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Evidence-Based Review of Sport-Related Concussion: Basic Science

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Abstract: The evidence base for sport-related concussive brain injury is reviewed in this paper. In the past, pathophysiological understanding of this common condition has been extrapolated from studies of severe brain trauma. More recent scientific study demonstrates that this approach is unsatisfactory, and the clinical features of concussion represent a predominantly functional brain injury rather than manifest by structural or neuropathological damage. Such understanding of this condition remains incomplete at this stage.

Key Words: Concussion—Traumatic brain injury—Sport.

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INTRODUCTION

Although concussion is a well-recognized clinical entity, its pathophysiological basis remains a mystery. The clinical syndrome of concussion with a relatively short-lived period of posttraumatic neurologic dysfunction followed by full recovery has been described for over 3,000 years. Although many extensive and well-planned research studies conducted in the past have provided some understanding of the pathophysiological changes to the brain following mild head injury, the nature of these changes has not yet been resolved.[1,2]

DOES EXPERIMENTAL CONCUSSION TRULY REPRESENT CLINICAL CONCUSSION?

Since most brain injuries do not result in death, the study of human brains is necessarily limited in attempting to identify the neuropathologic changes occurring after clinical concussion. For this reason, experimental concussion using a variety of animal models has been the principal research tool. It remains controversial as to whether the results observed from these studies are an accurate representation of human concussion. Difficulty in interpretation of such studies include:

1. The use of anesthetized animals, which makes it difficult to characterize the acute clinical effects of brain trauma. In addition, the interpretation of posttraumatic amnesia and other cognitive symptoms cannot be readily evaluated in animals.[3–6]
2. Because the quantitative biomechanics of impact force is not yet established for the human case, the ability to compare experimental biomechanical and/or mathematical models is limited.[2,3,6–9]
3. Animals with small brains can tolerate much higher acceleration or deceleration forces due to certain mechanical factors such as the amount of extracellular space, posture, and differing geometry of the brain–spinal cord axis.[10–12] Similarly the use of cervical collar restraints may enable the animal to sustain much higher linear accelerations without the production of concussion.[4]
4. Most animal models use loss of consciousness as the principal evidence for the presence of concussive injury. Given that this occurs in the minority of cases of sport-related concussion,[13] the validity of such models using this domain as the sole determinant of concussion is open to doubt.

Despite these criticisms, in severe brain injury there is substantial evidence that animal models of traumatic brain injury provide reliable and valid information that may be applicable to human patients.[14] However, basic scientific research needs to focus on the physiological changes to the brain following milder forms of head trauma such as those sustained in sporting environments.

THE BIOMECHANICS OF CONCUSSION

Concussion is the result of acceleration–deceleration forces applied to the moving brain. This in turn causes shearing forces or distortion of the vascular and neural elements of the brain. The precise mechanism and bio-

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mechanical parameters that occur in response to neural tissue strain has not yet been determined.[15]

Applied loads to the head may be either static (with an impact time duration exceeding 200 ms) or dynamic (less than 200 ms).[7] When the head is immobilized, there is considerably more force needed to produce a concussion than when it is free to move.[2,16] Experimental animal concussion could only be produced at tested levels of acceleration up to 1,230 *g* when the moving head was free to rotate; no concussion was observed when head rotation was prevented or allowed only to translate.[11] It was also demonstrated that wearing a neck collar protected the brain during impact to the head presumably due to a reduction of the angulation of the head on the neck, which minimizes the shear strains in the brain.[11]

It has been shown in primate animal models of brain injury that static loads seldom result in loss of consciousness even with severe skull fractures and brain contusions.[2,7] On the other hand, dynamic loads (particularly angular acceleration) have been shown to be the common cause of head injury. Rotation, particularly in a coronal plane, appears to be necessary for loss of consciousness as well as diffuse and focal lesions in the brain.[11]

