2019 ICORD TRAINEE SYMPOSIUM

Full Abstract Booklet

ICORD at the Blusson Spinal Cord Centre

818 WEST 10TH AVE

icord 2019 Trainee Symposium Schedule

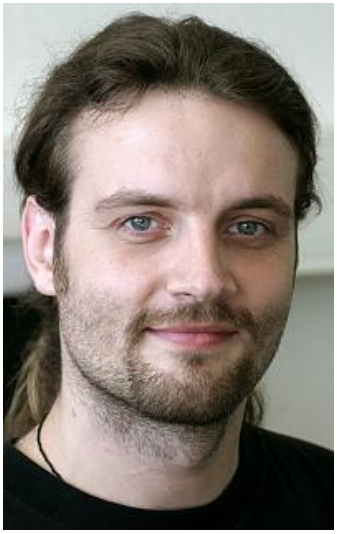
Time	Session	Location
9:00	Registration Opens	Main Entrance
9:00 – 9:45	**Breakfast**	Atrium
9:45 – 10:00	**Welcome and Opening Remarks**	Lecture Hall
10:00 – 11:00	**Plenary Lecture: Dr. Kathleen Martin Ginis** From Guidelines to Practice: Development and Implementation of SCI-Specific Exercise Guidelines	Lecture Hall
11:00 – 11:15	Break + Trivia	Atrium + Lecture Hall
11:15 – 12:00	**Trainee Presentations**	Lecture Hall
12:00 – 13:00	**Lunch**	Atrium
13:00 – 13:45	**Trainee Presentations**	Lecture Hall
13:45 – 14:00	Break + Trivia	Atrium + Lecture Hall
14:00 – 14:45	**Trainee Presentations**	Lecture Hall
14:45 – 15:00	Break + Trivia	Atrium + Lecture Hall
15:00 – 16:00	**Plenary Lecture: Dr. Kristian Franze** The mechanical regulation of neuronal growth and regeneration	Lecture Hall
16:00 – 17:45	**Poster Session**	Atrium
17:45 – 18:00	**Award Presentation and Closing Remarks**	Atrium
18:00 – 21:00	**Social**	Atrium

Plenary Speakers

Dr. Kathleen Martin Ginis

Dr. Kathleen Martin Ginis holds the Reichwald Family Chair in Preventive Medicine at University of British Columbia's Southern Medical Program. She is also a UBC Distinguished University Scholar, Professor in the Department of Medicine (Division of Physical Medicine and Rehabilitation), Professor in the School of Health and Exercise Sciences, and an ICORD Principal Investigator. Dr. Martin Ginis has received over $12 million in research funding and has published over 250 peer-reviewed research articles. Her research program focuses on physical activity behaviour change, and the psychosocial consequences of physical activity participation, particularly among people living with spinal cord injury. In 2014 Dr. Martin Ginis was awarded the Ontario Medal of Good Citizenship in recognition of her long-standing contributions to research with the spinal cord injury community.

Dr. Kristian Franze



During development and pathological processes, cells in the central nervous system (CNS) are highly motile. Despite the fact that cell motion is driven by forces, our current understanding of the physical interactions between CNS cells and their environment is very limited. We here show how nanometer deformations of CNS tissue caused by piconewton forces exerted by cells contribute to regulating CNS development and pathologies. *In vitro*, growth and migration velocities, directionality, cellular forces as well as neuronal fasciculation and maturation all significantly depended on substrate stiffness. Moreover, when grown on substrates incorporating linear stiffness gradients, glial cells migrated towards stiffer, while axon bundles turned towards softer substrates. *In vivo* time-lapse atomic force microscopy revealed stiffness gradients in developing brain tissue, which axons followed as well towards soft. Interfering with brain stiffness and mechanosensitive ion channels *in vivo* both led to similar aberrant neuronal growth patterns with reduced fasciculation and pathfinding errors. Importantly, CNS tissue significantly softened after traumatic injuries. Ultimately, mechanical signals not only directly impacted neuronal growth but also indirectly by regulating neuronal responses to and the availability of chemical guidance cues, strongly suggesting that chemical and mechanical signaling pathways are intimately linked, and that their interaction is crucial for neuronal development and regeneration.

Trainee Oral Presentations

11:15 **Spatiotemporal Distribution of CSPGs and Myelinated Axons in Porcine SCI**

SS Dalkilic, XY Zhao, A Allard-Brown, E Okon, F Streijger, BK Kwon

Anatomical similarities of larger animals to humans enable translation of findings from rodents to humans in spinal cord injury (SCI) research. Studying cellular events in larger models could identify potential therapies. A key obstacle to recovery is believed to be the failure to regenerate myelin: insulating layers that allow efficient neural signaling. Chondroitin sulphate peptidoglycans (CSPGs), within the central nervous system's extracellular matrix, also affect neuroregeneration. We used immunofluorescence to investigate how SCI affects the cord, including axons, myelin, and CSPGs in a pig model. Yucatan pigs received a mechanical thoracic (T10) injury, and recovered for either 1 or 12 weeks. A control group did not receive injury. Cords were cryosectioned and antibody-stained for axons (neurofilament and βIII-tubulin/NF200+βIIIT), myelin basic protein (MBP), and CSPGs (CS56). Injury epicenters and distal sites (5mm and 15mm from epicenters) were imaged. Structural integrity of myelin and axons, clearly observed in controls, decreased with proximity to the epicenter, indicating neurodegeneration. Disintegration was observed even at 15mm from epicenter, a site typically assumed to remain undamaged, although MBP and NF200+BIIIT signals increased with longer recovery duration at 5mm and 15mm from epicenters. Native CSPG structure disintegrated at epicenters, accompanied by decreased CSPG levels. However, CSPG levels increased distally from injured epicenters, higher at 5mm compared to 15mm; overlapping NF200+βIIIT and CSPG signals also increased at 5mm. Our findings describe patterns of degeneration—with potential explanations for inhibited recovery—in a large animal following traumatic SCI, and shed translatable insights into mechanisms of neurodegeneration in humans.

11:30 **Investigating the Role of Granzyme K in Cutaneous Inflammation**

CT Turner, S Hiroyasu, MR Zeglinski, RI Crawford, A Burleigh and DJ Granville

Granzyme K (GzmK) is a serine protease recently elucidated as a mediator of inflammation. GzmK is upregulated in inflammatory diseases including sepsis and endotoxemia. However, the pathological role of GzmK in cutaneous inflammation is limited. In the present study, we hypothesized that GzmK is elevated in cutaneous injury and disease and contributes to increased severity through the augmentation of inflammation. GzmK expression was evaluated histologically in tissue from patients with cutaneous injury and disease and compared to healthy skin controls. The role of GzmK was investigated in murine models of cutaneous injury and disease, comparing GzmK knockout to wild-type mice. Affected tissue severity was assessed macroscopically. Affected tissue was examined histologically for epidermal thickness, GzmK expression, collagen organization (Masson's Trichrome, picosirius red, Collagen I/III), inflammation (markers of T-cells, macrophages, NK cells), angiogenesis (CD31) and fibrosis (α-SMA). To further verify the role of GzmK in cutaneous inflammation, we are currently culturing keratinocytes with GzmK for assessment of cellular proliferation, cytokine expression and the GzmK degradome. GzmK positive cells were markedly elevated in biopsies from patients with cutaneous inflammation compared to healthy control skin. Lymphocytes and dendritic cells were identified as the predominant cell type responsible for GzmK expression. Preliminary data show GzmK-/- mice to have reduced severity compared to equivalent WT mice. In summary, GzmK, an important mediator of inflammation, is elevated in human cutaneous inflammation, and may contribute to the development of cutaneous injury and disease.

11:45 **Left Ventricular Function in Individuals with Acute and Chronic Spinal Cord Injury**

SJT Balthazaar, TE. Nightingale, M Walter, KD Currie, CR West, AV Krassioukov

Chronic spinal cord injury (SCI) results in impaired cardiac function. However, there is still very limited knowledge of whether cardiac dysfunction is present in humans during the

acute phase post SCI. Therefore, the goal of this study was to compare various cardiac indices using a cross-sectional study design between acute SCI (1 year). Seventy-one participants (age: 18-60 years) with acute (96 ± 33 days, n=33) and chronic (13 ± 21 years, n=38) motor-complete SCI (C4-T6, AIS A/B) underwent echocardiography. These groups were age-matched. A two-tailed Mann-Whitney U Test revealed a significantly higher EDV ($p = 0.039$), higher ESV ($p = 0.010$), SV ($p = 0.025$), and Q ($p = 0.005$) in the acute group compared to the chronic group. When groups were further divided into cervical and thoracic subgroups, a significantly higher EDV ($p = 0.040$), ESV ($p = 0.020$), SV ($p = 0.017$), and Q ($p = 0.025$) was found in the acute cervical subgroup compared to the chronic cervical subgroup. Q was significantly higher ($p = 0.024$) in the acute thoracic group compared to the chronic thoracic group, while other parameters did not reveal significance between thoracic subgroups. Results suggest that ventricular size and cardiac output may change over time following SCI. Diminished cardiac function in cervical groups may be due to the loss of supraspinal sympathetic control. These data suggest changes in different cardiac function indices are seemingly dependent upon lesion level, i.e. reduction in LVID (thoracic SCI) versus reduction in contractile tissue velocity (cervical SCI).

