Lessons from NATURE: methods for traumatic brain injury prevention

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Abstract

Multiple species obtain repetitive head collisions throughout the course of their lifetimes with minimal neurologic deficit. Nature has allowed the unique development of multiple protective mechanisms to help prevent neurotrauma. In this review, we examine the concept of rapid brain movement within the skull ‘Slosh’ and what nature teaches on how to prevent this from occurring. We look at individual animals and the protective mechanisms at play. Marching from macroscopic down to the molecular level, we pinpoint key elements of neuroprotection that are likely contributing. We also introduce new concepts for neuroprotection and address avenues of further discovery.

Keywords

Neurotrauma; Slosh; Nature; Neuroprotection; Emerging strategies

Introduction

Lessons from Nature

In nature, it is common for certain animals to experience repetitive head impacts with minimal to no head damage and/or long-term consequences. Specifically, birds such as the woodpecker and the diving gannet, along with horned/antlered animals like the bighorn sheep and deer engage in activities that necessitate head impacts on a routine basis [1]. Woodpeckers strike trees to look for food and develop nests. Diving gannets strike the water at high speed to catch prey. Horned animals compete for mates by head butting.

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On average, woodpeckers slam their beak into tree trunks at a rate of 18–22 times per second, to either search for food or to create a nest [2]. This translates to woodpeckers moving their heads at 15 miles per hour. With each peck, a woodpecker undergoes a force between 1,200–1,400 times that of Earth’s gravity (g) [3]. To put this into perspective, a sudden implementation of 50 g would detach the connective tissue that surrounds much of a human’s organs [3]. Another bird that frequently experiences head impacts are the diving gannets. Diving gannets forage for food in the ocean. Diving gannets make 20–100 dives per foraging trip, and with each dive, the head of a diving gannet can collide with the surface of the water at speeds up to 20 meters per second [4]. Furthermore, animals such as the big-horned sheep use their horns as weapons in combat to compete for mates or guard territory. The cranial impact of a collision of horns between two big-horned sheep can be up to 3400 newtons per collision [5].

Unique anatomical characteristics of these animals enable the repetitive head collisions with limited deleterious consequences. Specifically, the woodpecker has a small subdural space and a unique tongue structure that limits brain movement [6]. The tongue of a woodpecker is notable because it extends posteriorly from the base of the mouth, around the neck, over the occiput, and into the right nostril. This creates a muscular sling inside the head of woodpeckers which has previously been identified as a possible shock absorber. In addition, the hyoid bone has been shown to aid the dissipation of energy during impact. Similarly, the horn of a big-horned sheep is a large, hollow curled structure primarily composed of keratin [7]. The distinctive tapered spiral horn geometry reduces the load more efficiently than other geometries, such as a tapered bar [7].

In contrast, although the human anatomy clearly differs from that of a woodpecker or big-horned sheep, the tightening of the muscles around the internal jugular vein (IJV) may possibly reduce the trauma experienced by an individual during head collision (Figure 1). The proposed principle is that by increasing venous engorgement, the ability for the brain to move within the cerebrospinal fluid becomes limited. This phenomenon of constricting neck muscles for impact is commonly observed amongst boxers and may indicate why they are able to sustain repeated forces of great magnitude. The development of collars that can aid athletes and warfighters is also a topic of ongoing investigation. The remainder of this review will look at the principles that mediate brain protection in association with traumatic brain injury (TBI).

