Itinerary

SFU Theatre

09:00 - 09:30  Registration and Coffee
09:30 - 09:45  Welcome and Introductions

Selected Student Oral Presentations:

09:45 - 10:00  Shane Virani, Colin Russell, Megan Bruschetta, Kevin Hua, Brigitte Potvin, David Cox, Stephen Robinovitch: The Effect of Shoulder Pad Design on Head Impact Severity during Shoulder Checks in Ice Hockey

10:00 - 10:15  Matthew Lloyd, Michael Koehle, Rebecca Skillen, Rob Drapala, Victoria Claydon: Cardic and Vascular Responses to Carotid Sinus Massage are Unrelated to Baroreflex Stimulation via Neck Suction

10:15 - 10:30  Samrat Thouta, Yen M. Cheng and Tom W. Claydon: Mechanistic insight into the human cardiac hERG potassium channel activation gate

10:30 - 10:45  Colin Peters, Alec Yu, Peter Ruben: An Updated Model for the Cardiac Voltage-Gated Sodium Channel

10:45 - 11:00  Break

Keynote Speaker:

11:00 - 12:00  Dr. Grace Lee: Building a legacy of leadership by (re-)defining success

12:00 - 13:00  Lunch
13:00 - 14:30  Poster Session 1 (EVEN numbered boards)
14:30 - 16:00  Poster Session 2 (ODD numbered boards)
16:00 - 16:30  Awards
16:30 - 17:30  Social at the SFU Highland Pub
Welcome Note

Dear all,

We are excited to welcome you to the 7th Annual Biomedical Physiology and Kinesiology Research Day! We have a full program of events in store for the day, including 4 oral presentations from graduate students, a keynote address from Dr. Grace Lee, 39 poster presentations, lunch, and a social at the end of the day.

We hope you share our excitement about what promises to be an excellent day that will showcase and celebrate the breadth and quality of research being conducted in our Department by talented undergraduate and graduate students and post-doctoral fellows.

We would like to thank the companies that have generously donated door prizes – make sure you get your ticket for a chance to win! To make this day possible, funds were also generously donated by the BPK Department, the Graduate Student Society, the BPKSA, and the BPKGSA. I would also like to specifically thank Sabrina Azaria, our talented BPK Alumni and Engagement Officer, for her time, effort, and creativity to design and create the abstract submission site, advertising materials, and this program booklet.

Enjoy the day!

Dawn Mackey
On behalf of the BPK Research Day Organizing Committee
Featuring Keynote Speaker

Dr. Grace Lee

Grace Lee, PhD, completed her graduate studies in Neuroscience from the University of Edinburgh and the University of British Columbia. She completed a certification program in health care ethics at the University of Washington during her postdoctoral fellowship.

Elected President of the UBC Postdoctoral Association, she led seminars and workshops on areas of career development, financial literacy, and entrepreneurship. Frustrated with the academic system, she launched a marketing business and resigned from her fellowship to translate her experience into e-commerce. In addition to running her business, she works in biotech at STEM-CELL Technologies Inc. as a senior manager and is also an Executive at the Vancouver Board of Trade Small Business Council. She regularly takes on speaking engagements in both the academic and business communities.

Keynote Topic

Building a legacy of leadership by (re-)defining success

Dr. Lee will share her perspectives on the fundamentals to discovering your passion, personal branding with intellectual capital, and mindsets in career transitions. She hopes to inspire meaningful career transitions by revealing the lessons she has learned from disrupting academia.
Oral Presentations

Shane Virani, Colin Russell, Megan Bruschetta, Kevin Hua, Brigitte Potvin, David Cox, Stephen Robinovitch

The Effect of Shoulder Pad Design on Head Impact Severity during Shoulder Checks in Ice Hockey

Forty-two percent of concussions in ice hockey are caused by hits involving shoulder-to-head contact. Our goal was to determine, how shoulder pad stiffness affects head impact severity by conducting laboratory experiments where players delivered checks to an instrumented dummy.

Fifteen participants administered “the hardest shoulder checks they were comfortable delivering” to the head of a dummy. Trials were conducted with participants wearing two common types of shoulder pads, with and without a 2 cm thick layer of polyurethane foam over the shoulder pad cap.

We found that a 2 cm thick foam layer overlying the shoulder cap can reduce peak linear accelerations experienced by the head by 21.6–27.7%, peak rotational velocities by 10.5–13.8%, while causing no significant increase in shoulder impact velocity. Therefore, integration of foam padding on top of or in replacement of plastic caps warrants further examination as a method for preventing brain injuries in ice hockey.
Cardiac and Vascular Responses to Carotid Sinus Massage are Unrelated to Baroreflex Stimulation via Neck Suction

The arterial baroreflex is crucial for short-term blood pressure control – impaired baroreflex function predisposes to fainting and falling. Carotid artery baroreceptors are central to the baroreflex response to changes in blood pressure during orthostasis. In older adults, clinical carotid baroreceptor stimulation using carotid sinus massage (CSM) has a high false positive rate, and it is unclear how these responses compare to other baroreflex tests. Furthermore, previous work has focused on cardiac responses to CSM, and neglected the arguably more important vascular resistance responses. We aimed to compare the vascular resistance and R-R interval (RRI) responses between CSM and neck suction (NS).

In 8 participants, carotid baroreceptors were stimulated with -60mmHg NS and with ultrasound-guided CSM to compare cardiac (RRI; electrocardiography) and forearm vascular resistance (FVR; mean arterial pressure [Finometer]/brachial blood flow velocity [Doppler ultrasound]) responses between the two tests. We hypothesized that CSM responses would correlate with NS responses.

Responses to CSM were smaller than to NS (RRI: +80±60ms and +356±60ms, p=0.03; FVR: -14±0.04% and -27±0.04%, p=0.03). There was a significant positive correlation between RRI responses to both stimuli when expressed as ΔRRI (R2=0.61, p=0.02), and maximum RRI prolongation (R2=0.70, p=0.01). FVR responses were not correlated between CSM and NS (R2=0.08, p=0.48). There was a significant negative correlation between the FVR and RRI responses to CSM (R2=0.44, p=0.02) but not to NS (R2=0.03, p=0.6).

Together, these results suggest that responses to CSM do not reflect baroreflex responses to other tests, which questions the clinical interpretation of hypersensitive responses to CSM.
Mechanistic insight into the human cardiac hERG potassium channel activation gate

Cardiac arrest is an electrical disturbance in the heart resulting in the abrupt loss of heart function. Loss of function of human-ether-a-go-go-related-gene (hERG) potassium channels due to inherited mutations or pharmacological blockade leads to sudden cardiac death by reducing cardiac repolarization. Unlike other voltage-gated potassium (Kv) channels, hERG channels display unusual gating characteristics that are crucial for their physiological function. hERG channels slowly activate (open) and deactivate (close) with rapid inactivation and recovery from inactivation. These unique gating properties provide robust repolarizing current that aids terminal repolarization of the action potential. In addition, hERG channels have an unusually high sensitivity towards a wide variety of commonly used drugs. The molecular bases of these unusual gating events and drug binding are poorly understood. In other Kv channels, the activation gate is formed by the convergence of the inner S6 helices near a conserved Proline-Valine-Proline (PVP) motif which introduces a kink that allows opening of the activation gate. hERG channels lack the PVP motif and the location of the activation gate and how it is coupled to voltage sensor movement is less clear. Here, we performed a proline-substitution scan of the inner S6 helices to determine the position of the gate. Proximal substitutions (I655P-Q664P) impeded gate closure trapping channels in the open state, while distal substitutions (R665P-Y667P) preserved normal gating. These data suggest that the activation gate is formed at Q664 and provide the first detailed map of the position of the gate in hERG. Using voltage clamp fluorimetry and gating current analysis we also characterize voltage sensor movement in a trapped-open channel to understand what underlies the unusually slow activation of hERG channels. We report what we interpret as intrinsic hERG voltage sensor movements, and demonstrate that these are uncharacteristically slow. We propose that this underlies slow activation of hERG channels.
An Updated Model for the Cardiac Voltage-Gated Sodium Channel

Voltage-gated sodium channels are responsible for the initial depolarization of neural, skeletal muscle, and cardiac tissues. Mutants in these channels cause epilepsy, cardiac arrhythmias, and muscle paralysis among other diseases. These channels are a target for pharmaceuticals including local anesthetics, anticonvulsants, and antiarrhythmics. Typically, experiments studying the effects of mutants and drugs on basic channel function are performed in heterologous expression systems, such as Xenopus laevis oocytes. Mathematical models based on these data can be used to make predictions about how these effects will impact electrical signalling in human tissue.

We have formulated a new modelling scheme for voltage-gated sodium channels that accurately replicates many of the aspects of our experimental data. Whereas other recent models in our field have relied on Markov schemes reflecting the channel as a single entity, we model the motion of the individual voltage-sensitive subunits that make up the channel. This method allows us to model more detail in channel gating without inflating the necessary number of states.

Thus far our new model is capable of replicating currents through the channel pore and the currents associated with movements of the voltage-sensitive subunits. One of our uses for this model is to ascertain whether specific channel mutants might be explained by altered rates within single subunits. Another is to accurately predict how changes to channel function by these mutants might impact sodium currents during a cardiac action potential.
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Session 1 | Even # Boards | 13:00 - 14:30
Session 2 | Odd # Boards | 14:30 - 16:00
Poster Presentations

01 Sabrina Abram, Jessica Selinger, Max Donelan

Can humans continuously optimize energetic cost in multiple gait dimensions?