Other animal research, using a frog model, has demonstrated that concussion closely correlated with the acceleration of the head during a concussive below. A minimum threshold acceleration beneath which there was no neuropathologic change, and the maximum acceleration beyond which the neuropathologic changes were not immediately reversible, were demonstrated.[17]

In 1974, Ommaya et al. developed the centripetal theory of cerebral "concussion" (i.e., acceleration concussion). This theory invoked the geometric, structural, and material properties of the cranium and its contents. In this theory, the clinical effects of rotational acceleration are produced by a centripetal progression of strains from the outer surfaces to the core of the brain (coinciding with the midbrain and basal diencephalon). At low levels of inertial loading, injurious levels of shear strain would not extend deeper than the cortex, while strains large enough to reach the well-protected mesencephalic part of the brainstem would result in loss of consciousness.[11] Although this model reflects the clinical aspects of moderate-to-severe brain injury, it does not explain the clinical features of mild brain injury or concussion in the historical sense.[2] Also, there is other animal research that casts doubt upon these findings. In a primate brain injury model, Jane et al. showed that axon degeneration was apparent in the inferior colliculus, pons, and dorsolateral medulla, whereas no degeneration was observed in the subcortical white matter.[18] From a clinical standpoint, cases of concussion with transient loss of consciousness in the absence of cortical symptoms are commonplace.[19]

WHAT ARE THE PHYSIOLOGICAL CHANGES TO THE BRAIN FOLLOWING CONCUSSION?

The effects of diffuse injury to axons and neurones sustained at the time of head injury may or may not be reversible depending on the magnitude of the blow. Some authors have suggested that strains produced by all head injuries result in axonal injury such that they become stretched and distorted, producing axonal dysfunction.[6,15,18,20,21] Recent experimental evidence suggests that the pathogenesis of axonal dysfunction resulting from head trauma is complex.[22] Alteration in axolemmal membrane permeability induced by impact may cause alterations in ionic flux and exert either direct or indirect effects upon the axonal cytoskeleton.[22]

In addition, Hovda et al. revealed that a cascade of neurochemical, ionic, and metabolic changes occur following experimental brain injury.[14] Most notably, an injury-induced ionic flux across the cell membrane due to the release of the excitatory amino acids has been shown to increase glycolysis with a dissociation of metabolism and cerebral blood flow, resulting in a state of metabolic depression.[14] Each element of the cascade has a different time window that may have important implications in both assessing and treating concussed individuals.[14]

Other investigators have shown that mechanical stress can produce a sudden neuronal depolarization, followed by a period of nerve cell transmission failure.[6] In animal experiments, this also has been consistently observed in the reticular formation of the midbrain following a concussive blow.[23] Trauma-induced membrane depolarization coupled with changes in cytoskeletal structure result in aberrant cellular signalling pathways that are reflected in the acute genomic response to injury.[24,25]

Brain vascular structures also may be vulnerable to injury. Neuronal cell loss in specific regions of the hippocampus, and breakdown of the blood–brain barrier, have been demonstrated in an animal study of severe brain injury.[26] The resultant ischemic degeneration in hippocampal cell fields was associated with significant memory impairment. Blood–brain barrier disruption also may allow a window of opportunity for compounds, such as excitotoxic amino acids, to cross this breach and cause local injury.[27]

In human brain injury cases, alterations in cerebral blood flow have been demonstrated. Where ongoing postconcussive symptoms have been present, reduced cerebral circulation time[28] and cerebral vasoconstriction with altered CO reactivity has been demonstrated.[29]

The relationship of alteration in intracranial pressure following head injury has also been studied. In severe brain injury or where "malignant" brain edema[30] complicates an acute injury, a prolonged and marked increase in intracranial pressure frequently occurs and may be sufficient to cause death due to respiratory arrest.[31] In concussive injury, no change in intracranial pressure has been demonstrated in animal models.[16] Similarly, it has been shown that diffuse axonal injury is not due to raised intracranial pressure.[32]

The traumatic coma of experimental cerebral "concussion" has been shown to be associated with failure of activity in the mesencephalic reticular formation.[11] Several studies in different animal models of experimental concussion have also demonstrated ultrastructural and biochemical alterations in the brainstem structures.[3,18,33]

Although experimental research has enhanced our understanding of the physiological changes to the brain following severe head trauma, there still remains uncertainty as to what is happening to the brain following minor concussive injuries and, in particular, sport-related concussion.

