Surgery
UNIVERSITY OF TORONTO

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A CASE FOR USING MACHINE LEARNING AND PREDICTIVE ANALYTICS TO IMPROVE DEDICATED SPINE TRAUMA OPERATING ROOM RESOURCE ALLOCATION

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Hypothesis and Purpose: The Dedicated Trauma Room (DTR) model is increasingly being used to address the challenge of scheduling trauma cases. However, insufficient DTR operating room (OR) time leads to after-hours care, while excess time leads to either unused or last-minute redistribution of OR time. We hypothesize a machine learning model (MLM) can predict trauma volume and allow for schedule optimization to better match supply and demand for the limited resource of OR time. In our study, we compare the current state of spine DTR scheduling to a proposed future state that may be further optimized using a MLM.

Methods: Demand on OR time was derived from a dataset of procedures completed by the orthopaedics department at a Level-1 trauma center. A regression model was used to determine the variables that significantly contributed to demand. These variables were integrated into a linear integer optimization to create a proposed future state DTR schedule that minimized the number of after-hours cases. This was then compared to the current DTR schedule.

Results: Seasonality and weekday-vs-weekend significantly affected demand on OR time. Under the current state spine DTR model (one DTR/week), there is an average of 3.4 (winter), 2.6 (summer), 1.3 (fall), and 0.8 (spring) after-hours cases being completed per week. Under the proposed future state spine DTR model, (two DTRs/week in winter and summer), the afterhour cases decrease to 1.4 and 0.6, respectively.

Conclusion: Seasonality and weekday-vs-weekend were determined to be variables that affect demand on OR time. A DTR optimization model has been identified which can meaningfully guide OR scheduling. Next steps of this work would be to predict the demand on the OR with a MLM to optimize the schedule.

INCIDENCE AND MORTALITY OF EMERGENCY GENERAL SURGERY CONDITIONS AMONG SOLID-ORGAN TRANSPLANT RECIPIENTS IN ONTARIO, CANADA

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Hypothesis and Purpose: Emergency general surgery (EGS) pathologies are perceived to be disproportionately high among solid organ transplant recipients (SOTR). However, this has not been adequately investigated at a population-level. Our objective was to characterize the incidence and mortality of EGS conditions amongst SOTR compared to non-transplant patients.

Methods: Data were collected through linked administrative population-based databases in Ontario made available through ICES. We included all adult SOTR (kidney, liver, heart, and lung) who underwent transplantation between April 2002 and December 2017. We then identified post-transplantation emergency department visits for EGS conditions (appendicitis, cholecystitis, acute diverticulitis with abscess or perforation, incarcerated or strangulated hernias, small bowel obstruction, choledocholithiasis, and perforated peptic ulcer). Age and sex standardized incidence (SIR) and mortality ratios (SMR) were compared between transplant and non-transplant patients.

Results: A cohort of 10,073 SOTR and 12,608,135 controls was analyzed. SOTR developed 881 EGS conditions (controls 552,194 events) and were 3.5 times more likely to develop an EGS condition (SIR 3.56, 95%CI 3.32-3.82). The SIR remained elevated when stratified by transplanted organ and specific EGS, except for perforated peptic ulcer. SOTR were also 1.5 times more likely to die within 30-days of EGS condition presentation (SMR 1.54, 95%CI 1.16-2.00) compared to non-transplant.

Conclusion: The incidence and mortality of EGS conditions is significantly higher in patients who have previously undergone solid organ transplant as compared to the general population.

THE UTILIZATION OF TELEHEALTH IN PRE-OPERATIVE ORTHOPAEDIC CONSULTATIONS AND ASSESSMENTS: A SYSTEMATIC REVIEW

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Hypothesis and Purpose: With the onset of the COVID-19 pandemic, telehealth (TH) for pre-operative orthopaedic care is expanding rapidly. However, the effectiveness with TH for pre-operative orthopaedic services is unclear. We aimed to identify the evidence describing the effectiveness, barriers, and clinical applications of TH in pre-operative orthopaedic care.

Methods: MEDLINE, PubMed, EMBASE, and Cochrane Library were search for studies reporting on satisfaction, feasibility, diagnostic accuracy, cost, wait-times, and barriers with TH in pre-operative orthopaedic care.

Results: Forty-seven studies were included with the most common conditions evaluated being trauma-related and the primary modality being videoconferencing. Seven of the 9 (78%) and 7/8 (88%) studies reporting satisfaction demonstrated moderate-to-high patient (78-100%) and provider satisfaction (73-98%), respectively. Nineteen of 25 (76%) and 7/7 (100%) studies reporting examination data found accurate radiographic and clinical examinations, respectively. Patient, provider, and health system costs were reduced in 8/8 (100%), 15/17 (88%), and 2/2 (100%) studies, respectively. Five of 8 (63%), 8/10 (80%), and 3/3 (100%) studies reporting clinic, consultation, and travel times, respectively, identified no difference or reduced times. Commonly reported concerns were professional liability, network security, and technical issues.

Conclusion: Given the COVID-19 pandemic, rapid uptake of TH has occurred. The available literature supports the use of pre-operative orthopaedic TH to provide patient and provider satisfaction, resulting in decreased wait/travel times and accurate, cost-effective treatment.

EFFECT OF SURGEON AND HOSPITAL FACTORS ON LENGTH OF STAY AFTER COLORECTAL SURGERY

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Introduction: Length of stay (LOS) after colorectal surgery (CRS) is a significant driver of healthcare utilization, costs and adverse patient outcomes. To date, little is known about the impact of the provider on LOS. In this study, we aim to identify the surgeon and hospital factors independently impacting LOS after CRS.

Methods: A retrospective cohort study was conducted, using administrative data, on Ontario CRS patients from 2008-2019. The independent effect of surgeon and hospital factors on LOS was assessed using multivariable regression, accounting for patient, surgery and system-related covariates as well as complications. To minimize unmeasured confounding, planned subgroup analysis was conducted on a cohort of patients undergoing homogeneous surgeries with no complications.

Results: 80,794 patients undergoing CRS were analyzed. Adjusting for the aforementioned covariates and complications, low surgeon volume was associated with increased LOS (RR 1.10 95%CI 1.02-1.18 p=0.009 for lowest quartile compared to highest quartile). In the 20,790 patients undergoing uncomplicated laparoscopic right hemicolectomy or ileostomy reversal, similar effects were seen (RR 1.17 95%CI 1.02-1.33 p=0.021 for lowest surgeon volume quartile compared to the highest quartile). In both models, surgeon years-in-practice (YIP) were associated with increased LOS (RR 1.02 95%CI 1.02-1.03 p<0.0001 for each five YIP).

Conclusion: Low surgeon volume and increasing surgeon years-in-practice displayed strong and consistent independent associations with prolonged LOS. These effects on LOS do not seem to be mediated by an increase in complications. Further standardization of care may minimize this apparently discretionary LOS.

MACHINE LEARNING PREDICTION OF SHOULDER PATIENT AT-HOME PHYSIOTHERAPY

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Hypothesis and Purpose: Physiotherapy is generally accepted as a critical component of the successful rehabilitation of common shoulder injuries. However, adherence to physiotherapy is often poor, especially in the home setting. Our team has developed a Smart Physiotherapy Activity Recognition System (SPARS) in which machine learning (ML) algorithms are trained to recognize physiotherapy exercises from inertial data captured by commercial wrist-worn smart watches. In this research, we validate the SPARS technology on labeled in-clinic patient data and unlabeled at-home patient data. We hypothesize that ML methods are effective for detection (AUROC > 0.95) and classification (accuracy > 90%) of exercises on unlabeled at-home patient exercises.

Methods: Inertial data was acquired from smart watches worn by 42 patients undergoing physiotherapy for symptomatic rotator cuff pathology as they performed physiotherapy exercises. The first stage of the analysis detected labeled in-clinic physiotherapy data from non-physiotherapy data as measured by the Area Under the Receiver Operating Curve (AUROC) metric. We tested a fully convolutional neural network (FCN) classifier with Softmax thresholding, a K-Nearest Neighbour (KNN) distance-based method, and a patient-specific method, where a KNN algorithm is trained on the next-to-last physiotherapy session with deep learning embedding. The second stage of the analysis tested algorithm accuracy for classifying exercises. Lastly, we examined non-physiotherapy activity detection and exercise classification on the unlabeled at-home dataset through qualitative ranking.

Results: A non-physiotherapy activity detection AUROC of 0.988 was achieved on the labeled in-clinic data. The patient-specific support method achieved the highest classification accuracy of 94.1%. Qualitative ranking of unlabeled at-home exercise data reflected the results of the quantitative analysis.

Conclusion: This research has demonstrated that physiotherapy exercises performed by patients at home can be accurately detected and classified by machine learning of inertial data captured by commercial smart watches.

GENETIC DELETION OF CX3CR1 TO IMPROVE SURGICAL OUTCOMES IN DCM

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Degenerative cervical myelopathy (DCM) is the most common form of spinal cord impairment worldwide and entails one or a combination of degenerative changes that compress the spinal cord. As the population ages, DCM is becoming increasingly prevalent and there is an urgent need for effective treatment approaches. Currently, DCM can be treated with surgical decompression (DEC) but functional recovery is limited by ischemia reperfusion injury (IRI), whereby restoration of blood flow perpetuates inflammation, causing activation of microglia and their subsequent release of nitric oxide, pro-inflammatory cytokines and interleukin factors that contribute to cytotoxic cell death. In the central nervous system, the fractalkine receptor CX3CR1 is expressed predominantly by microglia and plays a critical role in modulating neuroinflammation. We hypothesize that CX3CR1 is elevated following DEC and that its inhibition will attenuate inflammation and improve functional recovery. DCM is induced in C57BL/6 wildtype (WT) and CX3CR1-knockout (KO) mice at 8 weeks of age through the insertion of an ossification-inducing polymer under C5-6 that gradually compresses the cord. After 12 weeks of DCM progression, animals will be treated with decompression surgery (DEC) and then sacrificed at one of four time points, 24 hours, 1, 2, or 5 weeks post-DEC (n=20 per group per time). Neurobehavioral assessment of motor and sensory function will begin 4 weeks after DCM induction and will continue weekly until the experimental endpoint. Preliminary data from Western blotting and immunohistochemical analysis of wildtype (WT) samples after DEC indicate significant expression of CX3CR1 and CX3CR1-expressing cells relative to DCM controls ($p<0.05$), suggesting a role for fractalkine signaling in IRI. Determining the role of CX3CR1 in DEC will provide novel insight into the mechanism of DEC IRI and evaluate its inhibition as a therapeutic target. This study investigates a novel, clinically-relevant approach for improving functional recovery in DCM patients and paves the way for further research on IRI and inflammation-focused therapy.

A 3D MODELLING STUDY OF THE INTRAMUSCULAR ARCHITECTURE OF THE BELLIES OF THE FLEXOR DIGITORUM PROFUNDUS: IS THERE ARCHITECTURAL VARIATION?

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Introduction: To date, no studies have quantified 3D morphology/architectural parameters of the digital bellies of flexor digitorum profundus (FDP), both important determinants of relative excursion and force generation capabilities of a muscle. The purpose of this study is to model and quantify in 3D the morphology and architectural parameters of the digital bellies of FDP in situ to compare morphology, and excursion/force generation capabilities between bellies. **Hypothesis:** Each digital belly of FDP has unique architecture and different relative functional capabilities. **Methods**: The fiber bundles/ aponeuroses of the bellies of FDP were serially dissected and digitized (MicroScribe® Digitizer) in 5 embalmed specimens. The skeleton was laser scanned using a FARO® Quantum FaroArm®. The data were reconstructed into 3D models (Autodesk® Maya®). Fiber bundle length (FBL), pennation angle (PA) physiological cross-sectional area (PCSA) were quantified. The 3D morphology and architectural parameters were compared between digital bellies. **Results**: Fiber bundles of each digital belly had a distal attachment to the superficial and deep surfaces of an internal aponeurosis. Architectural parameters varied between the digital bellies. Mean FBL of the 2nd and 4th digital bellies were similar (78.9±18.5mm) and about 17 mm longer than the 3rd belly and 10mm longer than the 5th. The 2nd and 3rd digital bellies had the largest mean PCSA, and the 4th belly the smallest. Mean PA was similar between bellies. **Conclusions**: The relative functional capabilities of the digital bellies vary, with the 2nd digit having the greatest relative excursion and force generating capabilities as evidenced by the largest mean FBL and PCSA. Of the remaining digital bellies, the 4th had the greatest relative excursion capability and the 3rd the largest relative force generating capability. Further in vivo study is needed to document architectural changes during hand movements to enhance our understanding of the role of each FDP belly.

PREOPERATIVE NEUTROPHIL-TO-LYMPHOCYTE RATIO IS PROGNOSTIC FOR EARLY RECURRENCE AFTER INTRAHEPATIC CHOLANGIOCARCINOMA RESECTION

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Hypothesis/Purpose: Recurrence rates of intrahepatic cholangiocarcinoma (iCCA) after curative hepatectomy are as high as 50-70%. In fact, most of the recurrence occurs within two years. This emphasizes the need for biomarkers to detect early recurrence. We hypothesized that preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte-ratio (PLR), and systemic inflammatory index (SII) would be prognostic for early recurrence after iCCA resection. **Methods:** This is a single-centre retrospective cohort study of patients diagnosed with iCCA who had undergone elective hepatectomy at Toronto General Hospital between 2005 and 2017. The cut-off time point for differentiating early versus late recurrence of iCCA was estimated using piecewise linear regression model. This optimal cut-off was then used as the landmark timepoint to separate the analyses into early vs late recurrence time periods in Cox regression analysis with time-dependent covariates. Receiver operator characteristic curve was used to define the cut-off of prognostic biomarkers for early recurrence and re-evaluated with Kaplan-Meier methods. **Results**: 113 patients were included in this study. The optimal time point in differentiating early vs late recurrence was estimated at 12 months. NLR was significantly associated with increased risk of recurrence in the first 12 months [HR 1.4 (CI95% 1.1-1.7)] while PLR and SII were not. After 12 months, neither NLR, PLR, SII was associated with risk of recurrence. In the multivariable model, NLR, tumor size, and underlying cirrhosis remained significant for increased risk of recurrence in the first 12 months [HR 1.3 (CI 1.0-1.6), HR 1.2 (CI 1.1-1.4), HR 4.4 (CI 2.0-9.8), respectively]. Cutoff value for NLR was 3.35 and patients with high NLR (68%) had worse 12-month recurrence prognosis compared to the low NLR group (32%, p=0.01). **Conclusion:** Preoperative NLR, tumour size, and underlying cirrhosis were predictors of recurrence in the first 12-month period after curative iCCA resection. NLR could be a valuable addition to early recurrence risk stratification tools for guiding neoadjuvant or adjuvant therapies.

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IN VIVO PORCINE TENDON RELEASE USING HIGH-INTENSITY FOCUSED ULTRASOUND

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Introduction: Musculotendinous contractures are corrected with surgical resection of tendons. Given current trends towards minimally-invasive procedures, Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) is an ablation technique that provides an incisionless non-invasive treatment for contractures. This translates into less anesthetics and less prophylactic antibiotic use, among other benefits. The hypothesis of this study demonstrates that tendon disruption increases as a function of the amount of energy delivered to pig tendon *in vivo*.

Methods: Pig Achilles tendons (n=28) were each treated with powers of 20W, 30W, 40W and 50W for 30 seconds. Treatment planning and monitoring were achieved using the Achieva 3.0T Philips MRI. Ablation treatment was performed using a V1 Sonalleve (Profound Medical). Tendon disruption was confirmed both audibly during ranging and by comparing the range of motion (ROM) angles of the ankle joint, which the Achilles tendon spans, using goniometry before and after treatment. The changes of ROM angles were measured, and an ANOVA test used to determine statistical significance ($p<0.05$).

Results: Tendon disruption occurred in 2 out of 7 tendons, 6 out of 7 tendons, 7 out of 7 tendons, and 7 out of 7 tendons for 20W, 30W, 40W and 50W respectively. The average angle increase following treatment was 12.14 (SD=8.59), 15.71 (SD=6.72), 27.14 (SD=10.75) and 27.50 (SD=13.32) for 20W, 30W, 40W and 50W respectively with a statistically significant ANOVA test of $p= 0.017$.