People can continuously optimize step frequency to minimize energy use during walking. However, extending this optimization to multiple parameters may prove difficult for the human nervous system. Indeed, there are more conceivable gait strategies than there are atoms in the universe—a control challenge known as the ‘curse of dimensionality’. Our aim is to manipulate the relationship between energetic cost and multiple gait parameters and then test the hypothesis that people can optimize cost along multiple dimensions. Here we present our custom device, experimental design, and current progress towards testing this aim. We propose step frequency and step width as candidate dimensions—gait parameters that have distinct energetic optima in familiar conditions, and are unique to the individual, yet can be readily manipulated. Our custom device trades off a constant energetic reward, achieved by an aiding horizontal force to the waist, against a controllable energetic penalty, achieved by a treadmill incline. We use foot contact events to measure step frequency and width, and then command the incline based on the desired energetic penalty or reward. To validate our paradigm, we first sought to establish that subjects adapt to each dimension in isolation. We began by demonstrating that our step frequency controller can shift the energetically optimal step frequency lower than initially preferred. We tested three able-bodied subjects in the step frequency dimension and found that all subjects decreased their step frequency towards their new energetic optimum, on average by 4.79%+/-0.9% (mean+/-SD). We then verified that our step width controller can shift the energetically optimal step width wider than initially preferred. Next we will determine whether subjects also adapt their step width to converge on new optimum, and then combine controllers for these gait parameters to test our hypothesis that people can optimize energetic cost along multiple dimensions.

02 Loryn J. Bohne, Matt G. Lloyd, Robert Drapala, Michael Koehle, Victoria E. Claydon

Impact of respiration on responses to carotid sinus massage
The arterial baroreflex is crucial for short-term blood pressure control – abnormal baroreflex function predisposes to syncope (fainting). Carotid baroreceptors are particularly important in orthostatic cardiovascular control and are investigated clinically by determining heart rate and blood pressure responses to carotid sinus massage (CSM). Hypersensitivity to CSM (abnormally large decreases in blood pressure and heart rate) may be associated with syncope, with a prevalence of up to 62% in elderly populations. However, CSM has poor repeatability and a high false positive rate, which questions its utility as a diagnostic test. One source of variability may be a failure to standardize for breathing; as a result, cardiac and vascular responses to CSM may be obscured by concurrent changes in heart rate and intrathoracic pressure during respiration. We aimed to examine the effects of breath-holding versus normal breathing on the cardiac and vascular responses to CSM.

In three participants, supine and 70° head-up tilted CSM was performed for 10s each with a 60s rest between massages, in a randomized order. Massage conditions included left and right sides of the neck, during normal breathing and breath-holding, and sham massage. Throughout testing we continuously recorded beat-to-beat blood pressure (finger plethysmography) and heart rate (ECG). Our preliminary analyses demonstrated that the reduction in systolic arterial pressure during breath-holding was smaller (-4.1±0.87mmHg) than during spontaneous breathing (-5.8±1.2mmHg; p=0.03). During CSM the nadir systolic arterial pressure was lower (101.8±5.0mmHg; p=0.041) and RR interval prolongation smaller (0.83±0.04s; p=0.022) when tilted compared to supine (112.6±2.8mmHg and 1.15±0.02s, respectively), but were unaffected by breath-holding. Our preliminary data suggest that breath-holding may impact vascular responses to CSM. Further study is necessary in order to improve the repeatability of this method. Given that cardiac pacemakers are the current recommended treatment for carotid sinus hypersensitivity, it is imperative that this test is standardized.

Garveen Brar, Brooke Hockin, Ian Ruiz-Romero, Victoria Claydon

The Optimal Intermittent Calf Compression Paradigm to Improve Orthostatic Fluid Shifts and Cardiovascular Control

Orthostatic Hypotension (OH) is characterized by a significant reduction in blood pressure when upright, exacerbated by increases in venous pooling and capillary filtration that reduce the effective circulating volume. OH is prevalent in the elderly and associated with increased morbidity and mortality. Static calf compression garments are frequently prescribed for the management of OH, but are largely ineffective. We showed previously that low
frequency (LF) intermittent calf compression (0–100mmHg; 4s on and 11s off) is effective at reducing orthostatic fluid shifts, while simultaneously increasing stroke volume (SV), allowing cardiac output to be maintained at a reduced heart rate (HR). We aimed to determine the optimal calf intermittent compression paradigm to improve orthostatic fluid shifts and hemodynamic control. LF calf compression was applied in random order at inflation pressures from 0–40, 0–60, 0–80 and 0–100mmHg, with a placebo condition, in fifteen healthy controls during a series of five, ten-minute 60° head-up tilts. Strain gauge plethysmography was used to measure leg circumference changes. Cardiovascular responses were determined using finger plethysmography (Finometer). All compression paradigms significantly reduced leg circumference compared to placebo; after 10 minutes, inflation to 60 mmHg abolished the increase in leg circumference during orthostasis (−0.135±0.030%; p<0.05). Compared to the placebo (SV: 64.4±1.0mL; HR: 82.4±0.621bpm) and 0–40mmHg (SV: 65.0±1.1mL; HR: 81.0±0.67bpm) conditions, inflation of 0–60mmHg (SV: 69.5±1.0mL; HR: 77.4±0.62bpm) increased SV and reduced HR (all p<0.01) throughout tilt. Intermittent calf compression from 0–60mmHg is the optimal LF intermittent compression paradigm to ameliorate orthostatic fluid shifts and improve hemodynamic control.

Megan Bruschetta, Shane Virani, Kevin Ngoc Hua, Stephen N. Robinovitch

Development and Validation of a Tool for Analysis of Hockey Related Head Impacts Captured on Video

Objectives: Ice hockey accounts for the greatest number (44%) of sports-related head injuries in Canada. Improvements in prevention require a better understanding of the circumstances of head impacts in ice hockey. This study developed and tested the inter-rater reliability of a 32-item questionnaire that examines, based on video footage, the biomechanical, situational, and environmental aspects of these head impacts. Eight of the questions were adopted from Hutchison et al., Br J Sports Med, 2013, and eight from Mihalik et al., Pediatrics, 2010.

Methods: The questionnaire focused on head position, site of impact, nature of struck object, anticipation of collision, player trajectory and upper limb impact dynamics. Inter-rater reliability was tested using 30 randomly selected NHL hits. The videos were randomly assigned to two of seven trained, university-aged analyzers. For each question, we examined the percent agreement between analyzers, and the corresponding Kappa value, interpreted based on Landis & Koch’s recommendations (0.00–0.20 = slight agreement; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; 0.81–1.00 = almost perfect).
Results: All 32 questions had a percent agreement of 70 or higher (mean = 85, SD = 10) and 30 questions had a Kappa value of 0.40 or higher (mean = 0.71, SD = 0.15). Eight of these 30 questions were classified as having “almost perfect” agreement, 13 had “substantial,” 8 had “moderate,” and 1 had “fair.” Among the 30 videos, the head was contacted first in 76% of cases. The striking object was an opposing player’s shoulder in 33% of cases, hand in 17% and elbow in 13%.

Conclusions: Our 32-item questionnaire appears to be a reliable tool for analyzing the circumstances of head impacts in ice hockey. Future analyses with this tool should generate an improved understanding to aid in the design of strategies to decrease the risks for traumatic brain injury.

Cherlene E. Chang, Kimberley S. van Schooten, Stephen N. Robinovitch

An analysis of the spatial distribution of older adults’ falls in long-term care

Background: Falls are the leading cause of unintentional injuries in older adults, and are common in long-term care. Improved understanding of the spatial distribution of falls, and the factors separating high-risk and low-risk locations, may guide improved interventions. We determined the spatial distribution of falls in a single LTC unit and studied how this associated with intensity of use and environmental hazards.

Methods: We captured 233 falls from 46 individuals (mean age 78, SD 8) on camera in common areas of a single LTC unit in British Columbia, Canada. We calibrated each camera and mapped the location of each fall (imbalance onset) accounting for their calibration. We estimated fall density using a Gaussian kernel function and identified hot spots using nearest-neighbor hierarchical clustering. We also estimated intensity of use of space (resident density) and tested (using linear regression) whether this associated with the spatial distribution of falls. In ongoing work, we are studying whether environmental hazards further account for variations in spatial distribution of falls.

Findings: The dining room had the highest fall density (0.0465 falls/m2), followed by lounge areas (0.0403 falls/m2), and hallways (0.0111 falls/m2). We identified 11 fall location clusters in the dining and lounge areas. After correcting for resident density (explaining 86% of the spatial distribution of falls), we identified 4 high fall risk clusters in the hallways, and 15 low fall risk clusters in the dining and lounge areas.
Interpretation: Intensity of use explains 86% of the spatial distribution of falls by older adults in long-term care. 14% of the variability may relate to environmental hazards. By improving our understanding of where and why falls are most likely to occur, our results lead to more valid and effective approaches for targeting preventing falls in the long-term care setting.

Yuqi C. Chenliu, Xiaoye Sheng, Eric Lin, Shubhayan Sanatani, Glen Tibbits

Ischemia-Reperfusion destabilizes rhythmicity in immature atrio-ventricular pacemakers: A predisposing factor for postoperative arrhythmias

Introduction: Post-operative arrhythmias such as Junctional Ectopic Tachycardia (JET) and atrioventricular (AV) block are most often seen in neonate pediatric patients after congenital heart repair. While their etiology is largely unknown, we hypothesize that these arrhythmias originate in the immature atrioventricular (AV) node because of the combined effect of immaturity, ischemia-reperfusion (I/R) injury and postoperative β adrenergic agonist administration.

