Preclinical Models of Blast Injury

Pathophysiological Mechanisms Underlying Nervous System Damage by Blast Exposure

Research conducted at the Naval Medical Research Center (Silver Spring, Maryland) involves the effect of physical protection and increased intracranial pressure on the propagation of shock wave to brain in a rodent model. During blast exposure there is a direct transfer of shock wave through the skull to the brain. These waves can be transmitted from the body to the brain through blood vessels and cerebral spinal fluid. This study evaluated the contribution of head and/or body in transferring blast energy to brain by measuring intracranial (ICP), arterial (AP), and venous (VP) pressures in rodents exposed to blast overpressure (BOP). In view of the hypothesis that increasing the cerebral volume (CV) may have a protective effect against blast (by limiting the relative motion of intracranial content), the researchers increased CV by internal jugular vein (IJV) compression and investigated the resultant protection conferred.

The animals were exposed to BOP (~47 kilopascals) in a compressed air-driven blast tube with their body's orientation parallel (front) or perpendicular (side) to the blast. Animals were instrumented with pressure probes in the right lateral ventricle, femoral artery, and femoral vein, and exposed to BOP with/without protective shielding. Frontal exposure groups included no protection (F-NP), full body protection excluding tail, head protection (F-HP), and body protection excluding head (F-BP). Side exposure groups were exposed with no protection, or head protection (S-HP). In the Front BOP exposure with internal jugular vein compression group (F-IJV), the animal's neck was compressed by tightening Velcro tape immediately prior to exposure to BOP. The effects of protective shielding on ICP, AP, and VP are shown in Table 1. Body protection alone has no overall preventive effect, and for brain protection the head and neck need to be completely shielded.

A separate experiment was conducted to determine the BOP-induced (frontal-3 x 110 kPa, 30 minutes apart) effects on aquaporin-4 (AQP-4), 3-nitrotyrosine (3-NT), and endothelin receptor A (ETrA) in three groups of animals (control, blast, and blast-IJV). IJV prevented increase in 3-NT and ETrA in cortex, and attenuated the upregulation of AQP-4 and ETrA immunoreactivity in hippocampus.

This research also assessed the contribution of intensity of BOP as compared to the frequency of BOP on the resultant cellular impairment in the cortex. Blast-induced traumatic brain injury includes a variety of neuropathological changes depending on intensity of BOP, such as brain edema, neuronal degeneration, diffuse axonal damage, and vascular dysfunction with neurological manifestations of psychological and cognitive abnormalities. It is not well understood how the blast-induced brain injury depends on frequency and intensity of BOP. To address the relationship between single or repeated exposure to BOP and the resultant blast brain damage, animals were exposed to one or three (multiple blasts were separated by

30 minutes) blasts at two different intensities (72 and 110 kilopascals). Immunoreactivities of ferritin, occludin (Occ), neuronal nuclei (NeuN), AQP4, and 3-nitrotyrosine were analyzed to determine the effects on blast-induced hemorrhage, blood-brain barrier integrity, cellular loss, edema, and up-regulation of oxidative stress in the frontal cortex. Results to date showed that 110 kilopascal BOP induced a more significant increase of AQP4 and decrease of NeuN and Occ than exposure to 72 kilopascal at both single and repeated exposures. Quantitatively, it also appears that the animals subjected to single exposures exhibited similar degrees of damage as animals exposed to repeated BOPs. These results support previous findings that the blast-induced neuropathology depends more on intensity than on the frequency of BOP (*Kawoos et al. 2016*). A manuscript describing some of these findings were published (*Gu et al. 2017*).

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TABLE 1: Significant Effect of Protective Shielding/IJV Compression (Table used with permission from the authors)

Significant Effect of Protective Shielding/IJV Compression					
Parameters	Orientation				
	Front				Side
	F-FP	F-HP	F-BP	F-IJV	S-HP
ICP	Yes	Yes	No	Yes	Yes
AP	No	Yes	Yes	N/A	No
VP	No	Yes	Yes	N/A	N/A

REFERENCES:

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