13:00 **Granzyme B is a Novel Therapeutic Target for Atopic Dermatitis**

CT Turner, MR Zeglinski, KC Richardson, S Santacruz, S Hiroyasu, C Wang, H Zhao, Y Shen, R Sehmi, H Lima, GM Gauvreau, DJ Granville

Granzyme B (GzmB), a serine protease minimally expressed in normal skin, is drastically elevated in numerous autoimmune and/or inflammatory skin diseases. While long regarded as a pro-apoptotic protease, emerging studies indicate that GzmB accumulates in the extracellular milieu, retains its proteolytic activity, and cleaves extracellular matrix, cell adhesion- and basement membrane-proteins. GzmB levels correspond to disease severity in human atopic dermatitis (AD). We hypothesized that GzmB contributes to AD through the cleavage of extracellular proteins. Elevated GzmB was observed in lesional tissue from AD subjects. A causative role for GzmB was assessed in a murine model of AD, comparing GzmB-/- and wild-type (WT) mice. Significant reductions in inflammation, epidermal thickness and lesion formation were observed in GzmB-/- compared to WT mice. Topical administration of a novel, gel-formulated small molecule GzmB inhibitor also reduced AD severity compared to vehicle-treated controls. GzmB-impaired epithelial barrier function corresponded to reduced E-cadherin and desmoglein-1. In vitro, GzmB cleaved filaggrin, E-cadherin and desmoglein-1. Filaggrin, E-cadherin and desmoglein-1 were all decreased in AD mice compared to controls. Further, levels were significantly higher in GzmB-/- than WT AD mice. In summary, GzmB proteolytic activity contributes to impaired epidermal barrier function and represents a valid therapeutic target for AD.

13:15 **The Evolution of a Revolution: A Noninvasive Neuroprosthesis for Cardiovascular Recovery Following Spinal Cord Injury**

R Sachdeva, K Pawar, A Marwaha, AV Krassioukov

Objective: Spinal cord injury (SCI) results in life-threatening cardiovascular impairments that are among the highest priorities of recovery in this population. Majority of individuals with an SCI above T6 suffer from autonomic dysreflexia, a devastating condition where systolic BP can abruptly rise up to 300 mmHg in response to daily stimuli (e.g. full bladder), resulting in cerebral hemorrhage, seizures and even death. Because these BP fluctuations are rapid, current pharmacological options to manage BP are undesirable as they are slow-acting and exert prolonged unwanted effects. The objective of this study was to develop a noninvasive, fast-acting therapy to manipulate BP following an experimental SCI.
Methods: Adult male Wistar rats received a complete transection SCI at third thoracic spinal segment. Eight weeks post injury, transcutaneous electrical stimulation was delivered at 30Hz, 1ms pulses by electrodes placed on the skin at mid and lower thoracic levels. Hemodynamics were recorded at rest as well as during experimental autonomic dysreflexia (colorectal distension).
Results: Autonomic dysreflexia was mitigated (55 ± 16 vs. 13 ± 21 mmHg rise in systolic

BP) when stimulation was turned on prior to colorectal distension. Furthermore, already elevated BP during an autonomic dysreflexia episode was immediately ameliorated as soon as stimulation was turned on during the episode.
Conclusion: Transcutaneous spinal cord stimulation is a reliable, noninvasive, fast-acting and clinically adaptable therapy for potentially fatal cardiovascular consequences of SCI.
Support: Wings for Life Foundation (AVK), ICORD Seed Grant (AVK, RS, KP), Canadian institutes of Health Research (AVK), Craig H. Neilsen Foundation (RS)

13:30 **Cardia Mechanics are Exaggerated in Female versus Males with High-Level Spinal Cord Injury**

AM Williams, JK Ma, KA Martin Ginis, CR West

Introduction. High-level spinal cord injury (SCI) (i.e. ≥T5) causes significant autonomic dysregulation of the heart, ultimately leading to chronic cardiac remodeling with altered systolic and diastolic function. To date, no efforts have sought to compare the cardiac consequences of SCI between males and females, which is astounding considering females comprise of >25% of the SCI population. Left ventricular (LV) mechanics are important regulators of efficient ejection and filling function, and may be influenced differently between the sexes by the alterations to LV structure and autonomic control post-SCI. Aim. To assess the impact of SCI on sex differences in LV mechanics, structure and global function. Methods. Five females (47±8yr, 63.9±7.4kg) and five males (45±12yr, 71.5±10.6kg) with similar injury levels (i.e. two T4-T6, three C4-C6 per sex) were recruited. Two-dimensional echocardiographic images were acquired at rest and speckle tracking software was utilized to measure LV twist amplitude and velocity. Results. Females tended to have elevated LV twist (26.7±3.7° vs. 21.9±3.7°, p=0.09) and torsion (i.e. twist scaled LV length; 3.40±.53°/cm vs. 2.7±0.52°/cm, p=0.06) compared to males. Conversely, systolic twist velocity was faster in males (141±17°/sec vs. 117±14°/sec, p=0.04) without sex differences in diastolic untwisting. Absolute LV end-diastolic volume and stroke volume were larger in males, but did not differ between the sexes when scaled to body size. Conclusion. This preliminary work is the first to characterize important sex-related differences in LV mechanics and structure in SCI, which merit further investigation and may ultimately underpin differences in cardiovascular dysfunction (e.g. orthostatic hypotension).

14:00 **Spinal Cord Injury Research Participants' Views on Data Sharing**

McDougall, J., Ginis, K.L.M., McBride, C., Kramer, J.L.K.

Open sharing of participant data from research studies, such that a researcher can easily use de-identified data collected by another to address their own set of questions, has the potential to accelerate scientific discovery and reduce unnecessary costs of research (e.g., wasting participants' time). The primary argument against the notion of open data sharing are concerns for participant privacy. This has been raised chiefly by researchers and administrators, with little input, to this point, from the research participants themselves. To this end, we are surveying a broad sample of individuals with spinal cord injury about their views on open data sharing. The specific aims of this project are to:
1. Examine the concerns and views about open data sharing;
2. Determine whether data sharing beliefs differ by country (i.e., United States versus Canada);
3. Assess the influence that factors related to injury severity, socioeconomic status, overall psychological well-being, and secondary healthy complications have on data sharing beliefs.
We have developed a preliminary "open data sharing survey" which has been tested in approximately 50 individuals with SCI. This survey was based on two previous surveys; a data sharing survey conducted in a non-SCI cohort of research participants (Mello et al., 2018), and questions regarding socio-demographics, psychological factors, injury characteristics, and secondary health complications from the Canadian National SCI Community Survey (Noreau et al., 2014).
Preliminary results will be presented. Our sample of SCI research participants appear to

overwhelmingly support data sharing, but have a range of concerns that should be addressed.

14:15 **The effects of gabapentinoids on neurological recovery after spinal cord injury: A chart review**

FM Warner, JJ Cragg, CR Jutzeler, D Maier, L Grassner, O Mach, A Curt, JLK Kramer

A previous study using a large, prospective, multi-centre, cohort investigated the effects of pain medications after spinal cord injury. This analysis revealed an association between anticonvulsants and improved motor recovery. Anticonvulsants are a broad category of drugs, many of which are frequently administered after spinal cord injury for disorders including neuropathic pain. Upon closer inspection, the data revealed that this effect was driven largely by the early administration of a specific anticonvulsant group, gabapentinoids, and corroborated with recent preclinical discoveries. To further explore this association, we have conducted a chart review of patient charts from one of the cohort's participating centers and gathered specific information on type and timing of anticonvulsant administration. This examination has confirmed the beneficial effects of gabapentinoids, and the specificity of early administration. Together, these findings support the conclusion that gabapentinoids are a unique anticonvulsant that may represent a potential drug repurposing strategy to improve neurological recovery after spinal cord injury.

14:30 **A novel task to understand movement planning during obstacle crossing in individuals with and without iSCI.**

RN Malik, M Chow, G Eginyan, T Lam

Those with incomplete spinal cord injury (iSCI) remain limited community ambulators, partly due to their inability to correctly plan everyday skilled walking tasks. In this project, we developed a novel task to understand how able-bodied (AB) individuals and individuals with iSCI deploy covert spatial attention when planning an obstacle crossing task.
We developed a virtual reality environment which presented the participant with an obstacle within parallel bars. Participants were situated between real parallel bars of the same dimensions as they approached and stepped over the virtual obstacle. An arrow on the right or left side of the participants' fixation point on the obstacle indicated with which limb to step first. This dictated the areas of space the participant stepped into. Following the arrows disappearance, but prior to movement onset, participants were presented with a visual stimulus (i.e. Gabor patch) that was oriented either in a clockwise or counterclockwise direction. Participants were asked to discriminate its orientation. We expect covert spatial attention to be enhanced (better Gabor orientation discrimination) at all stepping locations compared to non-stepping locations. Moreover, we expect individuals with iSCI to deploy covert spatial attention to fewer stepping locations simultaneously, in comparison to AB individuals, due to proprioceptive impairments.

Trainee Poster Presentations

Undergraduate Trainee Posters

Effects of exercise interventions on blood pressure regulation during free-living in individuals with chronic, motor-complete spinal cord injury.