Methods: Whole heart optical mapping model of post-operative arrhythmias were generated encompassing these three primary risk factors: age, I/R exposure, and dopamine (DA) application. We used a custom optical mapping set up to capture 10 day (d) and 56-d rabbit whole-heart optical action potentials (OAP). The Langendorff heart preparations were loaded with RH-237, a potentiometric dye, excited with 532 nm light and the fluorescence was captured at > 700 nm on a Hamamatsu Orca Flash 4.0 digital CMOS camera. An ischemic mimetic solution was used, in addition to 90 min global no-flow ischemia, to reflect the ischemic condition the heart may experience during cardio-pulmonary bypass surgeries. DA was applied immediately upon reperfusion and OAP were captured periodically with continuous ECG monitoring.

Results: Neonate hearts experienced persistent post-ischemia arrhythmias of varying severity; while, in contrast, adolescent hearts did not develop reperfusion arrhythmias of comparable severity or duration.

Conclusion: Our data suggest that the combined deleterious effects of ischemic injury, which likely occurs during cardiopulmonary bypass, subsequent reperfusion and post-operative DA administration, specifically predispose neonates to AV nodal dysfunction making them susceptible to post-operative arrhythmias.
Grace Chun, Xiaoye Sheng, Leif Hove-Maden, Glen Tibbits

The Effects of a $\beta$-2AR Agonist on the Production of Arrhythmogenic Calcium Transient Activity in Cardiomyocytes

Calcium transients are the result of sarcoplasmic reticulum (SR) Ca$^2+$ release during a normal excitation-contraction cycle. Ca$^2+$ transients can be quantified to determine their role in arrhythmogenic events. The administration of $\beta$2 adrenergic receptor ($\beta$2AR) agonists can induce arrhythmogenic Ca$^2+$ events in cardiac myocytes. The extent of $\beta$2AR agonists in causing irregular Ca$^2+$ events leading to arrhythmias is important to determine proper dosages and effective counter measures for arrhythmic Ca$^2+$ events. Various ($\beta$2AR) agonists and antagonists were tested, to determine the basis of both normal and irregular Ca$^2+$ events. Ventricular cardiomyocytes from murine hearts were isolated through retrograde perfusion of collagenase type II solution via the Langendorff preparation. The dissociated cells were perfused with a modified Tyrode’s buffer with 1.8 mM Ca$^2+$ and loaded with Fluo-4-AM, a Ca$^2+$ indicator that exhibits increased fluorescence upon binding to free Ca$^2+$. The Ca$^2+$ transients were then recorded via the Leica SP5 16 MHz resonance scanning confocal microscope. With greater concentrations (3-10 $\mu$M) of fenoterol, a $\beta$2AR selective agonist, a greater fraction of cells exhibited greater spontaneous Ca$^2+$ releases and stimulated arrhythmic Ca$^2+$ activity (approximately 80% of cells). The fraction of cells with arrhythmogenic Ca$^2+$ events, however, were distinctly attenuated by KN-93, a calmodulin kinase II blocker (50%) and KT5720, a protein kinase A (PKA) inhibitor (30%). KN-92 (inactive analog of KN-93) had a slight lower fraction of cells with arrhythmogenic Ca$^2+$ events (60%). Together, our results suggest the clear role of CamKinase II and PKA in the etiology of these $\beta$2AR agonist-induced arrhythmogenic Ca$^2+$ events.

Ian Coccimiglio, Dave Clarke

Mathematical Modelling of AMP-Activated Protein Kinase During Contraction

AMP-activated Protein Kinase (AMPK) is an enzyme that senses shifts in intracellular energy balance. Its activity is regulated both by phosphorylation and allosteric binding of adenine nucleotides (ATP, ADP, and AMP). Until recently, the AMP:ATP ratio was considered the main determinant of AMPK activity in vivo. ADP has since been proposed as an additional regulator. Determining which of these adenine nucleotides is the principal regulator of AMPK during skeletal muscle contraction remains an open question. Here we report
the development and initial analysis of a mathematical model of AMPK regulation in contracting skeletal muscle. A system of ordinary differential equations (ODEs) incorporating the relevant molecules, protein complexes, and biochemical reaction rate expressions was used as the model framework. The model was constructed based on data from published studies in which the adenine nucleotide concentrations and AMPK phosphorylation and kinase activity levels were measured during muscle contraction. Kinetic parameters were estimated from published data. The ODEs were solved using the ode45 solver in MATLAB. Simulating the model with the nominal parameter values demonstrated that ADP is the primary regulator of phospho-AMPK levels in contracting skeletal muscle. The basis for this result is that while both AMP and ADP exhibit similar affinities for AMPK, the concentration of ADP is in far excess (10- to 400-fold) of AMP. A parameter sensitivity analysis determined that AMPK activity is most sensitive to parameters affecting AMPK Kinase. We conclude that ADP is the primary activator of AMPK activity in vivo.

Adeleke Fowokan, Iris Lesser, John Mancini, Scott Lear

The predictive relationship between baseline insulin and glucose with subclinical carotid atherosclerosis after 5 years in a multi ethnic cohort

Background
We sought to explore the relationship between baseline insulin and glucose and the progression of IMT in a multi ethnic cohort.

Methods/Results
Males and females between 30 and 65 years of age (n=545) of European, Chinese, South Asian and Aboriginal origin were assessed as part of the Multicultural Community Health Assessment Trial study for socio-demographics, smoking status and fasting insulin and glucose at baseline. Intima media thickness and total area were assessed after 5 years of followup using ultrasound.

Independent multiple regression models were used to explore the association between carotid IMT and total carotid area at 5 years with fasting insulin and glucose at baseline. Interactions between insulin and ethnicity, and glucose and ethnicity were additionally explored. Age, sex, ethnicity, education and smoking status were included as covariates.

A total of 545 participants (265 men and 279 women) were assessed. The mean (SD) age range of the male study participants was 47.3 (8.6) years while that of the female study participants was 47.6 (9.2) years. At baseline the geo-
metric mean for insulin was 62.7 pmol/L (95%CI: 59.8–65.8 pmol/L), glucose was 5.2 mmol/L (95%CI: 5.1–5.2 mmol/L).

For IMT, there was a significant insulin-ethnicity interaction such that this relationship was different between Aboriginals and Europeans (p=0.049). In the model with glucose as the variable of interest, glucose was a significant predictor of IMT (p<0.001) but there were no significant glucose-ethnicity interactions or main effects and ethnicity was not a predictor of IMT in this model. In models with total area as the outcome, there was no significant insulin-ethnicity interaction however, both insulin (p<0.001) and ethnicity were predictors of total area. In the model with glucose as the variable of interest, there was a significant glucose-ethnicity interaction such that this relationship was different between Chinese and Europeans (p=0.015).

Conclusion
Ethnicity modifies the predictive relationship between insulin and glucose with sub-clinical carotid atherosclerosis indicators but not consistently so.

Mohammad-Reza Ghovanloo, Mena Abdelsayed, Peter C. Ruben

Effects of Amiodarone and N-Desethylamiodarone on Cardiac Voltage-Gated Sodium Channels

Amiodarone (AMD) is a potent antiarrhythmic drug with high efficacy for treating atrial fibrillation and tachycardia. The pharmacologic profile of AMD is complex. AMD possesses biophysical characteristics of all of class I, II, III, and IV agents. Despite its adverse side effects, AMD remains the most commonly prescribed antiarrhythmic drug. AMD was described to prolong the QT interval and can lead to torsades de pointes. Our goal was to study the effects of AMD on peak and late sodium currents (INa,P and INa,L) and determine whether these effects change as AMD is metabolized into N-desethylamiodarone (DES). We hypothesized that AMD and DES block both INa,P and INa,L with similar profiles due to structural similarities. Given the inherent small amounts of INa,L in NaV1.5, we screened AMD and DES against the Long QT-3-causing mutation, deltaKPQ, to better detect any drug-mediated effect on INa,L. Our results show that AMD and DES do not affect WT or deltaKPQ activation; however, both drugs altered the apparent valence of steady-state fast-inactivation. In addition, AMD and DES preferentially block deltaKPQ peak conductance compared to WT. Both compounds significantly increase INa,L and window currents. We conclude that both compounds have pro-arrhythmic effects on NaV1.5, especially 1KPQ; however, DES seems to have a greater pro-arrhythmic effect than AMD.
Brain health in relation to physical health and the risk of dementia: Results from the Alzheimer Disease Neuroimaging Initiative

A better understanding of the relationship between physical health and brain health and their combined effect on dementia risks can benefit improved brain health in the aging population. To address this, we studied the Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset, which consisted of measurements on clinical assessments, brain MRI, cerebrospinal fluid biomarkers, and genetic risk factors. Brain health status was evaluated using the Brain Atrophy and Lesion Index (BALI); physical health status was assessed using the deficit accumulation based Frailty Index (FI). Both BALI and FI increased closely with age (p<0.01). Their mean values differed significantly among subjects in different diagnostics groups (p<0.05). Our study suggests that the aging brain subjected to dementia is particularly sensitive to the general health status of both the body and the brain, highlighting the role of health enhancement strategies in dementia prevention.

