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SPINAL CORD INJURY: TRANSLATING SCIENTIFIC DISCOVERY TO CLINICAL TRIALS

J Steeves (*Vancouver, Canada*)

The list of experimental interventions, therapies, and devices to facilitate improved functional outcomes after SCI is extensive. The International Campaign for Cures of spinal cord injury Paralysis (ICCP) hosted a workshop, held in Vancouver, in early 2004. The discussions were focused on the rapidly increasing number of experimental cellular-based and pharmaceutical drug treatments for the repair of SCI. Some of these clinical trials have already started and several more are at a late stage of pre-clinical maturity. There was a need for an international forum where participants, invited from 5 continents, could share information about their clinical trial ideas, plans, progress, and outcomes. It is hoped that these discussions will form the initial foundation for continued efforts to ensure all current and future SCI trials can be conducted in a consistent, safe, and effective manner. It is also hoped that such interdisciplinary forums will provide guidance for the translation of new scientific discoveries into valid clinical therapies. A brief summary of the workshop discussions and outcomes will be provided, outlining: 1) the general direction of current trial activities, 2) the preclinical validation process, 3) the variables associated with SCI trials, and 4) the progress on developing reliable and sensitive outcome measures.

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THE PRESENT AND FUTURE OF CLINICAL TRIALS IN TBI

AIR Maas, A Hernandez, E Steyerberg, A Marmarou, G, Murray (*Rotterdam, The Netherlands; Richmond, USA; Edinburgh UK*)

A systematic literature search for randomized controlled trials (RCT's) in adult patients with acute severe or moderate TBI, conducted over the years 1966 to 2004 yielded 18 studies in which 100 or more patients had been enrolled. Six trials reported positive results and five of these concerned single center studies investigating non-drug treatments. None of the multi center studies on neuroprotective agents showed convincing benefit in the overall population of moderate and severe TBI.

We are aware of various other large multi center studies, all with "negative" results, which have not (yet) been reported.

Difficulties in showing benefit may be related to the considerable heterogeneity of the patient population, and this has prompted a critical appraisal of the design and analysis of RCT's in TBI. We are currently investigating the extent of heterogeneity in 3 unselected prospective series and in 11 RCT's of moderate and severe TBI, encompassing over 10.000 patients, and are searching for solutions how best to deal with this complex problem. To this purpose extensive univariate and multivariate analysis of baseline predictors has been performed. This has confirmed the prognostic importance of many well-known baseline characteristics (e.g. age, motor score, pupillary reactivity, hypoxia, hypotension and CT parameters) but has also identified various other, currently less well-known predictors. Combining these predictors in a prognostic model shows that approximately 30% of patients in-

cluded in RCT's are in an extreme risk group, and do not contribute to the statistical power of a study. We propose that such extreme risk groups are excluded in future RCT's or that alternatively sample size calculations are adjusted for the confounding influence of including these risk groups. We further suggest that prognostic models should be used towards a more detailed classification of TBI. The common practice of dichotomizing the GOS in the primary efficacy analysis carries a risk of not detecting a clinically relevant difference. We propose to differentiate the point of dichotomy according to baseline prognostic risk (sliding dichotomy), and preliminary results show that this improves statistical power considerably. The concept of the sliding dichotomy has been applied in the analysis of the STICH study and will be further used in the final analysis of the phase III study on dexanabinol, in which enrollment was recently completed.

For the future we foresee more focussed and targeted trials with an important role for prognostic models, and a more refined use of the concept of the sliding dichotomy.

We hope to present final proposals for improving the design and analysis of RCT's in TBI during INTS 2006.

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SESSION 7.1*:* Neuroprotection

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THE FAS DEATH RECEPTOR AS A TARGET FOR NEUROPROTECTIVE THERAPY OF ACUTE SPINAL CORD INJURY

M Fehlings, S Casha, A Ackery, W Yu (*Toronto, Canada*)