Conclusions: Our results demonstrate that MRgFUS ablation disrupt tendons in pigs *in vivo*. With more power delivered to the tendon, the ratio of disruption and the angle of the ankle joint increased.

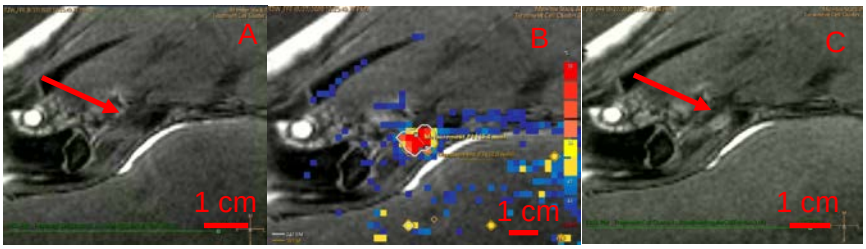

Figure 1: T2-weighted images for treatment of Achilles tendon (arrow) at 40W in the sagittal plane. The pre-treatment image (A), monitoring during treatment (B), and post-treatment image (C) show the change in area of hyperintensity (arrow), which corresponds to edema and successful delivery of FUS ablation onto the tendon.

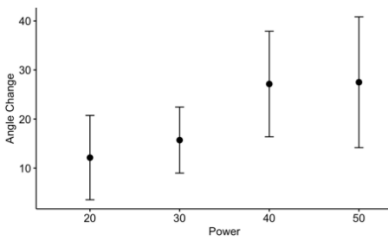

Figure 2: Change in ankle range of motion (ROM) following treatment at 20, 30, 40, and 50W. As power is increased, there is an increase in ROM.

IN-VIVO PORCINE TENDON RELEASE USING HIGH-INTENSITY FOCUSED ULTRASOUND LONG-PULSE HISTOTRIPSY FOLLOWED BY THERMAL ABLATION

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Hypothesis and Purpose: Musculotendinous contracture is the shortening of connective tissue in skeletal muscles causing pain and decreased mobility. This study investigates whether a Magnetic Resonance-guided Focused Ultrasound treatment of long-pulse histotripsy followed by thermal ablation can release tendons to improve lower leg range of motion, while minimizing thermal spread around the focus.

Methods: Treatments were planned using a Philips Achieva 3.0T MRI, performed using a Profound V1 Sonalleve system, and monitored using MR-thermometry. Each Achille's tendon from 20kg Yorkshire pigs received two adjacent treatments consisting of a 60s long-pulse histotripsy sonication (peak negative pressure of 13.5MP at 1.2MHz; DC=1%; PD=0.01s; 12000 pulses per burst) followed by 30s of thermal ablation at 20W (n=5), 30W (n=5) or 40W (n=5). Goniometry measurements assessed lower leg range of motion pre and post treatment.

Results: Tendon disruption was confirmed in 4 out of 5 tendons treated with 20W, and in all tendons treated with 30W and 40W. The average maximum temperature post sonication was 46.5°C±2.7 for 20W, 55°C±4.9 for 30W and 57°C±5.4 for 40W, with statistical significance ($p<0.05$) for 20-30W and 20-40W. Goniometry measurements showed that 20, 30 and 40W treatments increased lower leg range of motion by 5.2°±3.3, 12.0°±8.3, and 32.6°±6.6 with significance ($p<0.05$) for 30-40W and 20-40W. T2-imaging revealed precise lesions at the target.

Conclusion: Long-pulse histotripsy followed by thermal ablation produces precise tissue disruption in porcine tendons. Further work will optimize histotripsy parameters to minimize the thermal spread required for tendon disruption.

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THE USE OF PRIMARY SACROILIAC JOINT FUSION FOR LOWER BACK PAIN DUE TO SACROILIAC JOINT PATHOLOGY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Hypothesis and Purpose: We aimed to quantify the effect of sacroiliac joint fusion (SIJF) on patient reported outcomes in patients with chronic low back pain caused by sacroiliac joint (SIJ) pathology. We hypothesize that SIJF improves SIJ pain and disability.

Methods: This study was conducted according to the PRISMA guidelines. Databases were searched prior to August 18th 2020 involving the treatment of SIJ pathology. Primary outcome measure was the Visual Analogue Scale (VAS) for lower back pain. Secondary outcome measure was the Oswestry Disability Index (ODI). For single arm studies, treatment outcomes were analysed using the pooled mean VAS and ODI scores. For studies comparing SIJF to conservative management (CM), treatment outcomes were analysed using the standardized mean difference (SMD) for VAS and ODI scores.

Results: A total of 558 patients and six studies were included; two randomized controlled trials and four prospective cohort studies. Five out of the six studies were industry funded. Mean pooled VAS scores at baseline was 76.3 [95% confidence interval (CI) 68.4, 84.1] and at 6 month follow-up 31.0 [95% CI 27.9, 34.0]. Mean pooled ODI scores at baseline was 56.7 [95% CI 53.1, 60.2] and at 6 month follow-up was 32.4 [95% CI 30.4, 34.4]. According to VAS scores, the SMD between SIJF and CM at 6 months follow-up was -1.5 [95% CI -1.8, -1.1]. The SMD between SIJF and CM ODI scores at 6 months was -1.1 [95% CI -1.6, -0.5].

Conclusion: SIJF shows potential as a surgical treatment option for SIJ pathology, as improvements in post-operative patient-reported VAS and ODI were shown. However, there is a paucity of independent trials with long term follow-up in this field, therefore definitive conclusions about the efficacy of SIJF are limited. This work supports further exploration into the efficacy of SIJF through multi-centre comparative studies with long term follow-up.

TARGETED THERAPY AND INTRACRANIAL METASTATIC DISEASE: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

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Hypothesis and Purpose: Targeted therapies have been hypothesized to prolong survival in the management of patients with intracranial metastatic disease (IMD), but, paradoxically, to increase IMD incidence by improving systemic disease control and prolonging survival from the primary tumor. The purpose of this study was to assess the impact of targeted therapy and IMD on patient survival.

Methods: This retrospective cohort study included all patients in Ontario, Canada, diagnosed with IMD from 2005 to 2018 with primary diagnoses of lung or bronchus cancer, breast cancer, or melanoma, and primary disease-matched control patients. Kaplan-Meier and multivariable Cox regression analyses were performed to compare overall survival (OS) between patient sub-cohorts divided by primary disease and stratified by targeted therapy receipt or IMD status.

Results: Post-IMD targeted therapy was associated with prolonged OS in patients with HER2-positive breast cancer (HR 0.41; 95% CI, 0.33–0.5), EGFR-positive lung cancer (HR 0.28; 95% CI, 0.23–0.34), and BRAF-positive melanoma (HR 0.2; 95% CI, 0.14–0.29). Presence of IMD was associated with shorter OS in patients with metastatic HER2-positive breast cancer (HR 1.8; 95% CI, 1.56–2.08) and metastatic EGFR-positive lung cancer (HR 1.22; 95% CI, 1.08–1.39) but not metastatic BRAF-positive melanoma (HR 1.11; 95% CI, 0.77–1.61).

Conclusions: Targeted therapies resulted in prolonged OS in patients with IMD in the setting of HER2-positive breast cancer, EGFR-positive lung cancer, and BRAF-positive melanoma. Inclusion of patients with IMD in clinical trials and use of intracranial endpoints will be critical to determine the role of targeted therapies in the management of patients with IMD.

FETAL LUNG VASCULAR DEVELOPMENT IS DISRUPTED BY COMPRESSION IN A NOVEL EX VIVO MODEL OF CONGENITAL DIAPHRAGMATIC HERNIA

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Hypothesis and Purpose: The high morbidity and mortality rates of infants with congenital diaphragmatic hernia (CDH) are related to the degree of pulmonary hypoplasia and severity of pulmonary hypertension secondary to fetal vascular remodeling. We hypothesized that the compression exerted by the herniated organs on the lungs has a detrimental impact on pulmonary vascular development. The aim of the study was to evaluate the effects of mechanical compression on fetal lung vascular development using a novel *ex vivo* model.

Methods: We induced experimental CDH in fetal rats by maternal administration of nitrofen at embryonic day (E)9.5. Dams receiving olive oil at E9.5 served as control. Fetal lungs were harvested at E19.5 and cultured in 10% Matrigel for 24h. Explants were allocated to the following groups: Control, no compression; Control + compression; Nitrofen, no compression; Nitrofen + compression. Mechanical compression was applied to lung explants using a novel static micro-compression system. Factors involved in endothelial cell dysfunction (VEGFA, VEGFR2, PECAM-1) were assessed by RT-qPCR. Statistics: one way-ANOVA (Tukey post-test).

Results: Compared to non-compressed lungs, compressed lungs from both control and nitrofen exposed groups had lower levels of VEGFA ($p=0.024$, control vs. control + compression; $p=0.009$, nitrofen vs. nitrofen + compression), VEGFR2 ($p=0.013$, control vs. control + compression; $p<0.0001$, nitrofen vs. nitrofen + compression) and PECAM-1 ($p=0.003$, control vs. control + compression; $p=0.017$, nitrofen vs. nitrofen + compression).

Conclusion: Our study shows that mechanical compression has detrimental effects on markers that are critical for pulmonary vascular development regardless of nitrofen exposure. Further studies are underway to assess the effects of compression on vessel wall composition.

AUTOMATIC 3D PROSTATE CANCER INDUCED SARCOPENIA SEGMENTATION

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Purpose and Hypothesis: Highly prevalent in cancer patients, sarcopenia is a generalized and progressive loss of skeletal muscle mass, which is strongly correlated with surgical complications and mortality. This study tests the hypothesis that an automated ML-based tool can yield reliable, rapid, sensitive 3D quantification of sarcopenia using routine spinal prostate cancer CT imaging.

Methods: This retrospective study analyzed psoas muscle volume (from L2-L5) in prostate cancer patients from routine CT scans. Ground truth segmentations were created using a semi-automated approach with manual correction. Training was done on 26 volumes (21 unique patients') psoas muscles, and an additional 6 volumes (5 unique patients) were used for validation. A U-Net Convolutional Neural Network (CNN) architecture with additional batch normalization was trained with binary cross-entropy loss for 300 epochs (batch sizes = 6) with intensity augmentation, to segment psoas muscle within an ROI (voxel size=1.15x1.15x2.50mm^3, dimensions=128x128x64). Predicted masks were evaluated using a dice similarity coefficient (DSC).

Results: The model yielded DSCs of89% in the validation set. It took an average of 0.175s to segment the psoas muscle over the L2-L5 region (Nvidia Titan RTX GPU, Intel 9900X CPU). A strong linear relationship was found between the automated 3D and established manual 2D methods (R^2=0.93, $p<0.001$).

Conclusions: This automated ML-based 3D method yielded accuracy, speed and promise for greater sensitivity to initial development of sarcopenia will enable future study of large datasets. Accurate and precise measurement of sarcopenia will allow better disease and treatment monitoring, and allow for better prediction of patient outcomes.

IN VIVO ADMINISTRATION OF EXTRACELLULAR VESICLES DERIVED FROM AMNIOTIC FLUID STEM CELLS IMPROVES LUNG DEVELOPMENT IN EXPERIMENTAL PULMONARY HYPOPLASIA

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Hypothesis and Purpose: Poor outcomes for babies with congenital diaphragmatic hernia (CDH) are due to pulmonary hypoplasia and vascular remodeling. Using experimental CDH models, we showed that lung growth and maturation are restored via the administration of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs). We hypothesised that intra-amniotically (IA) injected AFSC-EVs would also rescue normal lung development. Herein, we aimed to evaluate whether IA injection of AFSC-EVs reaches fetal lungs and rescue lung growth and vascularization in experimental CDH.

Methods: AFSC-EVs were isolated from conditioned medium using ultracentrifugation, and characterized for size, morphology, and expression of canonical marker proteins. To reproduce fetal CDH, nitrofen was administered to rat dams at embryonic day (E) 9.5. At E18.5, we performed an IA injection with 100uL AFSC-EVs stained by ExoGlow™-Vivo or saline (control). Fetal lungs were imaged (IVIS) and harvested at E21.5. Groups were compared for: 1) airway branch density (mean linear intercept, H&E); 2) number of vessels per mm^2 (immunofluorescence); 3) mean wall thickness of 10-60um pulmonary arterioles (H&E).

Results: AFSC-EVs were found in the fetal lung and, compared to saline, restored airway branching density ($p=0.0029$), number of vessels per mm^2 ($p=0.04$) and decreased the mean wall thickness of pulmonary arterioles ($p<0.0001$).

Conclusion: Antenatal administration of AFSC-EVs improves fetal lung development by restoring airway branching and vascularization in experimental CDH. Ours findings demonstrate that AFSC-EV therapy is a promising strategy for the *in utero* regeneration of underdeveloped lungs in babies with CDH.

ID1 EXPRESSION IN GLIOBLASTOMA IS CORRELATED WITH ONE-CARBON MEDIATED PURINE SYNTHESIS

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Hypothesis and Purpose: In previous work, we have shown that inhibitor of DNA-binding-1 (ID1) is a critical regulator of the glioblastoma stem-like state and of glioblastoma tumorigenesis. Studies suggest that one-carbon (1-C) metabolism and de novo purine synthesis are metabolically essential to maintain rapid proliferation of glioma initiating cells. We hypothesized that ID-expressing glioblastoma cells have higher rates of 1-C mediated purine synthesis, and that this metabolic shift is necessary to maintain the stem-like cell phenotype.

Methods: Changes in metabolic programs were studied in ID1-knockout U251 glioblastoma cell lines ($ID1^{-/-}$). Protein expression analysis and mass-spectrometry were used to assess expression and concentration of metabolic enzymes and intermediates. Concomitant treatment with temozolomide (TMZ) and the metabolite AICAR was used to determine if metabolic changes mediate treatment resistance.

Result: The expression of DHFR, MTHFD2, PAICS, and ATIC – enzymes involved in 1-C metabolism and purine synthesis – were significantly reduced in $ID1^{-/-}$ cells. Enzyme expression was also reduced in a dose-dependent manner following chemical inhibition of ID1 with pimozide. The concentration of purine synthesis products IMP, AMP, and GMP were significantly lower in $ID1^{-/-}$ cells, while an accumulation of the AICAR intermediate was observed. Exogenous purine supplementation restored the proliferative capacity of $ID^{-/-}$ cells. Treatment with AICAR sensitized treatment-resistant U251 cells to TMZ.

Conclusion: The data suggest that ID1 expression correlates with an increase in 1-C mediated purine synthesis. As ID1 maintains a less differentiated phenotype in cancer cells and correlates with treatment resistance and recurrence, the metabolic phenotype observed may be a characteristic of less-differentiated glioma initiating cells and may potentially represent a therapeutic target for this cell population.

INDOCYANINE GREEN DISSOLVED IN NON-IONIC COMPUTED TOMOGRAPHY CONTRAST AGENTS ENHANCES SENTINEL LYMPH NODE MAPPING

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Hypothesis and Purpose: Multimodal sentinel lymph node (SLN) mapping combines complementary imaging techniques to improve SLN localization. Indocyanine green (ICG) is a near-infrared (NIR) fluorescent dye used for intraoperative SLN mapping. Integrating computed tomography (CT) would facilitate identification of deep SLNs that are otherwise difficult to localize by ICG alone. We hypothesised that dissolving ICG in CT contrast agents would enable combined CT-NIR SLN mapping.

Methods: Serial dilutions of ICG dissolved in distilled water (DW), serum (S), iohexol (IOX), and iodixanol (IOD) were evaluated *in vitro.* For *in vivo* evaluation, healthy BALB/c mice were injected intradermal into the dorsal hindfoot. Serial CT images (IOX-ICG, IOD-ICG, IOX, IOD) over 30min or serial NIR images (DW-ICG, S-ICG, IOX-ICG, IOD-ICG) over 180min were acquired to assess signal change within draining lymph nodes. For *in vivo* NIR imaging, mice were removed for sacrifice at set intervals to assess *ex vivo* lymph node fluorescence.

