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THEME TWO PLENARY

Penetrating and Blast Injury

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NEUROTRAUMA IN THE AFGHANISTAN AND IRAQ THEATERS OF OPERATION
JM Ecklund (*Washington, USA*)

Neurotrauma counts for 20 to 25% of all combat casualties. Since late 2001 the United States and Coalition Forces have been involved in ongoing combat and peacekeeping operations first in Afghanistan and later in Iraq. Battlefield care is different than peacetime or civilian care. The majority of wounds are penetrating and early care is delivered remote from advanced resources, often in austere environments. The ability to reach higher levels of medical care is often delayed by tactical, logistical, or environmental conditions. This presentation will first review the epidemiology of neurotrauma in both the Afghanistan and the Iraq theaters during different phases of the conflicts. Observations regarding the nature of injuries sustained and the relationship to current protective devices will be discussed. The current ability to deploy sophisticated management capabilities into austere environments and the resultant treatment outcomes will be summarized and highlighted. The use of telemedicine to enhance capabilities far forward in the treatment of neurotrauma will also be discussed. A review of the clinical observations describing the concussive effects of blast injuries will be presented based on the experience at Walter Reed Army Medical Center. Finally, preparedness in this age of terrorist threats will be emphasized, including a brief discussion regarding future emerging threats and potential injury patterns.

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BLAST(EXPLOSION)-INDUCED NEUROTRAUMA: A MYTH BECOMES REALITY
I Cernak (*Washington, USA*)

More than 50% of all action-related war injuries are caused by explosive munitions such as bombs, grenades, high-velocity missiles, mortar and artillery shells, antitank weapons and land mines. Increased terrorist use of such munitions has served to magnify this problem. Although exposure to blast overpressure that is generated during an explosion has been considered to damage primarily organs containing air or containing structures with different specific weights (ear, lungs, intestine), recent clinical and experimental data show that blast injuries cause significant brain damage, leading to cognitive and/or motor system deficits. While the majority of research has focused on the mechanisms of primary blast injuries inflicting gas-containing organs/organ systems, the possibility of blast-induced neurotrauma remains underestimated. The dogma that neurologic impairments following blast exposure are rare and solely a consequence of air-emboli in cerebral blood vessel has been challenged by recent clinical and experimental findings that resemble those observed following direct traumatic brain injury (TBI). The complexity of blast injuries can be explained by overwhelming local, general, and cerebral responses to the blast wave. As a part of a local response, parenchymal destruction, hemorrhage from ruptured blood vessels, and release of local mediators/modulators into systemic circulation occur. The general response includes homeostatic mechanisms aiming to counterbalance posttraumatic fluid loss, and maintain vital functions. My hypothesis is that alterations in brain function following blast exposure are induced by: 1) kinetic energy transfer of blast overpressure via great blood vessels in abdomen and thorax to the central nervous system; 2) hyperexcitability of the afferent nerves; 3) increased

release of neurotransmitters and autocoids from damaged peripheral tissue; and 4) ischemia caused by hemorrhage from injured organs. Our experimental studies demonstrate that blast overpressure causes cognitive deficit. Using three different experimental methods (whole-body shock tube, focal shock tube, open-air explosion), we demonstrated morphological alterations in the brain suggesting initiation of neurodegenerative processes, and related cognitive deficits. Blast overpressure also induces brain edema, as well as impaired energy metabolism, oxidative stress, and changes in neuroendocrine and second messenger systems; these alterations were comparable to those found after direct traumatic brain injury. Clarification of the mechanisms involved in explosion- (i.e. blast) induced neurotrauma may lead to effective novel treatment strategies to reduce long-term neurological deficits.