There is a critical need for effective neuroprotective approaches to treat spinal cord injuries. FAS receptor activation has been implicated in inflammatory responses, programmed cell death and Wallerian degeneration in neural injury although direct evidence for this mechanism in neurotrauma is lacking. We show that FAS receptor deficiency or inhibition of FAS activation reduces cell death and improves functional outcome after SCI. Studies were undertaken in FASLpr/lpr mutant mice and wildtype littermates subjected to a T5-6 clip compression SCI using the FEJOTA model. Complementary studies were done using an organotypic slice culture model of SCI. Post-traumatic apoptosis in the spinal cord, which is seen in neurons and oligodendrocytes, was decreased in the FAS deficient mice both *in vivo* and *in vitro*. FAS deficiency was also associated with improved locomotor recovery (assessed by BBB), preservation of axons (quantitative retrograde tracing with Fluorogold) and white matter preservation. *In vivo* oligodendrocyte counts were preserved in FAS deficient mice at seven days. Early evidence of neuronal preservation (Neurofilament 200 and MAP2 protein sparing) in mutant animals was not sustained and neuronal counts at the injury site were unchanged in chronically injured animals. Recent studies have shown that *in vitro* and *in vivo* inhibition of FAS activation (by soluble FAS receptor is neuroprotective after SCI. These results indicate that inhibition of the FAS death receptor pathway, predominantly in oligodendroglia, is associated with improved tissue sparing and enhanced functional recovery after traumatic SCI. Hence, inhibition of the FAS pathway may be a clinically attractive neuroprotective strategy.

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NEURON-ASTROCYTE INTERACTIONS FOLLOWING NEURONAL INJURY ACTIVATE A NOVEL, METALLOTHIONEIN BASED NEUROPROTECTIVE MECHANISM

RS Chung, J Dittmann, MI Chuah, JC Vickers and AK West (*Hobart, Australia*)

Recent studies have demonstrated the importance of cellular interactions between neurons and glial cells following brain trauma. In this regard, we have demonstrated that exogenous administration of the astrocytic protein metallothionein (MT) to injured neurons both *in vitro* and in animal models of CNS injury confers powerful neuroprotection by a direct, extracellular interaction with neurons (Chung et al, J Neurosci 2003). This suggests that the normal physiological role of metallothionein in the CNS involves a significant extracellular component, triggered by the initial neuronal injury. To investigate this, we have observed that MT immunoreactivity rapidly increases within the neocortex following focal cortical brain injury, primarily within astrocytes aligned along the injury site. At later time points, astrocytes, at a distance up to several hundred microns from the original injury tract, were MT immunoreactive. Induced MT was found both within the cell body and processes. Using a cortical neuron/astrocyte co-culture model, we observed a similar MT response following *in vitro* neuronal injury, with MT protein rapidly induced several hours after injury. Intriguingly, scratch wound injury in pure astrocyte cul-

tures resulted in no change in MT expression, at either RNA or protein level. This suggests that astrocytic MT induction was specifically elicited by neuronal injury, indicating that an important signalling interaction occurs between injured neurons and astrocytes, which we are in the process of identifying. To account for our observations, we have proposed a novel model of neuroprotective metallothionein action within the context of neuron-astrocyte interactions following injury (Chung and West, Neuroscience 2004).

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ADENOSINE A2A AGONISM ATTENUATES NEURONAL DAMAGE AND IMPROVES FUNCTIONAL OUTCOME FOLLOWING EXPERIMENTAL TRAUMATIC SPINAL CORD INJURY (SCI): COMPARISON TO METHYLPREDNISOLONE

DO Okonkwo, TB Reece, JJ Laurent, AS Hawkins, J Linden, JR Stone, GA Helm, JA Kern (*Charlottesville, USA*)

Steroids remain, in many respects, the lone pharmacologic treatment option for acute spinal cord injury, though their utility remains in dispute in the neurotrauma literature. Adenosine A2a receptor activation with ATL-146e, a selective A2a agonist, has shown potential benefit in SCI; however, it has not been compared to the gold standard of methylprednisolone. The current study evaluated ATL-146e and methylprednisolone for ability to preserve neuronal viability and motor function in experimental SCI. Three groups ($n = 10$) of New Zealand white rabbits sustained traumatic SCI using a 60 gm*cm Allen weight drop technique. Ten minutes postinjury, animals received ATL-146e (ATL, 0.06 mcg/kg/min IV for 3 hrs), methylprednisolone (Steroid, 30 mg/kg IV over 10 min), or saline (Control). Hind limb motor function was recorded q12h using the Tarlov scale (0 = paralysis to 5 = normal hop). After euthanasia at 48 hrs, fixed spinal cord tissue was evaluated for neuronal viability (neurons/high powered field).

