes in laser-Doppler flow (LDF) with MABP during hypobaric hypotension (data from our laboratory). Hypotension was induced by applying lower body negative pressure, thereby causing venous pooling in the lower body portions. Note that at MABPs above the lower limit of autoregulation, the pressure-flow relationship is initially passive, afterwhich the LDF returns to baseline over the course of 1 minute, thereby illustrating the autoregulatory response. Also note the transient overshoot in LDF when MABP is restored. Below the lower of autoregulation (30 mmHg), LDF remains passively decreased with a decline in MABP.

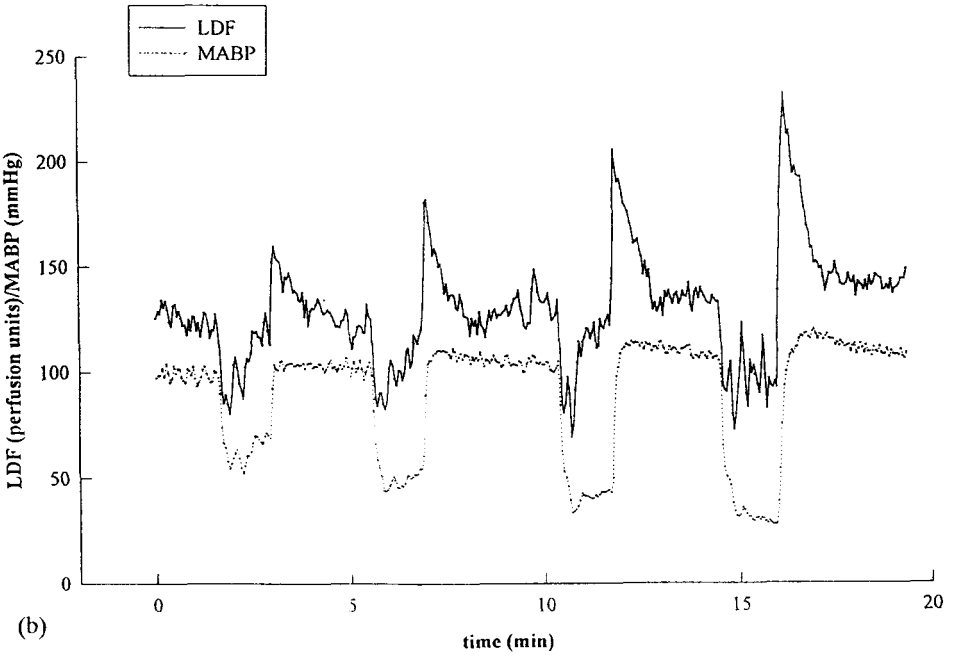

Figure 2 continued.

5.5. *The Concept of Cerebral Autoregulation*

Cerebral autoregulation (or more specifically *pressure autoregulation*) is defined as the capacity of the brain to maintain a constant CBF in the face of variations in systemic arterial pressure. This homeostatic mechanism is effective between systemic arterial pressures of approximately 50 and 150 mmHg, known as the lower and upper limits of autoregulation, respectively (45). Figures 2 (a) and (b) illustrate the concept of autoregulation. When CPP is reduced, cerebral vessels will compensate by dilating until a maximum limit is reached. Beyond this point, referred to as the lower limit of autoregulation, CBF will decrease passively in response to further reductions in CPP. Similarly, a rise in CPP will cause cerebral vessels to constrict until a limit is reached above which further increases in CPP cause an increase in CBF (upper limit of autoregulation). These limits can be modulated by sympathetic activity (46), the vascular renin-angiotensin system (47) and changes in carbon dioxide tension (48).

A number of factors have been proposed to account for the phenomenon of autoregulation. These include those factors that mediate changes in vascular resistance as mentioned above. However, the two most favored candidates are the local chemical factors (*metabolic mechanism*) and the *myogenic mechanism*, which has not been discussed previously in this review.

5.5.1. Local Chemical (Metabolic) Mechanism of Cerebral Autoregulation

According to this mechanism, metabolic factors act on the vasculature to produce dilations or constrictions in response to changes in CPP. A reduction in CPP causes CBF to decline, causing a shortage of O_2 and thereby allowing the build-up of metabolic waste products (vasoactive compounds). These products then act on the VSM to cause vasodilation and thus increase flow. The proposed factors have already been described (see above).

5.5.2. Myogenic Mechanism of Cerebral Autoregulation

The myogenic response is defined as the contraction of a blood vessel to increasing pressure or conversely, the relaxation of the vessel to decreasing pressure (49). The concept of the myogenic mechanism of autoregulation is based on the intrinsic property of vascular smooth muscle to contract in response to stretch. This has been demonstrated in isolated pressurized cerebral arteries which are free of any metabolic, endothelial (by denuding the vessel), or neural factors (by administering tetrodotoxin) (50, 51, 52, 53). Figure 3 illustrates the dynamic myogenic response of an isolated penetrating arteriole. While the cellular mechanisms mediating the myogenic response of blood vessels are still being elucidated, several hypotheses have been suggested including (i) activation of ion channels such as stretch activated channels, (ii) modulation of biochemical cell-signaling pathways within VSM, and (iii) length-dependent changes in contractile protein function (see 54 for review).

6. Cerebral Blood Flow Perturbations after TBI

Numerous clinical studies have documented transient decreases in CBF acutely following severe TBI (55, 56) which return to normal in patients that recover. In contrast, CBF

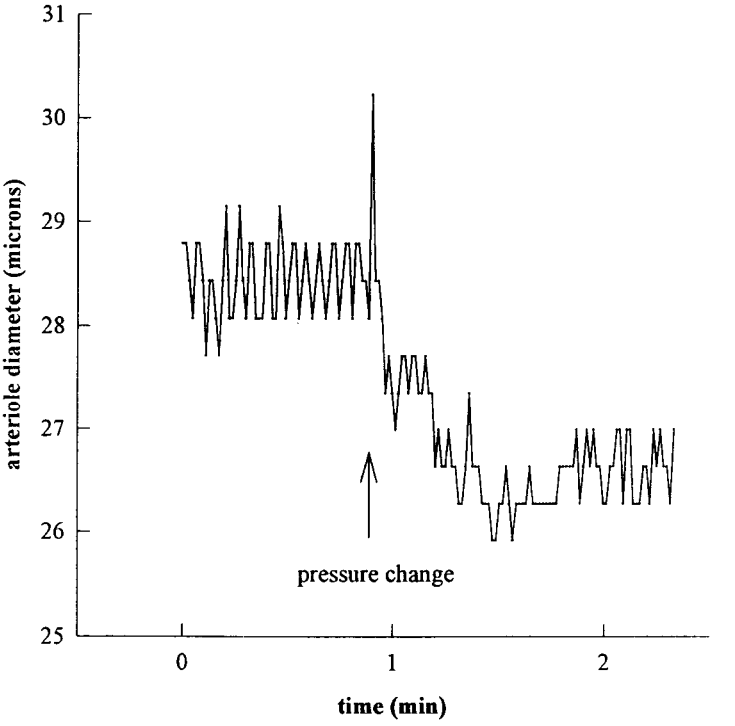

Figure 3: A real-time tracing showing the changes in diameter of an isolated penetrating rat arteriole when pressure was changed from 20 to 40 mmHg, thereby illustrating the dynamic myogenic response (data from our laboratory). The penetrating arteriole was mounted between two micropipettes on an arteriograph and changes in diameter of the vessel were projected on a monitor using a camera. Note the immediate passive dilation of the vessel when the pressure was increased to 40 mmHg, followed by the constriction of the vessel below the baseline, which represents the active myogenic response.

remains depressed in terminal patients. Interestingly, most studies have found that a decreased CBF is more common in adults than in children and adolescents (56, 57, 58). Moreover, a reduced CBF in patients has been associated with an unfavorable neurological outcome (59). In addition, Kelly and associates have recently reported that a phasic elevation in CBF acutely after head injury is a requirement for achieving functional recovery (60).