S Thomas, TE Nightingale, AA Alrashidi, M Franz, KD Currie, M Hubli, A Krassioukov

Objectives: to assess the impact of Arm-Cycle Ergometer Training (ACET) or Body-weight Support Treadmill Training (BWSTT), on autonomic blood pressure regulation in individuals with chronic (>1 year) spinal cord injury (SCI).
Design: Randomized controlled trial, with a 6-month ACET or BWSTT intervention.
Setting: Clinical research facility.

Participants: Sixteen individuals with motor-complete (C4–T5, American Spinal Injury Association Impairment Scale A-B) SCI, aged 39±11 years. Participants were randomly allocated to ACET (n=8) or BWSTT (n=8).
Outcome Measures: Mean day and night systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and nocturnal dip were measured, along with the frequency of Autonomic Dysrefelxia (AD) (including max pressor response, i.e. max SBP – mean SBP) and Orthostatic Hypotentsion (OH) episodes, using 24-hour ambulatory blood pressure monitoring (ABPM).
Results: Higher daytime SBP values were observed across both groups post intervention (day effect, P=0.023). Significant day*group interaction effects were noted for nighttime DBP (P=0.018) and daytime OH episodes (P=0.006). These interactions between groups were driven by; an increase in nighttime DBP for the BWSTT group (54±9 to 60±10 mmHg, P=0.028) and decrease in daytime OH episodes for the ACET group (11±10 to 7±5 per day, P=0.034).
Conclusion: These preliminary data demonstrate that 6 months of exercise, irrespective of modality, can increase free-living daytime SBP in participants with cervical and upper-thoracic SCI. Notable exercise modality-specific changes were observed for certain blood pressure parameters, which should be explored further with additional research. Exercise had no impact on the frequency or severity of spontaneously occurring AD.

Temporal and spatial pathogenesis of astrocytes and chondroitin sulfate proteoglycans in porcine spinal cord tissue following contusion injury

X Zhao, S Dalkilic, A Allard-Brown, E Okon, F Streijger, B Kwon

A critical challenge in spinal cord injury (SCI) research is to understand how to promote the regeneration of dystrophic axons beyond the glial scar. A major factor of the glial scar's extracellular matrix that limit regeneration are chondroitin sulfate proteoglycans (CSPGs) deposited by astrocytes. While elimination of CSPGs following SCI has proved efficacious, the spatial and temporal localization of CSPGs and astrocytes following SCI in human is still poorly defined. In the present study, we use our porcine model of SCI to capitalize on the anatomical and physiological similarities between humans and pigs to investigate the pattern of CSPG and astrocyte localization in the spinal cord.
Using female Yucatan pigs, a T10 contusion/compression SCI was induced. At 7 days and 12 weeks following SCI, spinal cords were harvested and processed for cryostat sectioning. The cross-sections were assessed for astrocytes (intermediate filament glial fibrillary acidic protein, GFAP), and CSPG's (CS-56) using immunofluorescent staining. Age- and sex-matched animals were used as controls and were subjected to similar surgery without the SCI.
Immunofluorescence labeling of spinal cords from SHAM animals demonstrated a mesh-like structure of CS-56 and GFAP. SCI was marked by an robust increase of CS-56 and GFAP immunoreactivity (IR) expression at 7 days and was still upregulated at 12 weeks post-SCI, as compared to the SHAM. This was demonstrated up to 15 mm rostral to the injury site. By 12 weeks after injury, the CSPG-GFAP meshwork increased in complexity. This suggests a broad inhibitory environment to regeneration for many months post-injury.

Continuous monitoring of spinal cord hemodynamics using an optical sensor

L Tu, B Shadgan, A Cheung, N Manouchehri, K So, M Webster, S Fisk, A Fong, F Streijger, A Macnab, BK Kwon

Current clinical guidelines suggest augmenting the mean arterial pressure (MAP) of acute spinal cord injury (SCI) patients during a week post-injury in order to improve spinal cord oxygenation and preserve neurologic function. However, it is difficult for clinicians to manage MAP without real-time physiological information on the effect of MAP alterations on spinal cord hemodynamics and oxygenation. To address this, we developed a non-invasive optical sensor based on near-infrared spectroscopy (NIRS). This well-established technology involves transmitting near-infrared light and then converting light absorption measurements into physiological parameters of interest. In this ongoing study, we investigate the feasibility and sensitivity of using NIRS as a spinal cord oxygenation and hemodynamics monitoring device by implanting a custom NIRS sensor into Yucatan pigs over a period of seven days after SCI. To validate the NIRS measurements, invasive intraparenchymal (IP) probes measuring oxygenation, blood flow, and tissue pressure are inserted into the spinal cord. Over the course of the experiment, changes in oxygen saturation and MAP are simulated to compare the measurements of the NIRS and IP sensors. The effect of these simulations was detected by both NIRS and IP methods, demonstrating that our novel

NIRS sensor can monitor changes in oxygenation and hemodynamics within the spinal cord. Based on the observed signals, the NIRS sensor is able to capture responses of spinal cord hemodynamics to MAP changes. With further development, the NIRS sensor could become a clinically relevant device used by spine surgeons to monitor spinal cord hemodynamics and improve clinical MAP management.

Duraplasty in Traumatic Thoracic SCI: The Impact on Spinal Cord Hemodynamics, Metabolism, Histology and Behavioural Recovery Using a Porcine Model

A Allard Brown, K So, N Manouchehri, K Shortt, EB Okon, C Morrisson, A Fong, R Gupta, S Tigchelaar, Y Kurtzke, L Kim, M Rizzuto, J Sun, E Liu, M Keung, KT Kim, F Streijger, BK Kwon.

Introduction: In this study, we sought to determine the effects of expanding the subarachnoid space through decompressive duraplasty surgery on intraparenchymal hemodynamics, tissue metabolism, histological and behavioural recovery outcomes in a porcine model of traumatic spinal cord injury (SCI). Methods: Female Yucatan pigs (n=36) were subjected to a contusion/compression SCI at T10 and then animals were randomized to either received a duraplasty or no duraplasty. Using micro-sensors implanted into the spinal cord parenchyma, SCI-induced changes in spinal cord blood flow, oxygenation, cord pressure, and glycolytic metabolites (glucose, lactate, pyruvate, glutamate, glycerol) were simultaneously monitored from the time of SCI to 7 days post-injury. After removal of the probes, behavioural recovery was tested over 12 weeks using the Porcine Thoracic Injury Behavior Scale (PTIBS), a 10-point locomotion scale. Thereafter, the spinal cords were harvested for histological analyses. Results: Following duraplasty surgery, the enlargement of the subarachnoid space at the T9-T11 level was observed in the hours, days and weeks following surgery. Duraplasty improved perfusion and reduced the L/P ratio within 3 hours post-SCI when compared to controls. Additionally, significantly greater white tissue sparing in the duraplasty group was observed 7 days post-SCI. Differences in PTIBS scores and in white matter and grey matter sparing were not evident at 12 weeks post-SCI, after adjusting for initial group differences in the dural sac height. Conclusion: Decompressive duraplasty following thoracic SCI may provide some benefits in the acute phase; however, our porcine model shows no clear evidence of any long-term physiological or behavioural benefits.

Near-infrared spectroscopy as a novel spasticity outcome measure: a systematic review

E Chow, J McDougall, RL Harris, PB Mills

Objective: To determine whether NIRS can: 1) detect differences between spastic and non-spastic muscles; 2) detect changes in spasticity in response to interventions; 3) correlate with other outcome measures of spasticity.
Background: Spasticity, characterized by involuntary muscle activation, can occur in over 60% of individuals following a spinal cord injury. Despite current therapies, spastic muscle overactivity can result in pain, joint contractures, functional impairments and decreased quality of life. There is a need to identify novel outcome measures for improved spasticity research. NIRS uses non-invasive optical methods for assessing real-time muscle hemodynamics (e.g. blood flow: total hemoglobin, [tHb]) and metabolism (e.g. muscle oxygenation: oxygenated Hb, [O2Hb]), which could be affected in spastic muscles.
Methods: A systematic search of MEDLINE, CINAHL, and EMBASE was conducted up to November 2018. Inclusion criteria: 1) humans/animals with limb spasticity; 2) NIRS used to examine spastic muscle hemodynamics and metabolism; 3) English language. Two authors independently reviewed the studies to determine eligibility, assessed risk of bias, and extracted data.
Results: Of 34 studies identified, five were deemed eligible for inclusion. NIRS was placed over muscles for monitoring at rest and during interventions intended to cause physiological change in musculature. NIRS parameters [O2Hb] and [tHb] were different between spastic and non-spastic muscles, in response to interventions, and correlated with other spasticity outcome measures (e.g. electromyography).
Conclusion: There is level 4 evidence that NIRS may be a novel objective outcome measure to provide real-time, non-invasive monitoring of spasticity. Further research in this field is warranted.

