CHAPTER 2

CONCUSSION MECHANISMS AND PATHOPHYSIOLOGY

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Abstract: Concussions are a frequent occurrence in athletic endeavors, its rate exceeding that occurring in the general population by 50 fold. The biomechanics and pathophysiology of concussion are still not well understood and may lead to potential significant sequelae from single or more commonly multiple concussions. Postconcussive symptoms, the second impact syndrome and the cumulative effects of concussions are all topics of interest in current concussion research in athletes and are leading to a more rational approach in determining policy aimed at returning athletes to their sport after a concussion. This chapter reviews current knowledge on the mechanisms, pathophysiology and sequelae of concussion in athletes.

Keywords: Concussion; Metabolic cascade; Glucose utilization; Ionic changes; Epidural hematoma; Subdural Hematoma; Intracranial Hemorrhage.

1.   INTRODUCTION

Most modern sports have made tremendous strides - through rules changes, equipment enhancements, and education - to minimize the occurrence of catastrophic head injury. Nevertheless, concussions remain a significant problem in all sports. A considerable amount of time and effort has been devoted to developing concussion grading scales and guidelines for return to play. While these scales are of use in the general sense, many sports medicine physicians are now advocating a highly individualized approach to decisions such as post-concussion testing and return to play. Recognizing the significant occurrence and impact of concussions on its players, the National Football League has funded considerable contemporaneous research on concussions in professional athletes, focusing on both short and long-term effects, and strategies for prevention. Such

information is, likewise, quite useful for athletes at other levels of skill and in other sports where a concussion may occur.

1.2.   Incidence of Concussion in Athletics

The exact incidence of concussion related to sports activities is not well-defined. This is primarily because of lack of recognition of concussion by the player, coaches, or trainers, and underreporting by players. Indeed, in many cases, a player may not even realize that they have suffered a concussion. Extensive education has been required to emphasize the fact that a concussion can occur in the absence of loss of consciousness. Indeed, more likely than not, the vast majority of concussions in sports fall into this category. The incidence of concussion seems to be rising in virtually all sports, but the higher numbers may reflect an increase in recognition and reporting by team physicians. The National Athletic Injury/Illness Reporting System began following all injuries in various sports in 1975. Their statistics indicate that the risk of a concussion is 2% to 6% in football and generally less than 2% in other sports (Buckley, 1988). For the sake of comparison, the risk of minor head injury for the general population in the United States is 0.1% or a rate of approximately 131 per 100,000 per year. The true incidence of concussion in sports may be significantly higher than these estimates suggest. Gerberich et al. (1983) reported that 19% of high school athletes had experienced at least one concussion during their career. A prospective study of 2500 college football players found the risk of a concussion to be approximately 10% (Macciochi et al., 1996).

An equally concerning issue is the occurrence of subsequent concussions in the same player over time. Various authors have reported a four to six fold increased risk for subsequent concussion in athletes who have suffered a prior concussion. Guskiewicz et al. (2000) reported that an athlete who has sustained a single concussion is three times more likely to sustain a second concussion in the same season. In the same article, he reported that there was an increased severity of symptoms with subsequent concussions. Powell and Barber-Foss (1999) reported that 10.3% of high school athletes who had sustained a concussion at some point during their high school career had a second concussion before ending their high school career; with 63.3% of the second concussions occurring in the same season and 19.4% in the following season. During the six-year period, 1996 to 2001, 787 concussions were reported in National Football League games - an incidence of 0.41 concussions per game. The highest risk was from helmet impacts, while 21% occurred from contact with other players' body parts, and 11% occurred from contact with the ground. In 91% of the cases, the concussion was not associated with a loss of consciousness (Pellman et al., 2004).

2.   **MECHANISMS OF CONCUSSION**

From a historical perspective, a concussion has been defined as a short lasting disturbance of neural functions provoked by a sudden acceleration and/or deceleration of the head usually without skull fracture (Denny-Brown and Russell, 1941; cf: Shaw, 2002). Sudden loss of consciousness and profound paralysis of neuronal functions which happen (although not always) in concussion accidents are at odds with the fact that no obvious sign of demonstrable lesion, including "laceration, edema, hemorrhage, or direct injury to the neuron..." (Symonds, 1974; cf: Shaw, 2002) can account for the observed symptoms. Cerebral concussion refers to disturbance or shock of impact (*Oxford English Dictionary*) and still the most puzzling and controversial phenomenon in sports medicine today. Currently the most common accepted definition of a concussion is an immediate and transient impairment of neural function, such as alterations in consciousness, disturbance of vision, memory, equilibrium, or other similar symptoms, caused by a direct or indirect (e.g. rotation) force transmitted to the head. Delayed symptoms of concussion may include chronic fatigue, tinnitus, sleep and eating irregularities, irritability, depression, inability to perform daily activities, and academic problems (Wojtys et al., 1999).