Hind limb function was significantly better in ATL-treated animals than controls (48 hr: ATL 3.2 $\pm$ 0.25 vs. Control 1.3 $\pm$ 0.62, $p < 0.02$). Motor function in steroid-treated animals was worse than ATL-146e and better than controls, but not significantly (48 hr: 2.5 $\pm$ 0.58, both $p > 0.05$). Neurons/hpf was significantly higher in treatment groups versus controls (ATL 12.1 $\pm$ 1.4 and Steroid 13.3 $\pm$ 1.4 vs. Control 7.5 $\pm$ 1.5 neurons/hpf, both $p < 0.04$). Neuronal viability did not differ between ATL- and Steroid-treated animals. ATL-146e was superior to steroids in preserving function and comparable to steroids in preserving histology following blunt spinal cord injury. Adenosine A2A receptor activation may be an effective treatment of acute SCI while avoiding adverse effects of steroids.

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QUERCETIN PRESERVES AXONAL INTEGRITY AFTER ACUTE SPINAL CORD INJURY

E Schültke, G Davies, RW Griebel, BHJ Juurlink (*Saskatchewan, Canada*)

Background: Previously, we have been able to demonstrate that administration of the flavonoid quercetin supports recovery of motor function after acute spinal cord injury in an animal model. The following experiments were designed to investigate possible mechanisms of action of quercetin early after injury.

Material and Methods: Adult male Wistar rats were submitted to mid-thoracic spinal cord compression injury, caused by 5 seconds closure of an aneurysm clip with a calibrated closing force of 50 g. One hour after injury, half of the animals received 25 micromol/kg quercetin i.p., while the remaining animals received saline vehicle only. All animals were sacrificed 72 hrs after injury. Spinal cord segments at several levels above and below the site of injury were harvested and homogenized. Western blots were performed for GAP-43, Amyloid Precursor Protein, phosphorylated neurofilament 200 (pNF), pan neurofilament 200 (both phosphorylated and non-phosphorylated) Neurotrophin-4. Spinal cord segments of four healthy animals were used as controls.

Results: We found that the amount of GAP-43 in segments adjacent to the site of injury was equal to that seen in uninjured, healthy animals, while the amount of GAP-43 in saline-treated animal was significantly reduced. Furthermore, we found significantly higher levels of pNF and Neurotrophin-4 in quercetin-treated animals then in those who received saline vehicle only.

Conclusions: The results of our experiments suggest that quercetin protects the morphological integrity of axons after acute spinal cord injury in our rat model.

This study was supported by the Christopher Reeve Paralysis Foundation and SSI.

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CALPAIN INHIBITION STRATEGIES FOR TRAUMATIC CNS INJURY
JW Geddes, T Sengoku, M Garcia, V Bondada (*Lexington, USA*)

Calcium-activated neutral proteases (calpains) are excessively activated soon after traumatic spinal cord and brain injury, and are ideally positioned in signaling and proteolytic cascades to help coordinate the postinjury secondary mechanisms leading to cell death. Unfortunately, current calpain inhibitors suffer from weak potency and poor specificity. As a result, it has been difficult to test the hypothesis that calpain inhibition will protect against the secondary damage and improve functional outcome following traumatic CNS injury. The endogenous calpain inhibitor, calpastatin, is a potent and specific calpain inhibitor but does not cross cell membranes. We developed novel calpain inhibitors consisting of calpastatin or its inhibitory domain I, fused to the protein transduction domain of the HIV trans-activator (Tat) protein (Tat47-57). The Tat-calpastatin fusion proteins were excellent calpain inhibitors in cell-free activity assays, but did not inhibit cellular calpain activity in several cell lines or in primary neurons. To determine the mechanisms underlying the inability of the Tat-calpastatin fusion proteins to inhibit cellular calpain, we examined their cellular localization. The fusion proteins were localized to endosomes, preventing their interaction with cellular calpains. Subcellular fractionation studies revealed that m-calpain is predominantly associated with membrane fractions in contrast to the cytosolic localization of mu-calpain and calpastatin. Together, the results demonstrate that endosomal uptake of proteins fused to the Tat protein transduction domain severely limits the applications of this methodology. The results further demonstrate that effective cellular calpain inhibition will require targeting both cytosolic and membrane-associated calpains.

