

## Blast Scaling Parameters: Transitioning from Lung to Skull Base Metrics

Lucke-Wold B<sup>1</sup>, Ryan CT<sup>1</sup>, Ogaga U<sup>1</sup>, Aric FL<sup>2</sup> and Charles LR<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, West Virginia University, Morgantown, WV, USA

<sup>2</sup>Department of Psychiatry, University of Washington, Seattle, WA, USA

**Corresponding author:** Lucke-Wold B, Department of Neurosurgery, West Virginia University, Morgantown, WV, USA, Tel: 304 293-5041; E-mail: bwold@mix.wvu.edu

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### Abstract

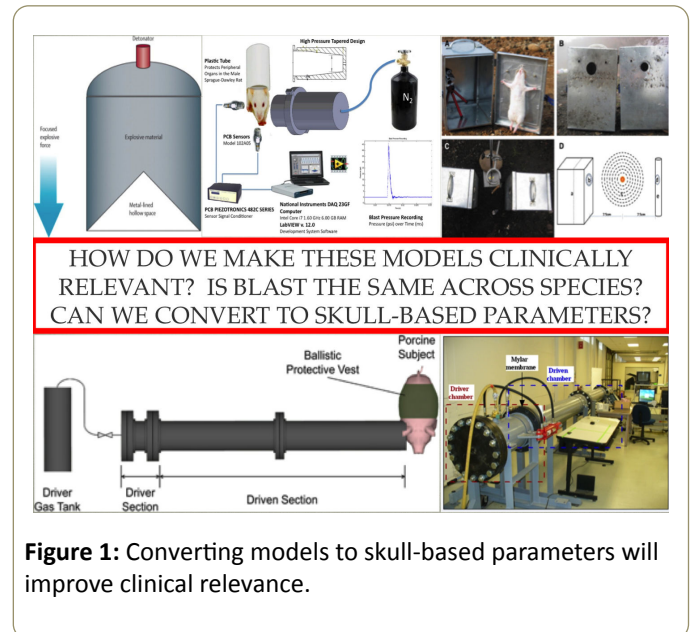
Neurotrauma from blast exposure is one of the single most characteristic injuries of modern warfare. Understanding blast traumatic brain injury is critical for developing new treatment options for warfighters and civilians exposed to improvised explosive devices. Unfortunately, the pre-clinical models that are widely utilized to investigate blast exposure are based on archaic lung based parameters developed in the early 20th century. Improvised explosive devices produce a different type of injury paradigm than the typical mortar explosion. Protective equipment for the chest cavity has also improved over the past 100 years. In order to improve treatments, it is imperative to develop models that are based more on skull-based parameters. In this mini-review, we discuss the important anatomical and biochemical features necessary to develop a skull-based model.

**Keywords:** Blast traumatic brain injury; Skull-based scaling; Clinically relevant models; Anatomical correlates; Biomarkers

### Introduction

Blast traumatic brain injury (bTBI) has been deemed the hallmark of modern warfare [1]. Unfortunately, limited treatment options exist to help warfighters who sustain bTBIs during conflict. In order to improve treatment options, it is imperative that pre-clinical models be designed to emulate real-time injury as closely as possible (Figure 1). The current models are primarily based off of lung-based scaling parameters developed back in the early 20th century [2]. Modern day improvised explosive devices however produce a different type of injury than the mortar shell explosions typical of the World Wars. In this mini-review, we discuss the relevant parameters for switching from lung-based scaling to the more relevant skull base metrics. By establishing better models

going forward, it will be possible to better test pharmaceutical treatments that will directly help patients with bTBI.



**Figure 1:** Converting models to skull-based parameters will improve clinical relevance.

### Anatomical Features

A recent literature review of blast exposure reports that 19.6 to 40% of victims, depending on the study, have injuries to the face [3]. Concurrent evidence from a porcine model also shows that face injury is common [4]. Head on blast exposure that injures the face in humans causes wave propagation through surrounding tissue into the brain [5]. Evidence of wave collision with the brain can be measured by increased intracranial pressure [6]. Singh and colleagues have shown that the location of exposure changes the extent of wave propagation into the brain [7]. The wave also dissipates as it travels throughout the brain indicating some intrinsic resistance [8]. Head orientation is also directly correlated with intracranial pressure changes following blast [9]. It is therefore imperative that when designing scaled blast models important variables should be addressed including distance from exposure, intensity of exposure, and location of primary

impact [10]. Below we discuss scaling principles in accordance to anatomical features. We begin at the macroscopic level with consideration for the skull, brain, cerebrospinal fluid, and vasculature. The discussion progresses to a focus on the role of cell types in scaling including neurons, glia, and endothelial cells.

