Scaling in Blast Neurotrauma

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Abstract The high incidence of blast exposure on today's battlefield has been strongly associated with traumatic brain injuries. Anecdotal evidence of prolonged apnea following blast exposure has been observed in military personnel and is commonly reproduced in animal neurotrauma models. Animal models have shown that apnea tolerance is both dose and species-dependent; important factors include primary blast characteristics (peak overpressure, P, and duration, Δt) and animal size. Experimental data on apnea from head exposure to primary blast were obtained from 121 tests using four different-sized animal models with thoracic blast protection: mouse, rabbit, ferret and pig with peak incident pressure and overpressure duration ranging from 99.7 to 1084.6kPa and 0.6 to 8.0ms, respectively. Apnea risk was assessed using logistic regression with a log-linear dose-response. Scaling procedures were explored based upon the body mass or brain mass of the animal. Scaling effects were largest in the small animal models. When scaling was applied to existing rodent neurotrauma models, scaled duration ranged from 17.65 to 540 ms, with most larger in duration than the typical blast exposure range seen in combat (~1-40 ms duration). It is imperative that appropriate scaling procedures between species are derived and implemented to properly correlate animal model pathophysiological outcomes with human response.

Keywords animal model scaling, apnea, blast neurotrauma, traumatic brain injury

I. INTRODUCTION

An increase in blast exposures in the recent military conflicts has spurred a focus on traumatic brain injury (TBI) in recent blast research. This recent effort contrasts with historical focus on pulmonary blast trauma since observed blast fatalities were clearly attributable to blast lung injury rather than blast brain injury (e.g. [1-3]). However, recent research has shown that modern body armor, especially body armor with hard inserts, is strongly protective against blast. The use of body armor allows an individual to withstand blast dosages above unprotected fatal levels for pulmonary injury, potentially exceeding brain injury blast thresholds. Further, an unexpected risk of mild neurotrauma for isolated blast exposure to the head was recently established at blast intensity levels comparable to the unprotected pulmonary threshold risk [4]. However, there are only a limited number of previous investigations available to support the development of cross-species scaling principles for blast neurotrauma owing to the presence of comorbid pulmonary trauma from blast exposure to unprotected animal pulmonary systems.

Animal models are an important tool in injury research as they provide physiological and behavioral measurements not afforded by cadaveric or dummy surrogates. Animal models have been used extensively in blast research since much of blast trauma is dependent upon physiological response which is only accessible in a living model. These models include: mouse (e.g. [5-7]), rat (e.g. [8-11]), rabbit (e.g. [2, 12, 13]), ferret (e.g.[4]), pig (e.g. [14, 15]). Large differences in size, structure, morphology and physiology between the injury models and humans necessitate the use of scaling procedures to relate the dynamic input and physical and physiological response from one species to another. Scaling methods are developed to match response of the animal model among species and to an equivalent human response. Scaling models have been developed for blast pulmonary trauma [16] and for blunt trauma [17]; however, blast neurotrauma scaling is unknown.

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Early in blast injury research, Bowen and others recognized that some form of scaling procedure was needed to compare injury endpoints across multiple species [18]. Scaling overpressure duration and peak overpressure was required to match equivalent injury response between different species [16]. Simple scaling models use a ratio of a reference mass (generally a human value) to an animal mass, where Δt is the duration of the positive overpressure phase. This form of scaling model increases the human equivalent value for animal models that are smaller than humans.

$$\Delta \mathbf{t}_{\mathbf{scaled}} = \left(\frac{\mathbf{Reference\ Mass}}{\mathbf{Mass}}\right)^{\mathbf{a}} \Delta \mathbf{t} \tag{1}$$

The work of Bowen covered many species of animals to investigate the differences in injury response[16]. Bowen developed a model for interspecies scaling of pulmonary injury risk [18]. Bowen's model related the animal body mass to a reference human body mass and was scaled by the cubed root, meaning the blast duration was effectively proportional to an animal model body length scale.

Panzer [19] recently developed a blast neurotrauma scaling methodology based upon simple FE models of the head and brain. For this study, five scaled-replica spherical head models comprised of skull, cerebrospinal fluid and brain were developed ranging in diameter from mouse to human head size. Strain, acceleration and peak pressure were calculated within the brain tissue during blast exposure. Both peak strain and peak acceleration were found to be larger in the smaller heads at the same blast condition, but peak brain pressures were fairly consistent between brain sizes. For instance, peak shear strain was observed to increase by 50% when halving the head size. From these results, Panzer developed a scaling model to relate the brain's relative biomechanical response (X) between two brain masses (M) to the applied peak overpressure (P) and duration (Δt):