2.1.   Biomechanics of Concussion

The biomechanics of concussion have been extensively studied and found to be primarily related to acceleration, deceleration, and translation or rotation of the head. It should be noted, however, that attempts to quantify the biomechanics of a concussion in general or of any comparatively simple type of brain injury is an extremely difficult task. Numerous factors need to be taken into consideration, including the shape of the skull, its size and geometry, density and mass of neural tissue, thickness of scalp and skull, extent/type and direction of the concussive blow, head–body relationships and mobility of the head and neck (Shaw, 2002). Recently, however, a sophisticated finite element analysis was undertaken using a detailed anatomic model of the brain to determine brain responses from concussive impacts occurring in National Football League games. With deceleration and rotation, a variety of "hot spots" were defined, indicating progressive areas of brain deformation subsequent to the impact, leading to the signs and symptoms of a concussion. There is an early response of the brain directly adjacent to the impact site (*coup* injury). In this linear case, a sufficient force in the form of an opposite velocity vector may cause the brain to strike against the inner skull in the direction it was initially traveling. Since the majority of NFL concussion impacts are oblique and lateral, the earliest signs of brain deformation or strain were in the temporal lobe.

Subsequently, a slightly delayed response was seen on the opposite side of the brain from the impact (*contrecoup* injury) - typically, the temporal lobe opposite the site of the impact, though, any brain area can be affected. In other words, the brain may be "rebounding" from the direction of the deceleration and hit the inner lining of the skull in the opposite direction. When rotational force is applied, the sites of brain contact with the skull can be manifold. It should be noted however, that there is a notion that no true coup or *contrecoup* brain injury may exist, and the magnitude of the brain tissue alteration (i.e., diffuse axonal injury, DAI) can be significantly larger when excessive rotational forces are applied (Barth et al., 2001).

Late in response to the concussive impact, deformations are seen in the midbrain above the brainstem. The study by Viano et al. concluded that concussive injuries occur from rapid displacement and rotation of the cranium after peak acceleration and momentum transfer in helmet impacts, and that various regions of the brain are serially affected by deformational strains as a result of this momentum transfer (Viano et al., 2005).

2.2.   Global Metabolic Cascade of Concussion

At present, there is a lack of complete understanding of the pathophysiology of cerebral concussions and explanations as to why after even mild concussions, the brain may become extremely vulnerable to secondary injury. It was initially felt that deformational strains produced by concussive forces will result in only a temporary disturbance of brain function related to neuronal, neurochemical, or metabolic function without associated structural brain injury. In recent years, however, it has been recognized that structural derangements may indeed occur, and that there may be a period of selective vulnerability to additional insults (e.g., second impact syndrome) or prolonged vulnerability to cumulative concussions and their long-term effects (i.e. *dementia pugilistica*). Indeed, during the minutes to few days after a concussion blow, brain cells that are not irreversibly damaged remain alive but exist in a vulnerable state (Woytys et al., 1999). Some patients suffering from a mild form of concussion may be extremely susceptible to the consequences of even minor changes in cerebral blood flow, as well as slight increases in intracranial pressure and apnea (Hovda, 1995). Metabolic dysfunctions during acute post-concussive events may be responsible for maintaining a state of brain vulnerability, characterized by increase in the demand for glucose and an inexplicable reduction in cerebral blood flow (CBF). In healthy controls, the CBF is tightly coupled to neuronal activity and glucose metabolism. This coupling may be disrupted as a result of acute brain injury. There are some supporting evidences for this. Experimentally induced fluid percussion following brain injury, may significantly reduce CBF up to 50% of normal

(Doberstein et al., 1992). In the setting of increased glucose use (i.e., hyperglucolysis), this mismatch in supply and demand may result in a potentially damaging energy crisis (Giza & Hovda, 2001). Acute brain injury induced increase in glucose utilization has been shown in the presence of low CBF in a number of animal studies (Pfenninger et al., 1989; Yanakami & McIntosh, 1989), and in humans with severe head injuries (Bergsneider et al., 1997). After the initial period of increased glucose unitization, the injured brain transitions into a period of depressed metabolism that may lead to long-lasting and worsening energy crisis. Specifically, in relation to evidence from experimental animals following the initial stage of hyperglycolysis where the CBF was found to be diminished by 24 hours post-injury and remained low for the next 5 to 10 days (Ballanyi et al., 1987). During the prolonged metabolic depression after traumatic brain injury (TBI), neurons are less able to respond metabolically to peripheral stimulation (Ip et al., 2003). The results of lateral fluid percussion injury (LFPI) clearly indicate that stimulation with impulses capable of inducing a vibrissa twitch resulted in an increase in the cerebral metabolic rate for glucose (CMR(glc) within 1-hour and was maintained up to day 7 post-injury. However, on day 1 LFPI stimulation induced a 161% increase in CMR (glc) and a 35% decrease in metabolic activation volume. Extracellular lactate concentrations during stimulation significantly increased from 23% to 55% and to 63% on day 1 and day 7, respectively, post-injury. Extracellular glucose concentrations during stimulation remained unchanged on day 7 but decreased 17% on day1 post-injury. The extent of cortical degeneration around the stimulating electrode on day 1 post-injury nearly doubled when compared with controls. In humans suffering from severe brain injury decreased glucose utilization may last up to four weeks post-injury (Bergsneider et al., 2000, PET study). Reduced cerebral glucose utilization was also found in comatose patients (Bergsneider et al., 2000), though it is still unclear how depressed metabolism may be related with acute neuropsychological and behavioral symptoms of traumatic brain injury. These neurobiological evidences may be at odds with common practices involving the clearing of brain injured athletes for sport participation within few days post-injury.