In experimental animals, a transient increase in CBF has been found immediately following TBI (61, 62, 63, 64). Global decreases in CBF have then been reported 15 mins following moderate FPI (65, 66, 62, 67) which recover to near control values by 2 h postinjury in all regions with the exception of the injured parietal cortex. In contrast, both moderate (5 m/s, 2 mm deformation) (63) and severe levels of CCI (68) have demonstrated ischemic levels of CBF on the ipsilateral side of injury. Following mild CCI, CBF is reduced to approximately 50% within the injured parietal cortex, however it does not reach ischemic levels (Giri et al, submitted for publication). This is illustrated in Figure 4 which presents an autoradiographic image reflecting blood flow in a coronal section of the rat brain at 1 hour following mild CCI. Unlike in FPI, CBF reaches ischemic levels at the impact site after moderate and severe levels of CCI. This discrepancy between the two models maybe attributed to the differences in transmitted force between these two models of TBI, suggesting that the biomechanical loading with CCI is more localized than with FPI, thereby producing focal ischemia. In other words, the solid piston applied in CCI focuses the injury at the contacted brain region. In contrast, the fluid pulse applied in FPI, although directed at a focal site, can dissipate its energy throughout the brain by nature of its physical properties. While no direct correlation studies have been reported between CBF and neurological outcome following experimental TBI, the degree of decline in CBF has been shown to be correlated with the severity of CCI injury (69).

Since both MABP and ICP are components of CPP (see Equation 3), perturbations of each of these components need to be addressed when considering changes in CBF in a pathophysiological condition.

6.1. Mean Arterial Blood Pressure Perturbations after TBI

Spontaneous episodes of hypertension are common in head injured patients and have been attributed to a massive release of catecholamines (70, 71). Other clinicians have also reported periods of systemic hypotension (72). Hypotension has been estimated to be present in 15-20% of patients following TBI (73). In addition to the clinical observations, alterations in MABP have been described in experimental models of injury. After severe CCI, an immediate transient hypertensive peak followed by sustained hypotension for the duration of the monitoring period has been observed (19, 69). A typical MABP profile

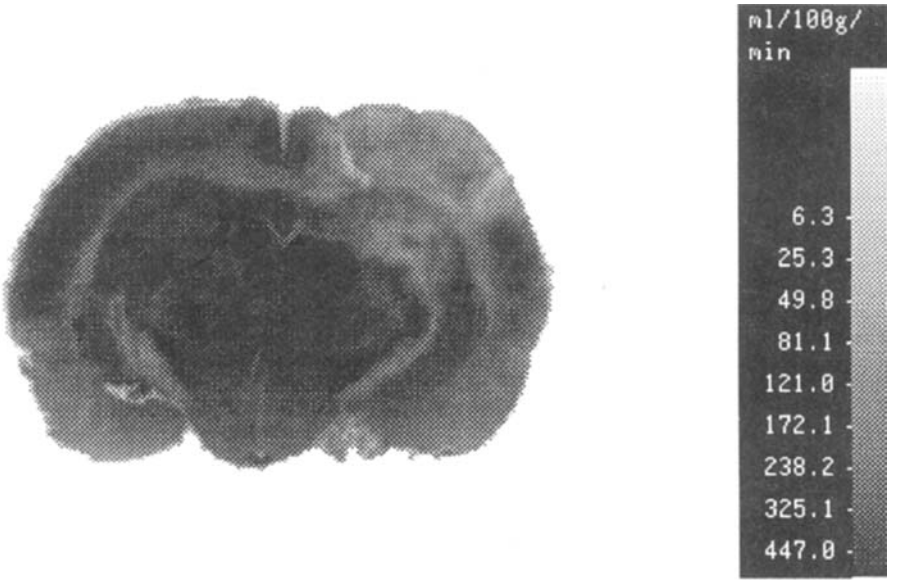

Figure 4: Typical autoradiograph at 1 hour following mild CCI (3 m/s, 2 mm deformation) in the rat, showing a marked reduction in CBF at the impact site (lighter shading), while CBF was maintained at preinjury levels in the remainder of the brain (darker shading). This data is from our laboratory.

observed at the time of severe CCI is shown in Figure 5. Such MABP responses have also been noted in FPI (74, 75, 76). In particular, the hypertensive episode has been attributed to free oxygen radicals associated with prostaglandin synthesis (77, 78).

The extent to which MABP perturbations affect CBF depends on several factors including changes in ICP, whether the change in CPP is beyond the limits of autoregulation, and whether or not autoregulation is intact. Assuming that ICP is unchanged, a decrease in MABP will cause a decrease in CPP (see Equation 3). In cases where these changes in CPP are within the limits of autoregulation (and autoregulation is intact), CBF will be maintained due to the compensatory changes in vascular resistance. Sustained levels of hypotension (CPP below the lower limit of autoregulation) will, however, result in significant decreases in CBF.

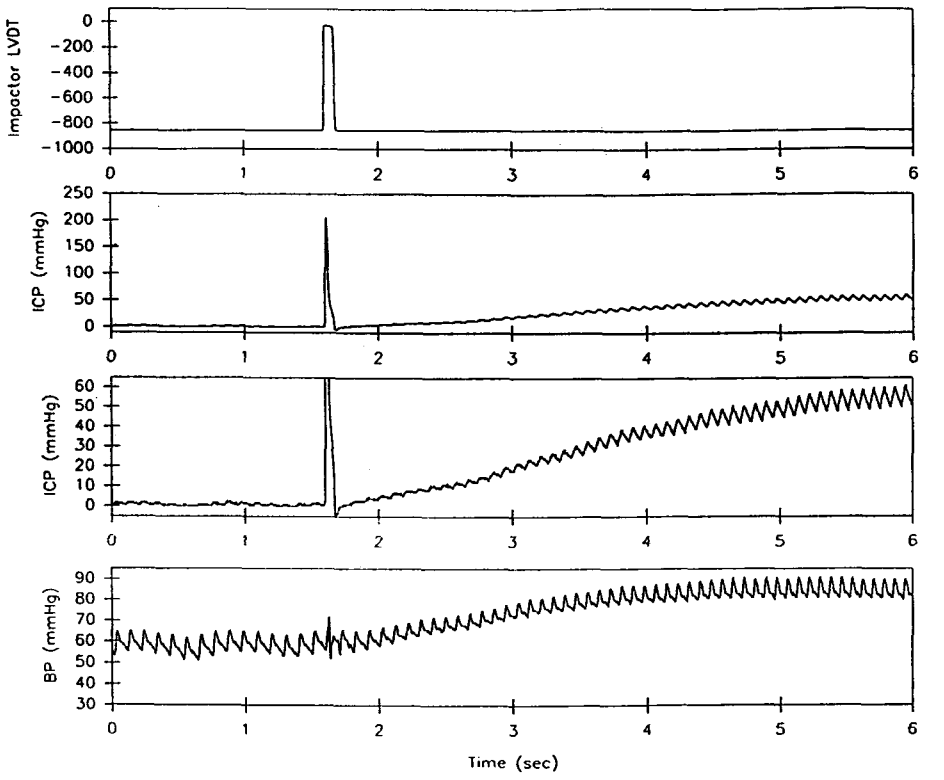

Figure 5: Changes in ICP and MABP following a severe CCI (5.7 m/s, 3 mm deformation, 132 ms duration). The top tracing is the output from the LVDT (linear variable differential transducer) which is connected to the CCI device. The change in voltage represents the changes in position of the impactor piston (data from our laboratory).

6.2. Intracranial Pressure Perturbations after TBI

Head injury to the brain is commonly associated with increases in ICP and develops in approximately 70% of patients with severe trauma (79). Increases in ICP may be caused by increased blood volume (either extravascular or intravascular), increased CSF volume or increases in tissue volume that result from vasogenic edema or space-occupying lesions such as intracerebral hematomas. Experimental studies following severe CCI have shown that the head insult is associated with a peak ICP (182±18 mmHg compared to 9.3±0.14 mmHg preinjury). This is illustrated in Figure 5. After returning to preinjury levels, ICP

then gradually increases, becoming significantly elevated from shams over a period of 5 hrs postinjury (69).