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THE US MILITARY'S RESEARCH EFFORT IN MILITARY RELEVANT NEUROTRAUMA

GSF Ling (*Bethesda, USA*)

Traditionally, for the US military, injury to the head and neck accounts for 20% of all wounds incurred in combat. Further, neurotrauma is the leading cause of death among casualties who have reached medical care. This experience continues in today's Global War on Terrorism. Current civilian research efforts are largely focused on closed head (concussive) and ischemic brain injuries. Although critically important, it is uncertain how these pertain to the injuries typically incurred in combat, i.e., penetrating and blast injuries. Furthermore, unconventional weapons, e.g., atypical explosives, chemical agents, etc, need more study. As the GWOT and similar threats to the civilian population increase, research into these and related issues is needed. The research conducted by military and Dept. of Defense scientists is now directed toward the acute and chronic effects of military relevant neurotrauma. All aspects are being studied ranging from elucidation of basic subcellular mechanisms of action to development of novel therapies and diagnostic methods. The greatest practical advance in military neurotrauma care is provided by material scientists through the current helmet. Similar success is needed from medical scientists as the clinical need is now.

SESSION 2.1: Models of Penetrating and Blast Injury

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INTRACRANIAL SOUND PRESSURE LEVELS DURING IMPULSE NOISE EXPOSURE

A Säljö, A Hamberger (*Göteborg, Sweden*)

Pressure waves, experienced as impulse noise, are produced by e.g. explosions, heavy weapons and by airbag deployment. We have shown, with immunohistochemical markers, damage in the central nervous system (CNS) after exposure of animals to impulse noise. Now we are monitoring amplitude, duration, rise time and frequencies of intracranial and intraabdominal pressures. The reflected part of a pressure wave results in a blow, which is recorded with an accelerometer. The portion of the pressure wave, which penetrates into the body, propagates the energy to various organs. The pressure was recorded with small pressure transducers (Samba Sensors, Göteborg, Sweden), implanted in the abdomen and brain of rats exposed to well characterized impulse noise. Part of this energy appears to be transferred from the abdomen and thorax to the brain, probably via the larger blood vessels.

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PENETRATING BRAIN INJURY IN THE RAT: I. MODELLING A SURVIVABLE, HIGH VELOCITY GUNSHOT WOUND TO THE HEAD WITHOUT USING A FIRED PROJECTILE

AJ Williams, X-C M Lu, JA Hartings, M Rolli, C Bautista, JR Dave, FC Tortella (*Silver Spring, USA*)

Penetrating brain injury (PBI) is a leading cause of mortality and morbidity in modern warfare and accounts for a significant number of traumatic brain injuries worldwide. However, PBI models replicating the ballistics of a high-velocity gunshot wound do not exist. In this study, rats (250–300 g) were subjected to a simulated (7.62 mm) ballistic wound utilizing a new PBI model developed for the USAMRMC combat casualty care research program. PBI was induced by inserting a metal probe into the frontal pole of the right cortex and terminating in the amygdala. A concentric ellipsoid air bladder ensheathing the probe was rapidly inflated and deflated ($<$ 10 msec) to 0, 5, 10 or 15% total hemispheric volume, mimicking the temporary cavity induced by energy dissipation. Evaluation of brain

(72 h post-PBI) revealed extensive injury to the ipsilateral frontal, insular, and piriform cortices as well as the caudate putamen and amygdala. Total lesion volumes (0 ± 0, 9 ± 3, 25 ± 3, 58 ± 5, and 86 ± 14 mm^3) and volumes of hemorrhage (0 ± 0, 5 ± 1, 7 ± 1, 12 ± 1, and 18 ± 2 mm^3) were progressive in size from a sham group to highest severity level evaluated, respectively. Remote neuronal degeneration (silver staining) was indicated in the white matter tracks of the cerebral peduncle. Astrogliosis (GFAP) was apparent adjacent to the injury region along with microglial (OX-42) and leukocyte infiltration (indicated from H&E). In conclusion, we have characterized the acute brain pathology associated with a survivable and highly reproducible PBI in the rat, demonstrating direct application as a new model for experimental PBI research.