Results: IOX-ICG and IOD-ICG had greater fluorescence *in vitro* compared to DW-ICG across all concentrations; S-ICG had similar peak fluorescence, but the optimal concentration range was narrower than with IOX-ICG and IOD-ICG. There was no impact on *in vitro* CT attenuation. *In vivo* CT imaging demonstrated no difference in SLN mapping kinetics. *In vivo* NIR imaging demonstrated greater initial SLN fluorescence intensity with IOX-ICG and IOD-ICG compared to DW-ICG and S-ICG. The staggered *ex vivo* NIR evaluation exhibited significant heterogeneity, although DW-ICG mice generally had lower fluorescence intensity.

Conclusion: ICG dissolved in CT contrast agents enabled CT-guided SLN mapping with improved NIR fluorescence intensity. However, significant *ex vivo* intra-group variability highlights that factors outside agent choice and injection technique affect mapping performance.

OPPORTUNITIES FOR ERROR REDUCTION IN TRAUMA CARE THROUGH SYSTEM-LEVEL INTERVENTIONS: LESSONS LEARNED FROM THE ACS TQIP MORTALITY REPORTING SYSTEM

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Hypothesis and Purpose: The importance of system solutions to overcome human fallibility and prevent medical errors has been recognized as critical for a safer healthcare system. Yet over time rates of preventable deaths have not changed, particularly in trauma care. The American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) developed a mortality reporting system (MRS) to aggregate deaths from > 300 trauma centers. This study evaluates the strategies used by centers to prevent future harm after such deaths.

Methods: Deaths are reported to the MRS if there is an identified opportunity for improvement (OFI), along with a mitigation strategy to avoid recurrence of the error. Using a validated framework and consensus by three independent reviewers, we mapped mitigation strategy effectiveness from person-focused to system-oriented interventions.

Results: Over a 2-year period, 395 deaths were reviewed. 33.7% of mortalities were unanticipated, and frequently occurred following failure to rescue (36.1%). Errors pertained to management (50.9%), clinical performance (54.7%) and communication (56.2%). Human failures were present in 61% of cases. Person-focused strategies like education were common, while more effective system-level strategies were seldom used. In 7% of cases, centers couldn't identify a specific strategy to prevent future harm.

Conclusion: Most strategies to reduce errors in trauma centers focus on changing the performance of providers rather than system-level interventions such as automation, standardization and fail-safe approaches. Centers require additional support to develop more effective mitigation strategies that will prevent recurrent errors and patient harm.

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SENSORY INNERVATION OF THE CERVICAL ZYGAPOPHYSIAL JOINTS C3-C7: IMPLICATIONS FOR IMAGE-GUIDED NERVE BLOCK AND RADIOFREQUENCY ABLATION

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Purpose: The purpose of this cadaveric study was to capture and model in 3D the course of the sensory innervation to C3-C7 cervical zygapophysial joints (CZP) and identify soft and bony tissue landmarks that could be used to localize capsular branches with image-guidance systems. **Hypothesis:** 3D modelling of the innervation of the C3-C7 CZP will enable precise localization of the sensory nerves to inform image-guided nerve block and radiofrequency ablation procedures. **Methods:** Two formalin-embalmed specimens were meticulously dissected. The branches given off the medial branches of C3-C7 posterior rami were serially dissected and digitized (Microscribe® G2X Digitizer) to their termination. Skeletal features were also digitized. The data were used to reconstruct the nerves in 3D using Autodesk® Maya®. The models were used to document the course of the nerves innervating C3-C7 CZP. The relationship of the nerves supplying the CZP capsules to soft and bony tissue landmarks were determined.

Results: The innervation pattern of the CZP varied regionally. C6/C7 zygapophysial joint was innervated by fine branches from C6 and C7 medial branches. C3 to C5 capsular branches formed a nerve plexus lying on the posterior surface of the articular pillar. Landmarks specifically localizing the capsular branches to the CZP include posterior aspect of the articular pillar and deep segmental intermuscular tendons of semispinalis capitis. The posterior intertransversarii can also be used as landmarks.

Conclusion: The results of this 3D pilot study provide the anatomical basis for the development of novel image-guided nerve block and radiofrequency ablation protocols that could enable precise targeting of capsular branches to the CZP.

TRIGEMINAL NEURALGIA IS ASSOCIATED WITH HIPPOCAMPUS DIFFUSIVITY ABNORMALITIES

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Hypothesis and Purpose: Chronic pain patients report changes in cognition and memory, functions associated with the hippocampus. We previously demonstrated that the volume of the hippocampus and its subregions differs in Trigeminal Neuralgia (TN) compared to healthy controls. We hypothesize that hippocampal subregions will demonstrate commensurate diffusion specific abnormalities in TN. To study this, we examine subfield hippocampal microarchitecture in surgically naïve TN patients using Diffusion Weighted Imaging (DWI) derived diffusivity metrics.

Methods: T1-weighted (T1w) images of 18 age and sex matched TN subjects underwent FreeSurfer v7.1.0 segmentation into anatomical substrates. Advanced Normalization Tool (ANTs) v2.3.1 was utilized to co-register T1w and DWI scans and transform hippocampal head, body and tail segmentations into DWI space. FSL v6.0.1 was utilized to extract fractional anisotropy (FA), mean diffusivity (MD), axonal diffusivity (AD) and radial diffusivity (RD) from bilateral whole hippocampi and subregions. Multiple t-comparisons were utilized to determine significance.

Results: TN subjects had significantly reduced FA in bilateral whole hippocampi, with a marked contralateral side reduction, ($p_{contra}<0.001$, $p_{ipsi}=0.014$). TN subjects had significantly lower FA in bilateral hippocampal heads, ($p_{contra}<0.001$, $p_{ipsi}=0.049$). Female TN subjects had significantly lower FA in contralateral whole ($p=0.005$), ipsilateral whole ($p=0.014$) and contralateral head ($p=0.0014$). No significant differences were observed for AD, RD and MD values.

Conclusion: We demonstrated a subregion specific reduction in hippocampal microarchitecture in TN subjects. This abnormal hippocampal architecture may provide a neuroanatomical substrate for cognitive reported by TN patients. Our future works aims to assess the role of pain in abnormal hippocampal diffusion and possible reversal of these abnormalities after surgical pain relief.

PRENATAL COUNSELLING FOR A SUSPECTED CLUBFOOT DIAGNOSIS REDUCES PARENTAL ANXIETY DURING THE CORRECTIVE PHASE OF PONSETI TREATMENT

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Hypothesis and Purpose: Accuracy of prenatal diagnosis of clubfoot during prenatal ultrasound screening is improving. When suspected, some parents are offered prenatal counselling. We aim to determine if counselling for parents of infants with clubfoot reduces parental anxiety regarding their child's diagnosis. We hypothesize that prenatal counselling improves parents' understanding of the condition and treatment thereby reducing anxiety.

Methods: This is a retrospective cohort study with prospectively collected survey data of patients in a clubfoot registry whose parents have completed ≥2 *Parent Experience Surveys* (PES) during their child's Ponseti treatment at a single pediatric hospital between 06/01/2019 and 05/31/2020. The PES is administered at initial consultation(1), completion of casting (2), initiation of bracing(3), transition to nighttime bracing(4), and annually to age 4 years(5). Three groups were compared: parents aware of their child's potential clubfoot prenatally and received counselling (Group A), parents aware of the potential clubfoot but did not receive counselling (Group B), and parents unaware of their child's clubfoot until birth (Group C).

Results: Forty patients met inclusion criteria, with 18 in Group A, 11 in Group B, and 11 in Group C. Anxiety scores in all groups decreased significantly between points 1 and 2 ($p=0.005$) corresponding with lessening anxiety, but the decrease in Group A was significantly greater than in Group B ($p=0.046$). There were no significant decreases in anxiety scores at subsequent time points in any group. Treatment satisfaction scores were high across all groups at all points.

Conclusions: Parental anxiety decreased from initial consultation to the end of Ponseti casting in all groups. The reduction was greatest in parents who received prenatal counselling. We recommend counselling for parents of children with prenatal diagnosis of clubfoot as it may provide needed reassurance in the early phase of treatment.

ENHANCED OUTCOMES AND REDUCED PERIOPERATIVE NEUROLOGICAL COMPLICATIONS IN THE SURGICAL MANAGEMENT OF DEGENERATIVE CERVICAL MYELOPATHY: EXAMINING THE IMPACT OF REMOTE ISCHEMIC PRECONDITIONING

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PURPOSE AND HYPOTHESIS: Degenerative cervical myelopathy (DCM) is caused by progressive compression of the cervical spinal cord. Surgical decompression (DEC), while effective in most cases, results in ischemia reperfusion injury (IRI) and hinders a return to baseline function. Remote ischemic preconditioning (RIPC) is a non-invasive intervention that uses transient ischemia distal to the site of injury to protect the host from ischemic insult. In this study, we posit that RIPC prior to DEC will enhance neurological recovery through the amelioration of DEC-induced IRI.

METHOD: DCM was induced in mice and at 12-weeks they either underwent: 1) RIPC prior to DEC; or 2) DEC alone (n = 50, respectively). Acute (24h post-DEC) and chronic (5wk post-DEC) cohorts were subjected to molecular and Catwalk gait analysis.

RESULTS: Acutely, RIPC resulted in a significant decrease of nearly all proinflammatory markers relative to DEC alone ($p < 0.05$) and markedly reduced astrogliosis. Chronically, RIPC animals significantly outperformed both DEC and DCM groups in nearly all gait metrics and returned to pre-DCM baselines ($p < 0.05$). RNA-seq revealed that RIPC negated the change of thousands of DEC-associated genes and combined with Western blotting we show that RIPC upregulates PPARγ, an inhibitor of STAT3, which is a critical activator of IRI-mediated astrogliosis.

CONCLUSIONS: In conclusion, RIPC when performed prior to DEC, reduces neuroinflammation and confers robust long-term neurological recovery relative to DEC alone. We are currently planning to move into a Phase I/II clinical trial.

PRECLINICAL EVALUATION OF A BEDSIDE IMAGE-GUIDANCE SYSTEM FOR EXTERNAL VENTRICULAR DRAINAGE

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Purpose: External ventricular drainage (EVD) is a life-saving procedure required to drain cerebrospinal fluid from the ventricular system in response to elevated intracranial pressure. Malpositioning of the EVD catheter occurs in up to 45% of standard, freehand EVD procedures. The aim of this study was to evaluate the visualization accuracy of a novel structured-light-based, image-guidance system in a preclinical cadaveric model of EVD catheter placement.

Methods: A pre-interventional computed tomography (CT) scan was acquired on 3 cadaveric heads. A guidewire (simulating the catheter) was inserted as in a clinical EVD procedure (n=6, left and right sides). A 3D-printed button ("Bullseye") was placed over the guidewire on the surface of the scalp and an optical image of the Bullseye and experimental area was captured with a structured-light scanner (Einscan, Shining 3D). The guidewire position was segmented from a post-interventional CT image (actual guidewire position). A virtual model of the Bullseye was aligned with a co-linear representation of the intra-operative guidewire (predicted guidewire position). A series of image registrations aligned the actual and predicted guidewire positions utilizing the pre- and post-interventional CT images, optical image and the virtual Bullseye model (3D Slicer). Angle and offset errors were calculated between predicted and actual guidewire positions. The registration procedure was repeated with optical images that captured distinct cranial features to determine the effect of different anatomy on registration accuracy.

Results: The lowest angle error (1.27 ± 0.38°) and offset error (0.33 ± 0.19 mm) were observed for optical images which included the face & scalp surface surrounding the guidewire entry point.

Conclusion: This novel image-guidance system presents a precise, rapid method to identify EVD positioning. Use of facial features are key to improved accuracy in the registration. Future work will consider workflow automation and clinical implementation.

TRENDS IN LOWER EXTREMITY REVASCULARIZATION AND AMPUTATION FOR PERIPHERAL ARTERIAL DISEASE OVER THE LAST TWO DECADES: A POPULATION-BASED TIME SERIES ANALYSIS

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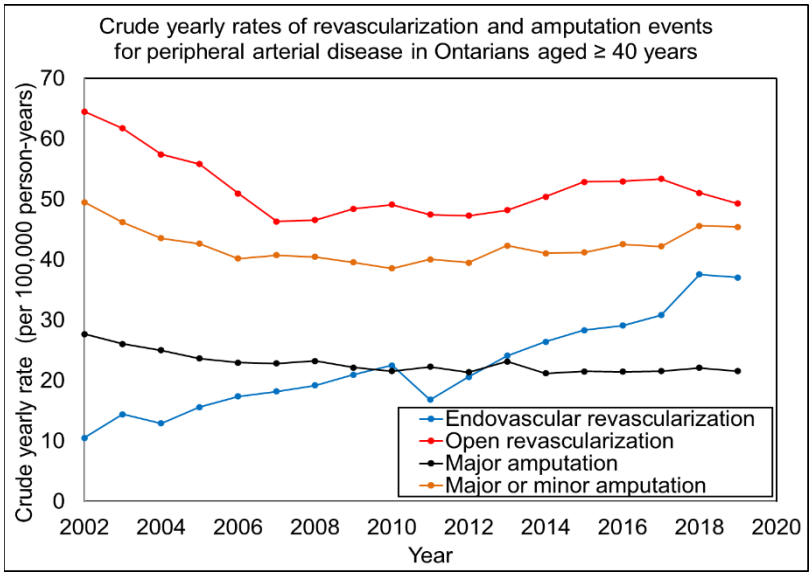
Hypothesis and purpose: While considering changes over time in population demographics and comorbidity, our objective was to describe temporal trends in lower extremity revascularization and amputation for peripheral artery disease (PAD) in Ontario, Canada from 2002 to 2019.

Methods: In this cross-sectional time series analysis of all Ontario residents aged residents ≥40 years between 2002 and 2019, we computed crude annual rates of lower extremity revascularization (endovascular, open) and major amputation for PAD. Annual rates relative to 2002 (RR) adjusted for changes in demographics and comorbidities were estimated using generalized estimating equation models.

Results: The rate of endovascular revascularization increased from 2002 (10.55/100,000 person-years) to 2019 (37.08/100,000 person-years; Adjusted RR=2.79, 95% CI=2.63-2.97). For open revascularization, rates decreased from 2002 (64.53/100,000 person-years) to 2019 (49.27/100,000 person-years; Adjusted RR=0.64, 95%CI=0.62-0.66). The rate of major amputations decreased from 2002 (27.70/100,000 person-years) to 2019 (21.60/100,000 person-years; Adjusted RR=0.56, 95% CI=0.53-0.58).



Conclusions: An increase in revascularization for PAD, driven by an increase in the usage of endovascular modalities, coincides with a decrease in rates of major amputations for PAD.

ADIPOSE-SPECIFIC ATGL ABLATION REDUCES THE PATHOLOGICAL BROWNING OF SUBCUTANEOUS WHITE ADIPOSE TISSUE

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Hypothesis and Purpose: Hypermetabolism following severe burn injuries is associated with adipocyte dysfunction, elevated beige adipocyte formation, and increased energy expenditure. While the phenomenon of pathological white adipose tissue (WAT) browning is well-documented in cachexia and burn models, the molecular mechanisms are essentially unknown. Here, we report that adipose triglyceride lipase (ATGL) plays a central role in burn-induced WAT dysfunction and systemic outcomes.

Methods: This study assessed the physiological relevance of adipose ATGL in burn-induced systemic dysfunction. To do so, adipose-specific ATGL knockout (AKO) and ATGL floxed (WT) mice were subjected to a 30% total body surface area (TBSA) thermal injury and then select biomarkers studied at 1-week post-burn. Atglistatin, an ATGL inhibitor, was administered to determine the therapeutic potential of ATGL targeting.

Results: Targeting adipose-specific ATGL in a murine AKO model resulted in diminished browning, decreased circulating fatty acids, and mitigation of burn-induced hepatomegaly. Furthermore, we demonstrate that the selective ATGL inhibitor atglistatin mimics the AKO results.