The early findings regarding depressed metabolism in acute brain injury have been supported by a number of recent studies. Specifically, it has been clearly shown that brain trauma is accompanied by regional alterations of brain metabolism, reduction in metabolic rates and possible energy crisis (Vespa et al., 2005). In this study, microdialysis markers of energy crisis were found during the critical period of intensive care despite the absence of brain ischemia. Patients underwent combined positron emission tomography (PET) for metabolism of glucose (CMRglu) and oxygen (CMRO(2)) and cerebral microdialysis (MD) at a mean time of 36 hours after injury. Microdialysis values were compared with the regional mean PET values

adjacent to the probe. The data revealed a 25% incidence rate of metabolic crisis (elevated lactate/pyruvate ratio (LPR) > 40) but only a 2.4% incidence rate of ischemia. Positron emission tomography imaging revealed a 1% incidence of ischemia across all voxels as measured by oxygen extraction fraction (OEF) and cerebral venous oxygen content (CvO(2)). In the region of the MD probe, PET imaging revealed ischemia in a single patient despite increased LPR in other patients. Lactate/pyruvate ratio correlated negatively with CMRO(2), but not with OEF or CvO(2). It was concluded that traumatic brain injury leads to a state of persistent metabolic crisis as reflected by abnormal cerebral microdialysis LPR that is not related to ischemia. In another recent study, the course of cerebral blood flow (CBF) and metabolism in traumatic brain injury (TBI) patients was examined with special focus on changes in lactate and glucose indices in the acute post-traumatic period (Soustiel et al., 2005). Global CBF, cerebral metabolic rates of oxygen (CMRO2), glucose (CMRGlc), and lactate (CMRLct) were calculated. In all patients, CBF was moderately decreased during the first 24 hours in comparison with normal controls. Both CMRO2 and CMRGlc were significantly depressed and correlated to outcome of Glasgow Coma Scale (GCS) gradings. Moreover, CMRLct analysis revealed positive values (lactate uptake) during the first 48 hours, especially in patients with a favorable outcome. Both CMRO2 and CMRLct correlated with GCS gradings. These findings emphasize the clinical significance of monitoring the CBF and metabolic changes in TBI and provide evidence for metabolic coupling between astrocytes and neurons. These findings are also consistent with a more recent animal study examining the effects of traumatic brain injury (TBI) on brain chemistry and metabolism in three groups of rats using high-resolution (1)H NMR metabolomics of brain tissue extracts and plasma (Viant et al., 2005). Evidence was found of oxidative stress (e.g., a decrease in ascorbate of 16.4% in the cortex and 29.7% cortex and hippocampus combined in TBI rats versus the untreated control group. Also there were indicators of excitotoxic damage (e.g., a decrease in glutamate of 14.7% and 12.3% in the cortex and hippocampus, respectively), membrane disruption (e.g., a decrease in the total level of phosphocholine and glycerophosphocholine of 23.0% and 19.0% in the cortex and hippocampus, respectively) and neuronal injury (e.g., decreases in N-acetylaspartate of 15.3% and 9.7% in the cortex and hippocampus, respectively). Significant changes in the overall pattern of NMR-observable metabolites using principal components analysis were also observed in TBI animals.

It is important to note that the pathophysiology of peri-lesion boundary zones in acute brain injury is highly dynamic, and it is now clear that spreading-depression-like events occur frequently in areas of cerebral cortex adjacent to contusions in the injured human brain (Parkin et al., 2005). In this study, an automated method to assay microdialysate from peri-lesion cerebral cortex for assay of glucose and lactate in 11 patients with