The Effect of Experimental High Thoracic Spinal Cord Injury on the Morphology of Cardiomyocytes in the Right Ventricle

RK Azad, M Fossey, M Poormasjedi-Meibod, B Hayes, E Erskine, CR West

High thoracic spinal cord injury (SCI) is a devastating condition that results in severe paralysis and elicits significant cardiac dysfunction. It has previously been demonstrated that SCI results in a significant decrease of left ventricle (LV) cardiomyocyte dimensions, yet the effect of SCI on cardiomyocytes in the

right ventricle (RV) are still unknown. In this study, we use a clinically relevant rodent model to investigate the effects of high thoracic SCI on cardiomyocyte morphology in the RV. Initially, 10 Wistar rats were assigned to one of two groups: dorsal durotomy with intact spinal cord (8-Week SHAM; n = 5) or complete transection at the third thoracic segment (T3) (8-Week SCI; n=5). After 8-weeks, the rats were euthanized and an assessment of the cardiac morphology was completed using ex vivo, histological techniques. To assess the acute temporal effects of high thoracic SCI, an additional 33 rats were assigned to either a dorsal durotomy group (7-day SHAM; n=5) or one of the following SCI groups that were terminated at different time points post-injury: 12-hour SCI (n=5), 1-day SCI (n=7), 3-day SCI (n=5), 5-day SCI (n=5) or 7-day SCI (n=6). After termination at each respective time point, an assessment of the cardiac morphology was completed. The results show that at 8-weeks post- SCI there is a significant decrease in the length and width of cardiomyocytes found in the RV. The results of this study also show that at up to 7-days post-SCI there is no significant change in the dimensions of RV cardiomyocytes.

The Therapeutic Potential of Cannabis in Persons with Spinal Cord Injury: A Systematic Review

KJ Nabata, E Tse, A Lee, JJ Eng, M Queree, Spinal Cord Injury Research Evidence (SCIRE) Research Team, M Walter, TE Nightingale, and AV Krassioukov

Objective

This systematic review aims to: 1) understand usage patterns and reasons for cannabis use, and 2) the treatment efficacy and safety of cannabis use, in individuals with SCI.

Methods

Studies reporting on cannabis use in individuals with SCI were searched electronically via PubMed, Embase and Web of Knowledge. 6,700 studies were screened and 26 were included in this review. Eighteen studies addressed questions regarding cannabis usage in individuals with SCI. Eight studies investigated the therapeutic potential of cannabis on secondary medical conditions commonly experienced by individuals with SCI, such as pain, spasticity and bladder dysfunction.

Results

Studies investigating cannabis use; concluded that the most common usage method was smoking and the frequency of use was predominantly daily in individuals with SCI. Relief of spasticity and recreation were the most common reasons for use. Although the magnitude of effects were inconsistent, the overarching evidence reports cannabis can be used to reduce pain and spasticity in individuals with SCI. Despite these promising results, cannabis use was also associated with adverse events such as sedation and psychosis.

Conclusion

Current evidence suggests that cannabis is effective in the management of pain and spasticity in individuals with SCI. However, at present there is a lack of rigorously designed, high quality evidence in this population. Longer-term, double-blind, randomized controlled trials, assessing a wider-range of outcomes, should be conducted in the future to further our understanding of the beneficial and detrimental effects of cannabis in individuals with SCI.

The Effect of Experimental High-thoracic Spinal Cord Injury on Left-Ventricular Systolic Function

R Gupta, BD Hayes, MS Poormasjedi-Meibod, M Fossey, E Erskine & CR West

Introduction

The deleterious effect of spinal cord injury (SCI) has been previous explored using various rodent models. These studies, however, have been largely delimited to the acute or sub-acute setting and used older ‘conductance’ based technology to estimate volumetric indices. This study extends the previous work by investigating the effect of SCI on left-ventricular (LV) systolic cardiac function at a more chronic time-point and using a more robust ‘admittance’ based catheter to estimate volumetric cardiac data.

Methods

Thirteen male Wistar rats were randomly divided into two groups: Sham injury (SHAM, n=6) & T3 spinal cord transection (T3 SCI, n=7). Following a 10-week period, LV catheterization was performed under urethane anesthesia with a pressure-volume admittance catheter to assess the pressure-generating capacity of the LV at rest (load-dependent function). We also assessed the pressure and volume response to occlusions of the inferior vena cava for the subsequent determination of load-independent systolic function.

Results

Following a T3 spinal cord transection, there was a significant reduction in the maximum rate of LV

pressure rise (dP/dtmax, p = 0.0104) and the LV developed pressure (Pdev, p = 0.0095). The T3 SCI group also exhibited a significant reduction in the load-independent end-systolic elastance (Ees, p < 0.001).
Conclusion
A 10-week chronic study using a complete T3 SCI transection model demonstrates significant reductions in the load-dependent and load-independent indices of LV systolic function. This implies that changes in the heart's intrinsic function are likely a major contributing factor to the observed reduction in the LV pressure-generating capacity.

*** Spatiotemporal Distribution of CSPGs and Myelinated Axons in Porcine SCI**
SS Dalkilic, XY Zhao, A Allard-Brown, E Okon, F Streijger, BK Kwon
Anatomical similarities of larger animals to humans enable translation of findings from rodents to humans in spinal cord injury (SCI) research. Studying cellular events in larger models could identify potential therapies. A key obstacle to recovery is believed to be the failure to regenerate myelin: insulating layers that allow efficient neural signaling. Chondroitin sulphate peptidoglycans (CSPGs), within the central nervous system's extracellular matrix, also affect neuroregeneration. We used immunofluorescence to investigate how SCI affects the cord, including axons, myelin, and CSPGs in a pig model. Yucatan pigs received a mechanical thoracic (T10) injury, and recovered for either 1 or 12 weeks. A control group did not receive injury. Cords were cryosectioned and antibody-stained for axons (neurofilament and βIII-tubulin/NF200+βIIIT), myelin basic protein (MBP), and CSPGs (CS56). Injury epicenters and distal sites (5mm and 15mm from epicenters) were imaged. Structural integrity of myelin and axons, clearly observed in controls, decreased with proximity to the epicenter, indicating neurodegeneration. Disintegration was observed even at 15mm from epicenter, a site typically assumed to remain undamaged, although MBP and NF200+BIIIT signals increased with longer recovery duration at 5mm and 15mm from epicenters. Native CSPG structure disintegrated at epicenters, accompanied by decreased CSPG levels. However, CSPG levels increased distally from injured epicenters, higher at 5mm compared to 15mm; overlapping NF200+βIIIT and CSPG signals also increased at 5mm. Our findings describe patterns of degeneration—with potential explanations for inhibited recovery—in a large animal following traumatic SCI, and shed translatable insights into mechanisms of neurodegeneration in humans.
***Also featured as an oral presentation**

Masters Trainee Posters

A Reduction in Cardiac Function Precedes Structural Adaptations in Experimental Spinal Cord Injury
M Fossey, MS Poormasjedi-Meibod, B Hayes, E Erskine, DJ Granville, MS Ramer, CR West
Introduction
Chronic high-thoracic spinal cord injury (SCI) is associated with systolic dysfunction, cardiomyocyte atrophy and the upregulation of major proteolytic pathways in the heart. How such dysfunction manifests with time post-injury is presently unknown.
Methods
Male Wistar rats underwent complete SCI at the 3rd thoracic spinal level (T3-SCI; n=29) or dorsal durotomy alone (SHAM; n=6). T3-SCI rats were euthanized at different time points: 24 hours (24-hours SCI; n=7), three days (3-day SCI; n=8), five days (5-day SCI; n=7) or seven days post-SCI (7-day SCI; n=7). SHAM rats were euthanized at seven days post-durotomy. In terminal experiments, left-ventricular (LV) catheterizations were performed to assess cardiac function. Additionally, cardiac tissue was collected for histological analysis to quantify cardiomyocyte dimensions.
Results
Relative to SHAM, all SCI groups exhibited reduced maximal rate of LV systolic pressure increment (dP/dtmax; p=0.0002), and SCI rats at 3-day, 5-day and 7-day post-SCI exhibited reduced stroke work (SW; p=0.0036). The maximal rate of LV relaxation (-dP/dtmin; p<0.0001) was reduced at all SCI time points vs. SHAM; however, tau (time constant of isovolumic relaxation) was not different (p=0.28). Histological analysis indicated no significant decrease in cardiomyocyte dimensions in any SCI group vs. SHAM, although length tended to be lower in 7-day SCI vs. SHAM (p=0.058).
Conclusion

Systolic cardiac function decreased significantly in all SCI groups vs. SHAM. This indicates a rapid onset of cardiac dysfunction following T3-SCI. Cardiomyocyte atrophy was not significant post-acute SCI, implying a reduction in cardiac function precedes structural remodeling.
Acknowledgments
Heart and Stroke Foundation of Canada.

Investigating the influence of repetitive noxious stimulation on pain sensation: A systematic review and meta-analysis.
A Enzler, J Archibald, JL Kramer
Identifying a reliable, non-invasive human pain model which shares features with clinical pain is crucial in order to investigate pain modulation mechanisms. Different repetitive painful stimulation paradigms over various days are currently used. Habituation, decreased pain perception, and sensitisation, increased pain perception, are important physiological mechanisms occurring in response to repeated noxious stimulation and have been examined in various studies. However, not all studies have reported consistent findings. Therefore, this meta-analysis aims to compare changes in pain intensity ratings and pain thresholds in healthy individuals related to repetitive noxious stimulation. Overall, 82 studies were identified in a systematic search, among which 15 were eligible for the quantitative analysis. An unbiased summarized mean difference was calculated for both outcome measures and a study evaluation was conducted. Moreover, detailed information about participants and the repetitive painful stimulation paradigms was extracted. The meta-analysis showed lower pain intensity ratings after repetitive stimulation in 92 % of the studies. Further, summarized mean differences were considered to be large, after both 4 and 8 days of prolonged noxious stimulation (0.85 and 1.25 resp.). Pain thresholds were augmented after the stimulation in 78 % of the studies. However, these results varied across studies and summarized mean differences were only considered to be large after 8 days of repeated painful stimulation (-0.73). Although, this pattern of habituation seems to be consistent and therefore promising, the outcome measures confound sensory and emotional components. Thus, further research is needed to disentangle sensory and emotional contributions to the pain response.