Conclusion: Here, we demonstrate the clinical applicability of targeting ATGL post-burn, suggesting a path forward for improving patient outcomes.

AUTOPHAGY IS IMPAIRED IN EXPERIMENTAL CONGENITAL DIAPHRAGMATIC HERNIA LUNGS AND RESTORED BY ADMINISTRATION OF AMNIOTIC FLUID STEM CELL EXTRACELLULAR VESICLES

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Hypothesis and Purpose: We recently reported that administration of amniotic fluid stem cell extracellular vesicles (AFSC-EVs) promotes epithelial cell homeostasis in hypoplastic lungs of fetal rats with congenital diaphragmatic hernia (CDH). We hypothesized that autophagy, a cellular mechanism that is crucial for fetal lung development, is impaired in pulmonary hypoplasia and can be restored with AFSC-EV administration. Herein, we aimed to assess the degree of autophagy at different stages of lung development and to evaluate the impact of AFSC-EVs on each of these timepoints for an eventual clinical translation of this cell-free therapy.

Methods: EVs were isolated from rat AFSC conditioned medium by ultracentrifugation and characterized by size (nanoparticle tracking analysis), morphology (transmission electron microscopy), and expression of canonical markers (Western blot). At embryonic day (E)9.5, dams received nitrofen to induce CDH or olive oil (control). Fetal lungs were harvested at E12.5 (embryonic), E14.5 (pseudoglandular), E17.5 (canalicular) stages, grown as explants for 72h, and treated with medium (control and nitrofen groups) or AFSC-EVs. Groups were compared for autophagy activation (BECN-1, ATG5) and impairment (SQSTM1) levels using qPCR. **Results**: Compared to control, nitrofen lungs had lower levels of BECN-1 and ATG5 at E12.5 ($p=0.04$), E14.5 ($p=0.04$; ATG5, $p=0.02$; BECN-1), and E17.5 ($p=0.04$; BECN-1, $p=0.03$; ATG5). SQSTM1 levels were upregulated in nitrofen lungs at E14.5 ($p=0.01$) and E17.5 ($p=0.04$). AFSC-EV treatment restored autophagy markers ($p=0.04$ at E12.5, $p=0.02$; ATG5, $p=0.04$; BECN-1, $p=0.01$; SQSTM1 at E14.5 and, $p=0.03$; ATG5, $p=0.01$; BECN-1, $p=0.04$ for SQSTM1 at E17.5).

Conclusions: This study demonstrates that lungs of rat fetuses with CDH have impaired autophagy mainly during the pseudoglandular and canalicular stages, and that AFSC-EV administration can effectively rescue the autophagy levels at these timepoints.

NEW METHODS FOR DIAGNOSING ASPIRIN RESISTANCE IN PATIENTS WITH ATHEROSLCEROTID DISEASE

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Hypothesis and Purpose: Between 25-30% of patients are non-sensitive to their 81 mg Aspirin (ASA) therapy and are at a four-fold higher risk of adverse cardiovascular events. In this study we investigated if Platelet Works, a point-of-care platelet function test, could detect ASA non-sensitive patients and we determined the optimal cut-off point (COP) needed to diagnose patients with ASA non-sensitivity. Methods: In the first discovery study, a total of 60 patients were recruited. In order to establish the utility of Platelet Works in detecting ASA sensitivity, we simultaneously evaluated each sample with light transmission aggregometer (LTA), the gold standard for ASA sensitivity testing, in addition to testing with platelet works. ASA non-sensitivity was defined as ≥20% maximal platelet aggregation after induction with arachidonic acid by LTA. For the validation study, a new cohort of 40 patients taking 81 mg of ASA were recruited. These patients were analysed by Platelet Works and LTA to validate the COP determined in the discovery study. Results: In the discovery study, LTA analysis determined that 10 out of the 40 patients were non-sensitive to their 81 mg ASA therapy. Our data from the Platelet Works analysis demonstrated that the non-sensitive patients had 23.44 ± 5.414 percent (95% CI: 11.87 to 35.02, p=0.0006) higher platelet aggregation in response to AA when compared with sensitive patients. After conducting receiver operating characteristics curve analysis, two COPs for ASA non-sensitivity using Platelet Works were chosen based on the Youdin Index (YI). When validating the COPs using platelet aggregation in response to arachidonic acid, we noted a sensitivity and specificity of 91 and 69 percent, respectively. Conclusion: Platelet Works is able to identify ASA non-sensitive patients through a point-of-care test with a good sensitivity and specificity.

ADIPOSE TISSUE AS A CENTRAL REGULATOR OF BURN-INDUCED METABOLIC DYSFUNCTION

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Hypothesis and Purpose: Adipose tissue is a highly plastic and dynamic organ, capable of modulating whole-body energy homeostasis. Harnessing this ability, namely by inducing the activation of brown and beige adipocytes, has become a promising means to combat metabolic disorders. However, under catabolic conditions such as cancer cachexia and severe burns, the chronic activation of beige adipose tissue is thought to be a driving factor in perpetuating the hypermetabolic response. Given that inguinal white adipose tissue (iWAT) has been shown to have a tissue-autonomous influence on systemic metabolism, we sought to determine whether the transplantation of healthy iWAT could improve the catabolic condition in a mouse model of thermal injury. **Methods:** At 7 days post-burn, which burn mice display peak metabolic activity, iWAT from either burn mice inflicted with a 20% total body surface area burn (BB) or healthy controls (BS), was dissected, minced and grafted into the subcutaneous cavity of recipient burn mice. We then compared various metabolic and immune parameters by mass cytometry between groups at 30 days post-burn. **Results:** We show that BS mice were protected against burn-induced hyperphagia, fat loss, glucose intolerance and liver dysfunction displayed by BB mice. Moreover, in the endogenous iWAT, BS showed significant decreases in browning and lipolytic markers and a restored immune profile within the stromal vascular fraction of iWAT in comparison to BB mice, which was overwhelmed with dysfunctional proportion of B cells, T cells and NK cells and macrophages. **Conclusion:** Our data reveals that tissue-autonomous factors from adipose tissue, such as adipokines or resident immune cells, influence the local and systemic environment to improve metabolic dysfunction in thermally injured mice.

RISK OF REVISION SURGERY FOLLOWING CERVICAL DISC REPLACEMENT VS. ANTERIOR CERVICAL DISCECTOMY AND FUSION: POPULATION-BASED COHORT STUDY

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Hypothesis/purpose: In recent years, cervical disc replacement (CDR) has gained popularity for cervical degenerative disorders. The rationale for CDR over anterior cervical discectomy and fusion (ACDF) is preservation of segmental motion and physiological spinal kinematics, which is hoped to delay development of adjacent segment disease and re-operation rates. Superiority of CDR over ACDF in rates of secondary surgeries has not been demonstrated in long-term follow-up. This study compares rate of re-operation in CDR and ACDF for treatment of cervical degenerative disc disease using population-based data for the province of Ontario. **Methods:** A population-based cohort study was conducted using health administrative databases including patients undergoing ACDF or CDR between October 2005 to March 2018. Patients receiving CDR vs. ACDF were identified using physician service claims and hospital discharge abstracts. The primary outcome was revision surgery in the cervical spine defined as an operation more than 30 days after the index procedure. Secondary outcomes were immediate/ acute complications within the first 30 days after the index operation, readmissions and length of hospital stay. Cox proportional hazard models were used to identify predictors of time to revision surgery. Predictors of the binary outcome of an immediate complication within 30 days were estimated using logistic regression. **Results:** 5,207 patients were included. Mean follow-up was 2,728 days for CDR and 2,542 days for ACDF. Among 4,937 ACDF procedures, 7.5% underwent subsequent revision surgery and among 270 CDR procedures, 8.9% had revision surgery. While the study groups did not differ in their risk of revision surgery (adjusted HR 1.20, 95% CI 0.78-1.85), CDR was associated with a lower probability of an acute complication (adjusted OR 0.41, 95% CI 0.21-0.80). Among other factors, multi-level surgery was an independent predictor of acute complication [OR= 1.33 (95% CI 1.06 – 1.66)]. CDR patients experienced shorter mean (±SD) length of hospital stay [1.42 (±0.87) vs. 2.00 ± (3.08) d for ACDF]. **Conclusions:** This study does not demonstrate superiority of CDR over ACDF in revision surgery at the index and/ or adjacent level of the cervical spine for single and multi-level procedures**.** CDR may have an advantage over ACDF in the acute post-operative phase, with a shorter length of hospital stay and lower probability of acute complication.

AD-16 ATTENUATES BRAIN DAMAGE AND NEUROINFLAMMATION IN NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY THROUGH REGULATION OF TREM2 AND MX-1

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Hypoxia-ischemia (HI) brain injury in newborn infants is one of the most common causes of acute mortality and chronic neurologic morbidity worldwide. Neuroinflammation is a prominent feature in HI-related brain injury and plays a substantial role in disease progression.

Hypothesis: Inhibition of neuroinflammation exerts protective effects in HI brain injury *in vivo*.

Purpose: To assess inhibition of neuroinflammation as a potential therapeutic approach by evaluating AD-16, a novel, potent anti-inflammatory compound.

Methods and Results: We investigated the *in vivo* neuroprotective effects in a well-established neonatal hypoxic-ischemic (HI) brain injury model. We showed that a single dosage of AD-16 significantly reduced brain infarction volume and improved neurobehavioral outcomes, with a therapeutic window up to 6 hours after the injury onset. In addition, repeated daily administration of AD-16 significantly reduced the mortality rate of the animals while preserved whole-brain morphology. With Western immunoblots, we found AD-16 attenuated brain injury potentially through the regulation of neuronal survival (PI3K/Akt and MAPK/ERK), apoptotic (caspase-dependent and Bcl-2/Bax) and neuroinflammatory (JaK2/STAT3) signaling. We also reported for the first time that TREM2 and MX-1 are critically involved in mediating the HI-induced neuroinflammation in the neonatal brain.

Conclusion: Our study establishes the role of neuroinflammation in HI injury and suggests that AD-16 has promise as a potential therapeutic prevention and/or treatment for HI and its related brain injury in neonates.

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LONG-TERM FOLLOW-UP REVEALS THE NEED FOR ONGOING NUTRITIONAL MONITORING AND GUIDANCE AFTER PROPHYLACTIC TOTAL GASTRECTOMY

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Hypothesis and Purpose: Individuals harboring a pathogenic cadherin-1 germline mutation have an 80% life-time risk for hereditary diffuse gastric cancer and prophylactic total gastrectomy (PTG) is recommended in young adulthood. We previously demonstrated good recovery of body image and social functioning by one-year post-PTG. Here, we seek to determine the long-term impact of PTG on gastrointestinal function and nutrition, which is not well documented.

Methods: Consecutive patients who underwent PTG between 2009 and 2019 were identified from an institutional database and charts reviewed to determine perioperative (<30 days), early (<1 year) and late (>1 year, up to 7 years) anastomotic and nutritional outcomes.

Results: 31 patients (23 female, 8 male) underwent PTG at a median age of 35 years (range 20-63). Prior to discharge from hospital, all patients received nutritional counselling from a registered dietitian. Median follow-up after PTG was 28 months (IQR 9-48). At 1 year postoperatively, median weight loss was 19% (10-48%) of preoperative weight. Dumping was the most common early and late postoperative complication (42%); 2 (6%) patients transiently required TPN to address resultant nutritional compromise. Esophago-jejunal anastomotic stricture was diagnosed in 10 (33%) patients, and 8 (26%) required a median of 4 (4-9) endoscopic dilatations within the first postoperative year. 4 (13%) patients had persistent problematic dumping and weight loss more than 2 years postoperatively. 2 (6%) required repeat dilatation for anastomotic stricture at 3- and 6-years post-PTG.

Conclusions: The majority of PTG patients were able to maintain acceptable nutritional status despite long-term GI dysfunction. However, these data reveal a need for vigilance regarding anastomotic stricture, dumping and weight loss, even after 2 years post-PTG. Ongoing nutritional guidance and support for these individuals are required.

TICAGRELOR USE AND PRACTICE PATTERN AMONG CARDIAC SURGEONS

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Hypothesis and Purpose: Despite the widespread application of Ticagrelor as an antiplatelet agent in ACS, variability still exists amongst surgeons in its exact clinical utilization. In this study, we probed the knowledge, attitudes, and practices of surgeons in their use of ticagrelor amongst patients with ACS undergoing CABG.

Methods: A survey for surgeons was developed by established content experts, including cardiac surgeons and methodologists. The survey examined domains of knowledge, attitude, and practice patterns in Ticagrelor use.

Results: We received responses from 70 of 70 surgeons (100% response rate). The majority of included surgeons (51%) perform 100-150 CABG procedures each year. 90% of surgeons identified bleeding risk as the most concerning complication amongst patients requiring CABG in the context of ACS, while 10% of those surveyed reported both bleeding and ischemic risk as important considerations. Despite 91% of respondents communicating a willingness to use a ticagrelor reversal agent, 53% of surgeons disclosed a lack of awareness of the existence of such an agent.

Conclusion: Surgeons consider bleeding risk as the most important complication to consider in patients undergoing CABG surgery for ACS. While over half were not aware of a ticagrelor reversal agent, the majority confirmed its potential for use in clinical practice and considered it a major advance. Clinical trials examining the effects of the reversal agent in patients requiring CABG will inform practice.

THE ROLE OF HEDGEHOG SIGNALING IN BASAL-LIKE BREAST CANCER

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Hypothesis and purpose: Basal-like breast cancer (BLBC) is an aggressive breast cancer subtype with poor prognosis and no known targeted therapies. Although cancer research has traditionally focused on cancer cells in isolation, non-malignant cells in the tumor microenvironment (TME) also contribute to the growth and metastasis of cancer[1]. A strong correlation exists between tumor associated macrophage (TAM) infiltration and poor prognosis in BLBC[2]. We hypothesize that the Hedgehog signaling pathway is responsible for not only proliferation and progression of BLBC, but also shaping the TME.

Methods: In a mouse tumor-derived cell line encompassing the loss of BRCA1 and p53 in the presence of k14Cre (termed KBP cells), Hedgehog intracellular signaling components GLI1 and GLI2 were knocked down/inactivated using either siRNA, doxycycline inducible shRNAs, or the GLI1/GLI2 inhibitor GANT61. Proliferation and cancer cell stemness were analyzed *in vitro*. *In vivo,* KBP cells were injected into immunocompetent mice and tumor growth, tumor weight and immune infiltrates were examined in the presence or absence of GANT61.

Results: GANT61 decreased the proliferation of KBP cells ($p = 0.003$) *in vitro*. Knockdown of GLI1 but not GLI2 decreased the number of cancer stem cells (CSCs) using both siRNA ($p = 0.0044$) and inducible shRNAs ($p < 0.001$). As well, inhibition of GLI1 and GLI2 using GANT61 significantly decreased CSCs ($p = 0.001$). *In vivo*, GANT61 treatment of KBP allografts resulted in decreased tumor growth ($p = 0.0422$), tumor volume ($p = 0.0407$), and TAM infiltration ($p = 0.0287$).

Conclusion: Hedgehog signaling components GLI1 and GLI2 are important for BLBC cell proliferation, with GLI1 also important in CSC promotion. Inhibition of GLI1 and GLI2 resulted in decreased tumor growth and inhibited the recruitment of TAMs. Therapies that target GLI1 and GLI2 or downstream signalling could be used as novel treatments for BLBC.

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RELATIONSHIP BETWEEN HEMODYNAMIC INDICES AND ARTERIAL WALL MECHANICAL PROPERTIES IN ASCENDING THORACIC AORTIC ANEURYSMS

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Hypothesis and Purpose: Hemodynamic indices derived from magnetic resonance imaging may be linked to arterial wall mechanical properties in ascending thoracic aortic aneurysms (ATAAs). Determining this relationship may lead to development of novel metrics for ATAA complications.