SESSION 7.2*:* Hypothermia

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THERAPEUTIC HYPOTHERMIA FOLLOWING BRAIN AND SPINAL CORD INJURY
WD Dietrich (*Miami, USA*)

The beneficial effects of mild to moderate hypothermia have been reported in various experimental models of CNS injury. With these established benefits, investigations have concentrated on clarifying temperature-sensitive pathomechanisms, including excitotoxicity, oxidative stress, free radicals, blood-brain barrier damage, inflammation, and apoptotic cell death. Recently, this research has been translated to the clinic, where specific patient populations have been reported to benefit from hypothermic treatment. The degree of injury severity is an important factor in determining whether a specific treatment strategy will be effective. Thus, increased ischemic or traumatic severity may limit the beneficial effects of any therapy, including hypothermia. In this regard, recent studies have shown that, in a model of traumatic brain injury complicated by secondary hypoxia, hypothermia was shown to be protective with slow rewarming. These and other studies indicate that hypothermia may be used as a protective strategy in situations where the patient may be at risk for a neurological insult as well as in the post-injury setting. Surface cooling strategies usually lead to whole body hypothermia that may have negative effects on multiple systems. Intravascular cooling catheters may be especially useful to control the rate of rewarming, an important factor in the beneficial effects of hypothermic therapy. In the area of spinal cord injury, systemic and local cooling approaches have also been undertaken, with variable results. Although the therapeutic effect of hypothermia has been demonstrated in some patient populations, negative findings have been reported in others. The limitations of the effectiveness of hypothermia may be related to several factors, including therapeutic window, optimal levels and durations of cooling, rewarming protocol, injury severity, and gender.

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EFFECT OF HYPOTHERMIA ON INTRACRANIAL PRESSURE, CEREBRAL PERFUSION PRESSURE, SYSTEMIC CONDITIONS, AND OUTCOME IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY
T Tokutomi, T Miyagi, K Morimoto, M Shigemori (*Fukuoka, Japan*)

Patients with Glasgow Coma Scale (GCS) scores of 5 or less after resuscitation following traumatic brain injury have a very high mortality rate and a low rate of favorable outcome as compared with patients having GCS scores of 6 to 8. Because there exists no effective treatment for patients with such low GCS scores, we initiated therapeutic hypothermia (33°C; for 48 to

72 hours) from 1994 to 1999. Contrary to our expectation, clinical outcome from this treatment showed no improvement, despite the intracranial pressure reduction effect of hypothermia. On the basis of this experience, we determined that cooling to 35°C; is sufficient to control intracranial hypertension, and that hypothermia below 35°C; may predispose patients to persistent cumulative oxygen debt, which may associated with an increasing risk of complications. Persistently high levels of C-reactive protein (CRP) after rewarming from 33°C; was also observed. Since hypothermia was very effective in controlling intracranial hypertension, avoiding the adverse effects of hypothermia on systemic conditions might make it a more promising therapeutic tool. Hence, we altered the target temperature from 33°C; to 35°C; after 2000. The effect of 35°C; hypothermia on intracranial hypertension was similar to that of 33°C; hypothermia. Cerebral perfusion pressure was controlled at a higher level in the 35°C; hypothermic patients than in the 33°C; hypothermic patients. 35°C; hypothermic patients exhibited significant improvement in terms of systemic oxygen consumption and serum potassium concentration during hypothermia and increment of CRP after rewarming. However, there were no statistically significant differences between the 33°C; and 35°C; hypothermic patients in the incidence of infectious complications, changes of coagulation parameters, and clinical outcomes. Although further accumulation of the data is necessary, 35°C; seems to be the optimal temperature to control intracranial hypertension in patients with severe traumatic brain injury.

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TAI AND RESPONSE OF THE AXONAL CYTOSKELETON TO DIFFERENT RATES OF REWARMING AFTER MILD POST-TRAUMATIC HYPOTHERMIA.