**Mechanisms of Energy Transfer: Shortcomings of Helmets**

The injury process in traumatic brain injury often involves coup-contrecoup injury. The coup and contrecoup insults result in a focal contusion at the site and opposite site of impact, respectively. Direct head impact produces a focal cerebral contusion. Subsequent acceleration of the brain to the opposite side of the skull then results in a similar lesion opposite to the initial impact (Figure 2) [8]. Several other proposed mechanisms that likely contribute to the injury process exist. A study with balloons filled with fluids of different densities mimicking the brain and cerebral spinal fluid (CSF) suggest that the denser CSF shifts toward the impact site and displaces the brain to the opposite side of the skull [9]. Not surprisingly therefore, the contrecoup injury represents the initial impact of the brain.
with the skull and explains why the contrecoup injury site is often more severe [10]. Positive pressure theory suggests that contrecoup injury is a result of the brain lagging behind the skull and compressing against the opposite side of injury during the initial movement [11]. The negative pressure and shear stress theories on the other hand suggest that axial and rotational brain movements directly causing damage, respectively [12]. Helmets have largely proved successful in preventing skull fractures from primary and secondary impacts. However, they do not similarly protect against closed head injury, including focal contusions, hematomas, and concussions. The distribution of energy across the helmet and skull prevents fracture but may not adequately dissipate energy transmission affecting the brain [13]. Newton’s cradle is a device that uses swinging spheres in series to demonstrate the conservation of momentum and kinetic energy (Figure 3). Force is transmitted through the middle spheres, which remain stationary. Molecules partially connected by electrostatic forces constrain each other and transfer the pressure wave to the last sphere. This transfer can occur when a dense object is immersed in a less dense medium [14]. For example, in lithotripsy, shock waves can destroy kidney stones without the injuring intermittent structures. An ideal system would be one of elastic collision in which the head and brain transfer but do not absorb energy. A helmet with a soft outer layer covering the hard inner layer may take advantage of this concept. The soft layer may reduce the initial severity and facilitate the transfer of energy as seen in Newton’s cradle. Such helmets have been developed, though their efficacy is unknown, representing an opportunity for future research.

**Macroscopic Approaches for Preventing TBI**

The pathophysiology of TBI is complex and mitigated by various mechanisms that are interconnected; however, analysis of these mechanisms and their commensurate prevention may be simplified by examination through categorization of the pathophysiology into macroscopic, microscopic, and molecular causes. Macroscopically, TBI is mediated by direct force to the head as well as differences in the physical mechanics related to the components of the central nervous system and its surrounding structures [8,15]. Within the skull, there is the brain, CSF, and a system of vascular structures, which serves to perfuse the brain through various arteries. The system drains through a series of venous structures located within dura [8,16,17]. As the skull is an inelastic, rigid structure, interaction with the brain may cause mechanical injury [8]. Therefore, the skull is filled with a complex network of CSF, which circulates within the ventricular system and, notably, is present within the subarachnoid space. The CSF functions to prevent mechanical injury to the brain by acting as a buffer to absorb shock [16,17]. However, the suspension of the brain in CSF confers freedom of movement of the brain within the skull, which may also lead to mechanical injury [15]. For example, direct force to the head may cause a cerebral contusion and acceleration of the brain within the skull [8]. This aforementioned acceleration then may cause the brain to impact the side of the skull opposite to the injury [8,15,18]. Together, these injuries are known as, ‘coup contrecoup injury’ [17], and the mechanism of injury through which dynamic forces cause movement of the brain and its fluids within the skull is known as ‘slosh’ [6,15,19]. As most conventional protective methods, such as helmets, protect the skull but fail to mitigate the brain’s freedom of movement, slosh injury is
not addressed by these conventional methods [15,19]. To properly address slosh injury, protective methods must focus on the freedom of movement of the brain within the skull.

Increases in intracranial volume cause a reduction in intracranial compliance thereby reducing the brain’s movement within the skull, or slosh, and risk of TBI [6,15,19]. Of the components within the skull (the brain, CSF, and blood), blood is the component that is acquiescent to rapid changes in volume and, thereby pressure [15]. Therefore, an increase in cerebral blood volume would allow a reduction in intracranial compliance and confer protection to TBI through reduced intracranial collisions [6,15]. As previously mentioned, the cerebral vasculature drains through a series of venous channels with primary outflow via the IJV [16]. Constriction of the IJV alters intracerebral venous hemodynamics by reducing cerebral venous drainage, which increases intracranial volume as evidenced by an increase in intracranial pressure (ICP) and intraocular pressure (IOP) [20,21]. This is similar to the previously described Queckenstedt maneuver, where compression of the bilateral IJVs results in increased ICP [6]. Additionally, it is important to note the relationship between the intracranial volume and ICP as described by the Monro-Kellie doctrine (Figure 4) [22].

To assess the effect of IJV constriction, a rat model used a compressive collar to induce constriction of the IJV, which resulted in over a 30% increase in ICP and IOP within seconds [15]. Additionally, rats equipped with the compressive collar showed a reduced severity of TBI injury, as evidenced by the number of amyloid precursor protein-positive (APP-positive) neurons on autopsy: p <0.01 [15]. In a similar rat model, collar-induced IJV compression resulted in a 48.7%–59.1% reduction in degenerative neurons as evidenced by fluoro-jade B (FJB), a 36.8%–45.7% decrease in reactive astrocytes as measured by glial fibrillary acidic protein (GFAP), and a 44.1%–65.3% reduction in microglial activation as evidenced by ionized calcium-binding adapter molecule 1 (IBA1) [6]. This cerebral protection through venous constriction and resulting increased IOP is also found to be a protective element of woodpeckers [6,15,23].