The ability of persons with multiple sclerosis to adapt to altered visual input during visually guided walking

Multiple Sclerosis (MS) is a disease characterized by demyelination of central nervous system neurons resulting in weakness, fatigue, sensory loss, and visual deficits. There is no known cure for MS, rendering spontaneous recovery and rehabilitation of movement control essential. Here we identified the capacity for adaptation and retention in persons with MS (PwMS), as it is unclear whether these individuals retain these abilities. We compared the performance of 19 PwMS and 15 controls in a precision walking task while they adapted to altered visual input. This task required subjects to step to the center of two targets without stopping. After baseline trials with normal vision, subjects adapted to prism goggles (i.e., adaptation phase) which shifted the subjects perceived target location laterally. One post-adaptation trial followed. To determine retention, subjects came back one week later to perform the same task. To assess performance, we calculated foot placement error, defined as the medial-lateral distance between the middle of the foot and target. We quantified errors for the baseline phase (mean: last 10 trials), the initial adaptation trial, early adaptation (mean: adaptation trials two to
eight), late adaptation (mean: last 10 trials), and post-adaptation trial. We quantified retention as the percent change in foot placement errors across testing session for the initial adaptation trial error and early adaptation measures. We found a reduction in error from initial to late adaptation trials, and large errors in the opposite direction in the post-adaptation trial (i.e., negative aftereffect) in both groups on day one. Both PwMS and controls showed less error on the second day. Regardless of the measure, we found no differences between groups. These results indicate that high functioning PwMS are able to adapt and retain this adaptation over time.

Rachel Halipchuk, Jessica Selinger, Max Donelan

Distraction May Disrupt the Continuous Optimization of Human Gait

Recent findings have shown that humans adapt their gait in real-time to optimize energetic cost. Whether this energy optimization is accomplished by our conscious or subconscious nervous system remains unknown. Our purpose in this study was to investigate the conscious demands of optimization by creating a dual-task paradigm, where resources used for conscious thought must be divided.

The primary task replicated the paradigm used by Selinger et al. in which robotic exoskeletons are used to manipulate people’s energetically optimal step frequency. The secondary task was a 1-back audio discrimination test requiring subjects to continuously differentiate the pitch of audio tones. Subjects discriminated between tones while walking using a button held in each hand. In this preliminary analysis, we tested three naïve, able-bodied subjects. We first determined subjects’ preferred step frequency, prior to turning on the exoskeleton controller. Next, the exoskeleton controller was turned on and we determined if subjects would adapt their step frequency both spontaneously, and when primed to do so by perturbations toward higher and lower costs. Subjects performed the tone discrimination test throughout the entire experiment. We measured performance of both percent accuracy on the discrimination task and adaptations in preferred step frequency. Only one of the three subjects showed adaptation toward the new energetic optimum while executing the distraction task.

These findings contrast those of Selinger et al., where all tested subjects adapted in the absence of a distraction task. Subjects do not reliably adapt toward the optima, suggesting that conscious demands play a role in the continuous energy optimization of human gait.
The hERG potassium channel, found in cardiac tissues, is an important contributor to cardiac repolarization. Loss of function of hERG channels is associated with the life-threatening arrhythmia, Long–QT syndrome. HERG channel activators, which enhance current and may act to accelerate the repolarization phase of the cardiac action potential, have been proposed as a possible treatment for both congenital and acute drug-induced LQTS. One compound reported to have hERG activator properties is RPR260243. This compound has been shown to dramatically slow channel deactivation and to right-shift the voltage dependence of inactivation. Each of these would increase channel open probability. Although the electrophysiological characteristics of RPR260243 have been well described, the mechanism of action remains unclear, limiting further development. The N-terminus is known to play a critical role in the characteristically slow deactivation kinetics of hERG, likely through complex interactions with the S4–S5 linker and the C-linker/CNBD complex. Since, RPR260243 has been suggested to act to slow deactivation by interacting with the inner S5–pore domain and the C-linker, we hypothesized that both RPR260243 and the N-terminus share a similar site of action and molecular mechanism to slow channel deactivation. Using two-electrode voltage clamp, we have investigated the mechanism of action of RPR260243 on the deactivation properties of hERG channels by examining both wild-type hERG and hERG channels with the N-terminus deleted (ΔN). We found that the accelerated deactivation kinetics produced by the ΔN deletion were slowed in the presence of RPR260243. Interestingly, however, the dose-dependence of the effect of RPR260243 was right-shifted in ΔN channels compared to wild-type. These data suggest that RPR260243 acts to stabilize the open conformation independent of N-terminus interactions, but that the N-terminus stabilizes the interaction of the RPR260243 activator at the voltage sensor/pore domain interface.

Evan Hutcheon, Matthew Lloyd, Thomas Loughin, Victoria Claydon

META-ANALYSIS COMPARING HIGH ALTITUDE ADAPTATIONS IN ANDEANS, ETHIOPIANS, AND HIMALAYANS: UNCERTAIN ROLE FOR POLYCYTHAEMIA

Chronic Mountain Sickness (CMS) is a maladaptation to living at high altitude (HA), and is most prevalent in the Andes and Himalayas. We aimed to
compare HA adaptations between Andeans, Ethiopians, and Himalayans. A meta-analysis was performed using a keyword search in Pubmed to find information on CMS score, hemoglobin, arterial oxygen saturation, and altitude between Ethiopians, Andeans, and Himalayans. Data were compared from 63 manuscripts (n=12,052 participants), and multiple regressions analyses were performed. Values are means ± standard deviation. Andeans had higher hemoglobin levels than Himalayans (18.1±1.9 g/dL vs 16±1.5 g/dL, p<0.001) and Ethiopians (15.9±0.6 g/dL, p<0.037), with males having significantly higher hemoglobin levels than females in all ethnicities. Interestingly, arterial oxygen saturations were not significantly different between ethnicities and genders. Multiple regression analyses revealed that arterial oxygen saturation was the primary contributor to the CMS score (Qinghai CMS score = 69.338 - (0.836* arterial oxygen saturation) + (0.47*hemoglobin concentration), p<0.001 and R=0.942). Hemoglobin was related significantly to ethnicity, gender, and altitude (hemoglobin concentration =15.659 + (1.12*Ethnicity) + (1.32*Gender) + (0.001*Altitude) - (0.052*Arterial oxygen saturation), p=0.14 and R=0.865) whereas for arterial oxygen saturation only altitude was found to contribute significantly (arterial oxygen saturation = 103.923 - (0.0595*Age) + (0.234*hemoglobin concentration) – (0.00439*Altitude), p<0.001, and R=0.805). These data underscore the variable physiological adaptations of residents in the different mountainous regions of the world, and the uncertain role of polycythemia in the presentation of the disorder, despite it being considered a “hallmark” feature of the disease.

Nora Farag, Danielle Jeong, Jim Warwicker, Mark Boyett, Tom Claydon

Polyunsaturated fatty acids inhibit Kv1.4 by interacting with positively-charged extracellular pore residues

Increased levels of polyunsaturated fatty acids (PUFAs) during myocardial ischemia have a pathophysiological effect on the heart by modulating the function of cardiac voltage-gated potassium channels. Kv1.4 is a voltage-gated potassium channel that underlies the early repolarization phase of the cardiac action potential and helps determine the action potential duration. Using two-electrode voltage clamp, we report here the effects of ω-6 and ω-3 PUFAs on Kv1.4 channels heterologously expressed in Xenopus oocytes. PUFAs inhibited wild-type Kv1.4 channels during repetitive pulsing by slowing the recovery from inactivation. Using a Kv1.4 channel deletion mutant that lacks the N-terminus, we show that this effect of PUFAs is via a stabilization of pore-mediated C-type inactivation. We show that the stabilizing effect of PUFAs on C-type inactivation was similar to that of extracellular acidosis or a decrease in extracellular potassium, and indeed we found there was an
interaction among the three. Using site-directed mutagenesis, we identified two positively-charged residues in the channel pore (H508 and K532) of Kv1.4 channels that, when mutated, abolished the effects of the PUFAs (and extracellular H+ and K+) on C-type inactivation. Structural modelling and charge calculations suggest that the acidic head group of PUFAs raises the pKa of H508, which in turn reduces the K+ occupancy of the selectivity filter of the pore and stabilizes the C-type inactivated state. These studies provide the first description of a site and mechanism of interaction of PUFAs in Kv1.4 channels and offer a more general mechanism by which inactivation in voltage-gated channels may be enhanced by PUFAs.

Michal P. Jurkowski, Chantelle C. Lachance, Ania C. Dymarz, Dawn C. Mackey

Compliant Flooring to Prevent Fall-Related Injuries: Preliminary Results from a Scoping Review

BACKGROUND:
Compliant flooring systems may reduce the incidence and severity of fall-related injuries in older adults, but there is a lack of synthesized evidence about their performance. A scoping study is being conducted to answer: what is known about the biomechanical efficacy, clinical- and cost-effectiveness, and workplace safety associated with compliant flooring systems that aim to prevent fall-related injuries?

METHODS:
Academic (AgeLine, CINAHL, Cochrane Database of Systematic Reviews, MEDLINE, SportDiscus, and Web of Science) and grey literature (clinical trial registries, theses/dissertations, abstracts/conference proceedings, relevant websites) databases were comprehensively searched. Two independent reviewers screened records for inclusion in two stages: 1) title and abstract screening; and 2) full-text screening. Data will be charted and synthesized from records that pass both levels of screening, and results will be presented according to four pre-defined themes: biomechanical efficacy, clinical-effectiveness, cost-effectiveness, and workplace safety.