intracranial haematomas combined with electrocorticogram (ECoG) revealed several patterns of changes in metabolites. The number of transient lactate events was significantly correlated with the number of glucose events. In addition, progressive reduction in dialysate glucose was very closely correlated with the aggregate number of ECoG events. The authors suggested that adverse impact of low dialysate glucose on clinical outcome may be because of recurrent, spontaneous spreading-depression-like events in the perilesion cortex. Interestingly, abnormal metabolic cascades may be present at a remote site of brain injury, including subcortical brain regions. Specifically, a positron emission tomographic study examined the nature, extent, and degree of metabolic abnormalities in subcortical brain regions remote from hemorrhagic lesions using 16 normal controls and 10 TBI patients (Wu et al., 2004a). Sixteen normal volunteers and 10 TBI patients (Glasgow Coma Scale score, 4-10) participated in this study. Data from gray matter and (WM) white matter remote from hemorrhagic lesions, plus whole brain, were analyzed. There was a significant reduction in the subcortical WM oxygen-to-glucose utilization ratio after TBI compared with normal values, whereas the mean cortical gray matter and whole-brain values remained unchanged. WM metabolic changes, which were diffuse throughout the hemispheres, were characterized by a reduction in the metabolic rate of oxygen without a concomitant drop in the metabolic rate of glucose. This finding suggests that the extent and degree of subcortical WM metabolic abnormalities after moderate and severe TBI are clearly diffuse. Moreover, this pervasive finding may indicate that the concept of focal traumatic injury, although valid from a computed tomographic imaging standpoint, may be misleading when considering metabolic derangements associated with TBI. Moreover, the apparent loss of overall gray-white matter contrast (GM/WM) may be seen in TBI patients on FDG-PET imaging reflecting the differential changes of glucose metabolic rate (CMRglc) in cortical gray mater (GM) and subcortical white mater (WM) (Wu et al., 2004,b). In this study, the stabilities of the global and regional FDG lumped constants (LC) were examined. Parametric images (pixel unit: mg/min/100g) of FDG uptake rate (CURFDG) and CMRglc were generated and changes of CMR (glc) in whole brain, GM and WM were studied separately by using a MRI-segmentation-based technique. The GM-to-WM ratios of both CURFDG and CMRglc images were significantly decreased (>31%) in TBI patients that was highly correlated with the initial Glasgow Coma Scale score (GCS). The patients with higher CMRglc GM-to-WM ratios (>1.54) showed good recovery 12 months after TBI. There was also a selective CMRglc reduction in cortical GM following TBI. However, pathophysiological basis for the reduction in GM-to-WM CMRglc ratio seen on FDG-PET imaging following TBI remains unknown.

Abnormal metabolic cascades, in acute TBI patients, as evidenced by significant alteration of glucose utilization, may be also present in the

thalamus, brain stem, and cerebellum (Hattori et al., 2003). In this particular study, the regional cerebral metabolic rate of glucose (CMRglc) of cortical areas (remote from hemorrhagic lesions), striatum, thalamus, brain stem, cerebellar cortex, and whole brain was compared with severity of injury and the level of consciousness evaluated using GCSini (full form: Glasgow Coma Scale initial) and the Glasgow Coma Scale score at the time of PET (GCSpet). It was shown that regional CMRglc of the brain stem is relatively unaffected by the TBI. Compared with healthy volunteers, TBI patients exhibited significantly depressed CMRglc in the striatum and thalamus. CMRglc levels were not statistically lower in the cerebellum and brain stem. However, on comparison between comatose and noncomatose patients, CMRglc values in the thalamus, brain stem and cerebellar cortex were significantly lower than in comatose patients. It should be noted that CT or MRI findings were normal for the analyzed structures except for 3 patients with diffuse axonal injury of the brain stem. The presence of shear injury was associated with poor GCSini (full form: Glasgow Coma Scale initial). The metabolic rate of glucose utilization in these regions significantly correlated with the level of consciousness at the time of PET. It is feasible to assume that after traumatic brain injury (TBI), subcortical white matter damage may induce a functional disconnection leading to a dissociation of regional cerebral metabolic rate of glucose (CMRglc) between the cerebral cortex and deeper brain regions, including thalamus, brain stem and cerebellum. Not surprisingly patients suffering from TBI may experience long term behavioral deficits including abnormal balance and postural control.

2.3.   Neurochemical Cascade of Concussion

Direct evidence of diffuse abnormal neuronal excitation/inhibition in acute concussion can be obtained by examining depolarization of nerve cells soon after traumatic brain injury. This involves directly measuring ionic fluxes, in particular, the concentration of extracellular potassium (K^+) and the release of excitatory amino acid (EAA) neurotransmitters. The most common technique is the insertion of ion-sensitive microelectrodes into the animal brain immediately after the induction of experimental concussion (Takahashi et al., 1981). In a set of elegant experiments, microdialysis techniques were used to measure K^+ concentration in the hippocampus of an experimental rat right after mild or moderate induced concussions (Katayama et al., 1990). On a cellular level, several acute ionic changes may occur in concussed brains, such as the disruption of neuronal membranes, axonal stretching, and opening of voltage-dependent potassium channel leading to five fold increases of extracellular potassium (K^+). In addition, nonspecific membrane depolarization may disrupt neural