$$\frac{X_2}{X_1} = \left(\frac{P_2}{P_1}\right)^{\alpha} \left(\frac{\Delta t_2}{\Delta t_1}\right)^{\beta} \left(\frac{M_2}{M_1}\right)^{\gamma} \tag{2}$$

where α, β and γ are the scaling parameters. This model was fit to the 50th percentile peak brain strain and pressure results of the FE simulations. By combining the models for brain pressure and brain strain, blast pressure and duration scaling become separable and similar in form to Bowen's scaling model. The pressure and strain scaling models were combined in order to isolate pressure and duration scaling. From the isolated scaling models the peak pressure scaling factor was found to be 0.004, with small effect over the possible interspecies pressure conditions, while the duration scaling factor was found to be 0.248. This result is consistent with the expectation that peak intracranial blast pressure is relatively insensitive to animal model size while global strain response is sensitive to overpressure duration.

Other methods for scaling between species include simple empirical allometric scaling methods covering orders of magnitude in body size (e.g. [20, 21]). Many of these parameters (e.g. brain mass, metabolic rate, respiratory rate, etc.) are scaled across a large range of species, even between mice and elephants [22]. These scaling laws were derived by optimizing assumed scaling variables to fit large compilations of experimental data.

The goals of this study are to establish a clinical biomarker for central nervous system (CNS) overpressure mediated trauma using simple scaling methods to determine equivalent cross-species and human exposure in models of blast neurotrauma. The injury outcome of interest is apnea as it is known to occur as a result of primary blast exposure [4, 7, 13, 15] and may produce secondary injury from hypoxia. It is important to note that scaling may be different for different injury endpoints (e.g. apnea, death, axonal injury, etc.) and therefore injury scaling must be considered specific to the injury response.

II. METHODS

Animal Model Testing

Data were compiled for live animal model testing of 4 species subjected to primary blast: mice, rabbits, ferrets and pigs [4, 7, 13, 15]. The blast effects were associated only with the pressure wave applied using a compressed gas-driven shock tube. The shock tube consisted of a driver section filled with high pressure gas separated from an open-ended driven section by a diaphragm. By pressuring the driver section, the diaphragm is caused to rupture, propagating a pressure shock wave down the length of the shock tube. Peak overpressure

and overpressure duration were controlled by varying the driver gas used and the diaphragm thickness separating the driver from the driven section of the shock tube (Table 1). Incident pressure-time history was recorded at the exit of the shock tube for each test to determine blast dosage and the pressure wave characteristics of interest.

All animals were anesthetized and were provided with pulmonary protection to ensure isolation of injury to the head. The test animal was placed at the center of the shock tube exit face to maximize shock wave planarity while limiting pressure reflections. Animals were monitored for occurrence of apnea immediately post blast exposure. For this analysis 121 tests were used with 4 different species represented.

Table 1: Animal subjects for apnea risk assessment

	Mouse[7]	Rabbit[13]	Ferret[4]	Pig[15]
# of Tests	25	13	65	18
Peak Incident Pressure Range [kPa]	175.4-285.1	168.5-1084.6	99.7-831.5	111.1-893.9
Unscaled Duration Range [ms]	0.6-1.0	0.9-2.4	0.7-4.9	1.8-8.0
Body Mass (Ave ± SD)[kg]	0.026±0.001	4.2±0.6	1.2±0.2	61.7±9.5
Brain Mass (Ave ± SD)[g]	0.3	11	7	80

Scaling

Blast exposure data were scaled using four different methods. Each method scales the overpressure duration to account for differences between the animal model species and follows the form of Equation 1. The measured overpressure duration for each test was scaled to a human exposure equivalent according to each scaling method.

The first method uses the traditional pulmonary blast scaling model developed by Bowen [16]. The second method uses the blast brain scaling model derived by Panzer from computational models [19]. The third method is an allometric scaling relation of physiological parameters [20, 23], based on physiological time relations between small and large mammals that scales biometrics such as heart rate, breathing rate and life expectancy scale with mass. The fourth model is based on optimizing the parameters in the standard brain mass scaling model to the experimental apnea data.