Urodynamics and Histological Evaluation of the Bladder in a Porcine Model of Spinal Cord Injury
MS Keung, M Webster, EG Deegan, F Streijger, C Morrison, N Manouchehri, K Shortt, K So, KT Kim, LC Sherwood, A Herrity, C Hubscher, DR Howland, M Boakye, L Stothers, A Kavanagh, BK Kwon
Background: One of the most disabling and impactful consequences of spinal cord injury (SCI) is neurogenic bladder (NB) dysfunction. Studies on NB dysfunction have primarily utilized the rodent model of SCI. However, such small animal models of SCI are not suitable for the development and translation of novel human-sized devices. Objective: In this study, we investigated the functional and morphological changes occurring in the urinary bladder of SCI pigs to assess their applicability as a large animal model of NB dysfunction. Design: SCI was induced by a T10 weight-drop contusion on female Yucatan pigs. Urodynamic pressure-flow studies were performed in awake, slightly restrained pigs on various weeks post-SCI. Voiding efficiency was calculated as the ratio between voided and infused volume. Results: During micturition, pre-SCI pigs demonstrated voiding bladder contractions and a decrease in external urethral sphincter activity which resembles the normal human micturition cycle. In contrast, SCI pigs demonstrated signs of NB dysfunction such as detrusor overactivity. Furthermore, a 10-fold reduction in voiding efficiency was observed in the SCI pigs. Hematoxylin and eosin staining of the bladder post-mortem showed marked detrusor hypertrophy. Conclusions: A T10 contusion injury in Yucatan pigs induced bladder dysfunction similar to human bladder dysfunction after SCI. Overall, our pig model of SCI allows for repetitive measurements of bladder function at different time points in the same animal under fully awake condition.

Measuring Spinal Cord Hemodynamics in a Porcine Model of Acute Spinal Cord Injury Using a Novel Optical Technique
A Cheung, B Shadgan, N Manouchehri, K So, A Fong, L Tu, K Shortt, M Webster, S Fisk, F Streijger, A Macnab, and BK Kwon
Introduction: Current clinical guidelines suggest augmenting the mean arterial pressure (MAP) of acute spinal cord injury (SCI) patients to increase spinal cord perfusion and preserve neurologic function. However, it is difficult for clinicians to hemodynamically manage acute SCI patients without real-time

physiologic information about the effect of MAP augmentation within the injured cord. In this study, we developed an implantable optical sensor, based on Near Infrared Spectroscopy (NIRS), for non-invasive real-time monitoring of spinal cord tissue oxygenation and hemodynamics after acute SCI.
Methods: Nine Yorkshire pigs received a T10 contusion/compression injury. A multi-wavelength NIRS system with a customized optical sensor was implanted extradurally at T9. To validate the NIRS measures, the standardized method using an invasive intraparenchymal (IP) O2/blood flow sensor was inserted directly into the spinal cord at T11. Using NIRS, the spinal cord tissue oxygenation percentage (TOI%) and concentrations of oxygenated, deoxygenated, and total hemoglobin were monitored and compared to the IP measurements. Episodes of MAP alterations were performed to simulate the types of hemodynamic changes SCI patients experience post-injury.
Results/Conclusions: The non-invasive NIRS sensor identified changes in spinal cord hemodynamics and oxygenation levels in all subjects, in which measurements correlated with the invasive IP sensor. This pre-clinical demonstration of the potential of NIRS is the first step in developing a clinically applicable device that spine surgeons can use to monitor spinal cord tissue hemodynamics post-injury and optimize clinical MAP management.

Skilled reaching deterioration contralateral to cervical hemicontusion in rats is reversed by early pregabalin treatment

ELKS Erskine, BD Smaila, W Plunet, J Liu, EE Raffaele, W Tetzlaff, JLK Kramer, and MS Ramer

Introduction: Gabapentinoids are first-line treatments for painful traumatic and non-traumatic CNS disorders. Evidence from a large human study suggests that early use of gabapentinoids after spinal cord injury (SCI) improves motor scores. The underlying mechanism is unknown.
Objectives: We sought to examine the effects of early pregabalin (PGB, a gabapentinoid) treatment on performance in a fine motor task (skilled reaching) following cervical hemicontusion. We also asked whether early PGB administration affected PGB responsiveness later on.
Methods: Rats received C4/5 cervical hemicontusions. Injury severities ranged from 80-150kdyn. We monitored evidence of skin irritation (peri-incisional and elsewhere), and quantified food pellet retrieval using the modified Montoya staircase test. Behaviours were assessed in rats receiving early (for three weeks from injury induction) and/or late (resuming or beginning at week 8) PGB treatment in animals with 150kdyn injuries.
Results: Contralateral skilled reaching waned in control animals with 150kdyn injuries. This was prevented in animals which received early PGB as long as treatment continued. Deterioration of skilled reaching was reversed by later (week 8) PGB only in animals that had received early treatment. Ipsilateral reaching impairment was not improved by PGB. Relief of skin irritation verified early PGB efficacy.
Conclusion: Hemicontusive SCI produces a contralateral motor phenotype evocative of on-going neuropathic pain. Early PGB preserves sensitivity to subsequent PGB treatment, indicating that motor function is impaired by neuropathic pain, and can be improved indirectly by early PGB administration. Direct effects of PGB on motor circuitry cannot be excluded, but are not supported by our data.

Hypoxia mimicry augments axonal regeneration and functional recovery in the PNS

BD Smaila, EL Erskine, SD Holland, R Almadaran, F Babaeijandaghi, TP O'Connor, F Rossi, MS Ramer

Hypoxia inducible transcription factors 1a and 2a (HIFas) trigger changes in gene expression which maintain homeostasis under decreased O2. HIFa activity is negatively-regulated by prolyl hydroxylase domain proteins (PHDs 1-3), which during normoxia target HIFs for proteasomal degradation. Here we use genetic and pharmacological approaches to render individual or all PHDs non-functional to test the hypothesis that by mimicking hypoxia, axonal regeneration will be improved. In mice lacking PHD1 or PHD3, but not PHD2, regeneration distance was enhanced 2d following sciatic nerve crush. The same was true for mice treated with DMOG, a pan-PHD inhibitor. Functional sensory recovery (reflexive response to noxious toe pinch) likewise occurred earlier in PHD1-/- and PHD3-/- mice. DMOG-treated PHD+/+ mice also recovered nocifensive reflexes earlier than vehicle-treated controls, and their ability to grasp a wire cage lid with their hindpaws returned earlier with DMOG treatment. In terminal EMG experiments, while we did not find evidence of improved neuromuscular function 28 days following nerve crush in PHD null mutants, compound muscle action potential latency was reduced in DMOG-treated PHD+/+ mice. Immunohistological studies showed enhanced macrophage accumulation in the distal nerve following nerve crush in PHD1-/- and PHD3-/- mice, as well as DMOG-treated PHD+/+ mice, and

by FACS we show a skewing towards an M2-like macrophage phenotype following DMOG treatment. These results highlight PHD inhibition as a potential therapy for peripheral nerve injury.

Effects of ketogenic diet and ketone esters on remyelination in cuprizone/rapamycin model of demyelination

Nima Alaeiilkhchi, K. Kolehmainen, O. Seira, J. Liu, W. Plunet, N. Janzen, L. Raffaele, G. Duncan, W. Tetzlaff

Background: Multiple sclerosis (MS) is characterized by demyelination and axonal injury/degeneration. Demyelinated axons are thought to be more susceptible to degeneration, due to exposure to the inflammatory environment and metabolic stress. Therefore, promoting remyelination is a promising therapy, as it might mitigate axonal loss. As opposed to pharmacological therapies, diet-based treatments have fewer side-effects. The ketogenic diet (KD) (high in fat, adequate in protein, while very low in carbohydrates) increases ketone body production and decreases inflammation, which is thought to facilitate remyelination. KD is currently being used clinically for some treatment-resistant epilepsy, but its efficacy in MS models is unknown.
Objective: To assess the remyelination efficacy of KD and ketone esters (KE) in the cuprizone/rapamycin (cup/R) model of demyelination.
Hypothesis: KD/KE will promote oligodendrocyte differentiation and increase remyelination as compared to a standard diet (SD).
Method: Demyelination was induced by feeding the mice 0.3% cuprizone in the diet for 6 weeks accompanied by rapamycin injections. Animals were divided into 3 groups: (1) standard diet (SD), (2) ketogenic diet (KD), (3) ketone esters (KE). Groups 2 and 3 received their diets from day 1 to 9 after cup/R cessation. Animals were sacrificed 10 days-post-cup/R. Endpoints: Behavioural analysis was performed throughout (e.g. rotarod, resident intruder assay, and Barnes maze). Cerebral hemispheres were split for analysis: one half will be processed for immunohistochemistry and the other half for electron microscopy. Tissue samples will be analyzed for myelin pathology (i.e. demyelination, myelin decompaction, etc.), mitochondrial function, and general histopathological features (e.g. inflammation, microgliosis, etc.).