WHAT IS THE NEUROPATHOLOGY OF CONCUSSION?

The nature of transient loss of cerebral function following a blow to the head has excited much speculation over the centuries, directed as to whether microscopic neuropathologic changes occur or whether other cerebral pathophysiological processes manifest the clinical symptoms of concussion. At this stage these important issues remain unresolved.

Denny-Brown and Russell demonstrated the absence of neuropathologic change in a primate model of concussion, and suggested that concussion reflected a transient or functional disturbance in neurologic function.[16] Nevertheless, Sir Charles Symonds, an influential English neurologist, proposed that widespread irreparable damage resulted from cases of severe concussion, and that even in the slightest degree of concussion, there probably were a small number of perished neurons.[34] This idea was supported by Peerless et al., Povishlok et al., and Oppenheimer, who argued more specifically that diffuse axonal injury was the pathologic basis of traumatic unconsciousness or coma in concussion.[21,35,36] However, there are however a number of methodological problems with these studies.

Oppenheimer reported that diffuse microscopic lesions were evident in cases of "concussion."[35] This paper has subsequently become one of the most widely cited histologic studies of concussion in man. There are a number of concerns with this study, not least being the lack of clinical detail provided and the absence of exploration of potential confounding factors such as age or alcohol use. It also seems surprising that although Oppenheimer stated that it was not his intention to address "the meaning of the term concussion or its pathologic basis," his study continues to be cited to this day, often exclusively, as the basis for the notion of permanent damage following concussion. Gennarelli has offered an alternative analysis of these results suggesting that the number of damaged axons and neurons in this study was too small and not widely enough distributed to explain all of the clinical phenomena of concussion. He therefore concluded that many more axons must be affected at a functional level without permanent damage.[15]

In Peerless and Rewcastle's study, conclusions were drawn regarding the pathophysiology of concussion from histologic examination of only three cases of severe head injury.[21] Povishlok et al. is the other commonly cited paper in this area. The authors set out to demonstrate axonal injury in a fluid percussion cat model of minor head injury and then extrapolated their animal model findings to human concussion.[36]

Many authors have characterized the entity of diffuse axonal injury (DAI) in further animal and human studies; however, in these cases the clinical manifestation that they are studying reflect moderate-to-severe brain trauma rather than the entity of concussion.[37–45]

The duration of unconsciousness may reflect the likelihood of brain pathology. In one animal study, the length of unconsciousness was predictive of histologic damage at 48 hours after head injury. This pathologic change was particularly marked if loss of consciousness persisted for 4 minutes or more.[46] Limited studies in mild brain injury do not support the notion of loss of consciousness as a primary determinant of injury severity.[47]

IS THERE A GENETIC SUSCEPTIBILITY TO BRAIN INJURY IN SPORTS?

Recent research in boxers has suggested that chronic traumatic encephalopathy (CTE) or the so-called "punch drunk syndrome" may be associated with a particular genetic predisposition. The apolipoprotein E (ApoE) epsilon-4 gene (ApoE4), a susceptibility gene for late onset familial and sporadic Alzheimer's disease, may be associated with an increased risk of CTE in boxers.[48–51] In a nonboxing population, ApoE4 polymorphism was significantly associated with death and adverse outcomes following acute traumatic brain injury as seen in a neurosurgical unit.[52] In a recent prospective study of severe traumatic brain injury, ApoE genotypes were tested for their ability to predict days of unconsciousness and functional outcome after 6 months.[53] There was a strong association demonstrated between the ApoE4 allele and poor clinical outcome.