Table 2: Scaling Models

$$\Delta t_{scaled} = \lambda \Delta t \qquad \lambda = \left(\frac{\text{Reference Mass}}{\text{Mass}}\right)^{a}$$

Model	Scaling Mass	a
Pulmonary	Body	0.333
Computational	Brain	0.248
Physiological	Brain	0.400
Optimized	Brain	---

Following the application of each scaling method to the experimental data, apnea risk functions were developed. A logistic regression was conducted fitting a log-linear dose-response (Equation 3) to the scaled apnea outcome data (JMP Pro 10, SAS Institute Inc, Cary, NC). The regression model fit was assessed using the area under the receiver operating characteristic (ROC) curve for measuring the sensitivity versus 1-specificity for the model fit. Apnea risk curves (1, 50 and 99% risk) were generated for each scaling method. The optimized scaling model was found by simultaneously optimizing for the scaling parameter, α, and the dose-response model for apnea occurrence (Equation 3). This scaling model was used by Panzer [24] for functional forms chosen in this study for scaling and dose response.

$$\ln\left[\frac{\Pr(\text{apnea}|P_i)}{1-\Pr(\text{apnea}|P_i)}\right] = \beta_0 + \beta_1 \log_{10}(\text{Peak Pressure}) + \beta_2 \log_{10}(\Delta t) \quad (3)$$

III. RESULTS

Unscaled and scaled apnea outcome data are shown for each of the four scaling methods below. Scaling results are presented with 1, 50 and 99% risk of apnea curves. Since each of the species investigated were much smaller than humans, the result of scaling is a large shift of the experimental data to larger human equivalent durations. The unscaled data presented in Figure 1 is grouped together with no interspecies delineation between apnea and no apnea cases.

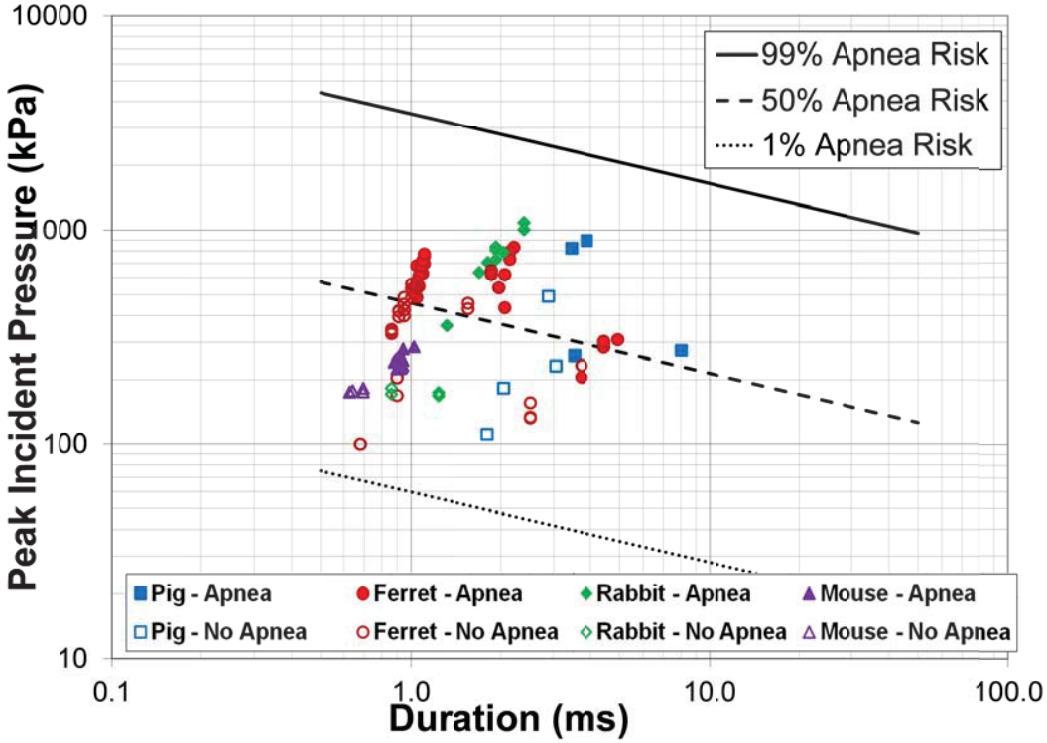

Figure 1: Unscaled experimental data with apnea injury risk curves

After scaling is employed for the different methods in Figure 2 through Figure 5, the apnea outcome data become organized and duration dependence is seen in the injury risk models. The effect of scaling is to increase the human equivalent duration and the effects are greatest for the smallest animal models. The optimized scaling exponent was found to be 0.383 and is shown in Figure 5 which is comparable to the physiological scaling value.