Non-Invasive Ventricular-Arterial Coupling in Athletes and Non-Athletes with Cervical Spinal Cord Injury

GA Alanis, AM Williams, CM Gee, AA Phillips, AW Sheel, CR West

Introduction. Cervical spinal cord injury (SCI) impairs both vascular and cardiac function due to loss of descending sympathetic control. A non-invasive approach to assess the cardiac-vascular interaction is by evaluating the “ventricular-arterial coupling” (VAC). A VAC ratio >1 reflects an “uncoupled” or ineffective interaction. To evaluate VAC in cervical SCI and the impact of chronic intense exercise, we evaluated VAC in non-athletes with chronic cervical SCI (SCI-na), wheelchair rugby athletes with cervical SCI (SCI-a), and able-bodied individuals (AB).
Methods. We recruited 11 SCI-na, 14 SCI-a, and 14 AB. The heart-vascular interaction was assessed by ultrasound. VAC was determined by the equation VAC=10*(Arterial elastance (Ea)/ventricular stiffness index(VSI)). Ea is an estimate of afterload and was calculated as end-systolic pressure/stroke volume. VSI is an estimate of cardiac contractility and was calculated as peak blood velocity/time-to-peak blood velocity.
Results. SCI-na showed significantly lower VSI compared to AB (9.7±2.4 vs 15.0±4.7 cm/s2; $p<0.01$), but not significantly different to SCI-a (12.4±2.3 cm/s2; $p=0.08$). SCI-na exhibited greater Ea (1.8±0.3 mmHg/mL) compared to AB (1.5±0.2 mmHg/mL; $p<0.05$) but similar to SCI-a (1.6±0.3 mmHg/mL; $p>0.05$). VAC ratio was the highest in the SCI-na group (2.0±0.5) compared to SCI-a (1.4±0.5; $p<0.05$), and AB (1.1±0.3; $p<0.001$). VAC was not signi□cantly different between SCI-a and AB.
Conclusion. The SCI-na group presented an uncoupled VAC ratio by a combination of both low systolic function and a higher load imposed on the ventricle. SCI-a showed a more optimal VAC ratio, presumably due to the bene□cial impact of exercise on the cardiovascular system.

Impact of Spinal Cord Injury and Simulated Orthostatic Hypotension on Left Ventricular Function

B.D. Hayes, M.S. Poormasjedi-Meibod, M. Fossey, E. Erskine, D.J. Granville, A.A. Phillips & C.R. West

Introduction

High level SCI impairs centrally-derived cardiovascular responses to postural change, leading to the development of orthostatic hypotension (OH). It was also recently shown that complete high level SCI causes significant reductions in left ventricular (LV) function. While it has been demonstrated that frequent bouts of OH cause impairments in cerebrovascular function and are associated with increased risk of coronary artery disease, it is not known whether this OH further exacerbates impairments in cardiac function following SCI.

Methods

22 rats were divided into four groups: 1. Sham injury (SHAM, n=5), 2. Sham injury and daily simulated OH (SHAM-OH, n=6), 3. T3 transection injury and daily simulated OH (T3-OH, n=5), 4. T3 transection (T3-SCI, n=6). 9 weeks after spinal surgery, LV pressure-volume (PV) catheterization was performed to assess LV function.

Results

Compared to both SHAM and SHAM-OH, the T3-SCI and T3-OH groups experienced significant reductions in systolic blood pressure, LV stroke work, cardiac output and LV contractility (all $p<0.04$). The T3-OH group demonstrated an increase in arterial elastance compared to both the SHAM-OH and SHAM groups ($p<0.014$). The ratio of ventricular-vascular coupling was significantly increased in the T3-OH group compared to all other groups (all $P<0.019$).

Conclusion

Complete high thoracic SCI causes a reduction in systolic LV function. Following the same SCI, simulated OH further impairs the cardiovascular system by uncoupling of the LV and the arterial system.

PhD Trainee Posters

Anterior cingulate cortex activity during noxious stimulation

J Archibald, E L MacMillan, C Graf, P Kozlowski, C Laule, and JLK Kramer

The pursuit of a physiological indicator of pain holds the potential to provide mechanistic information. Currently, there are no specific neurophysiological markers of pain (i.e., functional/structural magnetic resonance imaging, or electrophysiological techniques). Further understanding the biochemical mechanism of pain can provide the foundation for improving pain management strategies. Aim: The objective of this study was to determine changes in glutamate in the anterior cingulate cortex (ACC) in response to noxious stimulation. Methods: Fourteen healthy participants (6F/8M mean age=26.4) were recruited. Magnetic resonance spectroscopy (MRS) was performed using a 3-T (Philips) scanner, 3DT1 images, 1H-MRS (PRESS, TE/TR/NSA=22/4000/32, ACC voxel dimensions= 30/25/15mm3 =11.2mL) and T2-weighted data were collected. After baseline MR data collection, topical capsaicin-cream (active component of chili peppers) was placed on the inner part of the right forearm along with an inactivated thermo-pad. After 8 minutes, the thermo-pad was activated for 4 minutes. The participants provided pain ratings using an MRI device. MRS shots were saved and were pre-processed. LCModel (v6.3) was used to determined concentrations. Results: Spectra from data had good signal to noise ratio (mean 18.24), low linewidth (mean 4.11Hz) and low mean error estimate on the glutamate fit (4%), the quality of the spectra allowed for metabolite quantification of sufficient accuracy. A linear-mixed analysis revealed a positive relationship is seen between glutamate values and pain ratings ($p= 0.08$). Conclusion: This is the first study to report dynamic levels of glutamate in the ACC in relation to pain in healthy individuals using optimized MRS acquisition and processing methods.

Association between peak oxygen uptake and left ventricular systolic function in individuals with cervical and upper-thoracic spinal cord injury

Abdullah A. Alrashidi, Tom E. Nightingale, Shane Balthazaar, Katherine D. Currie, Kathleen Martin Ginis, Andrei V. Krassioukov

Individuals with spinal cord injury (SCI), particularly those with injuries at or above the sixth thoracic level (T6), are found to be less physically active as well as they exhibit reduced cardiorespiratory fitness (CRF). This is due to multiple factors, such as decentralization of sympathetic supraspinal control over the heart and peripheral vasculature, cardiac unloading, and reliance on upper extremities (smaller size relative to lower extremities). A recent systematic review revealed that individuals with SCI have reduced left ventricular (LV) mass, as well as altered some of global systolic function, compared to able-bodied individuals. In this study, we aim to investigate the associations between CRF [i.e. absolute and relative peak oxygen uptake ($\dot{V}O_2peak$)], and LV systolic function in individuals with SCI at or above T6. Methods: A total of thirty-two participants, aged 40±11 years, with motor-complete, chronic SCI between the fifth cervical and the T5, were recruited. $\dot{V}O_2peak$ was measured at volitional exhaustion during incremental arm-crank exercise testing using a metabolic gas analyzer. Indices of systolic function were obtained by echocardiography with participants resting in the supine position. Results: There were significant associations between absolute $\dot{V}O_2peak$ with LV end-diastolic/systolic volumes [r=0.492, (P=0.004) and r=0.386, (P=0.029),respectively)] and stroke volume (r=0.454, P=0.009). Relative $\dot{V}O_2peak$ was significantly associated with intraventricular septal wall thickness-diastole (r= −0.405, P=0.021). Conclusion: These associations between $\dot{V}O_2peak$ and indices of LV systolic function, while potentially mediated by body size, indicate the importance of maintaining a high CRF to minimize LV systolic dysfunction in individuals with cervical and upper-thoracic SCI.

MicroRNA Biomarkers in Cerebrospinal Fluid and Serum reflect Injury Severity in Human Acute Traumatic Spinal Cord Injury

SS Tigchelaar, R Gupta, C Shannon, F Streijger, S Sinha, S Flibotte, MA Rizzuto, J Street, S Paquette, T Ailon, N Dea, C Fisher, MF Dvorak, JM Mac-Thiong, S Parent, CS Bailey, S Christie, KR Van Keuren-Jensen, C Nislow, BK Kwon

Introduction: Spinal cord injury (SCI) is a devastating condition with high variability in injury mechanisms and neurologic recovery. Neurologic impairment following SCI is measured and classified by functional examination and is extremely challenging in the acute setting. Biological markers (biomarkers) for injury severity would represent a paradigm shift in the diagnosis of SCI patients. MicroRNA have emerged as attractive biomarker candidates in neurological disorders due to their stability in biological fluids, their phylogenetic similarities, and their tissue specificity.
Methods: We have used next-generation sequencing to identify microRNA associated with injury severity within the CSF and serum of human patients with acute traumatic SCI. Samples were obtained at 1 – 5 days post injury from 42 individuals with an acute SCI (22 AIS A, 10 AIS B, 10 AIS C) and 6 non-SCI control patients.
Results: We identified over one hundred human extracellular microRNAs that are dramatically elevated after SCI. We identified a set of microRNAs whose profiles and dynamics can discriminate injury severity between SCI patients and predict long term recovery.
Conclusion: CSF and serum microRNAs have the potential to serve as novel biomarkers for the evaluation of injury severity of SCI or other forms of traumatic, acute, neurologic injury.

