British Journal of Anaesthesia **99 (1):** 4–9 (2007)
doi:10.1093/bja/aem131

BJA

REVIEW ARTICLES

Pathophysiology of traumatic brain injury

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The knowledge of the pathophysiology after traumatic head injury is necessary for adequate and patient-oriented treatment. As the primary insult, which represents the direct mechanical damage, cannot be therapeutically influenced, target of the treatment is the limitation of the secondary damage (delayed non-mechanical damage). It is influenced by changes in cerebral blood flow (hypo- and hyperperfusion), impairment of cerebrovascular autoregulation, cerebral metabolic dysfunction and inadequate cerebral oxygenation. Furthermore, excitotoxic cell damage and inflammation may lead to apoptotic and necrotic cell death. Understanding the multidimensional cascade of secondary brain injury offers differentiated therapeutic options.

Br J Anaesth 2007; **99**: 4–9

Keywords: brain, cerebral blood flow; complications, vasospasm; head, trauma; inflammation; pathophysiology

Traumatic brain injury (TBI) still represents the leading cause of morbidity and mortality in individuals under the age of 45 yr in the world. Numerous experimental and clinical analyses of biomechanical injury and tissue damage have expanded the knowledge of pathophysiological events which potentially serves as the basis to define new or refine established treatment strategies. This review consolidates the current pathophysiological view of TBI predominantly derived from clinical work with particular emphasis on cerebral blood flow (CBF) and metabolism, cerebral oxygenation, excitotoxicity, oedema formation, and inflammatory processes.

Biomechanical and neuropathological classification of injury

The principal mechanisms of TBI are classified as (a) focal brain damage due to contact injury types resulting in contusion, laceration, and intracranial haemorrhage or (b) diffuse brain damage due to acceleration/deceleration injury types resulting in diffuse axonal injury or brain swelling.[2 40 46 49] Outcome from head injury is determined by two substantially different mechanisms/stages: (a) the primary insult (primary damage, mechanical damage) occurring at the moment of impact. In treatment terms, this type of injury is exclusively sensitive to preventive but not therapeutic measures. (b) The secondary insult (secondary damage, delayed non-mechanical damage) represents consecutive pathological processes initiated at the moment of injury with delayed clinical presentation. Cerebral ischaemia and intracranial hypertension refer to secondary insults and, in treatment terms, these types of injury are sensitive to therapeutic interventions.

General pathophysiology of traumatic brain injury

The first stages of cerebral injury after TBI are characterized by direct tissue damage and impaired regulation of CBF and metabolism. This 'ischaemia-like' pattern leads to accumulation of lactic acid due to anaerobic glycolysis, increased membrane permeability, and consecutive oedema formation. Since the anaerobic metabolism is inadequate to maintain cellular energy states, the ATP-stores deplete and failure of energy-dependent membrane ion pumps occurs. The second stage of the pathophysiological cascade is characterized by terminal membrane depolarization along with excessive release of excitatory neurotransmitters (i.e. glutamate, aspartate), activation of *N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate, and voltage-dependent Ca^{2+}- and Na^{+}-channels. The consecutive Ca^{2+}- and Na^{+}-influx leads to self-digesting (catabolic) intracellular processes. Ca^{2+} activates lipid peroxidases, proteases, and phospholipases which in turn increase the intracellular concentration of free fatty acids and free radicals. Additionally, activation of caspases (ICE-like proteins), translocases, and endonucleases initiates progressive structural changes of biological membranes and the nucleosomal DNA (DNA

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fragmentation and inhibition of DNA repair). Together, these events lead to membrane degradation of vascular and cellular structures and ultimately necrotic or programmed cell death (apoptosis).