Similar to the effect of MABP on CBF, the extent to which ICP perturbations will affect CBF depends on MABP changes, whether the change in CPP is beyond the limits of autoregulation, and whether or not autoregulation is intact. Assuming that MABP is normal, an increase in ICP will cause CPP to decrease (see Equation 3). In cases where the ICP perturbations are minimal, thereby resulting in a CPP within the limits of autoregulation (and autoregulation is intact), CBF will be maintained due to the compensatory changes in vascular resistance. Significant increases in ICP, thereby causing CPP to fall below the lower limit of autoregulation, will result in significant decreases in CBF.

6.3. Changes in Local Chemical Mediators of CBF after TBI

6.3.1. K^+ Perturbations after TBI

Although no clinical data is available, CCI has been shown to produce a massive release of K^+ into the extracellular space associated with a transient membrane depolarization (80). These observed changes resemble those seen during cortical spreading depression (81). It is possible that these alterations in potassium are solely due to neuronal depolarization. However, the ionic changes have also been attributed to the activation of ion channels as a result of the release of excitatory amino acids (EAAs). Both glutamate and aspartate increases have been reported after weight drop injury (23), CCI (24) and FPI (21, 22). EAAs can open channels permeable to sodium, potassium and calcium (82). In addition to K^+ changes, impaired K_{ATP} and K_{Ca} channel function has also been reported following FPI (83, 84).

6.3.2. pH Perturbations after TBI

Measurements of cerebral pH are difficult to determine *in vivo*. Intracellular pH can be measured noninvasively by ^{31}P NMR although it does have accuracy limitations (85). Nevertheless, transient increases in intracellular acidosis have been reported immediately following moderate and high levels of FPI, which recover to baseline levels after 1 hour (86). Although lactate measurements have been made both clinically (87) and

experimentally (88, 23), it is a misconception to assume that an increase in lactate reflects acidosis ("lactic acidosis"). Paschen and colleagues (89) have addressed this issue in detail and emphasized that the observed dissociation between pH and lactate is attributed to the fact that both parameters are regulated independently.

The response of the vasculature to changes in pCO_2 is mediated indirectly through changes in extracellular pH in the immediate vicinity of the VSM cells and in the cerebrospinal fluid (90). Clinically, CO_2 reactivity has been shown to be slightly depressed in the acute period after TBI, with restoration to normal after 24 hours (91, 92). Furthermore, Enevoldsen and Jensen (92) reported that preserved autoregulation associated with impaired CO_2 response indicated very severe brain damage, whereas impaired autoregulation associated with preserved CO_2 response suggested moderate or severe brain damage during recovery. Complete absence of CO_2 reactivity carries a poor prognosis and is usually a terminal event.

In animal studies, it has been demonstrated that mild TBI impairs and severe TBI abolishes the CBF response to increased CO_2 in the acute stages following injury (93, 94, 77). Figures 6 (a) and (b) illustrate the impairment of increased CBF to hypercapnia at 1 hour following mild CCI. Interestingly, Wei and colleagues demonstrated that the prevention of the rise in blood pressure following severe head injury, allowed vessels to maintain their responsiveness to pCO_2 (77). Cerebrovascular responsiveness to hypocapnia has also been shown to be restored by oxygen radical scavengers (95). Only one laboratory has yet undertaken chronic animal studies, and these investigators observed an attenuation in CO_2 reactivity even at 24 hours following severe CCI (96).

6.3.3. Adenosine Perturbations after TBI

Few studies have addressed adenosine perturbations following head injury. Nevertheless, increased levels of interstitial adenosine have been reported both clinically (97) and experimentally (23, 98). Moreover, administration of an adenosine agonist prior to FPI has been reported to attenuate metabolic disturbances and improve neurologic outcome (99). Future studies are required in order to determine whether adenosine perturbations play a significant role in mediating the CBF and pressure autoregulation changes seen following TBI.

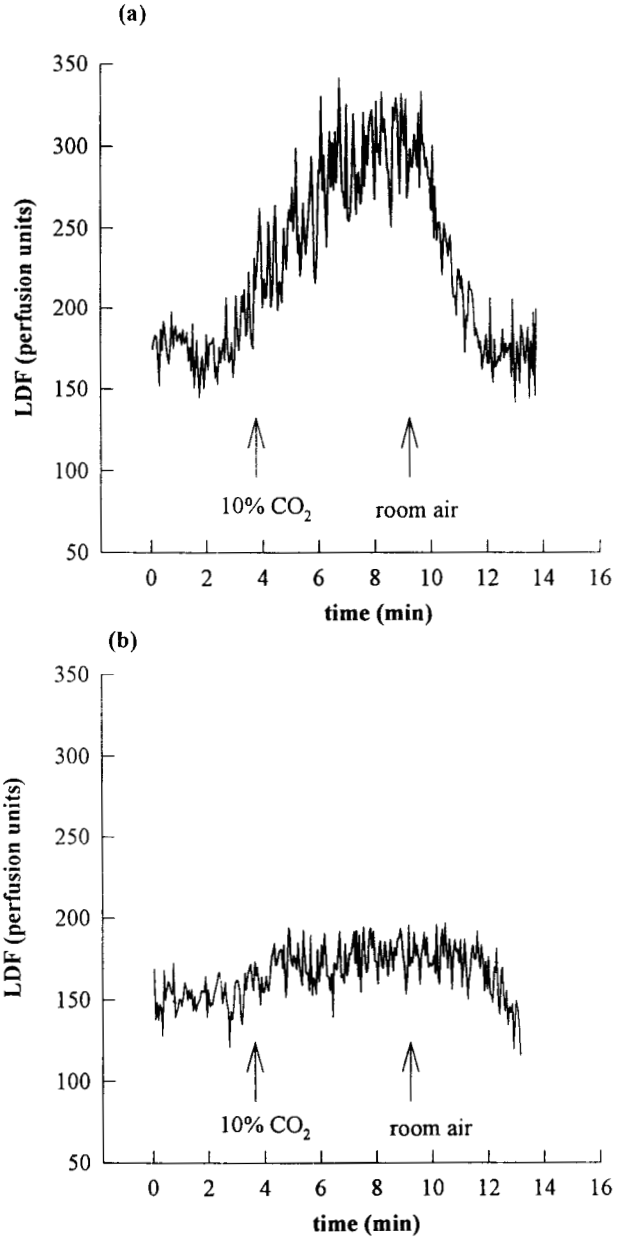

Figure 6: Response of LDF to hypercapnia (pCO_2= 63 mmHg) following (a) sham injury and (b) 1 hour following mild CCI in the rat. Note that in the sham animal, LDF increased by 78% LDF while in the CCI animal, LDF increased only by 20% (data from our laboratory).

6.4. Changes in Endothelial Mediators after TBI

Wei and colleagues have shown that morphological lesions in the endothelium accompany the cerebrovascular alterations seen following TBI, in the absence of overt damage to the VSM (77, 100). Moreover, this same group have demonstrated impaired endothelium-dependent function following FPI. Using the cranial window technique, both vasoconstriction in response to topically applied serotonin (101) and vasodilation in response to acetylcholine was reduced or abolished within the first 4 hours following FPI (102). Interestingly, following application of the free radical scavengers, superoxide dismutase and catalase, the normal responses to both serotonin and acetycholine were restored.

Two studies to date have been undertaken to examine the endothelial function of cerebral vessels following TBI *in vitro*. Bukoski and colleagues found that moderate FPI had no effect on the endothelium-dependent relaxation to acetylcholine or the contraction to serotonin (103). However, our laboratory has recently shown that after 24 hrs, severe CCI enhanced the sensitivity to 2MeSATP, a selective agonist for the $P2Y_1$ purinoceptors, while significantly reducing the constriction to the nitric oxide synthase inhibitor, L-NAME (104). These studies emphasize the relevance of studying different receptor systems and the importance of refraining from making generalizations regarding endothelium function following the study of selected agonists.