Furthermore, a similar mechanism may be capable in humans [6,15,19]. In humans, the IJV passes between the two muscle bellies of the omohyoid [6,24]. Therefore, constriction of the IJV by contraction of the omohyoid may result in this same alteration of intracerebral hemodynamics and protection from TBI [6,15]. Some researchers hypothesize that professional boxers are able to withstand expected blows much greater than unexpected by the contraction of the neck muscles, including the omohyoid [6]. Other research has demonstrated that muscle contraction prior to impact reduces head kinematics [25,26], and that neck strength is a protective factor against TBI [25–27]. This protective effect is likely related to biomechanical protection against head acceleration but may also include protective effects caused by neck muscle constriction of the IJV. To enhance the protective effect, IJV compressive collars have been examined in American Football and shown to reduce white matter changes after repetitive head impacts [28,29]. Similar jugular collars have also demonstrated the protective effect against slosh injury in military and police training during explosives training [30–32].
Microscopic Approaches for Preventing TBI

In nature, there are several animals that withstand repeated head impacts of significant force without resultant long standing injury. Birds and Bighorn sheep may both have developed unique respiratory adaptations that allow for increased carbon dioxide (CO$_2$) mediated cerebral blood flow alterations that have a neuroprotective effect during impacts.

The avian respiratory system is a unique and efficient system of gas exchange, delivering oxygen to tissue and removing CO$_2$ from blood. Physically distinct from the mammalian respiratory system it utilizes nine air sacs and a pair of lungs. Birds have two cervical air sacs, an unpaired clavicular sac, two cranial thoracic sacs, two caudal thoracic sacs, and two abdominal air sacs (Figure 5). The sacs are arranged into two groups, those coming off the anterior of the lungs and those arising from the posterior of the lungs. These thin-walled structures are composed of simple squamous epithelium, a thin layer of connective tissue and blood vessels. Unlike other vertebrates whose lungs allow for bidirectional flow of air due to expansion and contraction, the avian lungs are static with the air sacs functioning as bellows that expand and contract, forcing air though the lungs in a unidirectional fashion [33].

The respiration of birds consists of two cycles of inhalation and exhalation. In the first inhalation, air enters through the nares, goes down the trachea and into each primary bronchus. Some enters the lungs and participates in the exchange of oxygen and CO$_2$ through the air-capillary system, while the remainder enters the posterior sacs. When the bird exhales, the fresh air in the posterior sacs then enters the lungs, displacing the spent air. Thereby the process facilitates gas exchange. The spent air exits through the trachea. During the second inhalation, the air again enters through the trachea into the posterior sacs and lungs, displacing the spent air, but cannot yet exit through the trachea due to the inward flow of air. Instead, the CO$_2$ rich air enters the anterior sacs. During the second exhalation, air from the lungs and anterior sacs is expelled through the trachea [33].

Additionally, the respiratory sacs invade the bone via diverticula, thus pneumatizing them. When the diverticula come into contact with each other, they may unite, creating a continuous airway from the sacs into the bone. Pneumatic bones are common in the skull, humerus, clavicle, keel (sternum), pelvic girdle, and the lumbar and sacral vertebrae in birds that fly [33].

Bighorn sheep possess horns that are made up of an outer sheath that encases a bone core called the horncore. The outer sheath is made of keratin, the protein found in human hair and nails, and is organized into a protein-based matrix of lamellar sheets [7]. These sheets form hollow, elliptical tubules dispersed between layers that extend and grow forming the horn. Myers et al. has suggested that the horns of the bighorn sheep are themselves pneumatic organs, continuous with the respiratory system, thereby allowing the animal to rebreathe its air to increase the carbon dioxide within its blood. The increase in the partial pressure of CO$_2$ would induce vasodilation and subsequent increased intracranial volume, creating a tighter fit of the brain inside the cranium, reducing slosh, and thus, brain injury [34].
CO₂ is a mediator of cerebral blood flow (CBF), and this effect has been well studied. Physicians first started to explore the use of hyperventilation to lower cerebral blood volume and ICP during the 1920s [35]. CO₂ concentration is a key determinant of intracranial volume and elevated arterial CO₂ tension leads to a reversible relaxation and dilation of cerebral arteries and arterioles and increased CBF, whereas hypocapnia causes constriction and decreased blood flow [36]. The vasodilator effects of CO₂ in humans are demonstrated by the observation that inhalation of 5% CO₂ results in an 50% increase in CBF, and 7% CO₂ inhalation causes a 100% increase in CBF [37]. Cerebral blood volume is also impacted by alterations in the partial pressure of CO₂, but the relative change is less marked than CBF [38]. CO₂ is not only a potent dilator of cerebral vasculature; it is also an effective ocular vasodilator of retinal and optic nerve blood flow [39].