Methods: Four patients with ATAA underwent pre-operative magnetic resonance angiogram and 4D flow scans. Patient-specific computational fluid dynamic models were then constructed and the maximum time average wall shear stress (TAWSS) and average oscillating shear index (OSI) were recorded for the inner (IC) and outer curvature (OC) of the aorta. Resected IC and OC tissue samples underwent 1) biaxial tensile testing to determine energy loss (ΔUL) (a measure of hysteresis) and elastic modulus (E) in the circumferential and longitudinal directions, and 2) peel testing to determine delamination strength (S_d), a surrogate for aortic dissection risk.

Results: Maximum TAWSS positively correlated with ΔUL_{long} (rs=0.86, p=0.01), but not ΔUL_{circ} (rs=0.61, p=0.15). Maximum TAWSS did not correlate significantly with E_{long} (rs =-0.25, p=0.59), E_{circ} (rs=-0.71, p=0.07), or S_d (rs=-0.57, p=0.18). Average OSI negatively correlated with ΔUL_{long} (rs =-0.75, p=0.05) but not ΔUL_{circ} (rs=-0.50, p=0.25). No significant correlation was found between average OSI and E_{long}(rs=0.11, p=0.82), E_{circ}(rs=0.46, p=0.29), or S_d (rs=0.50, p=0.25).

Conclusion: Increasing maximum TAWSS and decreasing average OSI were found to be associated with increasing arterial wall energy loss for the investigated cohort of patients. These preliminary results provide evidence that hemodynamic indices may provide insight into the health of the arterial wall.

REGIONAL IDENTITY OF NEURAL STEM CELLS IS MAINTAINED THROUGHOUT THE CELL TRANSPLANTATION PROCESS

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PURPOSE: Neural Stem Cell (NSC) transplantation is a promising regenerative strategy to treat spinal cord injury (SCI) by replenishing lost cells and restoring motor/sensory deficits caused by injury. However, NSCs exhibit limited success to treat SCI when the identity of the NSC does not match the site of transplantation in the spinal cord. NSC identity is conferred through the expression of Homeobox (*Hox*) transcription factors, which regulate where the NSCs localize within the brain and spinal cord during development and throughout adulthood. This segmentation process can then promote the formation of appropriate neuronal circuits necessary to perform motor/sensory functions. If identity is maintained in NSCs post-transplantation, this may suggest their developmental role is recapitulated to promote success in all regenerative contexts within the Central Nervous System.

HYPOTHESIS: NSCs from the brain & SC will maintain regionally-specific *Hox* gene expression.

METHODs: Brain and SC-derived NSCs were dissected, expanded, and differentiation in culture, then transplanted into either the adult brain and SC. RT-qPCR and immunohistochemical markers of regional *Hox* markers were be used to confirm NSC identity.

RESULTS: After isolation & transplantation, SC and brain-derived NSCs exhibited region specific *Hox* expression (**SC**: *HoxA4-HoxD10;* **Brain**: Otx2, Emx2), with no overlap is identity-specific *Hox* markers.

CONCLUSIONS: These results will further support that NSCs derived from the brain and spinal cord retain their identity following proliferation and maturation both *in vivo* and *in vitro*. The maintenance of molecular *Hox* expression suggests that this genetic network may contribute to the success of cell-based therapies in the brain and spinal cord.

A SAFE PRE-CLINICAL STRATEGY TO DELIVER CONTINUOUS HIGH-DOSE OF INHALED NITRIC OXIDE *IN VIVO*

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Hypothesis and Purpose: The treatment of respiratory tract infections caused by viruses and resistant bacteria continues to be a major problem in clinical practice. In high doses (>160 ppm), inhaled Nitric Oxide (iNO) has been shown to act as a broad range antimicrobial agent, including its efficacy *in vitro* for the coronavirus family. However, there are still questions around the safe *in vivo* implementation of this therapy. Specifically, the formation of methemoglobin (metHb) and potential lung inflammation are major concerns. We hypothesized that by administrating intravenous (IV) bolus doses of methylene blue (MB) to avoid increasing metHb to toxic levels, we can propose a novel, feasible and efficient protocol for delivering continuous high-dose iNO for an extended period of time and in a safe way. **Methods:** 30kg Yorkshire pigs were anesthetized, intubated, proned, and randomized into two groups: Control (n=5), 6h of standard ventilation (pressure control 15 cmH_2O, PEEP 5, FiO_2 50%, heart rate 15 bpm); Treatment (n=5), standard ventilation + 6h of iNO 160 ppm + bolus (1mg/kg) MB was administered IV whenever metHb was close to 6%. We recorded blood gases and physiologic assessments to monitor lung function and biochemistry to evaluate possible systemic toxicity during the experiments and on the third postoperative day. **Results:** No significant adverse effects in lung function or pulmonary inflammation markers were observed. We maintained safe levels of metHb < 6% by giving MB IV. Nitrogen dioxide (NO_2) was also maintained at safe levels (< 5ppm). No significant changes were observed in coagulation status, urea, creatinine and sensitive enzymes (indicators of liver or kidney function). **Conclusion:** We show for the first time that uninterrupted 6h of high-dose iNO with adjuvant MB is safe and clinically feasible. Our study's main goal was to generate pre-clinical safety data to design early clinical trials in hopes of maximizing this therapy's antimicrobial effect, including against SARS-CoV-2.

NERVE TRANSFER SURGERY: INFORMATION SHARING IN SPINAL CORD INJURY ONLINE COMMUNITIES

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Hypothesis & Purpose: Nerve transfer is a new reconstructive option for improved upper extremity function in cervical spinal cord injury (SCI). This study evaluated the role of social media in information-sharing on nerve transfer surgery within the SCI community.

Methods: Data were collected from Facebook. Searched terms included 'spinal cord injury' and 'SCI'. Within public and private accessed groups, 'nerve', 'transfer', 'nerve transfer', and 'nerve surgery' were searched. Posts about nerve transfer, responses to posts, and comments about nerve transfer in response to unrelated posts were tabulated. Thematic analysis categorized data as seeking information, sharing information, sharing support, or sharing appreciation.

Results: Our search yielded 35 SCI groups (average size=2,007, largest=12,277). Nerve transfer was discussed in 9 groups (577 total mentions). In the seeking information axis, posts were related to personal experience (54%), objective information on nerve transfers (31%), surgeon/center performing the procedure (9%), and second opinion (4%). At least 13% of posts seeking information were from individuals learning about nerve transfers for the first time. In the sharing information axis, the posts: shared personal experience (52%); shared objective information on nerve transfer (13%); described alternative treatment (3%); tagged someone to share information (11%); linked to outside resources (12%); and recommended a specific surgeon/center (9%). We identified that patients wish to learn more on nerve transfer surgery, with a preference for peers' personal experience over objective data. Accuracy of information shared was variable.

Conclusion: Social media is an important source of information and support for people with SCI. There is a paucity of information on nerve transfers. These study findings will inform implementation of future patient education strategies.

TRANSCRIPTIONAL FOOTPRINT OF ISCHEMIA REPERFUSION INJURY AFTER DCM

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Background: Degenerative Cervical Myelopathy (DCM) is a chronic compression on the spinal cord that causes both pathobiological and functional complications. Decompression surgery (DEC) currently is the recommended treatment for this disorder. Although it is mostly useful, 44% of patients still show functional impairments within 6 months post-DEC. We hypothesized that the DEC-related complications are due to the secondary injury to the spinal cord known as Ischemia Reperfusion Injury (IRI), and deciphering IRI cellular mediators can minimize the adverse patient outcomes. **Purpose:** This project has three different aims: the first is to determine whether there is a defined transcriptomic hallmark for IRI after DEC relative to other IRIs. The second is to determine the role of neuroinflammation and specifically reactive astrocytes in mediating DEC-induced IRI. The third is to determine the role of STAT3-mediated astrogliosis on functional recovery after DEC. **Method:** DCM induction was performed on 8-weeks C57BL/6J mice. 12-weeks post-DCM, These animals underwent either DEC or sham surgery. Then, they were sacrificed for acute (24-hours post-DEC) and chronic (5-weeks post-DEC) time-points and were examined for protein and immunohistochemical readouts. The same analyses will also be done for STAT3 knock-out mice to reduce DEC-related behavioral and pathobiological complications. **Results:** By cross-referencing the differentially-expressed genes from our previous RNA-Sequencing data with those found in other IRIs, we found several common astrocytic-expressed genes. This outcome classifies post-DEC complications as an IRI and suggests the critical involvement of astrocytes in this process. Western blotting and immunostaining for astrocytic markers also confirmed the significant increase of astrogliosis in the DEC group relative to DCM. **Conclusion:** This study implicates astrogliosis as a critical mediator of IRI and may suggest STAT3 as a crucial acute therapeutic target for DEC-associated IRI attenuation.

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THE PUBLIC'S PERCEPTION OF SURGICAL TECHNOLOGY AND ROBOTIC SURGERY: A SOCIAL PSYCHOLOGY EXAMINATION

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Purpose and Hypothesis: Robotic surgery was approved for a broad range of procedures with limited compelling evidence demonstrating its benefits. Yet the utilization of robotic surgery has continued to increase over the years, and it is frequently sought out by hospitals, surgeons and patients. We hypothesize that the demand of robotic surgery by the public might be related to the public's perception of robotic surgery. **Methods**: We conducted a cross-sectional survey using a series of questions with an accompanying vignette designed to examine public's perception of robotic surgery and novel surgical technology compared to laparoscopic surgery. Eligible participants were English-speaking participants, 50 years or older, living in Canada or the United States. Participants and were recruited through Amazon Mechanical Turk's system. Participants were randomized to one of two vignettes:1) laparoscopic surgery and a 'novel surgical technology' or 2) laparoscopic surgery and robotic surgery. The vignettes were identical with the novel surgical technology describing robotic surgery without using the term 'robotic'. Outcome of interest was short- and long-term perceived postoperative outcomes and preferences. **Results**: Two groups were comparable in all baseline characteristics. The majority of the responders were male with a median age of 53 years old. Over 70% of the participants income was more than $50,000 USD and more than 55% identified as being white. There were no differences in the distribution of responses or the overall responses between the two surveys. All participants feared robotic and novel surgical technology more than laparoscopic surgery and perceived the surgeons using laparoscopic surgery as best technique. **Conclusion**: Using the term robotic surgery instead of novel surgical technology did not change the public's perception. The public fears post-operative recovery after Robotic surgery more and prefers laparoscopic surgery.

3D ANATOMICAL MODELLING STUDY OF SAPHENOUS NERVE DISTRIBUTION TO INFORM NERVE STIMULATION PROTOCOLS FOR TREATMENT OF OVERACTIVE BLADDER SYNDROME

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Purpose: Percutaneous saphenous nerve (SN) stimulation is an emerging treatment for overactive bladder (OAB) syndrome. The literature consists of descriptive accounts, photographs, and medical images of SN distribution. However, these resources are not adequate to construct high fidelity finite element models to simulate SN stimulation. The purpose is to document and model in 3D the course of the branches of SN relative to bony/soft tissue landmarks to enable assessment of electrode placement for percutaneous SN stimulation. **Hypothesis:** Finite element models constructed from high fidelity 3D data will provide a novel structural framework to optimize electrode placement protocols. **Methods:** The SN along with bony and soft tissue landmarks will be digitized (MicroScribe® G2X) and laser scanned (FARO® Quantum FaroArm®) in four embalmed specimens. The digitized and laser scanned data will be registered and modelled (Autodesk® Maya®). The 3D models will be used to determine optimal stimulation sites and to construct a finite element model of SN stimulation with engineering collaborators. **Results:** SN has an extensive subcutaneous network comprised of the infrapatellar and medial crural cutaneous branches (MCC). The MCC consist of an anterior (AB) and posterior (PB) branch, which further ramify to supply the medial aspect of the leg. The AB gives off multiple smaller branches as it courses distally deep to the great saphenous vein to the foot. Superiorly, AB lies just posterior to the medial border of the tibia and inferiorly, on its medial surface. The PB lies on the crural fascia superficial to the medial head of gastrocnemius and terminates superior to the ankle. **Conclusions:** The novel 3D data is the first providing a cartesian coordinate-based map of the distribution of the AB and PB of the MCC of SN. This high-fidelity data will facilitate more accurate modelling of electrode placement for percutaneous SN stimulation and provide the necessary detail to translate these findings to the clinical setting.

DETERMINING THE MECHANISMS OF TRANSPLANTED OLIGODENDROGENICALLY-BIASED NEURAL PROGENITOR CELLS

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Background: Myelin structure is particularly susceptible to dysregulation after spinal cord injury (SCI), ultimately contributing to impaired signal conductivity in the central nervous system (CNS). Neural progenitor cell (NPC) transplantation represents a potential regenerative approach for promoting remyelination following SCI, however the injury microenvironment predominantly directs NPCs to differentiate into astrocytes as opposed to myelinating oligodendrocytes. Our lab has successfully developed a protocol for priming human NPCs into oligodendrogenically-biased NPCS (oNPCs), which effectively differentiate into a greater ratio of oligodendrocytes. However, a detailed analysis of the mechanisms of these cells post-transplantation has not been conducted to date.

Hypothesis and Purpose: We aim to utilize RNA sequencing approaches in order to determine the mechanisms by which oNPCs promote recovery following SCI. We hypothesize that oNPC transplantation decreases the expression of negative myelin molecules following SCI.

Methods: Female immunodeficient Rowett Nude (RNU) rats were subjected to a cervical SCI, and half of the rats were transplanted with oNPCs 1 week post-injury. The oNPCs were prepared from human NPCs by mimicking oligodendrogenic developmental cues *in vitro*. The animals were sacrificed 9 weeks following injury and RNA was isolated from the injury epicenter for subsequent bulk RNA sequencing and analysis.

Results: It is expected that oNPC transplantation reduces the expression of negative myelin molecules when compared to the non-transplanted control group.

Conclusion: This project will provide us with a greater understanding of oNPC mechanisms, which will help us optimize NPC interventions for SCI in the future.

ENHANCING NEURAL REGENERATION AND LOCOMOTOR RECOVERY WITH NX PEPTIDE ADMINISTRATION IN A CERVICAL SPINAL CORD INJURY (SCI) RAT MODEL

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Background: NX is a peptide derived from a conserved region of sub-commissural organ (SCO)-spondin, a protein proposed to be involved in spinal cord regeneration in vertebrates. NX has demonstrated increased neural growth *in vitro* and exhibits anti-inflammatory properties. **Purpose:** To examine the neuroprotective and regenerative properties of NX in a pre-clinical SCI model, through two main aims. Aim 1: assessing locomotor recovery and bladder function, and aim 2: determining cellular anatomical changes at the lesion site. **Hypothesis:** NX will reduce inflammation, allowing for enhanced neural repair and regeneration at and across the injury site, and improved neurobehavioural recovery. **Method:** Female adult Wistar rats (250-300g) will receive a clip compression-contusion SCI at the C6/C7 level of the spinal cord to model traumatic SCI in humans. 72 injured rats will be randomized into 4 groups, in a blinded manner, to receive one daily dose of either NX (8mg/kg) or vehicle, starting 4 hours (h) or 8 h post-SCI. NX or vehicle will be administered intraperitoneally over 8 weeks. 12 sham rats will only receive a laminectomy with no clip-induced SCI, and vehicle treatment beginning at 4 h post-surgery. Neurobehavioral assessments will be performed at numerous intervals until 8 weeks post-SCI, where animals will be sacrificed for histological and biochemical assessments. **Expected Results:** As heightened inflammation is associated with chronic pain; it is predicted that the anti-inflammatory properties of NX will reduce neuropathic pain. Reduced scar formation and fewer astrocytes near the lesion site are also anticipated, allowing for enhanced neural survival and improved motor function.

Conclusion: Compared to other proposed treatments for SCI, NX provides a multi-faceted approach that mitigates various aspects of SCI. By reducing inflammation and improving regeneration, NX treatment will enhance functional recovery, reduce neuropathic pain, and improve SCI patients' quality of life.

A ROBOTIC MRI-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND NEONATAL NEUROSURGERY PLATFORM: ASSESSMENT OF TARGETING ACCURACY AND PRECISION

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Hypothesis and Purpose: A robotic MRI-guided high-intensity focused ultrasound (MRgHIFU) platform was developed to treat the neonatal brain. This platform positions the transducer above the head of the patient, which eliminates awkward patient positioning while providing a greater treatment area. This study investigates and quantifies the targeting accuracy and precision of the robotic MRgHIFU platform; we hypothesize it will hit an intended target within a distance of 2mm.