transmission by depolarizing neurons, leading to excess release of excitatory amino acids (EAA) such as glutamate, which exacerbates the potassium flux into the extracellular space by activating kainite, NMDA, and D-amino-3 hydroxy-5-methyl-4-soxazole-propionic acid (AMPA) receptors (Giza & Hovda, 2001). It seems that only when extracellular potassium reaches a critical threshold, does this trigger the release of EAA and other neurotransmitters from nerve terminals. Normally, excessive concentration of extracellular potassium is neutralized by surrounding glial cells allowing the brain to maintain physiological equilibrium of K^+ following mild disturbances. In fact, the EAA inhibitor drugs (i.e., kynurenic acid) may significantly reduce the post-traumatic potassium efflux in rats (Katayama et al., 1990). Moreover, EAA release may be unaffected by administration of TTX modified by cobalt, implying a role for neurotransmitter release. Within the scope of this pathological cascade the excessive extracellular K+ may trigger neuronal depolarization, release of EAAs and ultimately even greater concentration of extracellular K^+. Post-synaptic EAA receptors subsequently activate the opening of associated ligand-gated ion channels therefore permitting the rapid outflow of large amount of K^+ accompanied by the influx of extracellular calcium (Nisson et al., 1993). In other words, initially there is a massive excitatory process (due to excessive concentration of potassium) and this is ultimately followed by an abrupt wave of relative neuronal deactivation (outflow of K^+), and this phenomenon is known as *spreading depression.* There is a notion that acute loss of consciousness, memory loss and cognitive abnormalities are direct manifestations of post-traumatic *spreading depression* (Giza & Hovda, 2001).

Through a phenomenon known as excitotoxicity, glutamate activation of NMDA receptors open calcium (Ca^{2+}) channels and allows an influx of calcium into cells. Excessive accumulation of Ca^{2+} can damage intracellular organelles, especially the mitochondria resulting in aberrant oxidadative metabolism and ultimately energy crisis or failure. In fact, a potent N-type calcium channel blocker, SNX-111 may significantly reduce post-concussive calcium accumulation and may be suggested as a treatment with NMDA receptor antagonists (Samii et al., 1999; Giza & Hovda, 2001). Another trigger for influx of Ca^{2+} may be mechanical stretching of axons resulting in membrane disruption and mitochondrial swelling (Maxwell et al., 1995). Increased Ca^{2+} has been shown to lead to microtubule breakdown up to 24 hours post-injury and along with focal axonal swelling may lead to secondary axotomy and formation of axonal bulbs. These are other intra-axonal cytoskeletal pathologies that are commonly considered within the scope of diffuse axonal injury as a result of head trauma. It is important to note that post-traumatic increase in Ca^{2+} may not necessarily lead to immediate cell death, although, this may for sure lead to an impairment of mitochondrial metabolism. The detailed discussion of neurochemical cascades associated with excessive accumulation of intracellular Ca^{2+}

triggering the cell death is beyond the scope of this chapter. Again, electrolyte homeostasis is usually restored within minutes to hours post acute traumatic brain injury. However, long-term perturbations may occur, resulting in neuronal vulnerability to further insults and/or be responsible for post-concussive symptoms (Katayama, 1990). See Fig. 1 for details.
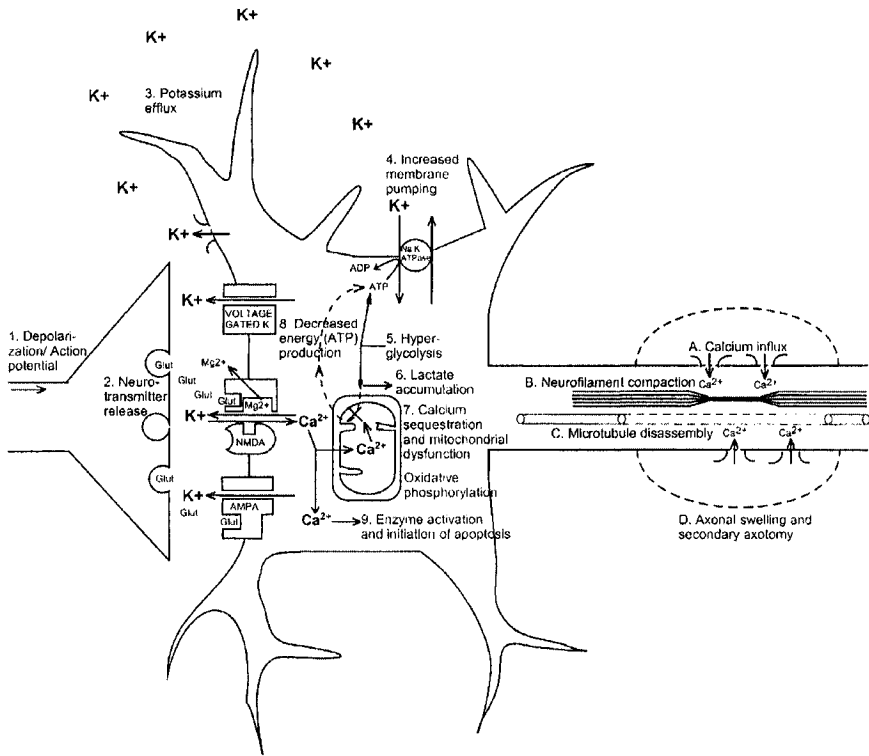

Fig. 1. Neurometabolic cascade following traumatic brain injury. (1) Nonspecific depolarization and initiation of action potentials. (2). Release of excitatory neurotransmitters (EAAs). (3). Massive influx of potassium. (4) Increased activity of membrane ionic pumps to restore homeostasis. (5) Hyperglucolysis to generate more adenosine triphosphate (ATP). (6) Lactate accumulation. (7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. (8). Decreased energy (ATP) production. (9) Calpain activation and initiation of apoptosis. A, Axolemmal disruption and calcium influx. B, Neurofilament compaction via phosphorylation or sidearm cleavage. C, Microtubule disassembly and accumulation of axonally transported organelles. D, Axonal swelling and eventual axotomy.