Techniques to quantitatively assess cerebral nitric oxide (NO) levels are not yet optimal, and so clinicians have only indirect methods to estimate NO production in the plasma (105) and CSF (106). Experimental studies are few in number, however increased levels of interstitial nitrates and nitrites have been observed maximally 20 min following TBI (107). Furthermore, Cobbs and associates have reported that FPI results in a marked induction of endothelial nitric oxide synthase (eNOS) (108). In addition, treatment with L-arginine, the substrate for NO synthase, has been shown to prevent the posttraumatic hypoperfusion (109). The beneficial effects of NO may be multifactorial. First, NO acts as a vasodilator, thereby having the potential to reverse the hypoperfusion seen after TBI. Second, NO may inactivate free radicals which contribute to the pathophysiology of TBI. Indeed, in this same study, administration of a free radical scavenger did restore CBF to baseline after a brief period of hypoperfusion. Another possibility is that other vasoactive

products of arginine metabolism such as polyamines or agmatine may be contributing to the beneficial effects of L-arginine following TBI (110). While the results of these recent L-arginine experiments appear very promising, it should be mentioned that the evidence to date suggests that NO may be either beneficial or detrimental to the brain depending on the cellular source of NO (see 111 for review). Not only can NO act as a vasodilator, but it can also trigger programmed cell death by reacting with superoxide anion to form peroxynitrite (112). Therefore, there may be a particular therapeutic window following TBI in which the effects of NO are beneficial, afterwhich detrimental effects may emerge.

6.5. Changes in Neurogenic Mediators after TBI

No studies to date have addressed the levels of VIP, substance P or CGRP following TBI. Rather, the majority of reports are concerning catecholamines and serotonin. These factors have already been addressed with respect to endothelial mediators after TBI, but also deserve some mention here. Significantly elevated catecholamine levels have been observed following human TBI (113, 70) and have been correlated to neurologic outcome (114, 115). Experimental studies have corroborated these clinical findings, demonstrating that hypothalmic levels of norepinephrine and dopamine remain significantly elevated up to 1 week following FPI (116). Activation of catecholamines have also been implicated in the cerebrovascular and metabolic changes during cortical freeze lesions (117). Catecholamines may contribute to the pathophysiology following TBI by altering cerebral oxidative metabolism (118), by effecting pressure autoregulation (46), by modification of CBF (119, 120) or by modulation of EAA neurotransmitters (121, 122). In addition to increased catecholamine concentrations following TBI, elevated levels of CSF serotonin have been reported clinically (123, 124). Further studies are required in order to determine whether they play a major role in contributing towards cerebrovasculature alterations after TBI.

6.6. Cerebral Pressure Autoregulation after TBI

In the clinical setting, impairment or absence of the autoregulatory response is often reported in patients with severe head injury (125, 126, 92, 127, 128). Impaired autoregulation has even been reported following mild levels of TBI (129), but clearly this

study demonstrates that a heterogeneous population exists where some patients autoregulate (72%) and others do not (28%). Disturbed autoregulation has been shown to be correlated to an unfavorable outcome (130). Although a similar association has not been found following mild TBI clinical studies (129), this may have resulted from small sample size.

Loss of autoregulation has also been reported in fluid percussion injury (94, 131, 132). There is evidence suggesting that the lower shoulder of the autoregulatory curve is shifted to the right following TBI (94). If this is the case, this would indicate that a higher CPP is required for a TBI patient to maintain normal CBF and that these patients would not be able to tolerate hypotension in contrast to an uninjured patient, thereby making them more susceptible to episodes of secondary ischemia or hypoxia.

Interestingly, several investigators have observed preserved autoregulation with a concomitant defective CO_2 reactivity both in animals (133, 134) as well as patients suffering from acute severe head injury (135, 136, 92). These *apparently* contradictory observations have given rise to the suspicion that the preserved autoregulation seen in severely injured brain tissue is a "false autoregulation" which is succeeded by a period of impaired autoregulation during clinical improvement. This phenomenon has been ascribed to interstitial edema, however a more likely explanation perhaps is that CO_2 and pressure autoregulation are mediated by different physiological mechanisms. To support this notion, there is evidence suggesting that while NO mediates CBF regulation during hypercapnia (137), it does not play a role in autoregulation during hypotension (138, 139, 140).

The underlying mechanisms affecting abnormal cerebral autoregulation are not yet fully understood (92). Endothelial dysfunction (141), vasospasm (142), and release of free radicals (32) have all been implicated (130). It has also been suggested that loss of pressure autoregulation may be related to damage of brainstem vasoregulatory centers (135). The sudden rise in arterial blood pressure often observed following TBI can break through cerebrovascular autoregulation and even damage the arteriolar endothelium (77). However, impaired pressure autoregulation has been observed in the absence of transient hypertension at the time of injury (131).

While the prevailing concept is that pressure autoregulation is absent or greatly impaired following TBI, the reality may be towards a mixed population. Both clinical

(129) and experimental studies (94) have too often ignored this fact and have instead concentrated on the subset of subjects with impaired autoregulatory capacity. This emphasizes the fact that the status of autoregulation cannot be presumed and the importance of routinely testing autoregulatory responses by the bedside.

6.6.1. Myogenic Perturbations after TBI

Reports of the myogenic capacity of cerebral vessels in the literature under pathophysiological conditions are extremely limited. Alterations in myogenic tone and/or response have been shown in hypertensive rats (50), under conditions of high glucose concentration (143) and following focal ischemia (144). Our laboratory has recently reported that the myogenic response of middle cerebral arteries isolated from the brain 24 hrs after severe CCI is compromized (Golding et al, J. Neurotrauma, in press). Such experiments are impractical to carry out *in vivo* due to the complicating factors of blood flow and other metabolites. The abovementioned studies utilized an *in vitro* method whereby cerebral vessels are cannulated and pressurized (145). This technique can be employed as it allows one to examine the intrinsic mechanisms of cerebral vessels without the complications of flow, influence of the parenchyma and other possible stimuli of the vasculature.

7. Ramifications of Cerebral Autoregulatory Perturbations following TBI

When cerebral autoregulation is disturbed following TBI, the brain may be uniquely vulnerable to the effects of secondary insults and less capable of maintaining an adequate CBF and a correct metabolic balance. An abolition or shift of the autoregulation curve to the right after TBI would indicate that even mild levels of hypotension, that normally one could contend with, may cause critical reductions in CBF in head injured patients. Maintenance of adequate perfusion is imperative: a decrease in CPP may induce brain ischemia (146, 147) while an increase in CPP can provoke brain edema in injured tissue (148). Obviously, clinical treatment must find a delicate balance between the two extremes.

Knowledge of the status of autoregulation will be important in deciding on the optimal cerebral perfusion pressure management, which is a subject of ongoing controversy (149,

150). Moreover, the status of autoregulation will determine the effect of certain treatment modalities used to control ICP. For instance, it has been shown that the effect of mannitol (in treating cerebral edema) on ICP is more pronounced when autoregulation is intact (151). Information on autoregulatory capacity would also be vital if surgical intervention is required, at a time when fluctuations in MABP are more likely.

8. Concluding Remarks

The present review has highlighted the fundamental role of cerebrovascular function in contributing towards secondary insults following TBI. It is necessary to emphasize the importance of recognizing autoregulatory impairment in the head-injured patient in order to prevent such secondary events from occurring. Further experimental studies will perhaps shed more light on the biochemical mechanisms contributing to perturbations of CBF, autoregulation and metabolism following TBI. Future strategies to prevent secondary ischemia in these patients may include identifying patients with impaired autoregulation, optimizing cerebral perfusion, and avoiding extremes of CPP. Such an approach will hopefully contribute to dramatically reducing the mortality and improving outcome following TBI.