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PENETRATING BRAIN INJURY IN THE RAT: III. INTRACRANIAL PRESSURE, BRAIN SWELLING AND PHYSIOLOGICAL PARAMETERS

C Yao, AJ Williams, M Rolli, X-C M Lu,, FC Tortella (*Silver Spring, USA*)

The management of brain injury includes monitoring and maintaining physiological parameters in an effort to improve outcome. In the present study, we evaluated changes in several physiological variables following experimental penetrating brain injury (PBI). Rats were subjected to PBI by introducing a rigid catheter into the right frontal lobe and rapidly inflating a concentric ellipsoid balloon to one of four different severity levels (0, 5, 10, and 15% brain volume). The percent brain swelling (ipsilateral/contralateral hemispheric volume) in tissue collected at 72h was 2.9 ± 0.6, 2.8 ± 1.2, 5.7 ± 1.4, and 13.6 ± 1.7% at the 0, 5, 10, and 15% severity levels, respectively. In a subsequent series of preliminary experiments we evaluated the changes in ICP, mean arterial blood pressure (MABP), brain temperature, and rectal temperature in anesthetised rats post-10% PBI. Baseline ICP measurements were 9.8 ± 0.2 mmHg. Post-PBI, ICP progressively increased from the initial 2 h post-injury (10–11.5 mmHg) to 13 ± 0.5, 16 ± 3.5, and 18.3 ± 0.3 mmHg on days 1, 2, and 2 post-injury, respectively. In contrast, MABP dropped 8–14 mmHg during the initial 2 h following PBI, indicating a decrease in cerebral perfusion pressure at the early stages of injury. Body temperature was maintained throughout the surgery with a homeothermic heating system but brain temperature dropped post-PBI by 0.9–1.9°C over the initial 30 min period. In summary, we have evaluated changes in physiological variables including brain swelling, ICP, MABP, and brain temperature associated with experimental PBI in the rat that may relate useful information and provide an experimental basis for the clinical management of PBI.

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LEAKAGE OF S-100 PROTEIN AFTER HIGH VELOCITY PENETRATION INJURY TO THE BRAIN

M Risling; MSkold; I Larsson; M Angeria, J Davidsson (*Stockholm, Gothenburg, Sweden*)

Traumatic penetration injuries to the brain lead to tissue damage, edema formation, inflammation and bleeding. We have developed a model for penetration injuries to the brain, at high velocity with good reproducibility. During experiments, a lead bullet was accelerated by air pressure in a specially designed rifle and impacted a secondary projectile. The second projectile consisted of a metal cylinder with an attached carbon fibre pin (length 24 mm, diameter 2 mm) with a tip angle of 30 degrees. The pin of the secondary projectile, guided by a narrow tube, approached the surface of the brain of anesthetized adult female rats ($n = 21$) with a speed of 150 m/s. The shape of the narrow tube provided good control of the penetration depth into the brain, which was 5 mm from the dura. In other experiments, the secondary projectile was accelerated to a speed of 1.5 m/s, by the impact of a pendulum. The animals were allowed to survive for 6 hours – 7 days. Blood samples were collected for S-100 analysis. Sections from the brain were cut perpendicular to the lesion and stained for immunohistochemical examination. S-100 in blood peaked at 6h and 7 days. ED-1 positive macrophages peaked at 5 days after the lesion whereas a down regulation of blood-brain barrier (BBB) associated proteins was detected in the penumbra zone surrounding the lesion at 7 days. Cell death, as detected by TUNEL labeling and Fluoro Jade-B staining, peaked 1-3 days after the injury.

SESSION 2.2*:* Clinical Management

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DEVELOPMENT OF INNOVATIVE PORTABLE DEVICES FOR THE TREATMENT OF MILITARY TRAUMA CASUALTIES