K+, potassium; Na+, sodium; Glut, glutamate; Mg2+, magnesium; Ca2+, calcium; NMDA, N-methyl-D-aspartate, AMPA, d-amino-3-hydroxy-5-methyl4-isoxazole-propionic acid.

(Re-printed with permissions from: Giza, C., & Hovda, D. (2001). The neurometabolic cascade of concussion. *Journal of Athletic Training, 36(3)*, 228-235.)

2.4. Second Impact Syndrome

In 1984, three athletes died from massive brain swelling after a minor concussion. In all three cases there had been an antecedent concussion from which they were still symptomatic- this typifies the second impact syndrome (Saunders & Harbaugh, 1984). Since then more than 50 such occurrences have been reported (Cantu, 1992; Cantu & Voy, 1995). The postulated pathophysiology is a defect in cerebrovascular autoregulation initiated by the initial concussion. Ongoing cerebrovascular vulnerability at the time of the second concussion triggers massive vasodilatation and subsequent lethal brain swelling due to a marked increase in cerebral blood volume. This notion has been called into question by autopsy findings of acute subdural hematomas in 15-20% of cases (Cantu & Voy, 1995). However, recent studies using transcranial Doppler ultrasonography to access cerebrovascular resistance and cerebral blood flow after concussion have demonstrated poor or absent cerebrovascular autoregulation in up to 30% of patients (Junger et al., 1997).

There are several potential pathophysiologies for the second impact syndrome. First, acute abnormal glucose metabolism and energy crisis shortly after traumatic brain injury indicate a window for potential vulnerability in the traumatized brain. Moreover, after the initial period of increased glucose unitization, the injured brain transits into a period of depressed metabolism (e.g., post-traumatic *spreading depression* (Giza & Hovda, 2001) that may lead to a long-lasting and worsening energy crisis. Thus, a secondary blow to the head delivered shortly after the first one may further exacerbate the energy crisis due to further demand in energy and previously impaired blood flow. Thus, an acute injured brain may be capable of recovering after the fist blow, but a second blow during energy failure can lead to irreversible neuronal injury and massive cell death. Another potential candidate for the second impact syndrome is that excessive Ca^{2+} accumulation that may irreversibly impair mitochondrial metabolism during the second blow to the head inducing massive cell death. Further development and elaborations on pathological mechanisms of second impact syndrome required additional empirical evidence and research.

2.5. Cumulative Effect of Concussion

Increasing evidence suggests that repeated concussions may have the potential for long term neurologic and cognitive sequelae. Several high profile athletes in recent years have ended their careers as a result of such concerns. The punch drunk syndrome or dementia puglistica was first described in 1928- and involved a spectrum of dementia, personality

disturbances and cerebellar or Parkinson-like symptoms (Martland, 1928). Subsequent retrospective studies of a number of former boxers with no neurologic or cognitive impairments found high rates of abnormalities on CT scans, electroencephalography and neuropsychological testing (Casson et al., 1984; 1982). One autopsy study found a high rate of neurofibrillary tangles, amyloid angiopathy and neuritic plaques (all markers of dementia) in 15 former boxers (Corsellis, 1973). Four of the 15 boxers' brains with clinically active Parkinson's disease demonstrated substantial substantia nigra depigmentation. There is also a line of evidence primarily from experience with boxers-, that there may be a genetic predisposition to both the severity of as well as the succeptibility to recurrent concussions. Jordan, et al. (1997) reported that the presence of a specific allele of the apolipopritein E (APOE) gene that was associated with an increased likelihood of severe cumulative effects in a study of 30 active and retired boxers.

Soccer players may also be susceptible to cumulative effects on cognition and neuropsychological functioning-, ostensibly from long term head to ball contact. Matser et al. (1998) found evidence of chronic neurocongitive impairments in 53 active European professional players. Retired soccer players have been found to have a variety of neuropsychological, CT scan and electroencephalographic abnormalities (Sortland & Tysvaer, 1989; Tysvaer & Lochen, 1991). In football, there is considerable ongoing debate over a cumulative effect of repeated concussions. Most studies, while finding significant neuropsychological impairment after single or multiple concussions have also found a resolution of these abnormalities within one to two weeks (Macciochi, 1996).