Given the potential physiologic explanations for the observed protection from brain injury in animals such as the hummingbird and bighorn sheep, it is no surprise that the search continues for a similar approach to manipulate CO₂ in humans. By increasing the partial pressure of CO₂, we may induce cerebral vasodilation and lead to increased ICP, thus reducing the shearing and cavitation caused by rapid acceleration/deceleration that are the hallmark of slosh-injury [34]. Increased partial pressure of CO₂ or hypercapnia not only mitigates macro-slosh injury, it also may also reduce molecular slosh of hemoglobin molecules present within red blood cells by reducing the absorption of forces by the tissue through an increase in the elasticity of collisions. Hypercapnia may be induced by a respiratory circuit which could be a breathing or non-breathing circuit mask, or a breathing circuit capable of controlling the amount of inhaled CO₂ (Figures 6 and 7).

Because of the interplay between intracranial volume, partial pressure of CO₂ and severity of TBI, it was suspected by Smith et al. that the physiologic acclimatization to increased altitude may lead to changes within the cranium that would reduce the rate of concussion experienced by high school athletes. These changes include increased ICP and would be a result of hypoxic vasogenic edema. They showed that among athletes playing at a higher altitude, there was a 31% reduction in the incidence of total reported concussions and 30% decrease in concussion rate for overall exposures, 27% for competition exposures, and 28% for practice exposures in football players. This study included nearly 6000 athletes from almost 500 schools with locations ranging from 2.1–2104 meters above sea level [40]. A follow up to this epidemiologic study was conducted by Myer and Smith et al. amongst National Football League (NFL) players, hypothesizing that games played at a higher elevation would have a lower rate of concussion than games played at a lower elevation. They found that the rate of concussion was 30% lower in games played at or above 196.3 meters. These results show that like bighorn sheep and other animals, a protective effect of hypercapnia induced increase in intracranial blood volume may be present in humans, albeit to a smaller degree [34].

**Molecular Approaches for Preventing TBI**

Targeted molecular modifications affecting erythrocyte membrane properties, hemoglobin structure, and blood viscosity are promising avenues to reduce TBI [41]. These therapeutic approaches are hypothesized to act via modulation of intracranial compliance, thus
minimizing the slosh effect. Erythrocytes cannot execute typical cellular repair processes like a nucleated cell; thus, many molecular alterations last the lifetime of the cell. After TBI, one of the primary injuries to erythrocytes is compromised cell membrane function \[42\]. Animal models of TBI have revealed an increase in markers of lipid peroxidation in RBCs as well as increased aggregation and decreased electrophoretic mobility, both markers of RBC function and membrane distensibility. Experiments with isolated human blood have shown similar trends; blast waves transmitted through steel containers cause lysis of erythrocytic cell membranes but can be mitigated by decreasing free space within the container to reduce the slosh effect \[43\]. Translation of this principle into \textit{in vivo} systems could be achieved with interventions which increase erythrocyte volume or blood viscosity (Figure 8).

As discussed in previous sections, the partial pressure of CO\(_2\) is a critical mediator of cerebral autoregulation as well as erythrocyte function \[44,45\]. Hypercapnia causes a right shift in the oxyhemoglobin dissociation curve, thus increasing O\(_2\) off-loading in hypoxic tissues. Further, increased pCO\(_2\) increases RBC volume through accumulation of bicarbonate, chloride, hydrogen, and other ions \[46,47\]. This effect serves to increase the viscosity of blood by increasing the proportion of total volume held within the cellular compartment \[48\]. Increased blood viscosity along with increased cerebral blood flow may be the crucial factors explaining the observation of fewer concussions during football games played at higher altitudes \[34,40\]. These factors are also consistent with the hypotheses explaining the innate neuroprotection seen in Bighorn Sheep. Hypercapnia induced by altitude and their unique respiratory anatomy allows Bighorn Sheep to minimize intracranial compliance and reduce the fluid slosh effect.