Specific pathophysiology of traumatic brain injury

Cerebral blood flow

Hypoperfusion and hyperperfusion

Studies in laboratory animals and humans have investigated the effects of TBI on CBF. Using ^{133}Xe scintillation detection, ^{133}Xe computed tomography (CT), stable xenon CT, or $^{15}O_2$ positron emission CT to assess CBF within a temporal range from ultra-early to late stages after TBI, many investigations have revealed that focal or global cerebral ischaemia occurs frequently.[6 13 26 52] Although the total ischaemic brain volume may be less than 10% on average,[6 14 69] the presence of cerebral ischaemia is associated with poor ultimate neurological outcome, that is, dead or vegetative state.[6 26 52] The frequent association between cerebral hypoperfusion and poor outcome suggests that TBI and ischaemic stroke share the same fundamental mechanisms. Although this assumption may be true to some extent, major differences exist between these two different types of primary injury. For example, the critical threshold of CBF for the development of irreversible tissue damage is 15 ml $100\,g^{-1}$ min^{-1} in patients with TBI compared with 5–8.5 ml $100\,g^{-1}$ min^{-1} in patients with ischaemic stroke.[15] While cerebral ischaemia predominantly leads to metabolic stress and ionic perturbations, head trauma additionally exposes the brain tissue to shear forces with consecutive structural injury of neuronal cell bodies, astrocytes, and microglia, and cerebral microvascular and endothelial cell damage.[7 16 55] The mechanisms by which post-traumatic ischaemia occurs include morphological injury (e.g. vessel distortion) as a result of mechanical displacement, hypotension in the presence of autoregulatory failure,[46 55] inadequate availability of nitric oxide or cholinergic neurotransmitters,[16 59] and potentiation of prostaglandin-induced vasoconstriction.[1]

Patients with TBI may develop cerebral hyperperfusion (CBF >55 ml $100\,g^{-1}$ min^{-1}) in the early stages of injury. Likewise, hyperaemia may follow immediate post-traumatic ischaemia.[30 34 43 57] This pathology seems as detrimental as ischaemia in terms of outcome because increases in CBF beyond matching metabolic demand relate to vasoparalysis with consecutive increases in cerebral blood volume and in turn intracranial pressure (ICP).[31]

It is important to note that diagnosing *hypoperfusion* or *hyperperfusion* is only valid after assessing measurements of CBF in relation to those of cerebral oxygen consumption. Both cerebral ischaemia and hyperaemia refer to a mismatch between CBF and cerebral metabolism. For example, low flow with normal or high metabolic rate represents an ischaemic situation whereas high CBF with normal or reduced metabolic rate represents cerebral hyperaemia.[5 30 43] In contrast, low CBF with a low metabolic rate or high CBF with high metabolic rates represents coupling between flow and metabolism, a situation that does not necessarily reflect a pathological condition.

Cerebrovascular autoregulation and CO_2-reactivity

Cerebrovascular autoregulation and CO_2-reactivity are important mechanisms to provide adequate CBF at any time. Likewise, both patterns are the basis for the management of cerebral perfusion pressure (CPP) and ICP and impairment of these regulatory mechanisms reflect increased risk for secondary brain damage.

After TBI, CBF autoregulation (i.e. cerebrovascular constriction or dilation in response to increases or decreases in CPP) is impaired or abolished in most patients.[20 24 25 27 29 32 33 58] The temporal profile of this pathology is as inconsistent as the severity of injury to produce autoregulatory failure. Defective CBF autoregulation may be present immediately after trauma or may develop over time, and is transient or persistent in nature irrespective of the presence of mild, moderate, or severe damage. Also, autoregulatory vasoconstriction seems to be more resistant compared with autoregulatory vasodilation which indicates that patients are more sensitive to damage from low rather than high CPPs.[16]

Compared with CBF autoregulation, cerebrovascular CO_2-reactivity (i.e. cerebrovascular constriction or dilation in response to hypo- or hypercapnia) seems to be a more robust phenomenon. In patients with severe brain injury and poor outcome, CO_2-reactivity is impaired in the early stages after trauma.[20] In contrast, CO_2-reactivity was intact or even enhanced in most other patients offering this physiological principle as a target for ICP management in hyperaemic states.[36 45]

Cerebral vasospasm

Post-traumatic cerebral vasospasm is an important secondary insult that determines ultimate patient outcome.[37 51] Vasospasm occurs in more than one-third of patients with TBI and indicates severe damage to the brain. The temporal profile and extent of hypoperfusion with post-traumatic vasospasm differs from vasospasm occurring after aneurysmal subarachnoidal haemorrhage. The onset varies from post-traumatic day 2 to 15 and hypoperfusion (haemodynamically significant vasospasm) occurs in 50% of all patients developing vasospasm. The mechanisms by which vasospasm occurs include chronic depolarization of vascular smooth muscle due to reduced potassium channel activity,[61] release of endothelin along with reduced availability of nitric oxide,[75] cyclic GMP depletion of vascular smooth muscle,[67] potentiation of

prostaglandin-induced vasoconstriction,[1] and free radical formation.[16 45]