In a prospective cohort study of 2905 football players from 25 US colleges, Guskiewicz, et al. (2003) looked at the incidence and effects of repeat concussion over the course of three seasons. During this time concussions occurred in 184 players (6.3%), with 12 (6.5%) of these having a second concussion in the same season. Of players reporting three or more concussions, the only substantive finding was a prolongation of post-concussive symptoms as compared to those with one prior concussion- 30% with > one week of symptoms compared to 14.6%. Iverson, et al (2004) also studied amateur athletes with three or more concussions, comparing them to a matched group never having suffered a concussion, utilizing the *ImPACT* computerized neuropsychological test battery. On testing two days post-injury significantly lower memory performance was manifested by athletes with multiple concussions compared to athletes with none. However there was no long term follow up provided.

Over 5 seasons, information was collected on concussions reported by 30 National Football League (NFL) teams, with a 6.3% incidence of single and 6.5% incidence of multiple concussions (Pellman et al., 2004). Slower recovery from post concussive symptoms was seen more frequently in

players who had sustained multiple concussions. Of those with 3 or more concussions, 30% had symptoms lasting more than one week, compared to 14.6% with a history of only one concussion. However, at least one study has demonstrated persistence of neuropsychological abnormalities up to 6 months after multiple concussions (Wilberger, 1989). Serial neuropsychological testing, of up to 6 months in players showed a correlation between not only the number of concussions but also the duration and severity of neurocognitive abnormalities. The long-term significance of these findings, if any, is yet to be known. A comprehensive health survey of former NFL players found a correlation between the frequency of concussions and depression but not with the incidence of dementia or Alzheimer's disease. (personal communication, Bailes, J.B.). Thus, further research is necessary to define the true significance of the possible cumulative effects of concussion and its underlying pathology. However, it is clear that repeated brain injuries developed within a short time frame can lead to much larger neuroanatomical, cognitive and behavioral impairments than isolated brain injuries.

3.   TRAUMATIC INTRACRANIAL LESIONS

3.1.   Epidural Hematoma (EDH)

Epidural hematoma (EDH) is the accumulation of blood between the dura and the inner table of the skull. Normally, because the periosteal surface of the dura is densely adherent to the inner table of the skull, no epidural space exists. Traumatic blow to the head, usually of the acceleration-deceleration type resulting in inward deformity with or without skull fracture may cause the dura to separate from the inner table. As mentioned before, the separation may occur on the side of the trauma (*coup injury*) or the contra lateral side (*contra-coup injury*). Mostly arterial, the lesion is almost invariably post-traumatic and associated with a skull fracture and tearing of the meningeal vessels. An epidural hematoma may result from a tear of the dural sinus and thus be venous in origin. The other sources of bleeding into traumatically created epidural spaces include injury to intradiploic veins, middle meningeal artery or its posterior branches. This type of hematoma is more common in the posterior fossa and results from a tear of the transverse or sigmoid sinus. The shape of an EDH is usually biconvex and not crescentic, unlike the majority of subdural haematomas. Unlike subdural hematomas, the epidural haematomas at frontal, occipital or at the vertex may cross the midline. The classic CT appearance of an EDH is a sharply defined, biconcave, high-attenuation density interposed between the inner table of the skull and the brain (see Fig. 2). The mass compresses the brain and may also cause compression or obliteration of the ipsilateral

lateral ventricle and a midline shift. The hematoma is limited in extent by the sutural dural attachments. Excessive linear (translational) and/or angular (rotational) forces delivered to the cranium and transmitted to the brain may induce an patient' unconscious state, although, EDH is often not associated with primary head injury unlike subdural hematomas. Therefore, from a clinical perspective, a patient with EDH may initially appear asymptomatic until the hemorrhage reaches a critically large size excessively compressing underlying brain tissues.

Fig. 2. MRI scan showing epidural hematoma with significant mass effect.

3.2.   Subdural Hematoma (SDH)

   Subdural hematoma (SDH) is a post-traumatic collection of blood in the subdural space, usually venous in origin. The blood comes principally from torn superficial cerebral cortical veins separating the arachnoid from the dura, in effect creating a subdural space. Rarely a subdural haematoma may be due to rupture of an aneurysm and subsequent laceration of the arachnoidal membrane. In this case the subdural haematoma is almost invariably associated with a subarachnoid haemorrhage. SDH may occur on the side of impact or, more commonly, the contra-coup side. SDH may also occur following ventricular decompression of communicating hydrocephalus. In this instance, the origin of the blood is due to rapid stretching and disruption of the same veins injured in post-traumatic SDH. Post-ventriculostomy SDH is usually bilateral. SDH is most commonly located over the fronto-parietal cortical convexity and, secondly, above the tentorium cerebelli, usually crescentic in shape, compared to the lentiform shape of epidural haematomas. The shape, however, depends on a patient's age and his/her trophic state of the brain. For example, in young patients a subdural haematoma may have a lentiform shape. Moreover, subdural blood may extend along the falx, in the midline, thus producing interhemispheric subdural haematomas. There are two forms of subdural hematomas as a