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REFERENCES

1. Selecki B.R., Simpson D.A., Vanderfield G.K., Ring I., Sewell M.K. The epidemiology of head injury in New South Wales. Proceedings of the 5th Annual Brain Impairment Conference, Lidcombe Hospital, Sydney 1980; (Abstr.)

2. Frankowski R.F., Annegers J.F.and Whitman S. Epidemiology and descriptive studies Pt 1: the descriptive epidemiology of head trauma in the United States. In Central Nervous System Trauma Status Report 1985. D.P. Becker and J.T. Povlishock, National Institute of Health, Bethesda. 33-43, 1985.

3. Waxweiler R.J., Thurman D., Sniezek J., Sosin D., O'Neil J. Monitoring the impact of traumatic brain injury: a review and update. J Neurotrauma 1995; 12: 509-516.

4. Kraus J.F. Epidemiology of head injury. In Head Injury. P.R. Cooper, Williams & Wilkins, Baltimore. 1-25, 1993.

5. Sosin D.M., Sniezik J.E., Waxweiler R.J. Trends in death associated with traumatic brain injury, 1979 through 1992. JAMA 1995; 273: 1778-1780.

6. Kraus J.F., Black M.A., Hessol N., Ley P., Rokaw W., Sullivan C., Bowers S., Knowlton S., Marshall L. The incidence of acute brain injury and serious impairment in a defined population. Am J Epidemiol 1984; 119: 186-201.

7. Kraus J.F. Nourjah P. The epidemiology of mild, uncomplicated brain injury. J Trauma 1988; 28: 1637-1643.

8. Max W., MacKenzie E.J., Rice D.P. Head injuries: costs and consequences. J Head Trauma Rehab. 1991; 6: 76-91.

9. Fearnside M.R., Cook R.J., McDougall P., Lewis W.A. The Westmead head injury project. Physical and social outcomes following severe head injury. Br J Neurosurg. 1993; 7: 643-650.

10. Gennarelli T.A. Animate models of human head injury. J Neurotrauma 1994; 11: 357-368.

11. Povlishock J.T., Hayes R.L., Michel M.E., McIntosh T.K. Workshop on animal models of traumatic brain injury. J Neurotrauma 1994; 11: 723-732.

12. Marmarou A., Foda M.A.A., van den Brink W., Campbell J., Kita H., Demetriadou K. A new model of diffuse brain injury in rats Part 1: Pathophysiology and biomechanics. J Neurosurg. 1994; 80: 291-300.

13. Soares H.D., Thomas M., Cloherty K., McIntosh T.K. Development of prolonged focal cerebral edema and regional cation changes following experimental brain injury in the rat. J Neurochem. 1992; 58: 1845-1852.

14. Yamakami I. McIntosh T.K. Effects of traumatic brain injury on regional cerebral blood flow in rats as measured with radiolabeled microspheres. J Cereb Blood Flow Metab. 1989; 9: 117-124.

15. Povlishock J.T., Becker D.P., Cheng C.L.Y., Vaughan G.W. Axonal changes in minor head injury. J Neuropath Exp Neurol. 1983; 42: 225-242.

16. Teasdale G. Jennett B. Assessment of coma and impaired consciousness. Lancet 1974; 2: 81-84.

17. Hamm R.J., Dixon C.E., Gbadebo D.M., Singha A.K., Jenkins L.W., Lyeth B.G., Hayes R.L. Cognitive deficits following traumatic brain injury produced by controlled cortical impact injury. J Neurotrauma 1992; 9: 11-20.

18. Baldwin S.A., Fugaccia I., Brown D.R., Brown L.V., Scheff S.W. Blood-brain barrier breach following cortical contusion in the rat. J Neurosurg. 1996; 85: 476-481.

19. Dixon C.E., Clifton G.L., Lighthall J.W., Yaghami A.A., Hayes R.L. A controlled cortical impact model of traumatic brain injury in the rat. J Neurosci Methods 1991; 39: 253-262.

20. Cooper P.R. Delayed brain injury: secondary insults. In Central Nervous System Status Report- 1985. D.P. Becker and J.T. Povlishock, William Byrd Press, NIH, Bethesda. 217-228, 1985.

21. Faden A.I., Demediuk P., Panter S.S., Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 1989; 244: 798-800.

22. Katayama Y., Becker D.P., Tamura T., Hovda D.A. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. J Neurosurg. 1990; 73: 889-900.

23. Nilsson P., Hillered L., Ponten U., Ungerstedt U. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. J Cereb Blood Flow Metab. 1990; 10: 631-637.

24. Palmer A.M., Marion D.W., Botscheller M.L., Swedlow P.E., Stryen S.D., DeKosky S.T. Traumatic brain injury-induced excitotoxicity assessed in a controlled cortical impact model. J Neurochem. 1993; 61: 2015-2024.

25. Shapira Y., Yadid G., Cotev S., Shohami E. Accumulation of calcium in the brain following head trauma. Neurol Res. 1989; 11: 169-171.

26. Hovda D.A., Yoshino A., Fireman I., Smith M., Becker D.P. Intracellular calcium accumulates for at least 48 hours following fluid percussion brain injury in the rat. Proc Am Assoc Neurol Surg. 1991; 1: 452 (Abstr.)

27. Vink R., McIntosh T.K., Demediuk P., Weiner M.W., Faden A.I. Decline in intracellular free magnesium concentration is associated with irreversible tissue injury following brain trauma. J Biol Chem. 1988; 263: 757-761.

28. Prasad M.R., Tzigaret C., Smith D.H., Soares H., McIntosh T.K. Decreased alpha-adrenergic receptors after experimental brain injury. J Neurotrauma 1993; 9: 269-279.

29. McIntosh T.K., Hayes R.L., DeWitt D.S., Agura V., Faden A.I. Endogenous opioids may mediate secondary damage after experimental brain injury. Am J Physiol. 1987; 253: E565-E574.

30. DeWitt D., Kong D.L., Lyeth B., Jenkins L., Hayes R., Wooten E.D., Prough D. Experimental traumatic brain injury elevates brain prostaglandin E2 and thromboxane B2 levels in rats. J Neurotrauma 1988; 5: 303-313.

31. Ellis E., Wright K., Wei E., Kontos H. Cyclo-oxygenase products of arachidonic acid metabolism in cat cerebral cortex after experimental concussive brain injury. J Neurochem. 1981; 37: 892-896.

32. Kontos H.A. Wei E.P. Superoxide production in experimental brain injury. J Neurosurg. 1986; 64: 803-807.

33. Quattrocchi K.B., Frank E.H., Miller C.H., MacDermott J.P.A., Hein L., Frey L., Wagner F.C. Suppression of cellular immune activity following severe head injury. J Neurotrauma 1990; 7: 77-87.

34. Goodman J.C., Robertson C.S., Grossman R.G., Narayan R.K. Elevation of tumour necrosis factor in head injury. J Neuroimmunol. 1990; 30: 213-217.

35. McIntosh T.K. Novel pharmacologic therapies in the treatment of experimental brain injury: a review. J Neurotrauma 1993; 10: 215-261.

36. Doppenberg E.M.R. Bullock R. Clinical neuro-protection trials in severe traumatic brain injury: lessons from previous studies. J Neurotrauma 1997; 14: 71-80.

37. Chesnut R.M., Marshall L.F., Klauber M.R., Blunt B.A., Baldwin N., Eisenberg H.M., Jane J.A., Marmarou A., Foulkes M.A. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993; 34: 216-222.

38. Ishige N., Pitts L.H., Berry I., Carlson S.G., Nishimura M.C., Moseley M.E., Weinstein P.R. The effect of hypoxia on traumatic head injury in rats: alterations in neurologic function, brain edema, and cerebral blood flow. J Cereb Blood Flow Metab. 1987; 7: 759-767.

39. Jenkins L.W., Moszynski D., Lyeth B.G., Lewelt W., DeWitt D.S., Allen A., Dixon C.E., Povlishock J.T. Increased vulnerability of the mildly traumatized brain to cerebral ischemia: the use of controlled secondary ischemia as a research tool to identify common or different mechanisms contributing to mechanical and ischemic brain injury. Brain Res. 1989; 477: 211-224.