### Skull dynamics

Characteristics of the skull tend to be more variable between species, particularly in regard to morphology and shape. For this reason, other skull characteristics must be considered when selecting the appropriate animal model to represent human skulls. It is most widely agreed that bone mineral density is the most important characteristic due to its direct correlation to bone elasticity and strength [11]. A recent study by Jean and colleagues investigated stress wave transmission through the skull interface of three species: mouse, pig, and human. They found distinct patterns of transmission based on skull density that correlated with observed spikes in intracranial pressure [12]. Other characteristics to consider are skull cavity volume, skull geometry, age, and structure [13,14]. Selection of an animal model with similar attributes to human bone density is required to be most accurate and clinically relevant. Studies show that the rabbit skull is the least comparable model to the human skull, with non-human primates being optimal [11]. Due to ethical and resource limitations, rodent models have emerged as the most feasible. Rodent models have many advantages such as low cost, ease of use, and available access. For scaling based on skull density, blast and shock waves must have low-amplitude and short duration for rodent models [2]. It is also important to consider the intensity of blast exposure. High-pressure and long-duration exposures can more readily transverse the bony cavity of the skull, but will not appropriately scale based on injury severity [15].

### Cerebral spinal fluid space

In order to understand injury expansion, extended research must focus on skull flexure and how it influences cerebral spinal fluid (CSF) post-blast in different models [16]. Recent evidence suggests that volume fractions vary between locations following blast exposure indicating multiple sites of pia-arachnoid complex disruption [17]. Detecting these areas of specific change is vitally important in understanding injury severity. Blast TBI is often associated with acceleration and subsequent deceleration of the brain and skull. The CSF responds differently than the brain to this rapid change in momentum due to its unique density gradient. The momentary lack of CSF cushioning allows the brain to collide with the skull [18]. Similar coup and contra coup effects have been observed in animal models including rhesus monkeys and rats [19,20]. Increasing the use of high throughput imaging modalities may enhance the ability to detect acute changes to the cerebral spinal fluid space following injury [21]. The transmission of the wave through the CSF has been linked to cavitation at the contra coup site of injury [22]. Finite element

modeling may be useful in predicting cavitation and CSF dynamics for different animal models of blast TBI [8].

### Brain size and architecture

White and Gray matter delineation are conserved across mammals. Even whales have similar axonal shearing following blast due to acceleration/deceleration forces [23]. The key components of interest for appropriate scaling are hierarchical neuroanatomy and metabolism [24]. In veterans, cortical thickness is significantly altered following blast exposure [25]. Areas consistently disrupted in human blast exposure are the prefrontal cortex and hippocampus [26]. The change in brain volume affects fluid-structure interactions [27]. In order to maintain clinical relevance, deformation of tissue due to pressure differences following blast must be consistent with scaling [28]. It was recently shown that when the top of a rat's head is facing the shock tube, skull flexure produces similar changes in intracranial pressure in the prefrontal cortex as that seen in human blast exposure [9]. The deformation of tissue was therefore conserved across species. Likewise, blast exposure in Macaca monkeys caused increased ICP that significantly damaged hippocampal cells and Purkinje neurons [29]. Although the use of non-human primates is ideal, the cost limitations and ethical considerations are prohibitive. In scaling for rodent models the key is using small blast tubes, which can focus the wave to more region specific areas of interest [15]. Finite element modeling done with computer simulation can be used to determine the peak pressure needed for deformation of tissue [30]. Tabletop blast models produce the short duration peak pressures necessary for sufficient scaling and are more reliable between trials than larger models [31].

### Vascular considerations

Because the brain has such a high demand for nutrients and oxygen, an extensive vascular network exists within the brain of all mammals. Brain tissue across all species have similar metabolic demands, therefore capillary length and ratio to cortical neurons will be conserved across mammalian species to provide the same demands for blood flow [32]. It is therefore assumed that the brain vasculature of a rodent, mouse, or rat would be an acceptable option for scaling with human vasculature. Blast can cause disruption of the vasculature, especially at the level of the blood brain barrier [33]. Thoracic exposure leads to a surge in venous pressure that contributes to chronic inflammation [34]. Blood vessels are susceptible to blast injury due to enhanced wave transmission through different density gradients [35]. Fluid/solid coupling algorithms can be used to map the temporal distributions of pressure across larger vessels following blast [36].