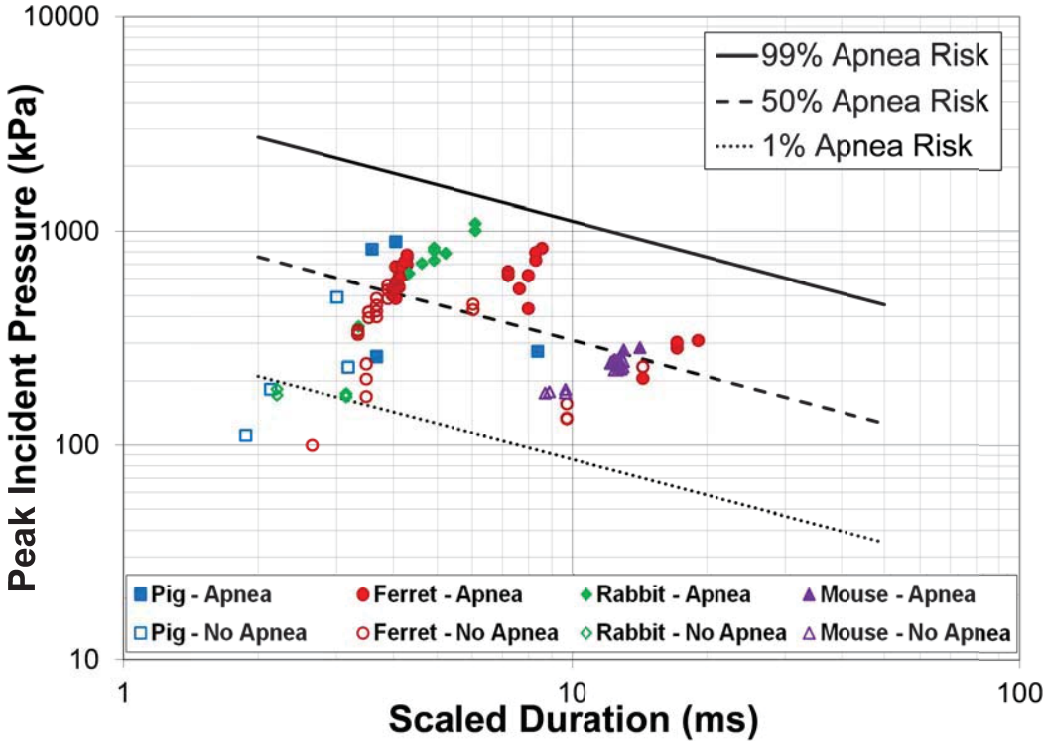

Figure 2: Experimental data with apnea injury risk curves scaled using pulmonary scaling

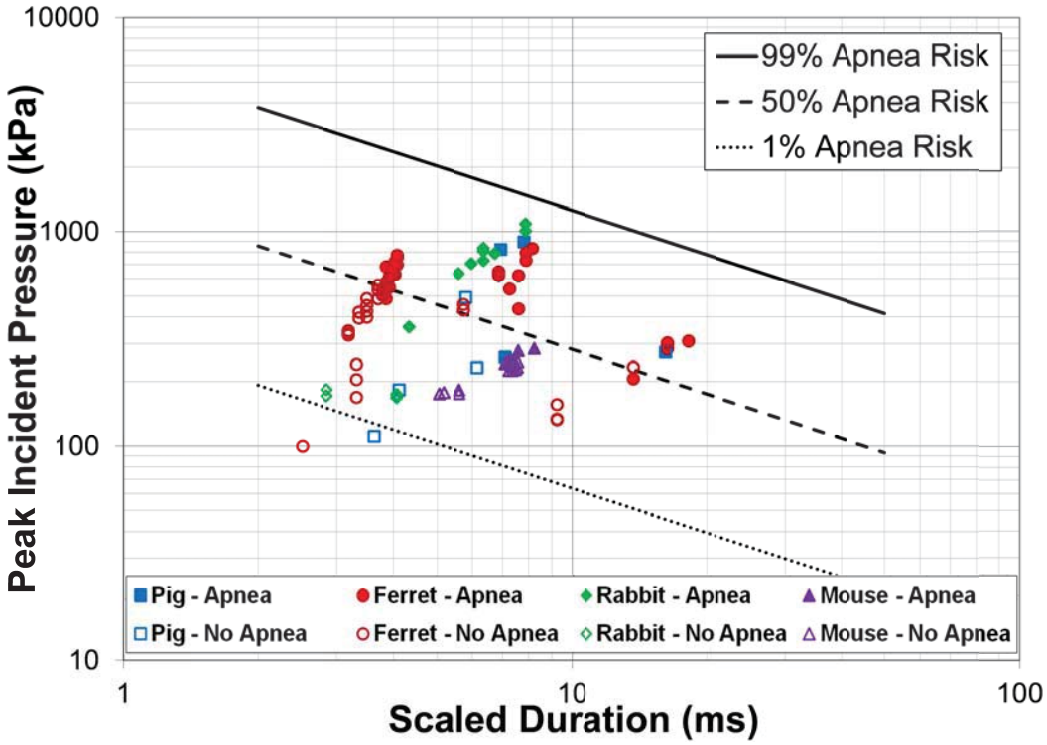

Figure 3: Experimental data with apnea injury risk curves scaled using computational scaling