Effect of ganglionic blockade on cardiac contractile function after experimental spinal cord injury

Mehdi Ahmadian, Malihe-Sadat Poormasjedi-Meibod, Matt Ramer, Christopher R West

Cardiac dysfunction is an undeniable consequence of high-thoracic spinal cord injury (SCI). This has been postulated to be largely due to absent supraspinal sympathetic control. We examined the cardiac response to acute SCI either before or after ganglionic blockade. Sprague Dawley rats underwent either hexamethonium infusion followed by complete transection at the T3 spinal level (n=4) or vice versa (n=4). Rats were anesthetised with urethane and ventilated via tracheotomy. Next, left ventricular function was assessed via a left-ventricular pressure-volume catheter that was inserted into the right carotid artery and advanced under pressure guidance into the left ventricle. Left ventricular pressure generating capacity (i.e., maximum pressure and dP/dtmax) were assessed at baseline, after spinal transection, and after intravenous hexamethonium infusion (20 mg/kg body weight). Both spinal transection and hexamethonium caused significant reductions in maximum pressure ($P < 0.001$) and dP/dtmax ($P < 0.001$), compared to baseline. The magnitude of reduction in maximum pressure and dP/dtmax did not differ significantly between hexamethonium infusion and spinal transection ($P < 0.05$). Interestingly, a further reduction in ventricular pressure was also noted when hexamethonium was given following SCI (maximum pressure, $P < 0.05$; dP/dtmax, $P < 0.001$). The fact that both SCI and hexamethonium reduce

cardiac function to a similar degree suggests that the loss of supraspinal sympathetic control is a key determinant of cardiac function after SCI. However, the additional reduction in cardiac function after hexamethonium infusion following SCI implies that there may be some ganglionic transmission post-SCI that partially maintains cardiac contractile function.

Effect of unintentional boosting on exercise performance in a tetraplegic athlete

Cameron M. Gee, Melissa A. Lacroix, Christopher R. West

Boosting is the induction of autonomic dysreflexia (AD) to reflexively activate otherwise dormant thoracolumbar sympathetic circuitry to 'boost' the capacity of the cardiovascular system and enhance exercise performance. AD is a life-threatening condition unique to individuals with spinal cord injury (SCI) characterized by a sudden increase in sympathetic activity below the level of the SCI. Here we report on the temporal heart rate response to an episode of unintentional boosting during a validated field-based exercise performance test in an athlete with tetraplegia.

An athlete with SCI (C6 motor-complete, sensory-incomplete) completed a 20x20m repeated sprint field test on two consecutive days. During the 13th sprint on day 2 the athlete unintentionally boosted via bladder emptying. Average heart rate (HR) when boosted (i.e. sprints 14-20) was considerably higher than before boosting (141±4 vs. 116±7 bpm) and compared to corresponding sprints on day 1 (141±4 vs. 120±1 bpm). Average time to complete 20m sprints when boosted were also faster than the corresponding sprints on day 1 (6.70±0.05 vs. 6.87±0.05 s).

This case report highlights the immediate effect of boosting on HR and field based exercise performance and supports the suggestion that exercise performance in athletes with SCI is limited by cardiovascular capacity.

Postdoctoral Trainee Posters

Long lasting benefits of faster neurological recovery

N Khosravi-Hashemi, JLK Kramer

We have investigated the impact of early neurological recovery gains on long-term functional outcomes in patients with spinal cord injury (SCI). To do so, we analyzed the data from more than 2300 patients with cervical SCI enrolled in European Multicenter study about Spinal Cord Injury (EMSCI). We classified the patients to two groups of "fast" and "slow neurological recovery" based on the measured American Spinal Injury Association (ASIA) motor scores at different times (acute, 4, 13, and 26 weeks) following SCI. This was done by applying an unsupervised clustering method called "K-means" to an index we developed to measure the "fastness" of recovery. The "fastness" index was calculated by fitting linear interpolation curves to motor scores and calculating the area under the curves after normalization. Then, we compared the Spinal Cord Independence Measure (SCIM) outcomes between the two groups at 6 months (26 weeks) and 1-year post injury. We found that the individuals recovering neurological function faster would be functionally more independent at 6-months post injury compared to individuals that recover slower, but to a similar, overall extent. Furthermore, the difference in functional independence between two groups remained significant at 1-year post injury. These results indicate that early neurological recovery during a critical window of opportunity (i.e., 1 to 3 months post injury) has consequential and long-lasting enhancing effect on functional returns (e.g., walking). The reason for such enhancement may lie in facilitatory impact of fast neurological recovery on intensive rehabilitation efforts during the early months post injury.

Biomaterial Scaffold-based Strategies for Spinal Cord Repair

K. Pawar, R. Sachdeva, N. Weidner, A. Anderson, and A. Krassioukov

After spinal cord injury (SCI) sensory, motor and autonomic functions are impaired and spontaneous regeneration and functional recovery is limited. Substantial recovery of function following SCI depends on longitudinally directed axon regeneration across the injury site, which requires a mechanical guidance providing scaffold. Biomaterial-based biodegradable implants using natural and synthetic material such as natural polysaccharide - alginate and synthetic copolymer - poly(Lactide-co-glycolide) (PLG) were used to create bridges as a carrier scaffold to support the regeneration of axons after SCI. Alginate-based anisotropic capillary hydrogels with defined capillary diameter formed via self-organizing process driven by unidirectional diffusion of divalent cations into sodium alginate solution. Axon outgrowth and cell

migration were investigated in term of axon length/density and cell density within the capillary structure. PLG based porous microchannel bridges were cast using gas foaming and salt leaching techniques. Aligned capillary and microchannel structures analyzed for axon outgrowth and cell migration in CNS in vitro and in vivo rodent spinal cord injury model. Robust regeneration of descending corticospinal tract was observed through PLG bridge crossing lesion site. Regenerated GFP fibers were co-localized with different neuronal markers. Finally, regeneration through implanted bridges was associated with functional recovery.

Diverse Cognitive Impairment After Spinal Cord Injury is Associated with Symptoms of Aberrant Cardiovascular Changes

TE Nightingale; MMZ Zheng; R Sachdeva; AA Phillips; AV Krassioukov

Objectives; to assess, 1) differences in cognitive functioning between individuals with chronic (>1 year) spinal cord injury (SCI) and non-SCI controls and, 2) associations between symptoms of autonomic dysreflexia and orthostatic hypotension with cognitive functioning in individuals with SCI.
Design; participants completed a motor-free neuropsychological test battery assessing 1) memory, 2) attention/concentration/psychomotor speed and, 3) executive function.
Setting; clinical research facility.
Participants; thirty-two individuals with SCI (C4–L2, American Spinal Injury Association Impairment Scale A-D) and thirty age, sex-matched non-SCI controls. Nineteen participants with SCI had injuries ≥T6 and a history of unstable blood pressure (BP) control.
Outcome Measures; seated BP; Rey Auditory-Verbal Learning Test (RAVLT); Digit Span Task; Stroop Test; Trail Making Test A&B; Symbol Digit Modalities Test; Controlled Oral Word Association Test; Autonomic Dysfunction Following Spinal Cord Injury (ADFSCI) questionnaire.
Results; systolic (107±7 vs. 126±10mmHg) and diastolic (62±5 vs. 77±9mmHg) BP were significantly lower in individuals with SCI compared to non-SCI controls. Significant differences were noted between SCI and non-SCI control participants for measures of memory and executive function. Furthermore, significant, moderate-to-large associations were observed between cumulative (frequency x severity) orthostatic hypotension symptoms scores, with measures of attention/concentration/psychomotor speed and executive function.
Conclusion; These data demonstrate differences in specific realms of cognitive functioning between an SCI cohort and non-SCI controls. Cumulative subjective scores for symptoms of unstable blood pressure control were associated with diverse cognitive deficits. These findings, in individuals without co-occurring traumatic brain injury, imply cardiovascular dysregulation plays a role in cognitive deficits observed in this population.

Effects of Ketogenic diet in mitochondrial function after Spinal Cord Injury

Oscar Seira, Kathleen Kolehmainen, Jie Liu, Robert Boushel and Wolfram Tetzlaff

Spinal Cord Injury (SCI) pathophysiology can be attributed to either primary physical injury, or the delayed, secondary injury cascades that can persist for several months. A better understanding of the secondary injury mechanisms is essential in developing of potential therapies to prevent damage, increase neuroprotection, restore metabolic deficits and finally promote functional recovery following SCI.
Indeed, previous studies have shown that a dysregulated metabolism and energetic deficits linked to mitochondrial bioenergetics deficiencies are severely affected after SCI. And the use of ketones after traumatic brain injury (TBI) it's been previously shown to improve secondary neuropathology by decreasing oxidative stress and increasing antioxidants.
We hypothesized that ketogenic diet (KD) will improve mitochondrial function after SCI. Using a C5 hemi-contusion model in adult male rats we examined the states of mitochondrial respiration and assessed the different components of the electron transport system (ETS).
Mitochondrial function was reduced after SCI, and administration of KD increased mitochondrial biogenesis and partially rescued function of Complexes I, II, and III at 7 days after SCI. KD also triggered changes in antioxidant pathways and signalling pathways previously associated with the activation of the nuclear and mitochondrial transcription machinery (i.e. mtFAM, ERK1/2) explain the partial bioenergetics recovery in our SCI model.