Furthermore, ApoE-deficient (knockout) mice have been shown to have memory deficits, neurochemical changes, and diminished recovery from closed head injury when compared with controls.[83] It is suggested that ApoE plays an important role in both neuronal repair[84] and antioxidant activity[83] resulting in ApoE knockout mice exhibiting an impaired ability to recover from closed head injury. Although only in early stages, the interaction between genetic and environmental factors may be critical in the development of postconcussive phenomena and/or sequelae.

WHAT IS THE RISK OF REPEAT CONCUSSIONS IN SPORT?

It has become a widely held belief that, having sustained a concussive injury, you are then more prone to future concussive injury; however, the evidence for this is at best slim. In a widely quoted study by Gerberich et al., which involved self-reported questionnaires relating the prior history of head injury in high school gridiron football players, it was found that there was an increased risk of subsequent concussions in players with a past history of concussion.[54] Significant methodological problems flaw this study. Not least is the fact that they not only included cases of concussion but catastrophic brain injury as well. Furthermore, the reliability of a self-diagnosis of concussion is questionable given that

only 33% of those with loss of consciousness and 12% of those with other symptoms were medically assessed. The majority of the diagnoses of "concussion" were by the coach, other teammates or by the players themselves. In fact, in a recent study (Delaney et al., unpublished observations), four of five concussions were not recognized as such by professional football players.

It would seem obvious that in any collision sport, the risk of concussion is directly proportional to the amount of time playing the sport. In other words, the more games you play, the more chance of an injury occurring. Therefore the likelihood of repeat injury may simply reflect the level of exposure to injury risk.

In addition, the authors acknowledge that the observed increased likelihood of concussion could also be explained by a player's style of play. Using dangerous game strategies and illegal tackling techniques may increase the player's risk of injury. In other words, players with more self-reported "concussions" may actually put themselves at further risk of head injury by their dangerous play, not because simply having one concussion necessitates a higher risk of subsequent concussions. Similar criticisms can also be levelled at another retrospective study, where it was reported that once an initial concussion was sustained, the probability of incurring a second concussion greatly increases.[55]

DOES REPEAT CONCUSSION RESULT IN CUMULATIVE DAMAGE?

Apart from boxing-related head injuries, the most widely cited studies of the cumulative effects of concussion have investigated patients who had suffered injuries sustained in motor vehicle accidents and injuries severe enough to warrant presentation to hospital. Generally, concussive injuries suffered in sports such as football involve lesser degrees of acceleration–deceleration forces than that experienced in motor vehicle accidents.[56–59] Athletes with sport-related injuries typically recover quickly and usually do not require acute hospital admission.

It is widely acknowledged that boxing carries with it a high risk of neurologic injury. Boxing, however, should not be considered as a model for cumulative head injury seen in other sports, since it presents unique risks to the athlete in terms of the frequency of repetitive head trauma.[60–63]

Limitations of retrospective studies in concussion, such as the widely cited motor vehicle accident studies by Gronwall et al., include diagnostic uncertainty relying on self-reported injury recall and the unreliability in the assessment of severity of previous injuries. For example, some head injuries in the cited studies were "assessed" up to 8 years after their occurrence with no medical documentation.[56–59] Although methodological problems flaw this study, however, the study supports the contention proposed by Symonds[20] that cumulative deficits may follow repeated concussive injury, such as evidenced by the "punch drunk" state of chronic traumatic encephalopathy seen in boxing.[62,64]

In another series of retrospective studies involving retired Scandinavian soccer players, although cognitive deficits were noted, significant methodological problems flaw the study,[65–68] notably, the lack of preinjury data, selection bias, lack of observer blinding, and inadequate control subjects. Approximately 40% of the control group were found to be cognitively impaired. The authors conclude that the deficits noted in the former soccer players were explained by repetitive trauma such as heading the ball. The pattern of deficits, however, is equally consistent with alcohol-related brain impairment, a confounding variable that was not controlled for. To date, no independent group has been able to duplicate these findings.