40. Cherian L., Robertson C.S., Goodman J.C. Secondary insults increase injury after controlled cortical impact in rats. J Neurotrauma 1996; 13: 371-383.

41. DeWitt D.S., Jenkins L.W., Prough D.S. Enhanced vulnerability to secondary ischemic insults after experimental traumatic brain injury. New Horizons 1995; 3: 376-383.

42. Harper S.L., Bohlen H.G., Rubin Y. Arterial and microvascular contributions to cerebral cortical autoregulation in rats. Am J Physiol. 1984; 246: H17-H24.

43. Kuschinsky W. Wahl M. Local chemical and neurogenic regulation of cerebral vascular resistance. Physiol Reviews 1978; 58: 656-689.

44. Brian Jr J.E., Faraci F.M., Heistad D.D. Recent insights into the regulation of cerebral circulation. Clin Exp Pharmacol Physiol. 1996; 23: 449-457.

45. Lassen N.A. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959; 39: 183-238.

46. Edvinsson L., Owman C., Siesjo B. Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cererbral blood flow. Brain Res. 1976; 117: 519-523.

47. Barry D.I., Jarden J.O., Paulson O.B., Graham D.I., Strandgaard S. Cerebrovascular aspects of converting-enzyme inhibition I: effects of intravenous captopril in spontaneously hypertensive and normotensive rats. J Hypertension 1984; 2: 589-597.

48. Ekstrom-Jodal B., Haggendal E., Linder L.E., Nilsson N.J. Cerebral blood flow autoregulation at high arterial pressures and different levels of carbon dioxide tension in dogs. Eur Neurol. 1971; 6: 6-10.

49. Bayliss W.M. On the local reaction of the arterial wall to changes of internal pressure. J Physiol. 1902; 28: 220-231.

50. Osol G. Halpern W. Myogenic properties of cerebral blood vessels from normotensive and hypertensive rats. Am J Physiol. 1985; 249: H914-H921.

51. McCarron J.G., Osol G., Halpern W. Myogenic responses are independent of the endothelium in rat pressurized posterior cerebral arteries. Blood Vessels 1989; 26: 315-319.

52. Harder D.R. Pressure-dependent membrane deploarization in cat middle cerebral artery. Circ Res. 1984; 55: 197-202.

53. Golding E.M., Robertson C.S., Bryan Jr R.M. Comparison of the myogenic response in rat cerebral arteries of different calibers. Brain Res. 1998; 785: 293-298.

54. Meininger G.A. Davis M.J. Cellular mechanisms involved in the vascular myogenic response. Am J Physiol. 1992; 263: H647-H659.

55. Gobiet W., Grote W., Bock W.J. The relation between intracranial pressure, mean arterial pressure and cerebral blood flow in patients with severe head injury. Acta Neurochir. 1975; 32: 13-34.

56. Langfitt T.W., Obrist W.D., Gennarelli T.A., O'Connor M.J., Weeme C.A. Correlation of cerebral blood flow with outcome in head injured patients. Ann Surg. 1977; 186: 411-414.

57. Bruce C.A., Raphaely R.C., Goldberg A.I., Zimmerman R.A., Bilaniuk L.T., Schut L., Khul D.E. Pathophysiology, treatment and outcome following severe head injury in children. Childs Brain 1979; 5: 174-191.

58. Muizelaar J.P., Marmarou A., DeSalles A.A., Ward J.D., Zimmerman R.S., Li Z., Choi S.C., Young H.F. Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GSC score, outcome, ICP, and PVI. J Neurosurg. 1989; 71: 63-71.

59. Robertson C.S., Contant C.F., Gokaslan Z.L., Narayan R.K., Grossman R.G. Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. J Neurol Neurosurg Psych. 1992; 55: 594-603.

60. Kelly D.F., Martin N.A., Kordestani R., Counelis G., Hovda D.A., Bergsneider M., McBride D.Q., Shalmon E., Herman D., Becker D.P. Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg. 1997; 86: 633-641.

61. Nilsson B. Ponten U. Experimental head injury in the rat. Part 3: cerebral blood flow and oxygen consumption after concussive impact acceleration. J Neurosurg. 1977; 47: 262-273.

62. Muir J.K., Boerschel M., Ellis E.F. Continuous monitoring of posttraumatic cerebral blood flow using laser-doppler flowmetry. J Neurotrauma 1992; 9: 355-362.

63. Bryan Jr R.M., Cherian L., Robertson C.S. Regional cerebral blood flow after controlled cortical impact injury in rats. Anesth Analg. 1995; 80: 687-695.

64. Nilsson P., Gazelius B., Carlson H., Hillered L. Continuous measurement of changes in regional cerebral blood flow following cortical compression contusion trauma in rat. J Neurotrauma 1996; 13: 201-207.

65. Yuan X., Prough D.S., Smith T.L., DeWitt D.S. The effects of traumatic brain injury on regional cerebral blood flow in rats. J Neurotrauma 1988; 5: 289-301.

66. Yamakami I. McIntosh T.K. Alterations in regional cerebral blood flow following brain injury in the rat. J Cereb Blood Flow Metab. 1991; 11: 655-660.

67. Pfenninger E.G., Reith A., Breitig D., Grunert A., Ahnefeld F.W. Early changes of intracranial pressure, perfusion pressure, and blood flow after acute head injury. J Neurosurg. 1989; 70: 774-779.

68. Kochanek P.M., Marion D.W., Zhang W., Shiding J.K., White M., Palmer A.M., Clark R.S.B., O'Malley M.E., Styren S.D., Ho C., DeKosky S.T. Severe controlled cortical impact in rats: assessment of cerebral edema, blood flow, and contusion volume. J Neurotrauma 1995; 12: 1015-1025.

69. Cherian L., Robertson C.S., Contant Jr C.F., Bryan Jr R.M. Lateral cortical impact injury in rats: cerebrovascular effects of varying depth of cortical deformation and impact velocity. J Neurotrauma 1994; 11: 573-585.

70. Rosner M.J., Newsome H.H., Becker D.P. Mechanical brain injury: the sympathoadrenal response. J Neurosurg. 1984; 61: 76-86.

71. Shiozaki T., Taneda M., Kishikawa M., Iwai A., Sugimoto H., Yoshioka T., Sugimoto T. Transient and repetitive rises in blood pressure synchronized with plasma catecholamine increases after head injury. Report of two cases. J Neurosurg. 1993; 78: 501-504.

72. Andrews B.T., Levy M.L., Pitts L.H. Implications of systemic hypotension for the neurological examination in patients with severe head injury. Surg Neurol. 1987; 28: 419-422.

73. Luerssen T.G., Klauber M.R., Marshall L.F. Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. J Neurosurg. 1988; 68: 409-416.

74. Dixon C.E., Lyeth B.G., Povlishock J.T., Findling R.L., Hamm R.J., Marmarou A., Young H.F., Hayes R.L. A fluid percussion model of experimental brain injury in the rat. J Neurosurg. 1987; 67: 110-119.

75. McIntosh T.K., Vink R., Noble L.J., Yamakami I., Fernyak S.E., Soares H., Faden A.I. Traumatic brain injury in the rat: characterization of a lateral fluid percussion injury model. Neurosci. 1989; 28: 233-244.

76. Yuan X., Wade C.E., Prough D.S., DeWitt D.S. Traumatic brain injury creates biphasic systemic hemodynamic and organ blood flow responses in rats. J Neurotrauma 1990; 7: 141-153.

77. Wei E.P., Dietrich W.D., Povlishock J.T., Navari R.M., Kontos H.A. Functional, morphological, and metabolic abnormalities of the cerebral microcirculation after concussive brain injury in cats. Circ Res. 1980; 46: 37-47.

78. Wei E.P., Kontos H.A., Dietrich W.D., Povlishock J.T., Ellis E.F. Inhibition by free radical scavengers and by cyclooxygenase inhibitors of pial arteriolar abnormalities from concussive brain injury in cats. Circ Res. 1981; 48: 95-103.