Capillary differences are also of interest in comparing mammalian species. Circulatory shock is common following blast exposure. The mismatch in ventilation/perfusion is prominently expressed at the capillaries where metabolic exchange occurs [37]. Damage to the endothelium of capillaries has been reported following blast exposure [38].

The damage can be indirectly observed through iron deposits in the parenchyma [39]. In addition to injury itself, other characteristics must be considered for appropriate scaling including capillary diameter, aging of vessel, endothelial cell and myocyte size differences between species, and coronary pressure. All of the aforementioned characteristics may vary between species [40]. For example, in humans, age leads to a widening of capillary diameter [41], but in rodents, age leads to a narrowing of capillary diameter [42]. Variability may be adjusted and accounted for with normalization to size, weight, or age using carefully organized mathematical equations.

### Red blood cells

The mean size of RBCs in humans is 9.65 microns. The smallest capillary is 4 microns meaning that RBCs must fold to fit through the capillary lumen [43]. Following blast injury, red blood cells can become structurally damaged limiting their ability to fit through the capillary lumen. The result is increased risk for hemorrhage and a drop in mean arterial pressure [44]. Post injury transfusions are often necessary following combat related blast injury to restore metabolic exchange [45]. Rats and humans have similar capillary diameters making rodent models viable for scaling [46]. Mammalian species often have different shapes of RBCs causing change in flow rate [47]. In rats unlike humans, RBCs decrease in size with age allowing more successful folding in young adult animals than neonatal animals [48]. The low-shear viscosity of young-adult rodent blood has similar dynamics to human blood despite aggregation being slightly different between the species [49,50]. The key similarity is that rat models have similar multifoci microhemorrhages following blast exposure, which is also seen in humans [51]. Not surprisingly, hemin, a heme oxygenase 1 activator, decreased injury severity when administered post-blast [52]. This finding indicates that red cell rupture is necessary for appropriate scaling in blast injury.

### Neurons

Neural tissue properties are more variable across species. Rodents gain white matter at a faster rate than primate species although relative neuronal density in gray matter is comparable [53]. Despite differences in neuron size and axonal connections between mammals, the cranial volume to brain volume ratio typically scales to the animal's body size [54]. Age is a key factor to consider as well. Aging typically results in shrinkage of brain volume, so the appropriate age of the animal must be selected for translational studies. Also, as rodent's age the brain gets larger but in aged humans the brain tends to shrink [55]. Blast injury in larger mammals results in periventricular and hippocampal damage [56]. The damage in rodents is found primarily within the cortex and white matter tracts. Occasionally neurons in the hippocampus become damaged resulting in abnormal function [57]. Despite differences in injury foci, neurons respond equally to injury across species by swelling and forming vacuoles [15]. A comparable amount of neuronal death also occurs across species [58]. Another important factor is that basal metabolic

rate conservatively scales across mammalian species according to body size, indicating the same cellular needs and energy expenditure [32]. Basal metabolic rate supports the use of mice as an affordable and practical model. DNA methylation rates are likewise similar between rodents and humans suggesting the validity of scaled models [59]. Neurodegeneration can occur at comparable rates between species, and higher severity of blast has been associated with  $\alpha$ -spectrin disruption in mice similar to the disruption seen in humans [60]. Of particular importance is the change within mitochondria post-blast. Mitochondrial dysfunction is common post-blast in mice, and recent human data supports disrupted mitochondria function as a mechanism of injury as well [61,62]. Select neuronal mitochondria genes are conserved between species indicating that the neuron may be an ideal cell to compare similar injury pathways across species [63].