PRELIMINARY RESULTS:
In our academic database search, 3611 records were identified, and 70 were included following the two stages of screening. 40 records were related to biomechanical efficacy, 20 to clinical effectiveness, 2 to cost effectiveness, and 8 to workplace safety. Several clinical effectiveness studies reported compliant flooring as a potentially effective intervention for reducing fall-related injuries in healthcare facilities, with variable effects on fall risk.
Both cost-effectiveness records simulated the effects of novel compliant flooring systems on fall-related injuries and reported favorable results. Most workplace safety records reported increased difficulty or force output when pushing carts on compliant surfaces, as well as increased injury rates associated with working on carpet; 1 study reported decreased pain intensity scores on 4mm vs. 2mm vinyl. Results from biomechanical efficacy studies have not yet been synthesized.

IMPLICATIONS:
This study will summarize evidence about compliant flooring as an intervention for preventing fall-related injuries in older adults and identify evidence gaps and new avenues for research.

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Sonal Kaushik
The Impact of Hypertension on Vascular Smooth Muscle Cells

Hypertension is associated with high circulating levels of Angiotensin II (Ang II). Ang II causes chronic inflammation and oxidative stress leading to mitochondrial dysfunction (MD) and remodeling of the vascular wall. In particular, Ang II has been shown to induce vascular smooth muscle cell (VSMC) hypertrophy in conduit arteries. The mechanism behind this phenotypic change is not fully understood but involves alterations in cell cycle regulation. Recent research in the Poburko lab has shown that chronic Ang II treatment of A7r5 rat aorta smooth muscle cells causes mitochondrial DNA (mtDNA) damage and the extent of mtDNA damage was linearly related to the fraction of cells showing increased nuclear DNA content. It has not been determined whether this increased nuclear DNA content was due to cells becoming polyploid or being in G2 arrest after DNA replication. Our current study aims to distinguish whether persistent low concentrations of Ang II and ddC, a replication blocking nucleotide analog, cause quiescent, differentiated A7r5 cells to undergo bona fide hypertrophy versus cell-cycle progression with arrest at G2 phase. We assessed the ploidy of A7r5 cells treated for 14, 20, and 28 days. Newly replicated DNA was labeled with Alexa-647 conjugated Click-iT® EdU (5-ethynyl-2-deoxyuridine) and ploidy was determined by staining nuclear DNA with Propidium Iodide (PI). The cells were imaged by epifluorescence microscopy. Ang II and ddC treated cells displayed polyploidy. Stimulation of growth with 10% serum at the end of drug treatment led to a net loss of 8N cells and increase in 2N cells in the 14 and 20-day experiments suggesting polyploidy may be due to cell cycle arrest in G2 phase. Further analysis into how mtDNA might promote a hypertrophic response would better our understanding of its role in the VSMC phenotype changes known to promote HT and could lead to preventative strategies.

Are long-term care staff within tolerance limits for safe pushing when using floor-based lifts over compliant sub-flooring?

Preliminary clinical studies suggest that compliant subflooring results in fewer and less severe fall-related injuries in acute care and long-term care (LTC) settings by decreasing the stiffness of the ground surface compared to standard flooring. Reduced ground stiffness may however increase the risk of care staff sustaining musculoskeletal injuries by increasing the push forces required to maneuver wheeled equipment. In this study, 14 female LTC staff performed 3.7 meter linear pushes of two floor-based lifts (traditional, motor-driven), loaded with mock residents of two different weights (67 and 90 kg), over two flooring systems (compliant+vinyl, compliant+carpet). Forces were recorded using a handlebar-mounted triaxial load cell and were compared to Snook & Ciriello’s (1991) tolerance limits for 90% of the female industrial population. For both the traditional and motor-driven lifts, all care staff exerted forces below tolerance limits when pushing 67 kg and 90 kg residents over compliant+vinyl flooring. However, care staff exerted forces above tolerance limits when using the traditional lift on compliant+carpet flooring for both 67 kg (29%; 4 of 14) and 90 kg (71%; 10 of 14) residents. In contrast, when pushing 67 kg and 90 kg residents using the motor-driven lift on compliant+carpet flooring, force values remained within the limits for all participants. Safety margins (tolerance limits – measured forces) were 2–3 times larger for the motor-driven lift than the traditional lift across conditions. In summary, care staff exceeded tolerance limits for pushing only when operating the traditional lift on compliant+carpet flooring.

Jacob Karamanian, Shane Virani, Colin Russell, Yijian Yang, Stephen Robinovitch

Head impact risk for older adults who fall with protective mechanisms seen in younger adults

Aging is associated with increases in the rate of fall related injuries such as traumatic brain injury. Our goal was to compare falls experienced by young versus older adults in terms of the movement profiles and sites of impact. Our second goal was to examine whether common protective responses led to avoidance of head impact. To accomplish this, video footage of older adult falls in long term care facilities and younger adult falls on a perturbation
platform in a laboratory setting were analysed with a validated questionnaire. Younger adults impacted their knees and hands significantly more often than older adults. However, rate for head injury was not different in older adults who impacted their hands and knees to older adults who did not. These results suggest that interventions that attempt to shift the falling behavior of older adults to similar to younger adults need to continue to be critically examined as physiological barriers, such as decreased reflexes, due to aging may not be able to be overcome.

Brian Li, Damon Poburko

Droplet Digital PCR Assay Optimization for Quantification of Multiple Nucleic Acids

Droplet Digital PCR (ddPCR) is the latest generation of polymerase chain reaction based on water-oil emulsion droplet technology that allows for absolute quantification of nucleic acids. The ddPCR working principle offers a unique method of quantifying nucleic acid copy number compared to traditional PCR because reaction samples are stochastically partitioned into one nanolitre oil droplets. This allows the amplification reaction to be carried out and measured in each droplet individually. In addition to offering higher precision versus quantitative PCR, ddPCR accommodates single-probe multiplexing quantification of multiple nucleic acid targets in one reaction. Multiplexing increases precision when measuring one target against a reference. Therefore, the first step for researchers that are starting to use ddPCR is to develop an optimized protocol for all variables to work harmoniously before quantifying nucleic acids in their sample of interest. We aim to address ways to overcome common hurdles when optimizing a multiplex protocol for ddPCR for starting users, which can be done with one sample of DNA. As an example, we will also demonstrate the ability of our ddPCR assay to detect sensitive changes in mitochondrial DNA (mtDNA) copy number in a7r5 rat aorta smooth muscle cells that have had their mtDNA depleted with 2',3'-dideoxycytidine (ddC). Because of the advantages that multiplexing brings, we hope to outline a step-by-step approach to optimization that new users can follow to develop a ddPCR protocol that is useful in their own research.

Somayeh Mojarad K., Jag Walia, Cynthia Gershome, Damon Poburko

Age-dependent role of CaV2.3 in sympathetic vasoconstriction of rat tail artery
Peripheral sympathetic nerves are essential for regulating homeostatic control of target organs, such as the tone of blood vessels. Advances in understanding the molecular organization of peripheral sympathetic nerves has not kept pace with our understanding of central synapses. Unlike central synapses, peripheral varicosities often exhibit co-transmission that is they release multiple neurotransmitters. Several lines of evidence show that CaV2.1 and CaV2.2 preferentially mediate the release of vesicles containing either norepinephrine (NE) or ATP, typical sympathetic co-transmitters, and that preferential interactions between different vesicle types and CaV2 isoforms underlies differential release of NE and ATP. CaV2.3 is a closely related channel that has been studied in several central synapses, but its role in peripheral sympathetic nerves is largely unknown. Using confocal microscopy to study perivascular nerves, we shown that ATP and NE are stored in segregated pools of vesicles. These studies revealed that CaV2.3 are present in rat tail perivascular sympathetic nerves and that they co-localize with vesicles expressing the vesicular nucleotide transporter (VNUT) that loads ATP into vesicles rather than the NE-transporting vesicular monoamine translocase 2 (VMAT2). However, a functional role for CaV2.3 to mediate ATP release from perivascular nerves has not been reported. We assessed the functional role of CaV2.3 in isometric force generated by rat tail arteries in response to field stimulation pulse-number ramps (1-100 pulses, 20 Hz). We stimulated caudal tail arteries of rats age 4-27 week with patterns shown to preferentially release ATP (low pulse number), and pharmacologically assessed neurogenic vasoconstriction by blocking CaV2.3 with SNX-482 or smooth muscle P2X receptors with Suramin. We further demonstrate that presence of CaV2.3, determined by immunofluorescence, is relevant with inhibitory effect of SNX-482 or Suramin ~ 50-60% of force generated by 1-10 pulses. Finally the contribution of Cav2.3-mediated neurotransmitter release increase with age. This is the first study to show a functional roll for CaV2.3 in sympathetic vasoregulation. Further detail of this study remain to be determined to examine the interplay between Cav2.3 and CaV2.1 in the regulation of ATP release.