Pharmacologic modulation of erythrocyte function and total cerebral blood flow with the carbonic anhydrase acetazolamide could leverage these principles to prevent TBI (Table 1). Single doses of acetazolamide are sufficient to increase cerebral blood flow \[49\], which could potentially beneficial in reducing brain slosh although this remains to be tested directly. Another study demonstrated acetazolamide treatment prior to exercise resulted in elevated arterial and venous CO\(_2\) partial pressures \[50\], which may impart all of the benefits of hypercapnia on brain dynamics during TBI. More investigation in disease-specific contexts is needed to fully evaluate the therapeutic potential of acetazolamide in TBI prevention.

**TBI & Hearing Loss: A Shared Mechanism**

The association of TBI of the blast variety with hearing loss is well established \[51\]. Within the subset of TBI patients, Lew et al. noted that those with blast-related TBI have significantly higher rates of hearing loss than those with non-blast-related TBI (62% vs 44%, \(p=0.04\)) \[52\]. Barotrauma-mediated tympanic membrane rupture is one well-characterized mechanism of hearing loss following blast exposure \[53\]. However, slosh-mediated damage to anatomical structures involved in audition may be another mechanism for hearing loss following blast exposure. Cochlear hair cells may be particularly susceptible to slosh-mediated damage in the setting of blast-related TBI, due to their relative fragility and mobility in the inner ear. Thus, mitigating slosh may help prevent damage to these structures.
during blast-related TBI. One proposed mechanism of slosh-mitigation in this setting is increasing intracranial volume via cranial venous sinus engorgement secondary to jugular vein compression. Increasing intracranial volume may be transmitted to the inner ear space, increasing volume and pressure surrounding the hair cells and attenuating slosh-mediated damage during a blast by reducing relative mobility of hair cells [31]. Other mechanisms involving redirecting energy from blasts may be similarly beneficial in mediating slosh-associated damage to anatomical structures and subsequently minimizing hearing loss.

Investigation of Slosh: A Way Forward

TBI is linked to cerebral edema, blood-brain barrier disruption, and neuroinflammation, all of which play a role in the severity of the injury and functional recovery. Recent advancements in TBI research imply that slosh mitigation, a method of limiting the brain’s ability to move inside the skull in both linear and rotational directions, may have the potential to prevent TBI [6,15,43]. The invention of a moderate jugular compression collar to enhance the resistance of the jugular vascular tree evolved from a better understanding of the mechanics of slosh as it applies to blood within the cranium [6]. More blood was hypothesized to be diverted to the vertebral veins (increasing CBF) and other capacitance arteries with higher vascular resistance, which occupied cerebral space and limited potential mobility [6,15,43]. Research studies have revealed that IJV compression significantly lowers signs of neurological injury, as measured by FJB levels and posttraumatic glial activation, with substantial reductions in the cortex, hippocampus, striatum, and cerebellum [6].

Other treatments have now emerged that follow the similar ideas of enhancing cerebral blood flow and cerebral perfusion pressure in the hopes of limiting brain impairment after a TBI by employing the principles of slosh mitigation. The strategies, to prevent subsequent injury after a TBI, range from postural adjustments to pharmacological interventions that can maintain cranial pressures, brain tissue perfusion, and reduce inflammation. Head immobilization and therapeutic positioning of the head (varying degrees of head of bed elevation (HBE)) have been advocated as a low-cost and straightforward method of preventing subsequent brain injury [54–57]. In a study by Winkelman et al., HBE of 30° has been reported to be a therapeutic technique to consider for preventing elevated ICP in TBI patients [55]. Other studies, on the other hand, have been unable to reach a consensus on therapeutic impact of HBE of 30°, and thus suggest that the optimum angle of HBE should be determined individually, with the desired clinical goal in mind, and after an analysis of the response of ICP, cerebral perfusion pressure (CPP), and CBF in each backrest positions [54–57].