W Maxwell, A Watson, B Conway, R Queen, D Graham
(*Glasgow, UK*)

Evidence has recently been obtained which suggests that mild, post-traumatic hypothermia may improve experimental and patient outcomes. But how hypothermia acts at 1) the level of the cytoskeleton of injured axons and 2) which rate or re-warming provides the optimal level of neuroprotection is controversial. The hypothesis that either slow or fast re-warming following mild hypothermia may cause secondary injury to axons was investigated. Twenty four animals were prepared for stretch-injury to the right optic nerve. Shams (3) were not injured and 3 maintained at normal core temperature (38.5C). All other animals were injured and cooled to a core temperature of 32.0–32.5 C as rapidly as possible. After 4 hours, 6 animals were re-warmed at a rate of 1C rise in core temperature every 10 mins (fast), 6 at a rate of 1C every 20 mins (medium) and 6 at 1C every 40 mins (slow). Animals were killed by perfusion fixation either for immunocytochemistry or for TEM. Damaged axons were labelled on paraffin sections either for accumulation of beta-amyloid precursor protein or for compaction of neurofilaments. The number of labelled axons was counted in the above experimental groups. Stereology was used to count numbers of and spacing between neurofilaments (NF) and microtubules (MT) within perpendicular transverse sections of axons at x 50,000 on a TEM. ICC labelling for damaged axons occurred in normothermic, fast and medium rates of re-warmed animals but not in slow re-warmed animals. There was compaction of NF and loss of MT in normothermic animals, total loss of MT with fast re-warming, a lack of NF compaction and a reduced number of MT with medium re-warming, but no difference from sham values with slow re-warming. The present study shows that re-warming at a rate of 1C core temperature rise every 40 mins retains normal axonal cytoskeletal architecture after TAI. Re-warming at a faster rate than the above results in pathology within the axonal cytoskeleton. Rapid re-warming induces a secondary insult to the axon. Thus slow re-warming provides the best hope for improvement of outcome for the head-injured patient.

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THE SIGNIFICANCE OF THE RELATION BETWEEN BRAIN TEMPERATURE AND CORE TEMPERATURE IN BRAIN HYPOTHERMIA TREATMENT FOR SEVERE TRAUMATIC BRAIN INJURY

E Suehiro, H Fujisawa, T Akimura, M Suzuki
(*Yamaguchi, Japan*)

Object: Brain temperature is influenced by cerebral perfusion pressure (CPP), metabolic processes in the brain, and the core temperature. This provides the disturbances in brain metabolism and in cerebral blood flow of traumatic brain injury (TBI) patients. Further, patients with TBI often need decompressive craniectomy or hypothermia treatment to control intracranial pressure (ICP). However the influences of these treat-

ments for brain temperature remains unclear. This study investigated the relation between brain and core temperature, and the effects of decompressive craniectomy in brain temperature.

Methods: This study involved 9 patients, suffering from TBI with a Glasgow Coma Scale (GCS) at admission of 8 or less. 6 patients (Group A) underwent decompressive craniectomy. 3 patients (Group B) underwent conservative treatment. All patients underwent hypothermia treatment. Brain temperature and ICP were monitored by an intraparenchymal catheters positioned at 2–3 cm depth from brain surface. Core temperature was measured using a bladder catheter with thermistor probe. The jugular venous oxygen saturation (SjO_2) was continuously measured. These were measured during hypothermia therapy.

Results: The temperature difference (delta T) between brain and bladder temperature was -0.20 ± 0.03°C (mean $\pm$ SE). Delta T in Group A (-0.23 ± 0.03) was lower than Group B (-0.15 ± 0.06). A significant correlation between delta T and SjO2 was seen in Group B ($R = 0.62$), but not in Group A. No relation was found between delta T and CPP.

Conclusion: delta T can be a reliable indicator of cerebral blood flow and metabolism in patients with a closed cranium.

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TOPICAL HYPOTHERMIA FOLLOWING SPINAL CORD INJURY: TRANSIENT NEUROPROTECTION BY DOWNREGULATION OF SECONDARY DAMAGE
CB Shields, YP Zhang, N Liu, LBE Shields, Z Zhang, L Xu, X Xu, Y Han (*Louisville, USA*)