Cerebral metabolic dysfunction

Cerebral metabolism (as reflected by cerebral oxygen and glucose consumption) and cerebral energy state (as reflected by tissue concentrations of phosphocreatine and ATP or indirectly by the lactate/pyruvate ratio) are frequently reduced after TBI and present with considerable temporal and spatial heterogeneity.[15 12 18 23] The degree of metabolic failure relates to the severity of the primary insult, and outcome is worse in patients with lower metabolic rates compared with those with minor or no metabolic dysfunction.[72] The reduction in post-traumatic cerebral metabolism relates to the immediate (primary) insult leading to mitochondrial dysfunction with reduced respiratory rates and ATP-production, a reduced availability of the nicotinic co-enzyme pool, and intramitochondrial Ca^{2+}-overload.[66 70] However, the use of hyperoxia in an attempt to correct for metabolic failure produces inconsistent results.[39 47] Interestingly, decreases in cerebral metabolic demand may[15] or may not be associated with matching decreases in CBF.[12 18] The latter reflects uncoupling of CBF and metabolism, probably due to increased adenosine availability.[12 54]

As an alternative pathophysiological event, hypermetabolism of glucose may occur.[4 9] This is driven by transient but massive transmembrane ionic fluxes with consecutive neuroexcitation that are not adequately met by (concomitant) increases in CBF. This type of flow-metabolism uncoupling supports the evolution of secondary ischaemic insults.

Cerebral oxygenation

TBI is characterized by an imbalance between cerebral oxygen delivery and cerebral oxygen consumption. Although this mismatch is induced by several different vascular and haemodynamic mechanisms as indicated earlier, the final common endpoint is brain tissue hypoxia. Measurements of brain tissue oxygen pressure in patients suffering from TBI have identified the critical threshold of 15–10 mm Hg $P_{t_{O_2}}$ below which infarction of neuronal tissue occurs.[28 56] As a consequence of this, the incidence, duration, and extent of tissue hypoxia correlate with poor outcome. However, oxygen deprivation of the brain with consecutive secondary brain damage may occur even in the presence of normal CPP or ICP.[65] In line with this, clinical protocols integrating the parameter of brain tissue oxygen pressure into management algorithms guided by ICP or CPP added important knowledge about the interaction between oxygen delivery and oxygen demand and demonstrated improved outcome from TBI when individualizing treatment based on critical brain tissue oxygenation.[27 33 35 47 63]

Excitotoxicity and oxidative stress

TBI is primarily and secondarily associated with a massive release of excitatory amino acid neurotransmitters, particularly glutamate.[8 54] This excess in extracellular glutamate availability affects neurons and astrocytes and results in over-stimulation of ionotropic and metabotropic glutamate receptors with consecutive Ca^{2+}, Na^{+}, and K^{+}-fluxes.[22 73] Although these events trigger catabolic processes including blood–brain barrier breakdown, the cellular attempt to compensate for ionic gradients increases Na^{+}/K^{+}-ATPase activity and in turn metabolic demand, creating a vicious circle of flow–metabolism uncoupling to the cell.[16 50]

Oxidative stress relates to the generation of reactive oxygen species (oxygen free radicals and associated entities including superoxides, hydrogen peroxide, nitric oxide, and peroxinitrite) in response to TBI. The excessive production of reactive oxygen species due to excitotoxicity and exhaustion of the endogenous antioxidant system (e.g. superoxide dismutase, glutathione peroxidase, and catalase) induces peroxidation of cellular and vascular structures, protein oxidation, cleavage of DNA, and inhibition of the mitochondrial electron transport chain.[3 11 60] Although these mechanisms are adequate to contribute to immediate cell death, inflammatory processes and early or late apoptotic programmes are induced by oxidative stress.[11]