Lauren Penko, Michael Rogers, Assaf Yogev, Matthew White

Influence of normoxic 30% nitrous oxide on timing of breathing following supra-maximal exercise

PURPOSE: To determine if the timing of breathing after supra-maximal anaerobic exercise is influenced by breathing of normoxic 30% nitrous oxide. HYPOTHESIS: It was hypothesized that normoxic N2O breathing would suppress exercise ventilation after a 30 s Wingate test. METHODS: Three college males of normal physique volunteered for the study that was approved by the SFU Office of Research Ethics. Participants were measured for exercise...
ventilation (VE), its timing components, tidal volume (VT) and frequency of breathing (FB). Each volunteer participated in two 30 s Wingate trials on an electrically-braked, seated, cycle ergometer, one trial while breathing air and one trial while breathing normoxic 30% N2O. Outcome variables included VE, VT, FB, inspiratory time (TI), expiratory time (TE) and total breath time (TTOT). Inspiratory time over TTOT gave the duty cycle (TI /TTOT) for breathing and VT /TI gave an index of inspiratory effort. A two-way repeated measures ANOVA was employed with factors of Gas Type (Air or normoxic 30% N2O) and Time (2, 4, 6, 8 and 10 min). RESULTS: During recovery in the air condition the mean TI /TTOT of 0.46±0.04 unitless was not significantly different (FGAS_TYPE, p>0.05) than TI /TTOT of 0.46±0.07 unitless in the normoxic 30% N2O condition. The mean VT/TI of 1.87±0.75 L/s in the air condition showed a trend to be significantly greater (FGAS_TYPE, p=0.06) than the VT/TI of 1.64±0.70 L/s in the normoxic 30% N2O condition. CONCLUSION: These preliminary results showed no influence of normoxic 30% nitrous oxide on the duty cycle for breathing but a trend for lower inspiratory effort during the recovery from supra-maximal anaerobic exercise.

Mahan Rahimi, Andrew Blaber, Carlo Menon

An Adaptive Compression System for Prevention of Lower Leg Oedema

One in 62 Canadians, especially the elderly, pregnant women and spinal cord injury patients, suffer from oedema or excessive leg swelling, a condition associated with pain, varicose veins, and hypotension that can lead to syncope and falls. The efficacious role of compression therapy in management of such disorders has been the subject of numerous studies. The shortcomings of the existing compression therapy products, such as lack of feedback on the applied pressure and inability to adapt to the changes in physiological conditions of the user, motivated us to develop a novel adaptive compression system (ACS) for prevention of lower leg swelling during stasis or ambulation. The proposed device is a motorized compression tool which is capable of delivering pressure in continuous and intermittent modes and adapts to physiological changes based on the feedback from flexible Force Sensing Resistors® (FSRs) which are used as a means to measure the interface pressure. We conducted a randomized study on 11 healthy participants to investigate the performance of the ACS in pumping blood back to the heart by monitoring its capability of preventing stroke volume decline. We created the needed shift in blood volume by graded LBNP and throughout testing continuously monitored beat-to-beat blood pressure, and electrical and mechanical activities of the heart via electrocardiography (ECG) and seismocardiography (SCG), respectively. Each subject completed two sets of experiments; one
Without donning the ACS, and another one having it on exerting intermittent compression at the onset of negative pressure. The results of the two-factor repeated-measures analysis of variance (ANOVA) with the Tukey-Kramer post hoc test showed there were statistically significant changes in mean responses of SCG-extracted data (including stroke volume). We assumed significance where $p<0.05$. This study showed that our device is capable of hindering stroke volume drop by facilitating blood circulation through compressing lower extremities.

**Kaveh Rayani, Charles M. Stevens, Yueh Alison Li, Christine E. Genge, and Glen F. Tibbits**

**Functional Characterization of Zebrafish Cardiac and Slow Skeletal Troponin C Paralogs by MD Simulations and Isothermal Titration Calorimetry**

Zebrafish hearts express two troponin C paralogs; differential expression of the genes for these paralogs is a response to environmental temperature. Ca$^2+$ binding to troponin C causes a conformational change that exposes a hydrophobic patch, which interacts with troponin I and initiates cardiac muscle contraction. Teleost-specific troponin C paralogs have not yet been characterized, to this end we have modeled the structures of these proteins using Molecular Dynamics (MD) simulation at 18 ºC and 28 ºC. The different Ca$^2+$ binding properties of cardiac (cTnC/ TnC1a) and slow-skeletal (ssTnC/ TnC1b) paralogs have been calculated through Potential of Mean Force calculations (PMF). Thermodynamic binding properties obtained through Isothermal Titration Calorimetry (ITC) provide an in vitro means of comparison.

MD simulations isolate the energetic contributions of Ca$^2+$ binding from those of the subsequent conformational change. The short timescale of MD means that the changes in PMF of the Ca$^2+$ interaction can be directly attributed to site II binding. In contrast ITC analysis includes Ca$^2+$ binding and the conformational change of TnC. ITC analysis has revealed that ssTnC has higher Ca$^2+$ affinity than cTnC. Moreover, each of the paralogs has increased affinity at higher temperature. Our data suggests that the change in affinity observed through ITC is due to modification of the energetic landscape of the conformational change upon Ca$^2+$ binding to TnC. Sequence substitutions and structural divergences in helices C and D of TnC are the main difference between structures of these proteins.

**Lauren Rietchel, Victoria Claydon**

**EFFECT OF BREATH HOLDING ON ORTHOSTATIC TOL**-
ERANCE DURING TILT TABLE TESTING: POSSIBLE INFLUENCE ON VALIDITY OF CAROTID SINUS MASSAGE TEST

The act of breath holding (BH) eliminates the influence of the respiratory muscle pump on venous return to the heart, and therefore we aimed to examine its effect on orthostatic tolerance (OT) and cardiovascular responses during tilt testing. This study also indirectly examined the validity of OT tests requiring BH such as the Carotid Sinus Massage Test (CSMT). Five healthy participants of normal height and BMI were recruited to participate in this study. The control tilt protocol consisted of a ten-minute tilt without BH. The BH protocol consisted of a tilt where individuals were asked to breath-hold eight times. BH occurred on an exhalation for fifteen-second periods at one-minute intervals. Protocol order was randomized and measurements were taken in a supine position on the tilt table for a ten-minute period prior to both tilts. Time matched paired t-tests revealed no significant difference (n = 5, p>0.05) in heart rate, stroke volume, mean arterial pressure, middle cerebral arterial flow, and systolic arterial pressure in both conditions. A two-way repeated measures ANOVA revealed evidence of an interaction of condition over time on cardiac output (CO) (Df: 7, F: 2.62, p=0.03). Post-hoc tests revealed decreased CO in BH conditions in the second and fourth breath hold. There was also a main effect of time on stroke volume (SV) (Df: 7, F: 3.01, p=0.02). It was decreased in the BH condition, which may have contributed to decreased OT over time. Evidence exists that BH dampens normal blood flow responses in healthy individuals and may weaken the validity of the CSMT depending on the length of the protocol.

Emily Ross, Brodie Sakakibara, Martha Mackay, Mustafa Toma, David Whitehurst, Harriette Van Spall, Kimber-ly Rutherford, Leon Jung, Bobby Gheorghiu, Alyson Ha-gan-Johnson, Jillianne Code, Iris Iannone, Scott A. Lear

The development of a text messaging intervention to improve the hospital-community transition in patients with cardiovascular disease

Background: Cardiovascular diseases are a leading cause of hospitalization. The transition from the hospital back to the community may make patients feel overwhelmed or alone in their care. In British Columbia, approximately 12% of patients are readmitted within 30 days of discharge. Increasing patient capacity for self-care is an effective way to reduce readmissions. Text messaging may be a low-cost and low-burden solution to help support patients. We are currently testing a 60-day text-messaging intervention
program for recently discharged acute coronary syndrome patients in a single-blinded randomized trial. The process for developing the text messaging program is outlined.

Methods: As part of the development process, we created a clinical advisory committee. The committee included researchers, health care providers, and patients. Initial messages were drafted based on interviews with patients, and discharge and support materials provided to patients. The text messages were revised based on the feedback from the committee, which included adding more topics and improving the ordering and wording of the messages. The messages were then discussed in focus groups with cardiac rehabilitation patients. The messages were revised again and finalized based on the findings of the focus groups and the input of the committee.

Results: This process allowed the input of key stakeholders and end-users participation in many stages of the development. The focus group participants liked the messages overall, in particular the texts supporting psycho-social needs. They also recommended that the texts include more specific resources they could follow-up with, and wanted the texts to be simply phrased. The finalized intervention included 50 texts to be sent over 60 days.

Conclusions: Many stakeholders contributed to the development of the messages to try to improve the acceptability. This model for development can be used for other programs that aim to support patients through information and communication technology.

Manpreet Ruprai, Mena Abdelsayed, Peter Ruben

Temperature Dependent Effects of Ranolazine on a Mixed Syndrome Cardiac Sodium Channel Mutant

Objective:
To determine how changes in temperature modulate the effects of Ranolazine on the mixed syndrome mutant E1784K.

Introduction:
The predominant sodium channel isoform in cardiac myocytes, Nav1.5, is responsible for the upstroke of the cardiac action potential. Mixed syndrome mutants in Nav1.5 lead to both gain-of-function and loss-of-function phenotypes. Ranolazine is a commonly prescribed antianginal drug that has been reported act as an antiarrhythmic. Since temperature has been shown to exacerbate the E1784K mutant, we sought to determine the effects of temperature on E1784K at varying Ranolazine concentrations.
Methods:
Whole cell patch clamp experiments were performed on Human Embryonic Kidney (HEK293) cells transiently transfected with NaV1.5-WT (wild-type) or E1784K α subunits, β1WT, and enhanced green fluorescence protein (eGFP). Recordings were performed at 22 ºC and 34 ºC.