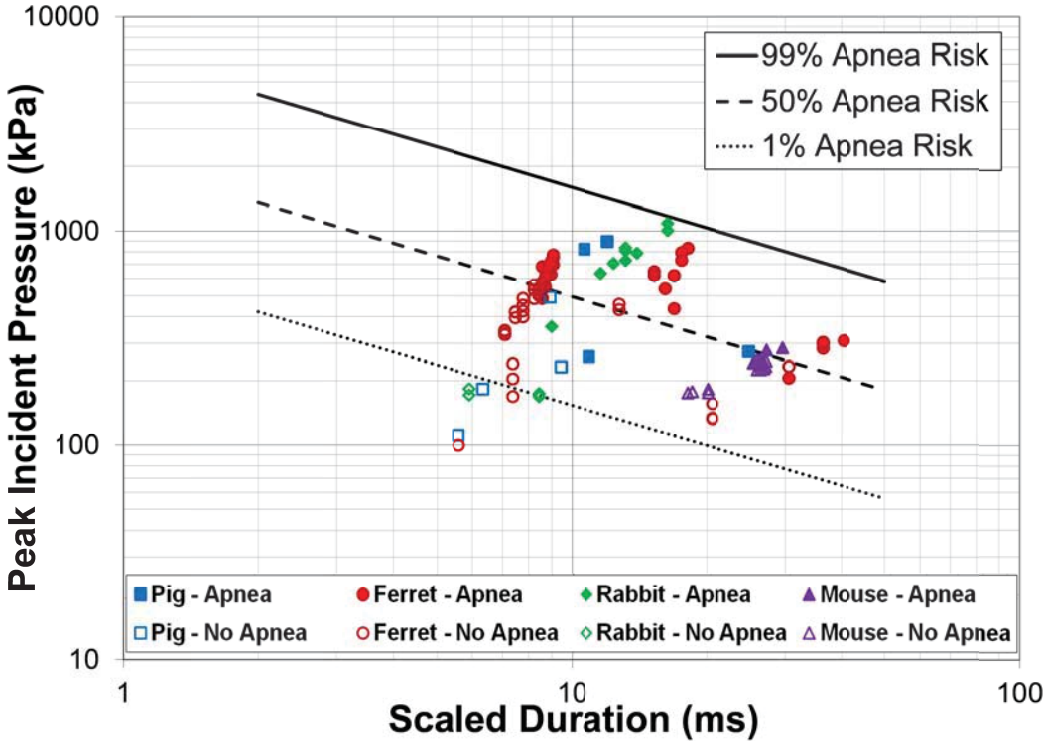

Figure 4: Experimental data with apnea injury risk curves scaled using physiological scaling