Monitoring ICP in individuals with TBI is critical for preventing further damage. An elevation in ICP is associated with a drop in CPP and, as a result, a decrease in CBF, which can lead to secondary ischemic phenomena. Hypocapnia is hypothesized to cause cerebral vasoconstriction and is commonly used to regulate ICP but chronic hypocapnia in TBI patients increases the risk of death and severe disability [58–60]. Mild hypercapnia, on the other hand, may enhance CBF by cerebral vasodilation, which has a therapeutic impact in cerebral ischemia following a TBI [58,59,61]. TBI is also known to cause cerebral bleeding and RBC lysis, which causes Hb and heme to be released and absorbed by
microglia and neurons [62,63]. This causes oxidative damage and inflammation in brain tissue, which can lead to cytotoxic edema [63–65]. Acetazolamide can target one of the molecular targets connected to cytotoxic edema, AQP4, in the astrocyte. In an in vivo mouse TBI model, acetazolamide was shown to reduce cytotoxic edema [64,66]. Another study looked at the effectiveness of the antioxidant methylene blue (MB) in decreasing inflammation and behavioral problems associated with diffuse brain damage [67]. This is especially noteworthy because antioxidant levels have been found to drop in both adult and pediatric TBI patients across several studies [65,67]. Hence, MB intervention is a good potential therapeutic approach that may reduce life-threatening complications of TBI, such as cerebral edema and neuroinflammation, and protect against the development of secondary and long-term neuropsychiatric complications [64–67].

After an injury, the brain’s ability to pressure autoregulate may be compromised, and CBF might passively follow shifts in CPP [6,15,43,54,60,61]. To maintain optimal blood flow and perfusion, it is critical to reduce inflammation, edema, and oxidative stress in the brain. In animal TBI models, the protective effects of Minocycline (a microglia activator) and DFX (an iron chelator) on protecting BBB and lowering inflammation through decreasing TNF-alpha and suppressive oxidative stress to avoid edema have been explored [68–70].

Conclusion

Further prospective studies are needed to determine the efficacy of the aforementioned strategies, as well as other theorized methodologies, in preventing and managing TBI patients. This could lead to new insights into therapies that can significantly reduce subsequent insult/injury after a TBI. Looking forward, slosh mitigation and early neuroprotective interventions, as opposed to extracranial protective equipment like helmets, appear to offer a fresh paradigm for preventing and managing TBI by successfully targeting the intracranial environment.

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Figure 1:
Anatomical relationship of omohyoid and internal jugular vein.
Figure 2: 
Coup-Contrecoup Injury.
Figure 3:
Newton’s Cradle.
Figure 4:
The skull confines the brain, cerebrospinal fluid, and intracranial blood. If volume increases in any of these dynamics, the system eventually loses ability to compensate and intracranial pressure peaks.
Figure 5:
Overview of avian lung sacs.
Figure 6:
Partial rebreather mask that could be used to increase CO$_2$ in humans.
Figure 7:
Respirator device that can acutely increase venous CO$_2$. 
Figure 8:
Mechanisms that increase CO$_2$, erythrocyte volume, and/or cerebral blood flow can have protective effects on the ‘slosh’ effect.
Table 1:
Overview of pharmaceutical treatments that target cerebrovascular dynamics.

| References | Study Design                          | Critical Observations                                                                 |
|------------|---------------------------------------|---------------------------------------------------------------------------------------|
| **Erythrocyte Disruption after TBI** |                                                      |                                                                                       |
| 41         | Randomized trial in a rat model of TBI | TBI causes increased erythrocytic lipid peroxidation and increases erythrocyte aggregation. |
| 42         | *ex vivo* analysis of human blood subjected to simulated explosive blast waves | Decreasing free space within a container (no slosh) reduces erythrocyte disruption and hemolysis compared to incompletely filled containers (slosh). |
| **Effect of CO2 on erythrocytes & CBF** |                                                      |                                                                                       |
| 47         | *ex vivo* analysis of whole blood from multiple mammal species | Erythrocytes increased in volume proportional to the relative CO$_2$ content of blood. |
| 48         | *ex vivo* analysis of human blood      | Increasing pCO$_2$ causes an increase in blood viscosity                                |
| 44         | Non-controlled clinical trial          | Transient hyperventilation is associated with increased cerebral autoregulation reactivity. |
| 50         | Randomized trial in horses             | Acetazolamide increases arterial and venous pCO$_2$ during exercise without significantly affecting oxygenation. |
| **Human Observational Studies & Pharmacologic Approaches** |                                                      |                                                                                       |
| 49         | Non-controlled clinical trial          | Single dose of acetazolamide increases CBF by ~40%.                                   |
| 19         | Observational studies of amateur and professional athletes | Altitude is inversely associated with risk of concussion during American football games |