79. Becker D.P. Common Themes in Head Injury. In Textbook of Head Injury. D.P. Becker and S.K. Gudeman, W.B. Saunders, Philadelphia. 1-22, 1989.

80. Nilsson P., Hillered L., Olsson Y., Sheardown M.J., Hansen A.J. Regional changes in interstitial K^+ and Ca^{2+} levels following cortical compression contusion trauma in rats. J Cereb Blood Flow Metab. 1993; 13: 183-192.

81. Leao A.A.P. Spreading depression of activity in the cerebral cortex. J Neurophysiol. 1944; 7: 359-390.

82. Cotman C.W. Iversen L.L. Excitatory amino acids in the brain-focus on NMDA receptors. TINS 1987; 10: 263-265.

83. Armstead W.M. Brain injury impairs ATP-sensitive K^+ channel in piglet cerebral arteries. Stroke 1997; 28: 2273-2279.

84. Armstead W.M. Role of impaired cAMP and calcium-sensitive K^+ channel function in altered cerebral hemodynamics following brain injury. Brain Res. 1997; 768: 177-184.

85. Roberts J.K.M., Wade-Jardetzky N., Jardetzky O. Intracellular pH measurements by ^{31}P nuclear magnetic resonance. Influence of factors other than pH on ^{31}P chemical shifts. Biochem. 1981; 20: 5389-5394.

86. Vink R., McIntosh T.K., Weiner M.W., Faden A.I. Effects of traumatic brain injury on cerebral high-energy phosphates and pH: a ^{31}P magnetic resonance spectroscopy study. J Cereb Blood Flow Metab. 1987; 7: 563-571.

87. DeSalles A.F., Kontos H.A., Becker D.P., Yang M.S., Ward J.D., Moulton R., Gruemer H.D., Lutz H., Maset A.L., Jenkins L., Marmarou A., Muizelaar P. Prognostic significance of ventricular CSF lactic acidosis in severe head injury. J Neurosurg. 1986; 65: 615-624.

88. Cohen Y., Sanada T., Pitts L.H., Chang L.H., Nishimura M.C., Weinstein P.R., Litt L., James T.L. Surface coil spectroscopic imaging: time and spatial evolution of lactate production following fluid percussion brain injury. Magn Reson Med. 1991; 17: 225-236.

89. Paschen W., Djuricic B., Mies G., Schmidt-Kastner R., Linn F. Lactate and pH in the brain: association and dissociation in different pathophysiological states. J Neurochem. 1987; 48: 154-159.

90. Wahl M., Deetjen P., Thurau K., Ingvar D.H., Lassen N.A. Micropuncture evaluation of the importance of perivascular pH for the arteriolar diameter on the brain surface. Pflugers Arch. 1970; 316: 152-163.

91. Cold G., Jensen F.T., Malmros R. The effects of $PaCO_2$ reduction on regional cerebral blood flow in the acute phase of brain injury. Acta Anesth Scand. 1977; 21: 359-367.

92. Enevoldsen E.M. Jensen F.T. Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg. 1978; 48: 689-703.

93. Saunders M.L., Miller J.D., Stablein D., Allen G. The effects of graded experimental trauma on cerebral blood flow and responsiveness to CO_2. J Neurosurg. 1979; 51: 18-26.

94. Lewelt W., Jenkins L.W., Miller J.D. Autoregulation of cerebral blood flow after experimental fluid percussion injury of the brain. J Neurosurg. 1980; 53: 500-511.

95. Ellis E.F., Dodson L.Y., Police R.J. Restoration of cerebrovascular responsiveness to hyperventilation by the oxygen radical scavenger n-acetylcysteine following experimental traumatic brain injury. J Neurosurg. 1991; 75: 774-779.

96. Forbes M.L., Hendrich K.S., Kochanek P.M., Williams D.S., Schiding J.K., Wisniewski S.R., Kelsey S.F., DeKosky S.T., Graham S.H., Marion D.W., Ho C. Assessment of cerebral blood flow and CO_2 reactivity after controlled cortical impact by perfusion magnetic resonance imaging using arterial spin-labeling in rats. J Cereb Blood Flow Metab. 1997; 17: 865-874.

97. Kochanek P.M., Clark R.S., Obrist W.D., Carcillo J.A., Jackson E.K., Mi Z., Wisniewski S.R., Bell M.J., Marion D.W. The role of adenosine during the period of delayed cerebral swelling after severe traumatic brain injury in humans. Acta Neurochir-Suppl 1997; 70: 109-111.

98. Bell M.J., Kochanek P.M., Carcillo J.A., Zaichuan M.I., Shiding J.K., Wisniewski S.R., Clark R.S., Dixon C.E., Marion D.W., Jackson E. Interstitial adenosine, inosine, hypoxanthine are increased after experimental traumatic brain injury in the rat. J Neurotrauma 1998; 15: 163-170.

99. Headrick J.P., Bendall M.R., Faden A.I., Vink R. Dissociation of adenosine levels from bioenergetic state in experimental brain trauma: potential role in secondary injury. J Cereb Blood Flow Metab. 1994; 14: 853-861.

100. Povlishock J.T., Becker D.P., Sullivan H.G., Miller J.D. Vascular permeability alterations to horseradish peroxidase in experimental brain injury. Brain Res. 1978; 153: 223-239.

101. Kontos H.A. Wei E.P. Endothelium-dependent responses after experimental brain injury. J Neurotrauma 1992; 9: 349-354.

102. Ellison M.D., Erb D.E., Kontos H.A., Povlishock J.T. Recovery of endothelium-dependent relaxation after fluid-percussion brain injury in cats. Stroke 1989; 20: 911-917.

103. Bukoski R.D., Wang S.N., Bian K., DeWitt D.S. Traumatic brain injury does not alter cerebral artery contractility. Am J Physiol. 1997; 272: H1406-H1411.

104. Golding E.M., Steenberg M.L., Cherian L., Marrelli S.P., Robertson C.S., Bryan Jr R.M. Endothelial-mediated dilations following severe controlled cortical impact injury in the rat middle cerebral artery. J Neurotrauma 1998; 15: 633-642.

105. Jacob T.D., Ochoa J.B., Udekwu A.O., Wilkinson J., Murray T., Billiar T.R., Simmons R.L., Marion D.W., Peitzman A.B. Nitric oxide production is inhibited in trauma patients. J Trauma 1993; 35: 590-596.

106. Goodman J.C., Tan D.H., Ritter A.M., Robertson C.S. Cerebrospinal fluid nitrate levels following head injury. J Neurotrauma 1995; 12: 971

107. Sakamoto K., Fujisawa H., Koizumi H., Tsuchida E., Ito H., Sadamitsu D., Maekawa T. Effects of mild hypothermia on nitric oxide synthesis following contusion trauma in the rat. J Neurotrauma 1997; 14: 349-353.

108. Cobbs C.S., Fenoy A., Bredt D.S., Noble L.J. Expression of nitric oxide synthase in the cerebral microvasculature after traumatic brain injury in the rat. Brain Res. 1997; 751: 336-338.

109. DeWitt D.S., Smith T.S., Deyo D.J., Miller K.R., Uchida T., Prough D.S. L-arginine and superoxide dismutase prevent or reverse cerebral hypoperfusion after fluid-percussion traumatic brain injury. J Neurotrauma 1997; 14: 223-233.

110. Reyes A.A., Karl I.E., Klahr S. Role of arginine in health and renal disease. Am J Physiol. 1994; 267: F331-F346.

111. Iadecola C. Bright and dark sides of nitric oxide in ischemic brain injury. TINS 1997; 20: 132-139.

112. Bonfoco E., krainc D., Ankarcrona M., Nicotera P., Lipton S.A. Apoptosis and necrosis: two distinct events induced, respectively, by mild and intense insults with N-methyl-D-aspartate or nitric oxide/superoxide in cortical cell cultures. Proc Nat Acad Sci. 1995; 92: 7162-7166.