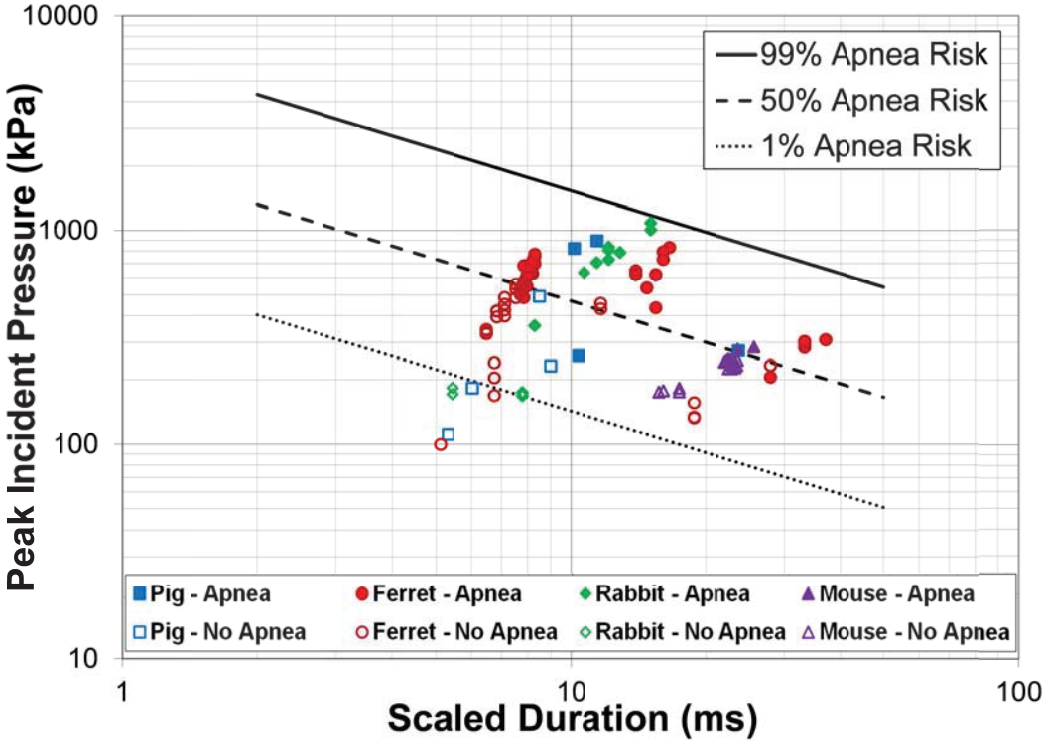

Figure 5: Experimental data with apnea injury risk curves scaled using optimized scaling

The resulting apnea risk curves demonstrate that the choice of scaling procedure can have large effects within the range of typical IED exposure as seen in Figure 6. The typical exposure range was calculated using CONWEP [25] to calculate blast exposure levels associated with charge sizes ranging from 0.25 to 1000kg of TNT at various standoff distances. At a constant duration of 4ms the 50% apnea risk occurs at peak overpressures of

500 for the computational and pulmonary scaling models, and 800kPa for the physiological and optimized scaling methods, respectively. Likewise, at a constant peak overpressure the duration resulting in 50% apnea risk varies from 4 for the computational and pulmonary models to 9ms for the physiological and optimized scaling.

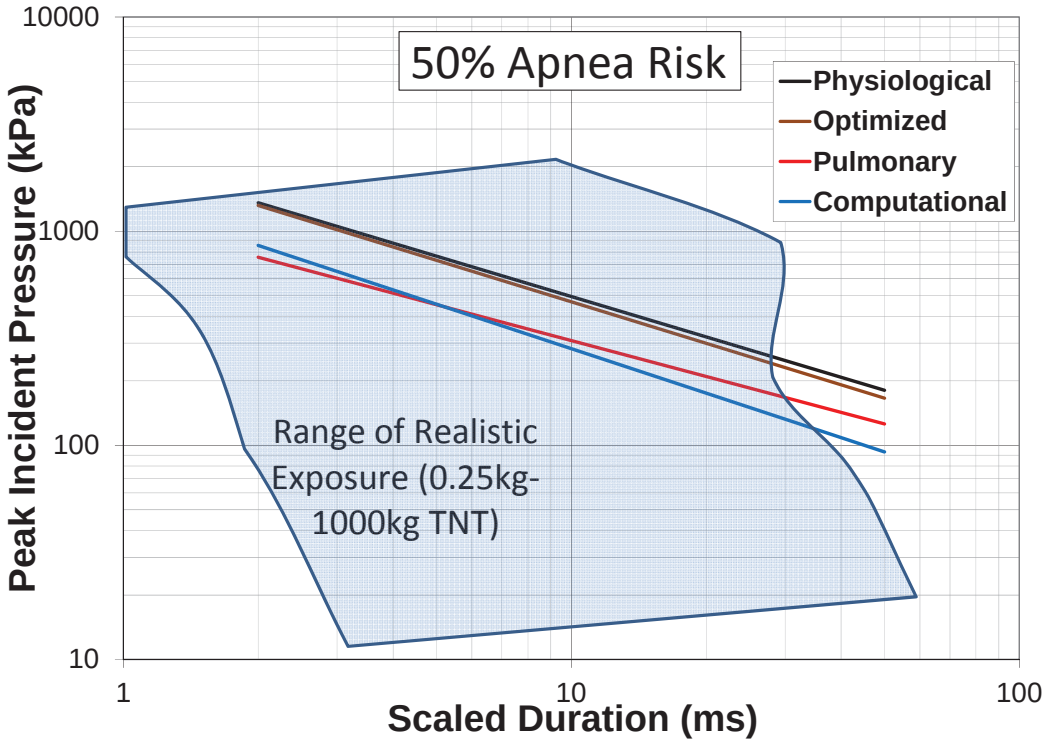

Figure 6: Comparison of 50% apnea risk curves with realistic human exposure range

Physiological scaling (Figure 4) shifted the experimental data furthest to the right of the plot as the higher scaling exponent results in higher scaled durations, especially for the small animal models. The result of using each scaling law for apnea risk is presented in Table 3.