Although hypothermia is neuroprotective following spinal cord ischemia, it seems to be ineffective in treating contusion spinal cord injury (SCI). We hypothesize that topical hypothermia of the spinal cord following contusion SCI delays but fails to abort destructive cascades leading to cell death. A moderate SCI (12.5 gm-cm) was created at T10 in Sprague-Dawley rats. The epidural space at the site of injury was irrigated for 8 hours with: 1) cooled Hank's solution (200°C) or 2) normothermic Hank's solution (37°C). Half the rats were killed immediately after 8 hours of irrigation, whereas the remainder was maintained at normothermia for an additional 16 hours. Injured spinal cords were assessed for myeloperoxidase activity (MPO) (neutrophil activity), IL-1 (cytokine activity), calpain (neurofilament protein degradation), and caspase-3 (apoptosis). MPO activity was 402.6 U/gram in the normothermic and 192.7 U/gram in the hypothermic group. IL-1 level in the hypothermic group was one-third that of the normothermic group. Calpain activity and caspase-3 levels were reduced in the hypothermic compared to the normothermic group. However, the parameters measured in the hypothermic group during the rewarming phase returned to those recorded in the normothermic group. SCI initiated a cascade of metabolic changes that initiates secondary degeneration and cell death. Hypothermia downregulates pathways resulting in secondary damage, however, it can only be administered for a limited duration. Hypothermia may be unsuccessful in treating SCI as there is a return of destructive metabolic activities to the normothermic levels after rewarming.

SESSION 7.3*:* Controversies in Clinical Management

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TARGETED THERAPY FOR BRAIN INJURY
P Reilly (*Adelaide, Australia*)

With the publication of evidence-based guidelines in the past 10 years, management of severe head injury can be based on generally accepted physiological end points. Standardized care may have resulted in improved outcomes however the global end points in current use do not take into account the variability of head injury between individuals, between regions of the brain and with time. Tissue oxygen electrodes and tissue dialysis measure regional changes following injury. With developments in CT and MRI the measurement of regional perfusion is more widely available. These techniques make it possible to follow the metabolic, functional and anatomical effects of injury regionally and globally. Miller and Dearden in 1988 proposed targeting hypnotic or osmotic therapy according to an interpretation of global pathology. Targeted therapy requires a determination of the correct target, whether this should be the dominant global pathology or vulnerable regions such as the penumbra of contusions and it requires delivery of the relevant therapy to the chosen target. Present challenges include using the global measurements available in most ICU to identify therapeutic end points appropriate to individual injury and secondly, determining whether regional measurements will identify more relevant treatment targets and therefore lead to better outcomes.

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THE AUSTRALIAN DECOMPRESSIVE CRANIECTOMY (DECRA) RANDOMISED CONTROLLED TRIAL: DESIGN AND PROGRESS REPORT

JV Rosenfeld, DJ Cooper, T Kossmann, L Murray, P D'Urso, A Davies, G Malham, V Pelligrino, P Reilly (*Melbourne; Adelaide, Australia*)

Aim: To determine the effect of early decompressive craniectomy (DECRA) on adult TBI patients with diffuse brain swelling and refractory intracranial hypertension on outcome.

Introduction: Severe traumatic brain injury patients with refractory brain swelling have very poor outcomes. DECRA lowers the ICP but it is often performed late. The question as to whether the clinical outcome is improved by DECRA is best addressed by a randomised controlled trial. The timing of the DECRA may also be important, therefore we are studying early DECRA to minimize the effects of prolonged intracranial hypertension.

Methods: Eligible patients have severe TB, GCS < 9, diffuse injury on CT, $<$ 72 hrs after injury, 16 to 60 yrs, ideally a ventricular drain, refractory ICP despite best medical management (ICP $>$ 20 mmHg. $>$ 15 minutes [continuous or accumulative over one hour]). The patient is then randomised to DECRA or continued intensive medical management. Late salvage DECRA is not excluded. A large bifrontal craniectomy is performed which is a slight variation from that described by Polin et al. (Neurosurg 1997; 41: 84–94). Outcomes are assessed by Extended Glasgow Outcome Score (GOSE), (6 and 12 months), and mortality. The plan is to recruit 210 patients by the end of 2006 from neurotrauma centres throughout Australia and New Zealand. The sample size is based on an increase in favourable neurological outcomes from 30% (current, adults) to 50%. Patients with no chance of survival are excluded.

Progress: A randomised pilot study was performed at the Alfred Hospital February to July 2003 and approximately one patient per month was enrolled. The consent process was successful in 93% of cases. The multi-centre DECRA trial is endorsed by the ANZICS Clinical Trials Group and supported by the Neurosurgical Society of Australasia. There are now 16 participating centres in Australia and New Zealand. Twenty-four patients had been entered into the study in April 2004. The Alfred Hospital is the co-ordinating centre. This is the first multicentre randomised controlled trial of this technique to be performed in the adult population.