Methods: A thermosensitive tissue-mimicking phantom (TTMP), that mimics brain matter, was developed to test the platform's capabilities in a controlled setting. A 3D printed alignment system was fabricated to keep the initial position of the robotic MRgHIFU platform and TTMP consistent. To quantify targeting, a rectangular grid pattern was sonicated within the TTMP, which was monitored by an MR thermometry sequence. Afterwards, the intended target locations were demarcated in the TTMP by inserted carbon fibre rods through a calibration template. Coordinates for each intended (carbon fibre rods) and actual (thermal lesions) targets were derived from T2-weighted MRI scans and their centroid distances were measured in three dimensions. The mean and standard deviation quantified the targeting accuracy and precision respectively.

Results: HIFU ablation resulted in distinct thermal lesions at the sonication points that appeared as discrete hypointense regions in T2-weighted scans. Measuring the distance between intended and actual target points (n=116) yielded a mean difference of [-0.1mm, -1.7mm, 0.0mm] with a standard deviation of [1.2mm, 0.8mm, 0.8mm].

Conclusion: These results demonstrate the robotic MRgHIFU platform's high targeting accuracy and precision in a brain-mimicking phantom, supporting its future neonatal neurosurgical application.

DETERMINATION OF OPTICAL PROPERTIES AND PHOTODYNAMIC THRESHOLD OF LUNG TISSUE FOR TREATMENT PLANNING OF IN VIVO LUNG PERFUSION ASSISTED PHOTODYNAMIC THERAPY

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Hypothesis and Purpose: Isolated lung metastases frequently occur in patients with sarcoma and colorectal carcinoma but are inadequately treated with current standard-of-care treatments. To develop personalized photodynamic therapy (PDT) for lung metastases, knowledge of the optical properties and maximal permissible PDT dose of lung tissue is required. In Vivo Lung Perfusion (IVLP) has been proposed as a platform to deliver targeted treatments. By using low cellular perfusate, IVLP could overcome PDT limitations to treatment volumes by removing hemoglobin, which greatly absorbs light at wavelengths necessary for PDT. This study presents quantification of the optical properties of the normal functioning lung during lung perfusion and the photodynamic threshold values for ALA induced PpIX mediated PDT and Chlorin e6. **Methods:** Porcine and human lungs were placed on an Ex Vivo Lung Perfusion circuit, as a surrogate for IVLP, and perfused with a low cellular perfusate or blood. Isotropic diffusers were placed into the bronchi and on the outside of the lung for light transmission measurements from which the absorption and light scattering properties were calculated at multiple wavelengths. In a second experiment, porcine lung tissue was exposed to increasing radiant exposures and the resultant lesion size was measured by CT and histology to quantify the photodynamic threshold. **Results:** Utilizing low cellular perfusate, resulted in a significant reduction in the absorption of light. The PDT threshold value for normal lung exposed to ALA induced PpIX mediated PDT is lower compared to thresholds reported for various malignancies. Chlorin e6 was undetectable in normal lung tissue and did not demonstrate PDT induced necrosis. **Conclusion:** IVLP, by using low cellular perfusate, allows for greater light penetration which may enable PDT treatment for diffuse metastases. This optical properties and threshold data will provide basis for clinical translation of PDT protocols for lung metastases during IVLP.

TEMPORAL EFFECT OF DOCETAXEL ON TUMOR GROWTH AND BONE QUALITY IN RAT MODEL OF VERTEBRAL METASTASES

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Hypothesis and Purpose: Bone is one of the most common sites of metastasis due to nutrient rich environment. The treatment is often multimodal, requiring systemic treatment in addition to focal therapy. Despite proven clinical efficacy in treating bone metastases, little is known about the impact of docetaxel on bone quality, especially during the metastatic development. This study evaluated the temporal effects of docetaxel on bone metastasis in a pre-clinical animal model.

Methods: Osteolytic (OL) bone metastases were introduced in athymic rats (n=40, 5 groups). Tumour development was evaluated with bioluminescent imaging (BLI) on day (d) 14 and d21 post tumor cell injection. Docetaxel (5mg/kg) was injected (i.v) in the early (d7) or late (d14) stages of metastases. Bone architecture was assessed in L2 vertebrae (μCT), and immunohistochemistry was used to visualize tumour burden in T11 and L5 vertebrae.

Results: Animals with OL metastases showed a significant decrease in body weight that was prevented by early docetaxel treatment (EDT) but not by late docetaxel treatment (LDT). The EDT group showed ($p<0.01$) less tumour burden (BLI and immunohistochemistry) and improved trabecular bone volume fraction compared to both untreated OL and LDT groups. Trabecular number was higher ($p<0.001$) and trabecular spacing was lower ($p<0.001$) in both EDT and LDT groups compared to OL. Despite large tumor burden in the LDT group seen in histology, overall bone histoarchitecture was well preserved with less trabecular damage.

Conclusion: This study showed that early docetaxel treatment prevented large metastases formation and decreased bone loss, while later treatment was not nearly as effective. These findings highlight the importance of early treatment of bone metastases with docetaxel when indicated.

THE ROLE OF EARLY WOUND CONTAMINATION ON DEEP WOUND INFECTIONS IN LUMBOSACRAL FUSIONS

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Hypothesis and purpose: It is unknown if early deep post-operative infection requiring surgical debridement in patients treated with lumbosacral fusion is usually caused by intraoperative or hematogenous contamination or by external inoculation (out-to-in). We hypothesize that the latter is more often responsible and suggest that aggressive dressing protocols could reduce the frequency of debridement surgery.

Methods: We conducted a retrospective review of adult patients treated with lumbosacral fusion between January 2014 and January 2021. Patients were included if they underwent at least 1 surgical debridement for infection or dehiscence. Cases of primary tumor and minimally invasive techniques were excluded.

Results: 363 eligible cases were identified. 14 patients underwent at least 1 debridement (4.1%) for dehiscence or deep infection. Mean BMI was 32.5 (20.7-44.4), surgical time was 369 mins (195-600) and blood loss 1800 mls (250- 4150). The median number of levels fused was 5. 3/14 patients showed no growth, 1 of which sustained durotomy. 2/14 showed S. aureus infection requiring debridement at a mean of 97 days. 9/14 showed infection with intestinal or urogenital pathogens requiring debridement at a mean of 15 days. Infection with intestinal or urogenital pathogens required significantly earlier debridement ($p= 0.03$) than S. aureus and dehiscence ($p= 0.037$).

Conclusion: External contamination was the principal cause of deep wound infection in this series. These present significantly earlier than hematogenous infections. Proximity to the bowel and bladder puts this region at risk. We should focus on barrier dressing and urinary diversion with a foley catheter to keep these pathogens from the wound.

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GLIOBLASTOMA IN ONTARIO: THE IMPACT OF REGIONALIZATION ON CARE DELIVERY AND TRAVEL BURDEN

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Hypothesis and Purpose: Ontario's system for delivery of neuro-oncology care has been historically centralized, at times requiring significant travel on the part of our patients. Toward the goal of patient-centred care and reducing patient burden, two regional cancer centres (RCC) for central nervous system oncology care delivery were introduced in 2016. This study aims to evaluate the impact of regionalization on healthcare utilization and travel burden for the glioblastoma (GBM) population in Ontario. **Methods:** We present travel patterns for a cohort of GBM patients diagnosed between 2010-2019 in Ontario. Patient postal codes were identified using the Ontario Cancer Registry and RCC postal codes were identified through Google Maps. Postal Code Conversion File was used to map locations. Travel times were calculated using the 2016 Census Road Network File and ArcGIS v10.6. We used Ontario's health administrative databases to identify information on receipt of treatment. Analyses were performed using Statistical Analysis Software. **Results**: Within the cohort of 5242 patients, 78.5% received radiation. Receipt of surgery and chemoradiation increased from 52% before 2016 to 63% after 2016. Median travel time to the closest RCC was higher for patients who did not receive radiation than for patients who did (p=0.03). After 2016, the median travel time to treatment RCC decreased (p=.0072). Overall, 65% of patients received care at the closest RCC, increasing from 62% (2010-2015) to 69% (2016-2019). Additional median travel time for patients not receiving care at the closest RCC was 17 minutes (p=.0442). The volume of local patients treated within the new RCC service areas increased from 4% and 6% to 35% and 41%, respectively. **Conclusion**: Regionalization resulted in changes in health care utilization patterns consistent with decreased patient travel burden. Focused regionalization did not come at the cost of decreased quality of care, as determined by delivery of standard of care.

IDENTIFICATION OF FACTORS PREDICTIVE OF BIRD-BEAK CONFIGURATION IN THORACIC ENDOVASCULAR AORTIC REPAIR USING COMPUTATIONAL MODELS

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Hypothesis and Purpose: Lack of proximal stent graft (SG) apposition to the inner curvature of the thoracic aorta during thoracic endovascular aortic repair (TEVAR) results in the formation of a wedge-shaped gap, called a bird-beak configuration (BB). BB can lead to complications such as type Ia endoleaks. The hypothesis is that aortic geometry and tissue properties, landing zone, and SG oversizing contribute to BB formation and size. The purpose of this work is to identify the most significant contributing factors of BB using computational models of TEVAR.

Methods: Five realistic computational models of the aorta with different values of aortic curvature and arch angle, and three commercial SGs with 4%, 12%, and 20% oversizing were developed. SG deployment simulations were performed for eight proximal landing positions along zones 0 to 4. For each simulation, the length and angle of the formed BB were measured.

Results: Using different combinations of parameters, 160 simulations were performed. An inverse correlation was found between the arch angle and BB size. The average BB length and angle per landing zone were largest in zones 0 (10.94 mm) and 2 (17.8°), respectively. Stiffer aortic tissue properties and larger SG oversizing reduced the size of BB. Statistical analysis of two regression models developed for BB length and angle with respect to the simulation parameters showed that the most significant contributors for BB angle were zone, aortic arch angle, and oversizing, and for BB length were zone, oversizing, aortic tissue properties, and aortic arch angle, respectively.

Conclusion: Previous studies have demonstrated direct correlation between BB length and angle with type Ia endoleaks. These results suggest that computational simulations of TEVAR may be useful in identifying patients at risk of BB and type Ia endoleak pre-operatively. Validation of the simulation results will be carried out using patient-specific geometries and clinical information.

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HIGH-INTENSITY HOSPITAL UTILIZATION AMONG ADULTS WITH DIABETIC FOOT ULCERS: POPULATION-BASED STUDY

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Purpose and Hypothesis: Diabetic foot ulcers (DFU) are a common and disabling complication of diabetes, often necessitating lengthy and recurrent hospitalizations. We sought to characterize modifiable determinants of high-intensity hospital care use among adults with DFU.

Methods: Three related case-control studies were conducted using Canada-wide cohorts of adults hospitalized with a DFU, 2011-2015. In Study 1, cases were the top-10% with the highest cumulative acute care hospital costs, and controls were a sample in the bottom-90%. Likewise, DFU cases and controls were those in the top-10% and bottom-90% for cumulative acute care hospital length of stay (LOS) (Study 2), and cumulative number of hospitalizations (Study 3). In each study, various predictor variables were assessed contrasting cases vs. controls. Age- and sex-adjusted excesses in acute care cost (Study 1, in CAD$), LOS (Study 2, in days) and number of hospitalizations (Study 3) were calculated using generalized linear models. **Results:** In Study 1, mean acute care costs among 8971 cases and 3174 controls were $71,757 and $13,687, respectively. Diagnosed sepsis generated the greatest excess mean cost ($38,790, 95% CI: 34,597 - 43,508), followed by chronic kidney disease (CKD) ($30,607, 95% CI: 28,389 - 32,825) and major lower limb amputation ($30,884, 95% CI: 28,613 - 33,155). In Study 2, the mean LOS was higher among the 8477 cases (69 days) than the 3467 controls (12 days). Major amputation generated the greatest adjusted excess in mean LOS of 28 days (95% CI: 27 - 28). In Study 3, there were 3 mean acute care hospitalizations among the 10,341 cases and 1 mean hospitalization among the 5509 controls. Peripheral artery disease (PAD) conferred the greatest excess in mean number of hospitalizations (1.3, 95% CI: 1.2 -1.4). **Conclusion:** Aggressive treatment of CKD and PAD, alongside guideline-based amputation prevention strategies, might reduce the high-intensity hospital care use among adults with DFU.

ENHANCED µCT IMAGING ENABLES HIGH RESOLUTION 3D VISUALIZATION OF MICRODAMAGE IN RAT VERTEBRAE

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Hypothesis and Purpose: Microdamage accumulation in metastatic bone can increase fracture risk. Backscattered electron imaging (BSE) provides very high resolution 2D images of bone with excellent contrast of $BaSO_4$ stained microdamage.[1] It is hypothesized that $BaSO_4$ labeled microdamage in enhanced µCT scans will be spatially correlated to damage in BSE images.

Methods: First lumbar (L1) vertebrae from nine 8-9 week old athymic rats (Hsd:RH-Foxn1rnu, Envigo, IN, USA) (3 healthy, 3 osteolytic, 3 mixed) were mechanically loaded (50N for 3hrs) and stained with $BaSO_4$. Twelve slides from the L1 vertebrae (6 healthy, 3 osteolytic, 3 mixed) were prepared for BSE imaging (2µm/pixel, Philips/FEI). The slides were imaged using µCT (µCT100, Scanco) under varied protocols for high contrast of the $BaSO_4$. The µCT and BSE images were aligned, resampled, registered (affine) and label fields of the $BaSO_4$ were generated. Spatial correlation, *g(r)*, was used to evaluate agreement between damage in the µCT and BSE images.[1] Convolution of the µCT label field (kernel *r=0.02mm*) created an inflated region. The distance between voxels in the two images were considered to be correlated if *g(r)>1*.

Results: Increasing data averaging reduced the grainy texture of the images and trabeculae were more clearly distinguished with low current. The enhanced scan parameters were 90kVp, 44uA, 200ms integration time, 8 data averaging and a 4.9µm voxel size. Spatial correlation (*g(r)=3.88-12.28*) was found between the µCT and BSE images. Examination of the µCT and BSE images shows microdamage that is obscured by noise in standard µCT images (Figure 1). **Conclusion:** Enhancement of µCT scanning parameters allows for rapid high-resolution 3D imaging able to quantify bone microdamage.

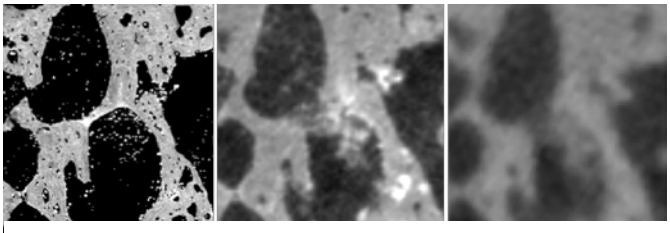

FIGURE 1: $BaSO_4$ labeled microdamage in BSE (left), enhanced µCT (middle) and µCT used in previous microdamage studies[1] (55kVp, 200µA, 7.4µm resolution, 300ms integration time, no averaging) (right).

References: 1. A. Atkins, et al. *Ann. Biomed. Eng.*, vol. 47, no. 4, pp. 980-989, 2019.

USING MACHINE LEARNING TO OPTIMIZE ON CALL SCHEDULING: AN INNOVATIVE WAY TO IMPROVE RESIDENT WELLNESS

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Hypothesis: Machine learning can be used to optimize resident call scheduling.

Purpose: There has been increased attention to excessive resident duty hours (RDH) and their corresponding effects on physician well-being and patient safety. One of the concerns of the RDH is the effect of on call work hours. The purpose of this study was to test a machine learning model to determine variables that drive on call demand and that potentially can be used to optimize call scheduling.

Methods: Daily handover emails of the orthopaedics department at a major academic hospital over a year were collected. A language-processing algorithm was used to extract information regarding numbers of procedures completed, admissions, consults, traumas and spine call duty. A linear regression model was used to determine the variables that influence call demand. Potential reduction capacity was measured by determining the number of "second-call" resident shifts that were not necessary, defined by days when the daily demand was less than 20 hours.