Table 3: Model brain weight and scale factor

$$\Delta t_{scaled} = \lambda \Delta t$$

Species	$\lambda_{Pulmonary}$	$\lambda_{Computational}$	$\lambda_{Physiological}$	$\lambda_{Optimized}$
Human	1	1	1	1
Pig	1.1	2.0	3.1	3.0
Rabbit	2.6	3.3	6.8	6.3
Ferret	3.9	3.7	8.2	7.5
Mouse	13.9	8.1	29	25

Apnea risk model coefficients and model fit statistics are presented in Table 4. All model coefficients were significant on a 0.01 level except for the duration coefficient for the unscaled data model fit. The area under the ROC curve was largest for the optimized and pulmonary scaling models; however, goodness-of-fit was similar for computation and physiological scaling. Goodness-of-fit was lowest in the unscaled regression model as expected.

Table 4: Logistic regression model coefficients and model fit statistics

	Regression Coefficients						Model Fit Statistics
Model	β_0	**p**	β_1	**p**	β_2	**p**	**Area Under ROC Curve**
Unscaled	13.8	<0.01	-5.2	<0.01	-1.7	0.026	0.81
Pulmonary	25.1	<0.01	-8.3	<0.01	-4.6	<0.01	0.86
Computational	22.1	<0.01	-7.1	<0.01	-4.9	<0.01	0.85
Physiological	30.0	<0.01	-9.0	<0.01	-5.7	<0.01	0.85
Optimized	29.6	<0.01	-8.9	<0.01	-5.7	<0.01	0.86

IV. DISCUSSION

This study is the first to empirically derive a blast neurotrauma scaling model for blast neurotrauma endpoint between common animal model species. These results show that the choice of scaling parameters influences the estimated human equivalent response. Scaling is needed to provide realistic input that replicates human biomechanical exposure and also to compare human and animal model endpoints. As expected, scaling effects were much larger for the smaller species due to the vast differences in body and brain mass between the animal model and humans. However, currently this model does not include species with brain size equivalent or larger than humans and therefore scaling to human levels is an extrapolation. As the use of blast neurotrauma models increases, the importance of employing proper scaling techniques during experimental design grows.

Comparing the 50% apnea risk functions between the different scaling exponents, a larger peak pressure is required for injury when using the physiological and optimized scaling factors compared to the pulmonary and computational scaling. At 1ms scaled duration the 50% apnea risk pressure value is 87% higher for the physiological scaling than the pulmonary scaling, 1115 to 2091kPa, respectively. At 10ms there is a similar increase of 72% from computational to physiological scaling, 290 to 500kPa, respectively. There is a potential that blast neurotrauma scaling is more prominent than blast pulmonary scaling (Table 3), therefore making consideration of scaling more important for blast TBI research.

There are many advantages which have made rodents the most popular animal models in blast neurotrauma research (e.g. expense, size, genetic knockouts). The majority of rodent blast models use shock tubes to introduce a primary blast with durations between 4 and 10ms [6, 26-30]. Even longer durations have been used in rodent models in excess of 10ms [31, 32]. When the optimized apnea scaling from this study is implemented, these rodent models correspond to scaled durations close to and exceeding 100ms. Overpressure durations of this magnitude are difficult to achieve without the use of nuclear weapons and are therefore of little interest in current neurotrauma research. The apnea outcome data used in this study are presented with scaled representative rodent neurotrauma conditions from literature in Figure 7.