Oedema

Oedema formation frequently occurs after TBI. The current classification of brain oedema relates to the structural damage or water and osmotic imbalance induced by the primary or secondary injury. *Vasogenic brain oedema* is caused by mechanical or autodigestive disruption or functional breakdown of the endothelial cell layer (an essential structure of the blood–brain barrier) of brain vessels. Disintegration of the cerebral vascular endothelial wall allows for uncontrolled ion and protein transfer from the intravascular to the extracellular (interstitial) brain compartments with ensuring water accumulation. Anatomically, this pathology increases the volume of the extracellular space.[16 68] *Cytotoxic brain oedema* is characterized by intracellular water accumulation of neurons, astrocytes, and microglia irrespective of the integrity of the vascular endothelial wall. This pathology is caused by an increased cell membrane permeability for ions, ionic pump failure due to energy depletion, and cellular reabsorption of osmotically active solutes.[64 68] Although cytotoxic oedema seems more frequent than vasogenic oedema in patients after TBI, both entities relate to increased ICP and secondary ischaemic events.[41 42]

Inflammation

TBI induces a complex array of immunological/inflammatory tissue responses with similarities to ischaemic

reperfusion injury. Both primary and secondary insults activate the release of cellular mediators including proinflammatory cytokines, prostaglandins, free radicals, and complement. These processes induce chemokines and adhesion molecules and in turn mobilize immune and glial cells in a parallel and synergistic fashion.[38 53] For example, activated polymorphonuclear leucocytes adhere to defective but also intact endothelial cell layers as mediated through adhesion molecules. These cells infiltrate injured tissue along with macrophages and T-cell lymphocytes.[74] Tissue infiltration of leucocytes is facilitated via upregulation of cellular adhesion molecules such as P-selectin, intercellular adhesion molecules (ICAM-1), and vascular adhesion molecules (VCAM-1). In response to these inflammatory processes, injured and adjacent tissue (based on 'spreading depressions') will be eliminated and within hours, days, and weeks astrocytes produce microfilaments and neutropines ultimately to synthesize scar tissue.[21] Proinflammatory enzymes such as tumour necrosis factor, interleukin-1-ß, and interleukin-6 are upregulated within hours from injury. The progression of tissue damage relates to direct release of neurotoxic mediators or indirectly to the release of nitric oxide and cytokines. The additional release of vasoconstrictors (prostaglandins and leucotrienes), the obliteration of microvasculature through adhesion of leucocytes and platelets, the blood–brain barrier lesion, and the oedema formation further reduce tissue perfusion and consequently aggravate secondary brain damage.

Necrosis vs apoptosis

Two different types of cell death may occur after TBI: necrosis and apoptosis (programmed cell death). Necrosis occurs in response to severe mechanical or ischaemic/hypoxic tissue damage with excessive release of excitatory amino acid neurotransmitters and metabolic failure. Subsequently, phospholipases, proteases, and lipid peroxidases autolyse biological membranes. The resulting cell detritus is recognized as an 'antigen' and will be removed by inflammatory processes, leaving scar tissue behind. In contrast, neurons undergoing apoptosis are morphologically intact during the immediate post-traumatic period with adequate ATP-production providing a physiological membrane potential. However, apoptosis becomes evident hours or days after the primary insult. Translocation of phosphatidylserine initiates discrete but progressive membrane disintegration along with lysis of nuclear membranes, chromatine condensation, and DNA-fragmentation. Likewise, very small particles derived from condensed intracellular material ('apoptotic bodies') are removed from the shrinking cell by excytotic mechanisms. The nature of apoptosis generally requires energy supply and imbalance between naturally occurring pro- and anti-apoptotic proteins. Consecutive activation and deactivation of caspases, which represent specific proteases of the interleukin-converting enzyme family, have been idientified as the most important mediators of programmed cell death.[10 19]

The clinical relevance of apoptosis relates to the delayed onset of cellular deterioration, potentially offering a more realistic window of opportunity for therapeutic (anti-apoptotic) interventions.[48 69]

Summary and conclusion

TBI combines mechanical stress to brain tissue with an imbalance between CBF and metabolism, excitotoxicity, oedema formation, and inflammatory and apoptotic processes. Understanding the multidimensional cascade of injury offers therapeutic options including the management of CPP, mechanical (hyper-) ventilation, kinetic therapy to improve oxygenation and to reduce ICP, and pharmacological intervention to reduce excitotoxicity and ICP. Yet, the unpredictability of the individual's pathophysiology requires monitoring of the injured brain in order to tailor the treatment according to the specific status of the patient.[62]

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