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Blast and penetrating injuries in the military frequently result in poor GCS outcome. Poor outcome, in turn, may be due to the lack of critical care provided by the medic. As the medic is limited by the training received, as well as the supplies he carries, quick diagnosis combined with effective treatment is critical in the survival of the wounded. To assist the medic in triage situations, our laboratory, working together with several biotechnology companies, have developed several medical devices to ease the critical care burden placed on the combat medic. The devices have been developed especially for the far-forward environment with portability and ease of use designed into each product. These devices include: 1) the Arrow-2 Microventilator measuring $6" \times 6" \times 2.5"$ weighing 3 lbs, designed to provide continuous ventilation (800 ml/breath and 12 breaths/min), over a 4-hr period; 2) the RFTT (radio frequency triage tool), a portable, noninvasive imaging system that can be used to detect the presence of air in the pleural cavity, and the presence of saline and/or blood within the fascia and muscle compartment; 3) the dysautonomia meter, a 3-lead ECG device is a battery operated, portable, hand held instrument capable of measuring the electrical impulses of the heart in real-time; and 4) the NOVA dermal hydration meter that measures hypovolemia in hemorrhage models. Our goal is to see all of these devices through human clinical trials for intended use in the battlefield to increase the survival and thus the eventual return of injured soldiers to the battlefield.

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POLY-NEUROTRAUMA: CLINICAL AND EXPERIMENTAL PERSPECTIVES OF DAMAGE CONTROL AND REPAIR

EAM Neugebauer (*Cologne, Germany*)

Polytrauma is the leading cause of death for persons between 15 and 44 years of age. From two own epidemiologic data bases we could show that 50% of all polytrauma patients sustain a combined poly-/neurotrauma. The injured brain is extremely vulnerable to hypotension, hypoxia, hyper inflammation and increased intracranial pressure which are causes of secondary brain injury. BBB disturbance contributes not only to secondary brain injury, but also to immune suppression with organ failure and death. The interaction between central and peripheral injuries is not well studied yet. We investigated the effect of different injury patterns in three groups of severely injured patients (TBI, Polytrauma without TBI, combined) on immunological parameters (IL6, IL10, TNF-receptors, PNM-elactase, PCT, Neopterin) and their relation to secondary damage (pneumonia, sepsis, MOF, mortality) by multivariate logistic regression analysis. We found a bidirectional increase in mortality and more MOF in the combined trauma group. Plasma PCT, age and ISS resulted in a MOF prognostic score.

For damage reduction and -repair volume therapy based on base-excess, the optimisation of fracture stabilisation (time, extend) and early psychotherapy after polytrauma were demonstrated by RCT's to improve outcome. Experimentally we could demonstrate that cell transplantation (neuronal and embryonic stem cells) in rat TBI models show beneficial effects on functional and cognitive outcome. We do need further studies to understand the mechanisms and to optimize treatment conditions for damage control and -repair.

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HYPERTONIC SALINE RESUSCITATION FOR SEVERE TRAUMATIC BRAIN INJURY PATIENTS.

DJ Cooper (*Melbourne, Australia*)

Long term outcomes of patients with severe traumatic brain injury continue to be unfavourable. We believe that secondary brain injury after trauma may be minimised and outcomes improved, by effective resuscitation and faster correction of secondary insults. Hypertonic saline (HTS) expands intra-vascular volume more rapidly than conventional resuscitation fluids, corrects hypotension, and decreases intracranial pressure. These features suggest that HTS may be an ideal resuscitation fluid for hypotensive patients with traumatic brain injury (TBI), especially in the pre-hospital setting. Previous trials have suggested benefit for HTS and HTS-dextran for pre-hospital TBI patients, and a commercial product is in use for pre-hospital resusci-

tation in many countries, but no randomised trial had been reported in this patient group. We completed the first prospective randomised trial testing pre-hospital HTS in addition to conventional resuscitation protocols in 229 patients with non-penetrating traumatic coma and hypotension in Victoria Australia. We found that neurological outcomes (Extended Glasgow Outcome Score) at both 3 and 6 months after injury were the same as in the patients receiving standard resuscitation protocols. There was a small trend to improved survival but favourable outcomes were the same. In the context of an efficient pre-hospital paramedic system in Victoria Australia, HTS did not improve patient outcomes. Hypertonic saline however continues to have likely advantages and be widely used for other indications in Intensive Care including the management of refractory intracranial hypertension.

1. Pre-hospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomised controlled trial, *JAMA* **291** (2004), 1350–1357.