113. Clifton G.L., Robertson C.S., Kyper K., Taylor A.A., Dhekne R.D., Grossman R.G. Cardiovascular response to severe head injury. J Neurosurg. 1983; 59: 447-454.

114. Hamill R.W., Woolf P.D., McDonald J.V., Lee L.A., Kelly M. Catecholamines predict outcome in traumatic brain injury. Ann Neurol 1987; 21: 438-443.

115. Woolf P.D., Hamill R.W., Lee L.A., Cox C., McDonald J. The predictive value of catecholamines in assessing outcome in traumatic brain injury. J Neurosurg. 1987; 66: 875-882.

116. McIntosh T.K., Yu T., Gennarelli T.A. Alterations in regional brain catecholamine concentrations after experimental brain injury in the rat. J Neurochem. 1994; 63: 1426-1433.

117. Inoue I., McHugh M., Pappius H.M. The effect of α-adrenergic receptor blockers prazosin and yohimbine on cerebral metabolism and biogenic amine content of traumatized brain. J Cereb Blood Flow Metab. 1991; 11: 242-252.

118. Feeney D.M., Sutton R.L., Boyeson M.G., Hovda D.A., Dail W.G. The locus coeruleus and cerebral metabolism: recovery of function after cortical injury. Physiol Psychol. 1985; 13: 197-205.

119. Kogure K., Scheinberg P., Kishikawa H., Utsunomiya Y., Busto R. Adrenergic control of cerebral blood flow and energy metabolism in the rat. Stroke 1979; 10: 179-184.

120. Weiss H.R. Milton E.B. Role of α-adrenoceptors in the control of the cerebral blood flow response to hypoxia. J Pharmacol. 1988; 148: 107-113.

121. Woodward D.J., Moises H.C., Waterhouse B.D., Hoffer B.J., Freedman R. Modulatory actions of norepinephrine in the central nervous system. Fed Proc. 1979; 38: 2109-2116.

122. Stanton P.K., Mody I., Heinemann U. A role for N-methyl-D-aspartate receptors in norepinephrine-induced long-lasting potentiation in the dentate gyrus. Exp Brain Res. 1989; 77: 517-530.

123. Nayak A.K., Mohanty S., Singh R.K., Chansouria J.P. Plasma biogenic amines in head injury. J Neurol Sci. 1980; 47: 211-219.

124. Markianos M., Seretis A., Kotsou A., Christopoulos M. CSF neurotransmitter metabolites in comatose head injury patients during changes in their clinical state. Acta Neurochir. 1996; 138: 57-59.

125. Cold G.E. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Acta Neurochir Suppl Wien 1990; 49: 1-64.

126. Cold G.E. Jensen F.T. Cerebral autoregulation in uncounscious patients with brain injury. Acta Anaesthesiol Scand. 1978; 22: 270-280.

127. Muizelaar J.P., Ward J.D., Marmarou A., Newlon P.G., Wachi A. Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation. J Neurosurg. 1989; 71: 72-76.

128. Paulson O.B., Strandgaard S., Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Revs. 1990; 2: 161-192.

129. Junger E.C., Newell D.W., Grant G.A., Avellino A.M., Ghatan S., Douville C.M., Lam A.M., Aaslid R., Winn H.R. Cerebral autoregulation following minor head injury. J Neurosurg. 1997; 86: 425-432.

130. Czosnyka M., Smielewski P., Kirkpatrick P., Menon D.K., Pickard J.D. Monitoring of cerebral autoregulation in head-injured patients. Stroke 1996; 27: 1829-1834.

131. DeWitt D.S., Prough D.S., Taylor C.L., Whitley J.M., Deal D.D., Vines S.M. Regional cerebrovascular responses to progressive hypotension after traumatic brain injury in cats. Am J Physiol. 1992; 263: H1276-H1284.

132. Proctor H.J., Palladino G.W., Fillipo D. Failure of autoregulation after closed head injury: an experimental model. J Trauma 1988; 28: 347-351.

133. Lewelt W., Jenkins L.W., Miller J.D. Effects of experimental fluid-percussion injury of the brain on cerebrovascular reactivity to hypoxia and to hypercapnia. J Neurosurg. 1982; 56: 332-338.

134. Reilly P.L., Farrar J.K., Miller J.D. Vascular reactivity in the primate brain after acute cryogenic injury. J Neurol Neurosurg Psych. 1977; 40: 1092-1101.

135. Bruce D.A., Langfitt T.W., Miller J.D., Schutz H., Vapalahti M.P., Stanek A., Goldberg H.I. Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients. J Neurosurg. 1973; 38: 131-144.

136. Miller J.D., Garibi J., North J.B., Teasdale G.M. Effects of increased arterial pressure on blood flow in the damaged brain. J Neurol. Neurosurg. Psych. 1975; 38: 657-665.

137. Wang Q., Paulson O.B., Lassen N.A. Effect of nitric oxide blockade by NG-nitro-L-arginine on cerebral blood flow response to changes in carbon dioxide tension. J Cereb Blood Flow Metab. 1992; 12: 947-953.

138. Wang Q., Paulson O.B., Lassen N.A. Is autoregulation of cerebral blood flow in rats influenced by nitro-L-arginine, a blocker of the synthesis of nitric oxide? Acta Physiol Scand. 1992; 145: 297-298.

139. Buchanan J.E. Phillis J.W. The role of nitric oxide in the regulation of cerebral blood flow. Brain Res. 1993; 610: 248-255.

140. Takahashi S., Cook M., Jehle J., Kennedy C., Sokoloff L. Preservation of autoregulatory cerebral vasodilator responses to hypotension after inhibition of nitric oxide synthase. Brain Res. 1995; 678: 21-28.

141. McCulloch J. Edvinsson L. Cerebrovascular smooth muscle reactivity: a critical appraisal of *in vitro* and *in situ* techniques. J Cereb Blood Flow Metab. 1984; 4: 129-139.

142. Compton J.S. Teddy P.J. Cerebral arterial vasospasm following severe head injury: a transcranial Doppler study. Br J Neurosurg. 1987; 1: 435-439.

143. Cipolla M.J., Porter J.M., Osol G. High glucose concentrations dilate cerebral cerebral arteries and diminish myogenic tone through an endothelial mechanism. Stroke 1997; 28: 405-411.

144. Cipolla M.J., McCall A.L., Lessov N., Porter J.M. Reperfusion decreases myogenic reactivity and alters middle cerebral artery function after focal cerebral ischemia in rats. Stroke 1997; 27: 2287-2291.

145. Bryan Jr R.M., Eichler M.Y., Swafford M.W.G., Johnson T.D., Suresh M.S., Childres W.F. Stimulation of α_2 adrenoceptors dilates the rat middle cerebral artery. Anesthesiology 1996; 85: 82-90.

146. Hamer J., Hoyer S., Stoeckel H., Alberti E., Weinhardt F. Cerebral blood flow and cerebral metabolism in acute increase of intracranial pressure. Acta Neurochir. 1973; 28: 95-110.

147. Lassen N.A. Control of cerebral circulation in health and disease. Circ Res. 1974; 34: 749-760.

148. Marshall W.J.S., Jackson J.L.F., Langfitt T.W. Brain swelling caused by trauma and hypertension. Arch Neurol. 1969; 21: 545-553.

149. Lang E.W. Chesnut R.M. Intracranial pressure and cerebral perfusion pressure in severe head injury. New Horizons 1995; 3: 400-409.

150. Unterberg A.W., Kiening K.L., Hartl R., Bardt T., Sarrafzadeh A.S., Lanksch W.R. Multimodal monitoring in patients with head injury: evaluation of the effects of treatment on cerebral oxygenation. J Trauma 1997; 42: S32-S37.

151. Muizelaar J.P., Lutz H.A., Becker D.P. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head injured patients. J Neurosurg. 1984; 61: 700-706.

152. Wahl M. Schilling L. Regulation of cerebral blood flow- a brief review. Acta Neurochir. 1993; 59: 3-10.