### Glia (astrocytes and microglia)

During injury, mouse brain tissue may behave similarly to human tissue. Inflammatory responses in both humans and mice can be activated by the release of similar chemokines [64]. Injury also leads to similar activation of glial cells, including astrocytes and microglia [65]. Because this reaction to neural injury has been shown to be similar in humans and mice, it can be further assumed that mice may be valuable for a translational model. Rats also have similar responses to humans. GFAP, a marker for astrocytosis, has been elevated within the rat hippocampus following blast exposure [66]. Astrocytosis and subsequent behavioral disturbance is most pronounced in rats at blast wave pressures greater or equal to 117 kPa [67]. Rat models show that astrocytic foot processes surrounding the blood brain barrier (BBB) swell following blast injury indicating damage [68]. Astrocytosis also plays an important role in human blast pathophysiology [69]. It may contribute to long-term degenerative disease such as chronic traumatic encephalopathy [70]. In humans, an acute response to blast exposure is often loss of consciousness. In rats, this transient response can be measured by loss of righting reflex. The loss of righting reflex is accompanied by microglia activation measured with IBA1 [71]. Similar microgliosis was observed in rats using the CD11b/c antibody. Activated microglia was found adjacent to areas of BBB disruption within the cortex [72]. Similar to humans, the pineal gland in rat serves as an exquisite sensor for microglia activation following neural injury [73]. Extended neuroinflammation mediated by microglia activation has been linked to cognitive decline in humans [74]. Understanding the mechanism of persistent microglia activation following axonal shearing, warrants the use of appropriately scaled rodent blast models [75].

### Endothelial cells

Blast exposure can disrupt tight junction proteins that interconnect endothelial cells [76]. The disruption is mediated by a vascular pressure surge and subsequent oxidative stress [33]. In vitro modeling has proved beneficial in detecting changes to endothelial cells post-blast. Findings suggest that damage occurs acutely and persists over a few days [77]. The

decrease in trans-endothelial electrical resistance is the result of the impulse transmitted instead of peak overpressure [78]. The use of in vitro modeling also enables blast to be directed to hippocampal slice sections allowing focused investigation into the vasculature in this area [79]. Another important consideration is that 30-80% of blast exposures result in some type of infection. The BBB is the primary defense for the brain and therefore disruption leads to increased risk for exposure to bacterial toxins [80]. Animal models allow focused investigation into the biochemical dynamics surrounding endothelial cells post-injury. Bacterial endotoxin has been shown to increase intracellular adhesion molecule 1 expression on endothelial cells post-injury allowing an influx of leukocytes [81]. Additionally, lipopolysaccharide can trigger an increase in adipokine genes following TBI [82]. In rabbits, the changes that occur to endothelial cells produce robust hemoconcentration post-blast [83]. Hemoconcentration has also been reported in sheep post-blast, which severely limits metabolic exchange and the clearance of toxins [84]. The use of appropriately scaled models will help elucidate these complex interactions that occur from endothelial cell damage post-blast.

## Biomarkers

Biomarkers have recently emerged as an important indicator of traumatic brain injury. Immediately following TBI in a porcine model, a panel of markers was increased in the CSF. These markers included neurofilament heavy chain, von willebrand factor, glia fibrillary acidic protein, brain-specific creatine kinase, and neuron-specific enolase [85]. Of particular importance are metabolomic biomarkers because they are altered following TBI in humans [86]. Metabolomic biomarkers must be similar between species exposed to injury to confirm that blast causes replicable and scaled injury [87]. Changes in blood flow drastically alter metabolic output [88]. The larger the brain volume the more metabolic capacity it has [32]. Metabolomic markers of interest for mammals include ascorbate, glutamate, phosphocoline, and N-acetylaspartate [89]. Another pathway of interest is neuroinflammation. Interleukin-5 offers to be a promising biomarker that is similarly elevated in CSF post-blast in multiple species [90]. Levels of interleukin-1a and erythropoietin have been shown to change in the CSF following blast in rodents, but further validation must be performed in human samples [91]. The vascular space often provides an appropriate venue to sample biomarkers. Changes in small nucleolar RNA within blood components is an important indicator of blast injury and may help indicate the progression towards neuropsychiatric disease in veterans [92]. Tau and TNF $\alpha$  changes are also detectable in serum and can offer acute sensitivity for acute injury [93]. DNA fragmentation is detectable in plasma and has been validated in a mouse blast model [94]. Scaled animal models offer an ideal option to screen potential biomarkers, which can then be validated in humans using multimodal magnetic resonance imaging [95].

## Conclusion

Moving forward, pre-clinical models will need to be based on skull-based parameters. In this mini-review, we discussed relevant features for scaling such as brain and skull anatomy, vascular considerations, and differences in response based on cell type. We highlighted relevant biomarkers that could be used to determine the appropriate outcomes of scaled pre-clinical models. By switching to skull-based models we will be better able to develop appropriate treatment options for warfighters. Skull-based models will provide the scientific community a better understanding of brain injury from blast exposure.

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