Results:
The voltage-dependence of activation in E1784K was hyperpolarized at both 10µM and 100µM Ranolazine at 34ºC compared to 22ºC. This effect opposes the depolarizing shift in E1784K induced by elevated temperatures. Ranolazine, at both 10µM and 100µM, also attenuated the large late INa in E1784K, which was exacerbated by elevations in temperature. The onset of use-dependent inactivation (UDI) was accelerated by 10µM of Ranolazine in E1784K at 34 ºC compared to WT. Elevated temperatures alleviated the stabilization of UDI seen in E1784K at 10µM Ranolazine and 22ºC.

Conclusions:
Increased temperature exacerbates the gain and loss-of-function properties in E1784K. Ranolazine is a potent antiarrhythmic in treating the thermosensitive E1784K channel. Additional studies are needed to further understand Ranolazine’s antiarrhythmic potential to treat E1784K under exercise conditions.

Sukhraj S. Sahota, Michael J. Rogers, Prabhjot K. Singh, Jingkai Pang, and Matthew D. White

Effects of Aging on Core Temperature Thresholds for Exercise Ventilation

Purpose: This study examined whether aging influences core temperature thresholds for exercise ventilation in humans.

Methods: The Simon Fraser University Office of Research Ethics approved the study. Prior to participating in the study, each volunteer was given a laboratory orientation, a 24 h reflection period, completed PAR-Q and medical history forms plus gave a signed, informed consent. A 62-year-old male volunteered for the study as did a control group of six college age males. A breath-by-breath metabolic cart was used to monitor ventilatory parameters including tidal volume (VT), minute ventilation (VE), breathing frequency (fB) and ventilatory equivalents for oxygen (VE/VO2). Core temperature was monitored using an esophageal probe (TES) that was positioned at the level of the left ventricle. Along with TES, skin temperatures were monitored on the forehead, chest, lower back, thigh, and forearm. Heart rate (HR) was
monitored with a pulse-oximeter. All volunteers completed a VO2max test. Each participant pedaled at a frequency of 70 revolutions per min, where the resistance was increased in steps of 40 Watts (W) every 2 min up until the point of exhaustion. A one-group t-test compared the control group’s mean to the TES threshold of the older volunteer. The level of significance was set at 0.05.

Results: The control group had an average TES threshold for VE/VO2 of 37.51± 0.100°C and it was significantly greater (p<0.0001) than the older volunteer’s TES threshold for VE/VO2 of 36.690°C.

Conclusion: These preliminary results support that core temperature thresholds for exercise ventilation are lower in older relative to younger males.

Valentine Sergeev, Eric Lin, Marvin Gunawan, Tom Claydon, Glen Tibbits

Investigating the role of Ikr in the excised zebrafish heart using dofetilide and optical mapping techniques

The cardiac ether-a-go-go gene (hERG) plays a key role in phase 3 of cardiac repolarization. Dysfunction of the channel increases action potential duration, making the myocardium susceptible to lethal arrhythmias. To date, functional studies of hERG have centered on heterologous expression systems: over-expressing the channel in a non-cardiac cell without native promotors or a complete profile of post translation modification. Furthermore, since arrhythmias are necessarily multicellular events, any study of the mechanism by which hERG dysfunction is arrhythmogenic necessitates studying the protein at the tissue or, preferably, at the organ level. Zebrafish (ZF) hearts have been shown to be a remarkable model of human cardiac electrophysiology; their cardiac tissue exhibits similar profiles of ion channel expression, heart rates and action potential duration compared to that of humans. Importantly, zebrafish express zERG in their myocardium, an ortholog of hERG. By applying voltage and calcium sensitive dyes to an excised ZF heart and recording their respective transients using optical mapping techniques, we have shown that dofetilide, a hERG blocker, prolongs the action potential of zebrafish myocytes. Furthermore, we show that there is relatively more block at higher temperatures suggesting that dofetilide may be used to assess functional Ikr current. Finally, we show that dofetelide may be arrhythmogenic – presumably through the prolongation of the action potential. In summary, excised ZF hearts may be a useful whole organ model of hERG function. Further, hERG dysfunction may be modeled in ZF using dofetilide.
Human induced pluripotent stem cells-derived cardiomyocytes (hiPSC-CMs) are important models of human cardiac physiology. Despite the number of advantages this model may offer over previous cardiac models, immaturity of these cardiomyocytes can hamper their adoption as an in-vitro model. The spontaneous and synchronous contraction of hiPSC-CMs is one of the principal indicators of these cells being differentiated into cardiomyocytes. The expression and functioning of several ionic channels, which occur during development, are important for generating action potentials. The human ether-a-go-go-related gene (hERG or KCNH2) encodes the voltage-gated potassium channels, which govern IKr and participates in the regulation of action-potential duration. Alternate transcripts of KCNH2 encode 1a and 1b subunits, each with different characteristics. Changes in the expression levels of hERG-1a and hERG-1b during development may also be apparent in pharmacological sensitivities of hiPSC-CMs’ action-potential dynamics, as well as their altered rates of spontaneous activity. The hERG current, IKr, which is active later in the action-potential plateau, has a strong effect on the thermodynamics of calcium efflux via forward-mode sodium-calcium (NCX) activity. Because forward-mode NCX activity is electrogenic, which results in a depolarizing current, changes in the calcium transient can potentially alter membrane-voltage dynamics. Quantitative RT-PCR and digital PCR were used to monitor transcript levels of hERG-1a and hERG-1b up to 150 days of maturation. Simultaneous voltage and calcium recordings, using the potentiometric dye RH-237 and the calcium indicator dye Rhod-2, were used to quantify the rates of spontaneous activity, action-potential profiles, and calcium transient dynamics. The findings show that changes in action-potential duration or increased susceptibility to pharmacological blockage of hERG channels correlate with changes in the expression level of two hERG subunits.

Myocardial ischemia occurs in response to partial or complete blockage of
coronary vessels that reduces blood flow to cardiomyocytes preventing adequate oxygen supply. One of the major consequences is acidosis, a reduction in local pH, in both intracellular and extracellular spaces. Studies in rabbit hearts subjected to ischemia showed that the external pH changes rapidly from 7.4 to as low as 6.1, and intracellular pH may drop from 7.0 to 6.6. The reduction in external and internal pH has profound effects on cardiomyocyte electrophysiology and contractility, and the, largely inhibitory, effects of acidosis on many ion channels has been widely reported. We have recently reported the site and molecular mechanisms of action of acidosis in cardiac hERG (human ether-a-go-go-related gene) potassium channels. hERG channels play a critical role in the repolarization phase of the cardiac action potential as a result of their unique gating properties. We have shown that extracellular, but not intracellular, acidosis has multiple, independent, effects on hERG channel open probability, voltage-dependence of opening, and the kinetics of closing and recovery from inactivation. Moreover, these effects appear to have differing dependence on pH. Having previously elucidated the sites and mechanisms of action for these effects, here we turn attention to the construction of a kinetic model based on our experimental data that may be used to describe the pathophysiological consequences of these multiple effects acidosis has on the hERG channel. Our model incorporates each of the effects of acidosis on the biophysical properties of hERG channels, as well as their differing pH-dependence and predicts that the overall effect of a pathophysiologically relevant acidosis on hERG channels acts to prolong the cardiac action potential duration, which may ultimately contribute to cardiac arrhythmia during myocardial ischemia.

Surabhi N. Simha, J. Maxwell Donelan

A mechatronic system for studying gait optimisation

In response to small energetic penalties, people continuously optimise their walking gait to minimize metabolic energetic cost. We aim to determine whether the nervous system similarly values energetic rewards, and whether it treats large changes in cost differently. Towards this aim, we designed a system to study gait optimisation in response to a wide range of energetic rewards and penalties. Ideally, such a system will rapidly transition between energetic costs, and target specific costs both accurately and precisely. To accomplish this, our mechatronic system manipulates the energetic cost of treadmill walking by applying forward and backward horizontal forces to a belt worn by users. A wall-mounted actuator generates the forces, and applies them to the user using long cables. A real-time controller processes signals from foot-mounted inertial measurement units to calculate step
frequency and then commands the appropriate actuator force depending on whether we want to reward or penalize the measured step frequency. We monitor the forces applied to the user using load-cells mounted to the belt. Respiratory gas analysis measures the energetic cost experienced by the user. We found that our system can indeed rapidly control applied forces—the force rise time when transitioning between a range of forces is 85 ms allowing for within-step force changes. It accurately and precisely applies constant forces to a walking subject—the steady-state and root-mean-square errors across a range of commanded forces are 1.25% body weight and 3.9% body weight respectively. Simulations of our system estimate energetic rewards of up to 49%, and penalties greater than 160%, relative to the cost of normal walking. We will next quantify actual energetic changes and then study gait optimization in response to energetic rewards.

**Prabhjot K. Singh**, Ian J. Foster, Michael J. Rogers, Elijah S. Willie, Sukhraj S. Sahota, and Matthew D. White

No effect of ketogenesis on mountain ultra-marathon performance times

PURPOSE: The purpose of this study was to assess the effect of ketogenesis on 50 km mountain ultra-marathon performance. The rationale was after glycogen depletion, when ketone body production and lower pH are evident, that this would decrease performance. We hypothesized a ketone producing group of runners would have greater finishing times in comparison with a non-ketone producing control group of runners.