result of head trauma. The acute subdural hematoma (ATSDH) presents within 24-48 hour post-injury while chronic subdural hematomas may present at a later time frame. Subdural haematomas are most often seen without fracture and develop as a consequence of shear stress forces leading to a rupture of subdural bridging veins (see Fig. 3). Subdural haematomas may develop subacutely or chronically or following a delay after trauma. Acute subdural bleeding usually develops by 1 of 3 mechanisms: bleeding from a damaged cortical artery (including epidural hematoma), bleeding from underlying parenchymal injury, and tearing of bridging veins which bridge the cortex to one of the draining venous sinuses. ATSDH is often associated with significant parenchymal injury and contusion, prompting some authorities to speculate that the associated mortality rate is unlikely to change despite new treatment plans for ATSDH. The contention is that the primary brain injury associated with subdural hematomas plays a major role in the patient's death. However, most subdural hematomas are thought to result from torn bridging veins, as judged by surgery or autopsy. Furthermore, not all subdural hematomas are associated with diffuse parenchymal injury. As mentioned earlier, many patients who sustain these lesions are able to speak before their condition deteriorates which is an unlikely scenario in patients who sustain diffuse damage.
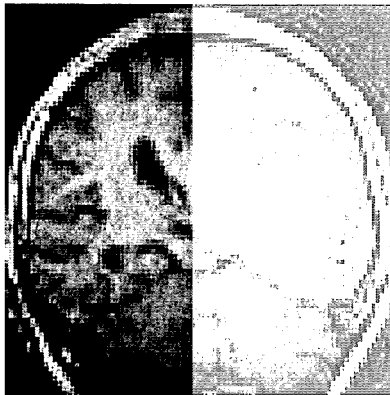

Fig.3. MR scan showing subdural hematoma

3.3. Intracerebral Hemorrhage (IH)

Intracerebral hemorrhage is bleeding into the cerebral parenchyma. It should be noted that the most common of causes of IH are non-traumatic hypertension, cerebral aneurysms, and vascular malformations. However, IH may occur following blunt trauma to the head resulting in cerebral contusion (e.g., a heterogeneous zone of brain damage that consists of hemorrhage,

cerebral infarction, necrosis, and edema). Contusions in athletes occur most often as a result of acceleration-deceleration mechanisms from the inward deformation of the skull at the site of excessive blows to the head. Contusions are often multiple and are frequently associated with other extra-axial and intra-axial hemorrhagic lesions. Extra-axial hemorrhage includes epidural and subdural hematomas, subarachnoid and intraventricular hemorrhages. Subarachnoid and intraventricular hemorrhage is often associated with severe cranial trauma. In the mildest forms the blood accumulates in the interpeduncular cistern and is often associated with the presence of blood in the ventricular occipital horns. It is important to note that even this mild form usually reflects severe brain trauma. Intra-axial hemorrhagic foci usually represent contused parenchymal tissue rather than true hematomas. Sometimes the hemorrhagic area extends, and this is believed to be the result of progressive hemorrhagic degeneration of primarily necrotic tissue. A particular type of intra-axial hemorrhage developing by an indirect post-traumatic mechanism is Duret's midbrain hemorrhage. This develops on an ischemic basis following compression of perforating arteries in the interpeduncular cistern owing to caudal displacement of the upper brain stem in case of severe brain swelling. The clinical course of patients with cerebral contusion varies greatly, depending on the location, number, and extent of the hemorrhagic contusion lesions. The patient may present with essentially normal function or may experience any type of neurologic deterioration, including coma. Frequently, behavioral or mental status changes exist due to involvement of the frontal or temporal lobes. The diagnosis of cerebral contusion is firmly established by CT scanning, which is also useful for following patients as the lesions evolve throughout their clinical course. Intracerebral hematomas along with subdural hematomas have been, the most common cause of sport-related lethal brain injuries (Bailes & Hudson, 2001).

CONCLUSION

Understanding the mechanisms, pathophysiology and potential sequelae of concussion is important for the proper protection of athletes, whether they be in recreational, collegiate or professional environments. Ongoing research is leading to an enhanced appreciation of this important problem in athletic endeavor and is providing new insights into prevention and treatment. Conventional wisdom considering concussion as a short-term phenomenon characterized by transient functional deficiencies is misleading given the scientific evidence presented in this chapter. Overall on the global level, normally cerebral blood flow (CBF) and metabolic demand for glucose utilization are coupled. However, there are obvious derangements in cerebral blood flow (CBF) as a result of traumatic brain injury. For

example, reductions in perfusion of up to 50% have been found while concomitant brain requirements for glucose may increase significantly (Yuan et al., 1988). The increased glucose requirement is related to the need for ATP production to power the ionic pumps to restore intra and extracellular electrolyte homeostasis. Thus, a significant uncoupling may occur. This generally resolves within minutes to hours, but can also be persistent and contribute to the brain's ongoing vulnerability. The abnormal metabolic cascade may be present at a remote site of brain injury, including the brain stem, thalamus and cerebellum. An acute injured brain may be capable of recovering after the fist blow, but a second blow during energy failure can lead to irreversible neuronal injury and massive cell death. These neurobiological evidences may be at odds with common practice to clear brain injured athletes for sport participation within few days post-injury solely based upon clinical symptoms resolution.

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