In summary KD improves the post-SCI metabolism by rescuing mitochondrial bioenergetics dysfunction, and might be a beneficial treatment for acute SCI.

Staff Posters

A Longitudinal Study of the Neurologic Safety of Acute Baclofen Use After Spinal Cord Injury

JJ Cragg, B Tong, JCR utzeler, FM Warner, N Cashman N, F Geisler F, JLK Kramer

The objective of our study was to determine whether treatment with baclofen is neurologically safe with respect to exposure during recovery from spinal cord injury. We performed a secondary longitudinal analysis of a cohort of adult patients with traumatic acute spinal cord injury. Cumulative baclofen dose was computed over the first 4 weeks following injury from concomitant medication information from a completed clinical trial. The main outcome measure was neurologic status, which was assessed over 52 weeks with "marked recovery" defined as the conversion to higher sensory and motor function. To complete the drug safety profile, drug toxicity was assessed with assays from standard blood work. Multivariable Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). Of the cohort (n = 651), 18% received baclofen within 4 weeks post injury. Baclofen use was associated with higher rates of marked neurologic recovery, even after adjustment for injury severity (HR = 2.1, 95% CI 1.5-3.0 for high dose vs none). Baclofen exposure was not associated with liver or renal side effects. The use of other medications indicated for spasticity was not associated with neurological outcomes. Overall, this longitudinal analysis provides level 3 evidence on the neurologic safety of baclofen and potential beneficial effects on recovery in the early days after acute traumatic spinal cord injury. The usefulness of concomitant medication files from completed clinical trials is highlighted. We also highlight the importance of incorporating logical patient questions and neurological outcomes into research addressing drug safety.

Cannabis use in women with spinal cord injury: physician and patient perspectives

AHX Lee, M Walter, TE Nightingale, R Sachdeva, AV Krassioukov

Background/Objectives: Spinal cord injury (SCI) results in devastating sequelae including paralysis, chronic pain and spasticity. As pharmacological treatment can be ineffective or have undesirable side effects, cannabis treatment has been explored in other countries. In non-SCI populations, cannabis is reported to alleviate anxiety, insomnia and neuropathic pain. Given the recent legalization of marijuana in Canada, it is imperative to characterize cannabis use after SCI and evaluate physician knowledge of cannabis use by patients with SCI.

Methodology: Women with SCI (n=20) completed an anonymous, online survey on their cannabis use. Physiatrists at GF Strong Rehabilitation Centre (n=15) completed a survey on their knowledge of cannabis to manage SCI.

Results: Before sustaining SCI, 21% (n=4) of respondents used cannabis compared to 35% (n=7) of women after SCI (35%). Primary reasons for cannabis use following SCI included: managing tone/spasticity (n=5), pain relief (n=3) and depression/anxiety (n=2). Two women used cannabis while pregnant or breastfeeding as a sleep aid or relief for morning sickness. The most commonly reported adverse effect was difficulty obtaining consistent, desirable effects (n=5). Up to 87% of physicians described their knowledge on SCI-related cannabis use as “none, very little or poor”. Physicians’ top priorities for research included: compound composition, quality control and establishing a database of available products.

Conclusions: Women with SCI in this pilot study used cannabinoid products primarily to relieve pain and spasticity. Cannabis use during pregnancy/breastfeeding indicated a need to evaluate impact on infant development. Safety and efficacy of medicinal cannabis use after SCI must be determined.

Lower Body Negative Pressure: a pre-clinical model of orthostatic hypotension following spinal cord injury

Marwaha A.S., Sachdeva R., Pawar K., Krassioukov A.V.

Spinal Cord Injury (SCI) is a devastating condition that permanently impacts quality of life. Majority of individuals with cervical or high thoracic SCI suffer from debilitating cardiovascular impairments that are the leading cause of disability and death among this population. A common challenge faced by individuals with SCI is of unstable blood pressure (BP). Shifting from a supine to upright position, BP drops to abnormally low levels, a condition called orthostatic hypotension (OH). The BP during OH can fall to

dangerously low levels, often resulting in blurred vision, dizziness, loss of consciousness, cognitive deficits, and an elevated risk of stroke. Despite OH leading to alarming increases in morbidity and mortality following SCI, there remains to be limited knowledge on therapeutic approaches for its management and prevention. This is partly due to the difficulty of generating an animal model of OH after SCI. We present lower-body negative pressure (LBNP) as a robust and clinically-relevant animal model of OH. Using a well-characterized rat model of T3 SCI, we evaluated the efficacy of LBNP to reduce BP. At 8 weeks post-SCI, a wireless pressure transducer was implanted into the femoral artery. The lower body of the anesthetized animal was placed in the LBNP chamber connected to a vacuum source. We observed a LBNP-induced decrease of 20.2 ± 6.0 mmHg and 15.1 ± 5.1 mmHg in systolic and diastolic BP, respectively. These findings suggest that an LBNP chamber may be a valuable tool to test the efficacy of various treatment strategies for mitigating OH.

Comparing skill performance between indoor and outdoor environments among experienced scooter users

S Jang, L Hurd Clarke, B Miller, WB Mortenson

Background: The Wheelchair Skills Test (WST) has been developed to assess scooter users' skill performance and mobility confidence. Traditionally, the WST has been performed using a standardized indoor course; however, it has been suggested that a community-based setting may be a suitable alternative. Objectives: To compare WST performance in the indoor and outdoor environments, to determine the utility of performing the WST in the community, and to learn about users' perspectives of performing the WST in different environments. Methods: For this mixed-methods study, 20 scooter users who have used their devices for ≥ 3 months were recruited. Each participant completed the WST twice – once in their community and once indoors within a two-week period. While testing in the community, detailed observations were made on the setting. Semi-structured interviews were conducted after completion of the WST in both environments. Results: Preliminary analysis revealed no differences in participants' WST performance scores between the two environments; however, participants were more confident performing in the community. When searching for WST obstacles in the community, the majority were easily found. While most participants preferred performing the WST in their community due to convenience and familiarity, they also perceived the indoor course as reflective of their community setting. Conclusion: These findings suggest that skills testing in the community is feasible; however, skills testing in indoor and outdoor settings are not comparable. Community-based testing may have better ecological validity, but testing in unfamiliar settings may encourage users to use their devices in novel settings.

Promotion of white matter repair after intoxication with cuprizone/ rapamycin by treatment with Metformin in mice

B S. Lashkari, W Plunet, F Miller and W Tetzlaff

Metformin stimulates adult neurogenesis and can promote neural repair and functional recovery in a model of hypoxia/ischemia of newborn mice (Miller and Morshead labs). Here we ask whether Metformin promotes remyelination when given after a 6 week regimen of cuprizone plus rapamycin to produce demyelination in the CNS, in particular the corpus callosum. Genetic fate mapping of oligodendrocytes in PDGFRa CreERT2::ROSAmTomato/ mGFP mice allows us to unequivocally identify areas of remyelination within the corpus callosum. Tamoxifen was given 4x during week 5 of intoxication. Metformin was injected (200mg_kg-1 _day-1) i.p. for seven days, and on day 8 the mice were perfused and processed for immunohistochemistry of Myelin Basic Protein (MBP), Green Fluorescent Protein (GFP) and axons (SMI-312 antibody). Four squares (100mm x100mm) within the area of remyelination in the corpus callosum anterior to the fornix were imaged at 63x magnification on a confocal microscope and immuno-reactivity quantified by thresholding using Image J.

Metformin treatment almost doubled MBP immunoreactivity (p=0.012) while the axonal signal remained the same. GFP immunoreactivity was also higher in the Metformin group suggesting a stimulation of the oligodendrocyte precursor pool. We are presently performing cell counts of Olig2 positive cells in these regions of interest and quantifications of myelinated axons in plastic sections of the contralateral brain hemispheres of the same mice by electron microscopy.

Taken together our data indicate that metformin stimulates oligodendrocyte turnover and remyelination and lends support to the ongoing clinical trial for white matter repair in children.

Supported by the Stem Cell Network

Thank You

supported by
Rick Hansen Foundation
THROUGH THE
Blusson Integrated Cures Partnership
icord
Rick Hansen Institute / Institut Rick Hansen

- ICORD Trainee Committee + Volunteers
- The ICORD Admin team especially Matthew Sahl and Cheryl Niamath
- Our two plenary speakers: Dr. Kathleen Martin Ginis and Dr. Kristian Franze
- Our many trainee presenters and our volunteer judges

Delicious Food and Drinks Supplied by:

ELYSIAN COFFEE ROASTERS
Fujiya
BREKA bakery & café
the Lazy Gourmet
EAST VAN ORIGINAL R&B BREWING CO.

And a Special Thanks to all our prize sponsors!

spade
AGRO ROASTERS
PALLET COFFEE ROASTERS
olive + ruby JUICE FOOD COFFEE
GREAT DANE COFFEE EST. 2012
JJBean COFFEE ROASTERS
MOVING COFFEE ROASTERY
MATCHSTICK
KAFKA'S
OUR TOWN
MODUS
ABADE
FRESH PRESS COFFEE BAR
nemesis.