Results: Three variables were demonstrated to significantly influence the call demand: spine call duty, weekday vs. weekend day, and season. Mean winter demand was 22.6 hours (SD 5.9) while summer demand was 25.9 hours (SD 6.4). Mean demand on spine call was 29.9 hours (SD 8.0) and mean demand off spine call was 17.5 hours (SD 3.9). When on spine call, the percentage of days with extra shifts per season was 19.0% in summer and 28.9% in winter. Overall, the number of extra resident shifts was 169 per annum.

Conclusion: Key drivers of resident demand have been identified using a regression model, demonstrating significant potential for optimization. If this model is applied city-wide, it would reduce the number of resident shifts per year by 507 days, which can significantly impact resident well-being while maintaining patient care.

A MOTION COMPENSATION ALGORITHM TO IMPROVE THERMOMETRY DURING MRgHIFU CONTROLLED HYPERTHERMIA

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Hypothesis and Purpose. Magnetic resonance guided high intensity focused ultrasound (MRgHIFU) can deliver hyperthermia for localized thermosensitive liposomal doxorubicin (TLD) release. Proteus is a custom hyperthermia software platform that modulates sonication to maintain steady hyperthermia. Motion artifacts can confound temperature measurements in MR thermometry. The objective of this work is to demonstrate that a motion compensation algorithm can negate motion artifacts from thermometry images obtained from a hyperthermia treatment.

Methods. An immunocompetent mouse (n=1) with hindlimb sarcoma received hyperthermia treatment for 20 min with TLD using the small-animal Bruker 7T MRI and IGT HIFU system. Proteus monitored a selected region of interest (ROI) to maintain a temperature of 40.5°C. The motion compensation algorithm used was a hybrid of principal component analysis and projection onto dipole fields (PCA-PDF) and was applied retrospectively.

Results. Proteus maintained an average ROI temperature of 40 ± 1.6°C and post-processing with the algorithm gave an average ROI temperature of 39 ± 3.5°C.

Conclusion. The PCA-PDF algorithm demonstrates its potential to improve temperature mapping accuracy in a MRgHIFU system for hyperthermia treatments in a murine model.

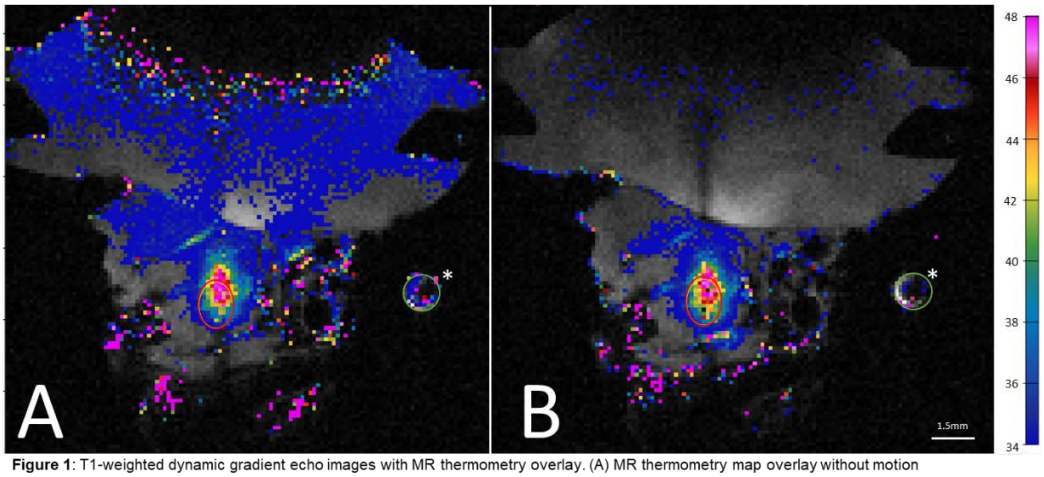

Figure 1: T1-weighted dynamic gradient echo images with MR thermometry overlay. (A) MR thermometry map overlay without motion compensation. (B) Retroactive motion artifact adjustment by the PCA-PDF algorithm at the same time point during hyperthermia treatment. ROI (ellipsoid) indicates the area being monitored by Proteus. Drift tube with a second ROI (*) measures any MR bore temperature shift over time.

RETROSPECTIVE MULTI-INSTITUTIONAL OBSERVATIONAL COHORT STUDY ON PREDICTORS OF SEIZURE REDUCTION FOLLOWING VAGUS NERVE STIMULATION

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PURPOSE: Vagus nerve stimulation (VNS) is a neuromodulation therapy that can modulate cortical excitability and reduce the severity of frequency of seizure in children with intractable epilepsy. Despite the widespread use of VNS, there is currently limited understanding to pre-operatively identify children who will benefit from VNS implantation. The purpose of this study is to retrospectively identify clinical and neural networked-based correlates of seizure reduction to better identify potential VNS responders.

METHODS: Data were gathered from patients (age ≤ 20) who have received VNS at four pediatric institutions: Hospital of Sick Children in Toronto, Nicklaus Children's Hospital in Miami, St. Louis Children's Hospital, and Texas Children's Hospital. The primary outcome was VNS response, defined as seizure frequency with a relative ≥ 50% decrease from baseline of all seizure types. Univariate and multivariate mixed-effects logistic regression stratified by institution was used to assess the relationship between predictors and main seizure reduction.

RESULTS: Across the four institutions, 564 patients were eligible for inclusion. The mean age of VNS insertion was 11.1 +/- 4.8 and 61.1% of the patients were male. The odds of being a VNS responder were decreased by two identified predictors: the presence of generalized onset of seizure (OR 0.39, 95% CI 0.17 – 0.88, p = 0.02) and previous epilepsy surgery (OR 0.43, 95% CI 0.21 – 0.87, p = 0.02).

CONCLUSION: This is the largest retrospective analysis of possible predictors of VNS effectiveness. Findings suggest that VNS response is less likely if a patient's seizure present with a generalized onset or have previously been treated with surgery. In the absence of randomized control trials, it is important to use observational data to guide management of children with intractable epilepsy.

MECHANICAL ACTIVATION DETERMINES FATE OF MESENCHYMAL STROMAL CELLS THROUGH EPIGENETICS MECHANISMS

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Hypothesis and Purpose: Mechanically imprinted myofibroblast memory of MSCs is preserved by DNA methylation. We aim to engineer MSCs with higher resistance to environment-induced fibrogenesis and thus, higher regenerative potential using manipulating epigenetics modifier.

Background*:* Patient-derived mesenchymal stromal cells (MSCs) are considered as cell therapy to accelerate the healing process of severe wounds (e.g., burns). However, during expansion on stiff cell culture materials, MSCs lose regenerative potential and develop a pro-fibrotic phenotype. Our lab revealed that prolonged culture ('priming') on tissue-soft substrates not only prevents acute MF activation but also imprints lasting 'mechanical memory'. We previously identified miR-21 as one factor preserving the mechanical memory and we will now explore if the mechanical priming induces even more stable epigenetic changes including DNA methyl transferases.

Methods: After priming rat bone-marrow-derived MSCs on substrates with the defined stiffness (soft versus stiff), we analyzed changes in DNMT expression and global DNA methylation. To explore the role of DNMTs in mechanical memory, the DNMTs activity was analyzed after transferring soft-primed MSCs to stiff environment and vice versa. Global chromatin states (compactness) were assessed by immunofluorescence imaging in the nucleus.

Results: Correlating with enhanced expression of the myofibroblast marker α-SMA, expression of DNMT3a increased upon stiff priming of MSCs, which persists even after switching to new environment. Concomitantly, global DNA methylation was higher and chromatin compactness was lower in stiff- compared to soft-primed MSCs. This suggests that higher DNA methylation in stiff-primed MSCs is preserved by DNMT3a.

Conclusions: Mechanical cues modulate the DNMT3a expression. We are currently studying how DNMT3a plays a role in mechanically induced memory of MSCs.

THE APPLICATION OF INTRATHECAL KCC2 GENE THERAPY IN TRAUMATIC SPINAL CORD INJURY

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Hypothesis: Traumatic spinal cord injury (SCI) impairs local neuronal conductance and induces a subsequent synaptic remodeling cascade in the rostro-caudal perilesional zone. K^+/Cl^- cotransporter 2 (KCC2) is a differentially expressed synaptic ligand-gated channel, which is pivotal for signal propagation in inhibitory spinal interneurons. Reduced KCC2 expression post-SCI disrupts the excitatory/inhibitory (E/I) ratio in the preserved spinal interneurons and blocks the relay of signals in the injured spinal cord. Gene therapy is a promising technique to alter the transcriptional profile of a cell, and recent advances in clinical translatability of adeno-associated virus 9 (AAV9) enables therapeutic KCC2 upregulation in the injured spinal cord. **Purpose**: The objectives of this study are to characterize KCC2 expression following traumatic cervical SCI and to examine the ability of gene therapy to induce KCC2 in a clinically relevant cervical SCI rodent model. **Methods**: AAV9s were injected to the injured rats via intrathecal administration. The rats were sacrificed 7 days following injection. The extracted spinal cords were prepared for transcriptional, histological, and protein analyses. **Results**: The results validate the early downregulation of KCC2 following clip-compression injury at both transcriptional and protein levels. The results also demonstrate the ability of intrathecal AAV9 administration to induce KCC2 expression in the preserved neural tissue without any deleterious off-target effects. **Conclusion**: This study validates the downregulation of KCC2 following clip-compression injury and demonstrate the efficacy of intrathecal AAV9 administration to induce KCC2 expression. Future optimization of AAV9 delivery to the injured spinal cord would further improve the therapeutic potency of KCC2 upregulation following traumatic cervical SCI.

INTERLEUKIN-6 BLOCKADE, A POTENTIAL ADJUNCT THERAPY FOR POST-BURN HYPERMETABOLISM

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Hypothesis and Purpose Severe burns remain a leading cause of death and disability worldwide. Despite advances in patient care, the profound hypermetabolic stress response induced by this trauma inevitably affects every organ system causing substantial morbidity and mortality. Recent evidence suggests interleukin-6 (IL-6) is a major culprit underlying post-burn hypermetabolism. Thus, pharmacological blockade of IL-6 may be a more favorable treatment option to fully restore metabolic function after injury. Here, we investigated the safety and effectiveness of blocking IL-6 for post-burn hypermetabolism using a validated anti-IL-6 monoclonal antibody (mAb) in our experimental murine model.

Methods: Adult C57BL/6 mice received a full-thickness scald burn and/or daily intraperitoneal injections of anti-IL-6 mAb (50 mg/Kg). The adipose, liver, and dorsal skin tissue were harvested on day 7 and 14 post-burn for histological analysis. Gene expression was analyzed via RT-PCR.

Results: Daily anti-IL-6 mAb administration protects against burn-induced weight loss ($p<0.0001$) without any adverse effect on mortality. At the organ level, post-burn treatment with the IL-6 blocker suppressed the thermogenic activation of adipose tissue ($p<0.01$) and its associated wasting ($p<0.05$). The reduction of browning-induced lipolysis ($p<0.0001$) indirectly decreased hepatic lipotoxicity ($p<0.01$) which improved liver dysfunction ($p<0.05$). Importantly, the beneficial effects of this anti-IL-6 agent extended to the skin, reflected by the decrease in excessive collagen deposition ($p<0.001$) and genes involved in pathologic fibrosis and scarring ($p<0.05$).

Conclusion: Collectively, we show that post-burn IL-6 blockade leads to significant improvements in systemic hypermetabolism by inhibiting pathological alterations in key immunometabolic organs. These findings support the therapeutic potential of anti-IL-6 interventions to improve care, quality of life and survival in burned patients.

UTILITY-BASED HEALTH RELATED QUALITY OF LIFE FOR CLEFT LIP AND PALATE FROM THE PATIENT AND SOCIETAL PERSPECTIVE: TWO CROSS-SECTIONAL STUDIES IN ETHIOPIA

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Purpose: Ethiopia has a population of over 112 million people with an estimated 1 in 672 born with cleft lip and/or palate (CLP). Yet, Ethiopia has only two multidisciplinary CLP centers. Utilities are a specific measure of health-related quality of life (HRQoL) used in economic evaluations which can help address systemic inequities. This study aims to assess the effect of CLP surgery on utility-based HRQoL from the patient and societal perspectives in Ethiopia.

Methods: Two cross-sectional studies, one from the patient-proxy perspective, and one from the societal perspective, were conducted in parallel within the capital of Ethiopia, between July 2019 and January 2020, to assess if treatment is associated with a statistically significant change in utility-based HRQoL. Standardized interviews for visual analogue scale (VAS), time trade-off (TTO), and standard gamble (SG) were conducted for both groups to measure utility-based HRQoL. Multivariate regression analyses assessed the effect of treatment on HRQoL after adjusting for pre-specified confounders.

Results: 304 patient-proxies and 130 societal participants were included. Patient-proxies reported a better VAS with treatment ($p=0.0001$) after adjusting for income ($p=0.02$) and cleft type ($p<0.05$), and a better TTO ($p=0.005$) after adjusting for income ($p=0.02$) and religion ($p=0.006$). Societal participants reported a statistically significant improvement in HRQoL with treated vignettes after adjusting for cleft type, income and sex in VAS, TTO and SG ($p<0.0001$).

Conclusion: This is the first study to assess utility-based HRQoL for a surgical disease in a low-resource setting. Surgery is statistically associated with a better HRQoL compared to no treatment. The application of utilities in economic evaluations can improve surgical access for children with CLP in Ethiopia and similar settings worldwide.

CLINICAL FEATURES AND OUTCOMES OF TRUNCAL VALVE REPAIR IN NONE-MILD VERSUS MODERATE-SEVERE TRUNCAL VALVE INSUFFICIENCY: A SINGLE INSTITUTION'S CASE-CONTROL STUDY SINCE 2000

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Purpose: To investigate the functional and survival outcomes of common arterial trunk (CAT) intervention in patients based on truncal valve insufficiency (TVI) severity. **Methods:** In this single-center retrospective matched case-control study, 16 consecutive CAT patients from 2000- 2018 with moderate to severe truncal valve regurgitation (TVR2-3) undergoing primary CAT surgery with truncal valve (TrV) repair were matched to 16 CAT patients with none to mild truncal valve regurgitation (TVR1-0). Survival, reintervention, biventricular function, and functional health status were comparatively analyzed by signed-rank, McNemar's and McNemar-Bowker tests. **Results:** Only one patient in the TVR1-0 required truncal valve (TrV) repair, for which complete adaption reduced the quadleaflet valve to trileaflet. In TVR2-3, 9 (56%) patients underwent complete adaptation to combine cusps, 4 (25%) received partial adaptation with commissuroplasty, and one patient (6%) had cusp thinning with annuloplasty. There was no significant difference between requirement of postoperative ECMO, ICU length of stay, and morality at median follow-up of 9.17 (1.40 – 15.12) years. Rate of subsequent TrV repair or replacement at 10 years postoperative was 8% (n = 1) and 67% (n = 11) for TVR0-1 and TVR2-3, respectively (p = 0.005). Incidence of interventional right heart catheterization at 10 years was 64.0% (n = 10) for TVR0-1 and 52.1% (n = 8) for TVR2-3 (p = 0.058). At discharge and latest follow-up, both groups reported comparable modified ROSS score and left ventricular ejection fraction. **Conclusion:** Irrespective of baseline TVI severity, complete repair of CAT can achieve reasonably low mortality. Multiple reinterventions are required for management of chronic TVI, without compromising long-term survival.

EVALUATION OF A NOVEL MEDICAL DEVICE FOR EARLY DETECTION OF ANASTOMOTIC LEAK

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Hypothesis & Purpose: Anastomotic leaks (AL) is a devastating consequence of gastrointestinal surgery, with a significant effect on morbidity and mortality. Early detection of AL remains a challenge despite a plethora of prediction. Accordingly, we evaluated a novel device ('NERv') for detecting changes in pH of drain effluent for the use of detecting AL in a porcine model.