METHODS: Six healthy males who were 53.6 ± 4.6 years of age and had a Body Mass Index of 22.3 ± 2.6 kg/m2 volunteered for the study. The Simon Fraser University Office of Research Ethics approved the study. Prior to participating in the study, each volunteer was given a laboratory orientation, a 24 h reflection period, completed PAR-Q and medical history forms plus gave a signed, informed consent. Using qualitative and semi-quantitative urine strips, pre and post-race urine samples were assessed for ketone body production and pH. A paired t-test was employed to compare urine samples taken after waking on race day and immediately following the race. The P value was set at 0.05.

RESULTS: The mean urine ketone body concentration was 15±0 mg/dL in the ketogenesis group while no ketones were evident in the control group’s urine. Prior to race the control group urine pH was 6.2±0.3 and it was not significantly different (p>0.05) than that of 6.8±0.6 in the ketogenesis group.
After the race the control group urine pH of 7.0±0.9 was not significantly different (p>0.05) than the pH of 5.8±1.4 in the ketogenesis group. The mean control group finishing time of 397±99 min was not significantly different (p>0.05) than of 468±64 min for the ketone producing group.

CONCLUSION: These preliminary results do not support the hypothesis that presence of ketone bodies in post-race urine samples gives longer finishing times in mountain ultra-marathons.

Sayed Naseel Mohamed Thangal, Jeremy Wong, Max Donelan

Continuous-time modeling of ground contact can approximate inelastic collision events in simulated bipedal walking

During walking, a leg is either in swing, in stance, or switching between the two roles. The latter event, termed the step-to-step transition, has traditionally been modeled as an instantaneous inelastic collision and then combined with continuous time models of swing and stance. While this hybrid dynamics approach has allowed for analytical analysis in bipedal models, it is not possible to model realistic ground contact dynamics. Furthermore, hybrid models suffer from a combinatorial explosion of events when extended to quadrupeds, which is our future goal. Here we consider an alternative, fully-continuous time approach to modeling the whole gait cycle that uses a spring-damper system to estimate the forces generated during ground contact. The goal of our present analysis is to test the ability of continuous-time modeling to reproduce results from hybrid models. To accomplish this goal, we compared the gait mechanics of two similar passive dynamic walking models; one used the hybrid approach to model step-to-step transitions, while the other used a spring-damper based continuous approach. We found periodic walking and similar gait behavior for a wide range of walking speeds in both models. The hybrid model had a slightly slower step period, longer step length and faster walking speed, as predicted by an extrapolation of the continuous model to theoretical values of infinite contact stiffness and zero ground compression. We also studied the effect of ground contact parameters on gait behavior in the continuous model by changing spring stiffness and found that a 50-fold increase only resulted in a 5.8% reduction in step period and a 10.0% increase in step length indicating that gait behavior is not very sensitive to ground contact parameters. In conclusion, the continuous approach can sufficiently approximate either instantaneous step-to-step transitions or more realistic ground contact dynamics, while being readily implementable in quadruped models.
**A technical approach to study how cardiac hERG potassium channels are controlled by the voltage-sensing domain**

The human-ether-a-go-go-related gene (hERG) encodes a cardiac voltage-gated potassium channel that is essential in cardiac myocytes to repolarize the action potential and relax the muscle tissue. Inherited mutations in hERG channels causing loss of function are associated with long QT syndrome, ventricular arrhythmia, and sudden death. Many therapeutic compounds (e.g. some beta-blockers) have a side-effect of binding to hERG channels and this also prolongs repolarization, inducing life-threatening arrhythmias. Despite its importance, the structural aspects of hERG channels that relate to their unique function are not entirely known. The hERG channel core is formed by two structural domains: 1) the voltage-sensing domain (VSD) senses the potential difference across the membrane electric field; 2) the pore domain (PD) allows ion permeation. Movement of the VSD drives PD opening, and it has been proposed that unusual gating of hERG channels derives from atypical VSD movement. However, mechanical coupling of the VSD and PD make this difficult to test. The objective of this study was to observe the function of the VSD independently, in isolation from the PD, in order to determine VSD mechanics. To do this, a stop codon was inserted in the linker connecting the VSD and PD (at residue 546) to produce a truncated hERG channel (G546X) comprising up to and including the VSD, but lacking the PD. Functional cell expression was then tested by injecting cRNA encoding the G546X construct into a model cell system (Xenopus oocytes). Enzyme-linked immunosorbent assay (ELISA) was used to detect surface membrane expression of wild-type or G546X mutant channels. Using this approach, we demonstrate that the VSD can express independently of the PD, thus creating the opportunity to study the function of this domain in isolation of the PD.

**Distinct Molecular Signatures of NE and ATP Containing Vesicles in Vascular Sympathetic Nerves**

Sympathetic vericosities release neurotransmitters including ATP and NE into the neuroeffector junction to regulate vascular smooth muscle cell contraction and ultimately blood pressure. Despite advances in cultured sympathetic neurons, few studies have characterized the molecular details of sympathetic terminals within intact blood vessels. Using immunohistochemistry (IHC) and epifluorescence microscopy, we focus on whether ATP and norepinephrine (NE) are co-stored in the same vesicles or in distinct pools of
vesicles and/or varicosities. Here we report IHC analyses to characterize the association of vesicular nucleotide transporter (VNUT) with other vesicular proteins: Synaptic Vesicle 2A (SV2A), Synaptophysin (Syp) and Synaptotagmin-1 (Syt1), the Ca2+ sensor for NE containing vesicles. We hypothesized that SV2A localizes to all vesicles of sympathetic nerve terminals, whereas Syp preferentially associates with VNUT-containing vesicles. Clusters of labelled vesicles were analyzed for fluorescent intensity using ImageJ and custom macros. Morphologically, VNUT labelled small and highly punctate pools of vesicles, whereas Syt1 labelled pools of vesicles the same size as varicosities. Syp- and SV2A-labelled vesicle pools were of intermediate size between VNUT and Syt1, with labelling consisting of small, round puncta within a varicosity. Visually, VNUT was anti-colocalized with all but a small subpopulation of vesicles labelled by Syt1, SV2A and Syp. In contrast, Syp and SV2A extensively colocalized with Syt1, but they also labelled small pools of vesicles lacking Syt1. Correlations in puncta intensities for Syt1 and SV2A (r=0.23) or Syp (r=0.36) and VNUT-Syp (r=0.29) were high relative to VNUT and SV2A (r=0.02) or Syt1 (r=-0.05). Thus we conclude that Syp and SV2A are preferentially localized with Syt1 to NE containing vesicles, but also associate with a small subpopulation of ATP containing vesicles. Moreover, ATP containing vesicles appear to lack Syt1, which may contribute to differential sympathetic release of ATP and NE as a function of stimulation frequency and duration.


Methods of Defining and Collecting Fall-Related Injuries in Long-Term Care for a Randomized Controlled Trial

Background: The Flooring for Injury Prevention (FLIP) Study is a 4-year randomized controlled trial (RCT) designed to test the effects of compliant flooring on fall-related injuries in resident bedrooms in long-term care (LTC). There is considerable variability among previous RCTs in how fall-related injuries are defined and collected. Here we examined methods of defining and collecting fall-related injury data from existing health records of LTC residents, and explored trends of serious and minor fall-related injuries in the FLIP Study.

Methods: Fall-related injury data were gathered from the LTC home’s fall incident reports, patient charts, and hospital records. Fall-related injuries could occur in FLIP rooms (n=150), non-FLIP rooms (n=86), and common areas of the LTC home. Serious fall-related injuries were defined as fractures and soft tissue injuries that resulted in an Emergency Department visit or a
hospital admission, and required any treatment or diagnostic evaluation (e.g. X-ray). All other fall-related injuries were considered minor.

Results: Over 27 months of follow-up, there were 40 serious fall-related injuries in FLIP rooms, and the most common types were pain requiring diagnostic evaluation (42.5%) and sutured lacerations (20.0%). There were 422 minor fall-related injuries in FLIP rooms, the most common types being pain (45.0%), contusions (19.0%) and lacerations (18.5%). Fractures were the most common serious fall-related injury in non-FLIP rooms (37.5% of 24 injuries) and common areas (32.4% of 37 injuries). Traumatic brain injuries were rare, with one reported concussion query and one unspecified internal head injury for all LTC home locations.

Conclusion: The evidence-based definition of fall-related injury developed for the FLIP Study, and associated methods of collecting fall-related injury data from a LTC home, may be useful for other intervention studies. The lack of TBI incidence suggests the need for further research to develop diagnostic tests for TBI among older adults in LTC.

Alec Yu, Colin Peters, Peter Ruben

Measurement of Intracellular pH During Cut-open Voltage Clamp

The cardiac voltage-gated sodium channel is responsible for the initial depolarization of ventricular cardiomyocytes. The channel mutant E1784K causes both type 3 long-QT syndrome and Brugada syndrome, inherited cardiac arrhythmias associated with sudden cardiac death and sudden infant death syndrome. Shifts in extracellular pH result in greater biophysical changes in E1784K than those in wild type channels. The effects of extracellular pH are unexpected, however, as residue 1784 is on the intracellular side of the channel. One potential explanation is that changing extracellular pH causes a corresponding change in the intracellular pH during experimentation.

We recorded ionic currents using the cut-open oocyte voltage clamp technique, modified to include a pH-sensitive electrode impaled in the oocyte. We measured current density and intracellular pH simultaneously at extracellular pH 7.4 and 6.0. Our C373F and C373F/E1784K sodium channel mutants show no significant change in intracellular pH when extracellular pH is changed from 7.4 to 6.0. From this, we conclude that interactions between extracellular protons and the mutant channel are the primary contributing agent to the biophysical changes seen at low pH.
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