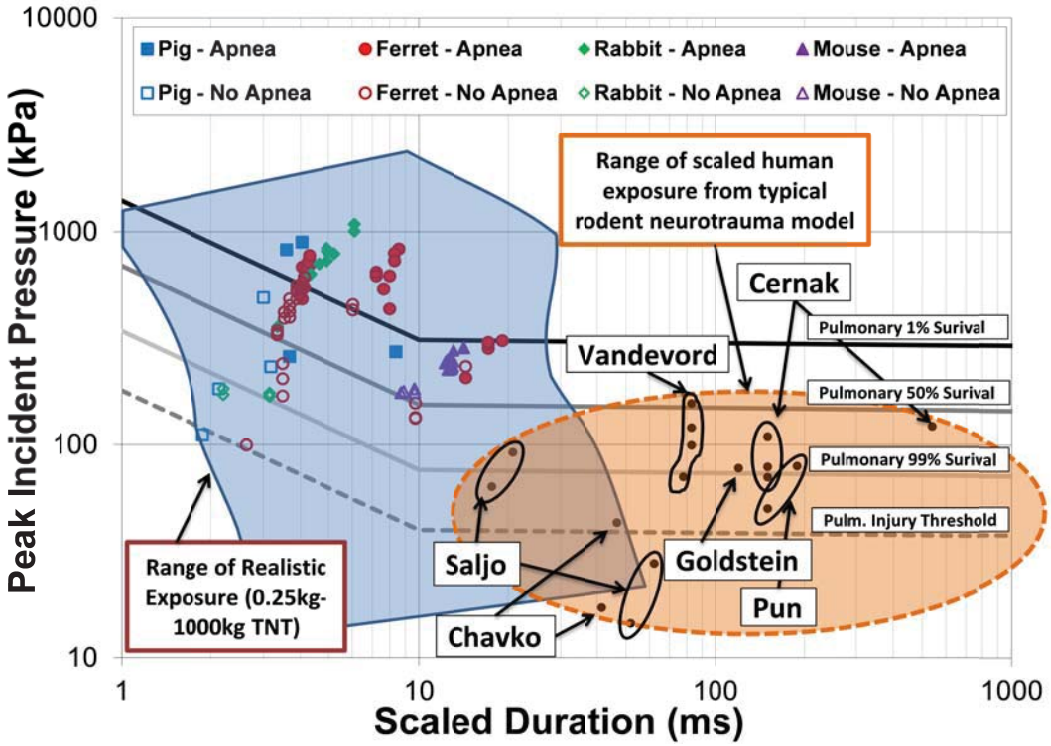

Figure 7: Scaled rodent neurotrauma test conditions compared to study data and range of realistic exposure

The range of realistic exposure presented corresponds to charge sizes ranging from 0.25 to 1000kg of TNT at varied standoff distances. As shown, the bulk of test conditions in literature greatly exceed the maximum

overpressure duration which can be realistically seen in combat. Complicating the interpretation of injury outcomes in these rodent models is the lack of pulmonary protection during blast exposure, resulting in an uncertain contribution to injury or fatality endpoints. Some studies mount the test animal within the shock tube on metal structures leading to pressure reflections and likely resulting in a more severe exposure (e.g. [33, 34]). Also, studies subject animals to pressure waves which plateau, therefore having a larger impulse for a given peak pressure and duration (e.g. [29]). It is also important to note that this range estimation is likely conservative as a majority of improvised explosive device (IED) threats are made up of artillery rounds equivalent to 7.5kg of TNT explosives or less [25].

The overall implication of large, scaled durations used in literature is that in some cases researchers are likely testing well outside the realm of likely human exposures. Compounding the problem is that for scaled durations that are orders of magnitude higher than normal exposure, there is a risk of changing the injury mechanism. For example, for pulmonary blast, injury mechanisms change from short duration to long duration (cf. [3]). For large duration and impulse, injuries more likely stem from acceleration-based mechanisms than primary blast injuries associated with the transmission of a blast wave through the tissue [24]. At extremely long durations enough momentum is transferred by the blast wave to cause large accelerations and displacements of the head and skull which are not seen at short durations (<10ms scaled), much like the change in injury mechanism seen with pulmonary blast injury. Pulmonary injury from short durations is associated with localized, spalling-type injury while long duration injury is associated with more diffuse crushing-type injuries [3].

This study is limited primarily by the range of species included. Ideally, more large animal species should be used, including species larger than human as scaling to human levels with the current model is an extrapolation. However, this is the largest range of scale to date for apnea risk assessment and additionally gyrencephalic (convoluted brain) and lissencephalic (smooth brain) species are included. Additional data are needed to validate the scaling model presented. Due to the large differences in structural anthropometry and pathophysiology between species, it is currently unknown if a unifying scaling procedure across all species is appropriate. Determination of whether multiple scaling methods are necessary for a single injury endpoint like apnea requires a larger set of tests animal species.

V. CONCLUSIONS

Blast animal model work has provided strong evidence that blast traumatic brain injury tolerance is dependent upon differences in body and brain size (e.g. [4, 7, 13, 15]). This study presents a risk model for apnea as a surrogate for the clinical presentation of blast neurotrauma. It also has derived the first empirical scaling for primary blast brain injury across animal species commonly used for blast brain research. Implications of this study are that many current studies are investigating blast doses well outside the realm of clinical interest. According to the derived apnea scaling of this study, unscaled blast test durations should be limited to approximately 1ms for mice, 3ms for rabbits and ferrets, and 6ms for pigs. Scaling provides realistic model inputs and the ability to scale for different injury endpoints or experimental outcomes. These findings emphasize that the choice of scaling method matters in the blast domain of interest and care must be taken to consider scaling during experimental design.

VI. ACKNOWLEDGEMENT

The authors gratefully acknowledge funding from the University of Pennsylvania through Army Research Office, Multidisciplinary Research Initiative (MURI) Grant W911NF-10-1-0526 and support from the Biomedical Engineering Department of the Pratt School of Engineering at Duke University.

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