Methods: Sus scrofa pigs were used in this study. Through a laparotomy, gastric and intraperitoneal fluid samples were obtained. A Jackson-Pratt (JP) drain was inserted into left paracolic gutter, as well as a secondary exteriorized catheter. A gastric leak was simulated by injecting 5cc of gastric fluid through the secondary catheter. The JP drain collected the effluent, which was measured in real-time by the connected NERv device.

Results: The NERv device measured an average trough pH of 6.99 $\pm$ 0.23 following leak simulation, significantly different than the physiologic fluid pH of 7.5 ($p<0.01$). This trough was seen an average of 3.6 $\pm$ 0.9 minutes following the injection of gastric fluid. This is compared the data seen in the control pig with physiologic fluid only, and there was minimal variability in pH. Multiple iterations and controls produced consistent, replicable data.

Discussion: This study demonstrates that the novel NERv device can accurately detect gastric AL in a simplified model. Its use does not alter current medical practice, being in-line with an existing para-anastomotic JP drain, and therefore has a lower barrier to adoption. However, it is a limited proof-of-concept study, and so additional experiments are required – particularly looking at intraluminal fluids with a more neutral pH, as well as a small, slow AL. Overall, this study has validated the potential applications of the NERv device and justifies its further investigation.

PORPHYSOME NANOPARTICLES ARE EFFECTIVE PHOTOSENSITIZERS FOR PHOTODYNAMIC THERAPY TREATMENT FOR CANCER

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Background: Photodynamic therapy (PDT) uses the excitation of photosensitizers with light to produce reactive oxygen species, which then cause cell death and tissue necrosis through a variety of mechanisms. Nanoparticles, like the “porphysome” (PS), inherently localize to tumours due to their size, and are attractive mechanisms to selectively deliver photosensitizers to tumours for ablation. The aim of this study was to determine whether or not PSs are viable photosensitizers for PDT ablation of tumours. **Methods**: Athymic nude mice bearing subcutaneous tumours of A549 cells on the right shoulder were enrolled when tumours reached 5 mm in maximum dimension. Animals were randomized into treatment groups: PDT with porphysome at various doses, drug-only and no drug negative controls, and positive controls using Photofrin (PHO) PDT (a clinically approved PDT agent). After treatment, animals were followed with volumetric tumour measurement and weight measurement three times per week for a total of 30 days post-treatment. **Results**: All PS doses demonstrated a significant tumour ablative effect compared to groups not receiving laser treatment; however, the greatest effect was seen in the 10 mg/kg PS group at a drug-light interval of 24 hours, with a cure rate of 67%. Negative control groups (both PS and PHO drug-only, and no drug no light groups) demonstrated uncontrolled tumour growth requiring sacrifice prior to the 30-day endpoint as tumours reached an *a priori* maximum volume. Direct comparison of PHO 5 mg/kg and PS 10 mg/kg demonstrated similar tumour growth suppression (MANOVA $p>0.05$), which was significantly different from the uncontrolled tumour growth seen in the untreated control groups. Complete cure was not different between PHO and PS treatment groups (15% vs. 25%, $p=0.52$). **Conclusion**: Porphysome nanoparticles are effective PDT agents with comparable efficacy to currently approved photosensitizers. Unlike existing therapies, porphysomes have the potential for multimodal diagnostic and therapeutic applications and may be the first single agent capable of both PDT and photothermal therapy.

PRIMARY CARE FOLLOW-UP IMPROVES OUTCOMES IN OLDER ADULTS FOLLOWING EMERGENCY GENERAL SURGERY ADMISSION

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Hypothesis & Purpose: While pre-operative optimization improves outcomes for older adults undergoing major elective surgery, no such optimization is possible in the emergent setting. Instead, surgeons must find post-operative interventions to improve outcomes among older emergency general surgery (EGS) patients. We hypothesized that post-discharge follow-up with an older adult's usual primary care physician (PCP) following EGS admission is associated with reduced 1-year mortality and nursing home admission compared to no such follow-up. **Methods:** This was a population-based retrospective cohort study of administrative data in Ontario (2006-2018). We evaluated all older adults (≥65 years) admitted to hospital for one of eight EGS conditions ranging from appendicitis to perforated viscus. Our main exposure was follow-up in the 14 days following discharge with the patient's usual PCP compared to no PCP follow-up. The primary outcome was days from discharge to nursing home admission or death, analyzed using a Cox proportional hazards model to adjust for known confounders. **Results:** Among 76,568 older adults admitted for an EGS condition, in the 14 days following discharge 32,087 (41.9%) were seen by their usual PCP. A total of 9,571 (12.5%) were admitted to a nursing home or died within 1 year. Usual PCP follow-up was associated with a significantly lower risk of nursing home admission or death compared to no PCP follow-up (HR 0.87, 95% CI 0.84–0.91). This effect was robust to different specifications of our risk-adjustment model. **Conclusion:** While frequently recommended to patients at discharge, greater effort should be taken during discharge planning to ensure that barriers to PCP follow-up are minimized. Surgical programs should create structures and processes of care to ensure that such follow-up is routinely arranged as part of ongoing efforts to provide senior-friendly surgical care.

THE SURVIVABLE ISCHEMIC PERIOD OPTIMIZING THE DONATION AFTER CIRCULATORY DEATH HEART MODEL USING THE NOVEL EX-VIVO HEART PERFUSION IN RATS

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Hypothesis: Donation after circulatory death (DCD) heart model with the optimal ischemic time can give high discriminability to further interventions using the model.

Purpose: We sought the optimal ischemic period for the DCD heart model in rats.

Methods: DCD hearts with different ischemic time: 0 (n=8), 15 (n=7), 30 (n=7), 45 (n=10), and 60 minutes (n=5), were used. After the designated ischemic period, the heart was harvested and then connected to the ex-vivo heart perfusion. Coronary reperfusion was maintained for 2 hours while cardiac function was monitored as maximum first derivative of left ventricular pressure (max+dp/dt) by using the intraventricular balloon technique. Blood gas analysis and western blotting were performed and analyzed by one-way ANOVA with Bonferroni post-hoc test.

Results: The group of 45 min ischemia showed significantly lower max+dp/dt and arterial lactate level than the group of 30 min ischemia ($p=0.03$, <0.0001, respectively), suggesting a theory that energy production was compensated and maximized by glycolysis added to impaired glucose oxidation in the group of 30 min ischemia, but this compensation was collapsed for the hearts with longer ischemia than 30 min which also accompanied with lower Akt phosphorylation.

Conclusion: DCD hearts with 45 min of ischemia demonstrated deterioration crossing over the point of no return from the view of hemodynamic, metabolic, and cellular functions ahead of other groups with shorter ischemia. Therefore, 45 min of ischemia is the optimal period for the DCD heart model with the highest discriminability to differentiate effects of further interventions as an ideal experimental model.

DEVELOPMENT AND TESTING OF A NOVEL ENDOVASCULAR TREATMENT FOR NEUROVASCULAR DISEASES USING PHOTO-MODULATED HYDROGEL EMBOLIZATION

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Hypothesis and Purpose: The goal of this project was to develop a novel embolization agent and delivery strategy using hydrogels, to address the limitations surrounding current embolization agents. It was hypothesized that this may improve the endovascular treatment for diseases including cerebral aneurysms, arterio-venous malformations, and tumours.

Methods: We compounded hydrogel formulations and preliminarily tested embolization in several acute animal model, including blood vessels of various sizes, an arterial-arterial network known as the rete mirabile, and in elastase-created saccular aneurysms.

Results: The hydrogels were designed to be low-viscosity, shear-thinning, photo-sensitive, and radio-opaque. We developed a method of intravascular microcatheter hydrogel delivery with dynamic modulation at the tip of the intravascular microcatheter, via photo-crosslinking using an adjustable integrated optical fibre. In a swine mode (n=3), the renal arterial tree, rete mirabile, and large to medium blood vessels were embolized successfully. In the rabbit saccular aneurysm model (n=2), hydrogel embolization was successful in one case, with hydrogel leakage out of the aneurysm into the downstream circulation in the second case.

Conclusions: We demonstrated a novel method of dynamic photomodulation and delivery of bioengineered hydrogels to address current limitations of endovascular embolization therapies. This method showed promise in successfully treating various neurovascular conditions, as seen in the proof-of-concept animal studies. The possibility of improving endovascular treatment in these pathologies with this novel strategy should be investigated further with direct comparative studies and longer-term animal trials.

GENDER DIFFERENCES IN FACULTY RANK AMONG ACADEMIC PHYSICIANS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: Many studies have examined gender inequity in academic medicine. However, no comprehensive synthesis of the literature has been performed. We conducted a systematic review and meta-analysis of gender differences in faculty rank among academic physicians. **Methods:** MEDLINE, Embase, Cochrane CENTRAL, ERIC, and PsycINFO were searched from inception to July 3, 2020. All original studies reporting faculty rank stratified by gender were included. Study screening, data extraction, and quality assessment were performed by two independent reviewers, with a third author resolving discrepancies. Meta-analysis was conducted using random-effects models. **Results:** Our search yielded 5,897 articles. Overall, 218 studies were included with 991,207 academic physician data points. Men were 2.77 times more likely to be full professors (OR 2.77, 95% CI 2.57-2.98). Although men practiced for longer (median 18 vs. 12 years, $p < .00002$), the gender gap remained after pooling 7 studies that adjusted for factors including time in practice, specialty, publications, h-index, additional PhD, and institution (adjusted OR 1.83, 95% CI 1.04-3.20). Meta-regression demonstrated improvement over time ($p = .0011$), however, subgroup analysis showed that gender disparities remain significant in the 2010-2020 decade (OR 2.63, 95% CI 2.48-2.80). The gender gap was present across all specialties and both within and outside of North America. Men published more papers (mean difference 17.2, 95% CI 14.7-19.7), earned higher salaries (mean difference $33,256, 95% CI $25,969-$40,542), and were more likely to be departmental chairs (OR 2.61, 95% CI 2.19-3.12). **Conclusions:** Gender inequity in academic medicine exists across all specialties, geographic regions, and multiple measures of success, including academic rank, publications, salary, and leadership. Men are more likely than women to be full professors after controlling for experience, academic productivity, and specialty.

OUTCOMES OF PEDIATRIC SEPTIC ARTHRITIS PATIENTS WITHOUT ROUTINE POST-OPERATIVE C-REACTIVE PROTEIN MONITORING

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Hypothesis and Purpose: Protocols that rely on CRP post-operatively to monitor resolution of pediatric septic arthritis are used variably among institutions due to the lack of evidence proving efficacy. SickKids Hospital currently does not routinely monitor CRP levels post-operatively. Despite this, we hypothesize that re-operation and re-admission rates are similar to other institutions'. Secondary outcomes are to explore predictors of re-operation and re-admission.

Methods: This is a retrospective cohort study of patients who underwent surgical treatment of septic arthritis between January 1, 2009 and January 1, 2019 at a single tertiary-care pediatric institution. Patients who were re-admitted and required re-operation were compared with patients who had uncomplicated courses post-operatively.

Results: The readmission rate was 5%. The re-operation rate was 14%. Unexpectedly, 23% of patients presented to the emergency department (ED) after discharge from the hospital. Post-operative CRPs were obtained in 88% of the cohort. Discharge CRP was not significantly different between any of the comparison groups. Having knee or elbow/wrist arthritis, higher presenting CRP, higher presenting WBC count, and culture positive serum increased the likelihood that the patient would require re-operation. There were no significant predictors for presentation to the ED or re-admission.

Conclusion: The re-admission and re-operation rates were comparable to the current published literature. Outcomes did not correlate with discharge CRP. There was a significantly high rate of 23% of children who returned to the ED after discharge. This finding deserves further investigation as does evaluation into the value of post-operative CRP monitoring.

OPTIMIZING THE SURGICAL INSTRUMENT TRAY TO IMMEDIATELY INCREASE EFFICIENCY AND LOWER COSTS IN THE OPERATING ROOM

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Introduction: Surgical trays are often poorly configured and can be ongoing sources of frustration and excess costs. We conducted an observational study to determine if a customized mathematical inventory optimization model would result in greater reduction of instruments than a clinician review of a surgical tray. **Methods:** Utilization of instruments on the Major Orthopaedic tray at a large academic hospital was documented over 80 procedures. Processes in the medical device reprocessing department and OR were observed to comprehensively quantify all associated costs. Results of the observations were applied to a customized mathematical model to determine ideal tray configuration. For comparison, a clinician review was also performed. **Results:** The mathematical model alone produced an ideal tray size of 47 instruments, a reduction of 41 from the original size of 88 (47% reduction). This represented $34,440 in annual savings. In contrast, clinician review suggested an ideal tray size of 67 (23% reduction), and $17,640 in savings. When clinicians were provided with the additional information from the model, they reduced tray size to 51 (42% reduction), producing $31,087 in savings. **Discussion:** The mathematical model yielded an additional 22% instrument reduction and $15,001 in savings compared to clinician review alone. This mathematical model is generalizable and can be applied to all specialities and hospitals to determine optimal tray configuration. As such, the financial implications are broad; at our institution, application to all surgical trays would result in $205,000 of savings annually. Surgeons and managers looking to streamline surgical trays should consider this evidence-based approach.

PREDICTORS OF SURVIVAL IN ELDERLY PATIENTS UNDERGOING SURGERY FOR GBM

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Hypothesis and Purpose: GBM has a median age of diagnosis of 64 years old and the incidence increases with age. An increasing number of elderly patients are being diagnosed with GBM and undergoing surgery. These patients often present with multiple medical comorbidities and have significantly worse outcomes compared to adult patients. The goal of this study was to determine clinical predictors of survival in elderly patients undergoing surgery for GBM.

Methods: A retrospective chart review of all consecutive patients 65 years of age and older that underwent surgery for newly diagnosed GBM over a 14-year period from 2005 to 2018 was performed. Patient characteristics, comorbidities, complications, and treatment were collected. A total of 150 patients were included, and subdivided into two age categories; 65-74 years old and 75 years or older.

Results: The median OS for all patients was 9.4 months. The number of preoperative medical comorbidities was not associated with decreased survival ($p = 0.09$). Patients in the older age category were more likely to experience a postoperative complication ($p < 0.001$) and the presence of a postoperative complication was associated with worse survival for all patients (HR = 2.34, $p = 0.01$).

Conclusions: The presence of medical comorbidities and advanced age are not reasons to exclude patients with GBM from surgical consideration. Postoperative complications are the most significant predictor of survival in elderly patients and these can be avoided by a short length of stay and discharge home.

LOSS OF H3K27ME3 IN MENINGIOMAS

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Purpose: There is a critical need for objective & reliable biomarkers of outcome in meningiomas beyond WHO classification. Loss of H3K27me3 has been reported as a prognostically unfavorable alteration in meningiomas. We sought to independently evaluate the reproducibility and prognostic value of H3K27me3 loss by immunohistochemistry (IHC) in a multi-center study.

Methods: IHC staining for H3K27me3 and analyses of whole slides from 151 meningiomas across three centers was performed. Staining was analyzed by dichotomization into loss, retained immunoreactivity, and a 3-tiered scoring system. Associations of grouping with outcome was performed using Kaplan-Meier survival estimates.

Results: A total of 21 tumours (13.9%) demonstrated complete loss of H3K27me3 staining in tumour with retained endothelial staining. Overall, loss of H3K27me3 portended a worse outcome with shorter times to recurrence in our cohort, particularly for WHO grade 2 tumours which were enriched in our study. There were no differences in recurrence-free survival (RFS) for WHO grade 3 patients with retained versus loss of H3K27me3. Scoring by a 3-tiered system did not add further insights into the prognostic value of this H3K27me3 loss. Overall, loss of H3K27me3 was not independently associated with RFS after controlling for WHO grade, extent of resection, sex, age, and recurrence status of tumour on multivariable Cox regression analysis.

Conclusions: Loss of H3K27me3 identifies a subset of WHO grade 2 and possibly WHO grade 1 meningiomas with increased recurrence risk. Pooled analyses of a larger cohort of samples with standardized reporting of clinical definitions and staining patterns is warranted.