In other retrospective studies involving a wide range of traumatic brain injury, loss of consciousness was associated with evidence of permanent change in fine motor control. The significance of this symptom in isolation from other cognitive domains is questionable.[69] Other studies have suggested that this may be an effect of environmental factors rather than due to the effect of injury.[70]

There have been few prospective studies of sport-related concussion.[13,71–74] In a study of American gridiron football, the authors found that, while information processing deficits were evident within 24 hours of injury, neuropsychologic function had returned to normal levels when it was retested within 5 to 10 days following injury.[71] Similar findings were reported in studies of Australian Rules football players. Concussive injuries in this sport tend to be mild, with neuropsychologic performance returning to preinjury levels within the first few days following injury.[13,72,73] Similarly, postconcussive symptoms such as headache, nausea, poor concentration, and fatigue also resolve within the first few days postinjury. The classic "postconcussive syndrome," which is frequently seen following brain trauma sustained in motor vehicle crashes, is seen less often in the sporting situation.

Similarly, there is little evidence that sustaining several concussions over a sporting career will necessarily result in permanent damage. The anecdotal approach was originally proposed by Quigley in 1945 and adopted by Thorndike, who suggested that if any athlete suffered three concussions that involved loss of consciousness for any period of time, the athlete should be removed from contact sports for the remainder of the season.[75] This approach has no scientific validity yet continues to be quoted to this day as the main rationale in most of the return-to-play guidelines.

In animal studies of experimental concussion, animals have been repeatedly concussed 20 to 35 times during the same day and within a 2-hour period. Despite these unusually high numbers of injuries, no residual or cumulative effect was demonstrated.[9]

The consensus on the cumulative effect of a concussion will not be resolved until there is a comprehensive definition and grading scale for concussion severity. With that established, whether repeated brain injury (or concussion) is cumulative will not be the question, but

rather what severity of an injury causes summation and for how long does this residual effect last?

DOES REPEAT CONCUSSION RESULT IN SECOND IMPACT SYNDROME?

Second impact syndrome (SIS) frequently is mentioned in the concussion literature but surprisingly has little scientific evidence for its existence. It is a term used to describe the potential catastrophic consequences resulting from a second concussive blow to the head before an individual has fully recovered from the symptoms of a previous concussion.[76,77] The second head injury is believed to result in loss of cerebrovascular autoregulation, which in turn leads to brain swelling secondary to increased cerebral blood flow.[30,78,79] Mortality in this condition approaches 100%.

In a recent paper, the evidence that repeated concussion was a risk factor for this condition was critically reviewed.[80] Published cases of SIS were classified as definite, probable, possible, or not SIS according to four criteria. In order for a case to be classified as definite SIS, all four criteria must have been satisfied. Seventeen published cases of SIS were identified. None were classified as "definite" SIS, five were considered to be "probable" SIS cases, and 12 were classified as "not" SIS, primarily because there was an absence of a witnessed second impact.[80] In addition, the veracity of team mate recall of concussive episodes, which is often the basis of a "first impact" in such cases, was shown to be unreliable. Based on these results, the investigators concluded that there is a lack of evidence to support the claim that SIS is a risk factor for diffuse cerebral swelling.

Even if there had been proper documentation that satisfied the four criteria listed above, the fact that there have been only a handful of published articles leaves many sport practitioners questioning the actuality of this syndrome.[81] In this paper, the central issue is whether repeated concussion was a risk factor for cerebral swelling, which is the putative definition of SIS. There is published evidence that acute (and delayed) brain swelling may occur following a single blow to the head and also in association with a structural injury such as a subdural hematoma.[82]

Although the scientific evidence for SIS is lacking, the repercussions of placing an athlete at risk for the potential consequences of a "second impact syndrome" is the basis of existing return-to-play guidelines that recommend removal of a concussed athlete from play. However, if SIS is not a real entity, such management recommendations may be inappropriate.

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