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OUTCOME AFTER DECOMPRESSIVE CRANIECTOMY DUE TO REFRACTORY INTRACRANIAL HYPERTENSION IN PATIENTS WITH TRAUMATIC BRAIN INJURIES

T Skoglund, C Eriksson-Ritzén, C Jensen, B Rydenhag (*Göteborg, Sweden*)

In patients with traumatic brain injury (TBI) intracranial hypertension secondary to cerebral oedema is a major problem. In our Tertiary University hospital we have used decompressive craniectomy since 1997 as a last tier treatment in patients who develop uncontrollable intracranial hypertension, despite maximal conventional surgery and medical treatment (including barbiturate sedation). Among the about 150 patients with severe TBI treated at our neurointensive care unit during the period from 1997–2002, nineteen patients were treated with decompressive craniectomy. All patients were young (mean $22+/-11$ years, range 7–46) and 68% were male. They underwent craniectomy between days 1–11 (mean $4.4+/-3.3$). The mean ICP was reduced from 32.7 to 14.8 mmHg after the craniectomy, twenty-fours hours after the craniectomy the mean ICP was 16.8 mmHg. The outcome of all patients could be assessed. The survival rate was 89%. Two patients died (both day 4 after the trauma). 68% of the patients had a favorable outcome (Glasgow Outcome Scale 4/5), 16% were severely disabled (GOS 3), and one patient (5%) was left in a vegetative state. All surviving 17 patients had their own bone flap electively reinserted. This procedure was performed 4.5 (range 1–7) months after the craniectomy was performed.

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COMBINATION OF VENOARTERIAL PCO2 DIFFERENCE WITH ARTERIOVENOUS O2 CONTENT DIFFERENCE TO DETECT ANAEROBIS METABOLISM DURING PROGRESSION TO BRAIN DEATH

E Roncati Zanier, R Nicolini, K Canavesi, V Conte, A Protti, L Gattinoni, N Stocchetti (*Milano, Italy*)

PURPOSE: In a condition of progressive irreversible ischemia, we hypothesize that for moderate perfusion reduction, oxygen extraction increases to maintain aerobic metabolism and arteriovenous O_2 content difference (AVDO2) rises; because of reduced CO_2 washout venoarterial PCO2 difference (DPCO2) increases with no changes in DPCO2/AVDO2 Ratio. With further

cerebral perfusion reduction, aerobic metabolism will begin to fall, AVDO2 will decrease while DPCO2 (due to buffered protons) will continue to rise, and the ratio rises. When brain infarction develops metabolism will be abated, no oxygen will be consumed neither CO_2 produced.

METHODS: Patients ($n = 12$) with acute cerebral damage that evolved to brain death were studied. Intermittent arterial and jugular blood samples were collected.

RESULTS: We observed 4 patterns: 1) AVDO2 4.1 $\pm$ 0.3 vol%, DPCO2 6.5 $\pm$ 0.71 mmHg and Ratio 1.55 $\pm$ 0.1, at a cerebral perfusion pressure (CPP) of 62.5 $\pm$ 5.5 mmHg suggesting a "normal state". 2) coupled rise of AVDO2 (5.8 $\pm$ 0.7 vol%) and DPCO2 (10.1 $\pm$ 1.0 mmHg) with unchanged ratio (1.92 $\pm$ 0.14), at a CPP $=$ 57.9 $\pm$ 5.8 mmHg, suggesting a "compensated hypoperfusion". 3) AVDO2 $=$ 5.1 $\pm$ 0.7 vol% with a DPCO2 increase (12.7 $\pm$ 1.2 mmHg), and associated rise in the Ratio (2.7 $\pm$ 0.2); CPP was 44.7 $\pm$ 10.5 mmHg. These values suggest an "uncompensated hypoperfusion". 4) Immediately before brain death diagnosis (CPP $=$ 17 $\pm$ 10.4 mmHg) there was a drop of AVDO2 (1.1 $\pm$ 0.1 vol%), and (to a lesser degree) of DPCO2 (5.3 $\pm$ 0.6 mmHg) with further ratio increase (5.1 $\pm$ 0.8).

CONCLUSION: Adequacy of cerebral perfusion should be evaluated adding AVDO2, DPCO2 and their Ratio to CPP values. Until compensatory mechanisms are effective, AVDO2 and DPCO2 remain coupled. However, when the brain's ability to compensate for reduced oxygen delivery is exceeded, the Ratio starts rising.