UW Medicine
SCHOOL OF MEDICINE

Department of Surgery

presents

The Sixteenth Annual Resident Research Symposium

Friday, January 22, 2010
7:45am – 12:30pm

Harborview Medical Center
Research & Training Building Auditorium
325 Ninth Avenue
Seattle, Washington

SCHEDULE OF PRESENTATIONS

Moderators: Jeffrey Matthews, M.D. and Alexander Clowes, M.D.

7:45am	Introduction	Alexander Clowes, M.D.
8:00am	Massarweh	A critical evaluation of the impact of Leapfrog's evidence-based hospital referral
8:15am	Foster	Organizational factors that promote successful implementation of the WHO Surgical Safety Checklist
8:30am	Farjah	Healthcare utilization among surgically treated Medicare beneficiaries with lung cancer
8:45am	Quade	Blunt aortic injury: the Harborview experience
9:00am	Mandell, K	Identifying risk factors for pulmonary embolism diagnosed during the initial trauma evaluation
9:15am	Mandell, S	Vehicle mismatch: a national estimate of preventable injuries
9:30am	Cheng	Early reinstitution of statin therapy in critically injured patients is associated with a reduction in post-injury development of organ failure
9:45am	Sakr	Plasma levels of non-esterified fatty acids predict the development of multiple organ disorder syndrome in trauma patients
10:00am	**BREAK**	
10:15am	Grabski	Smooth muscle α-actin: an inhibitor of proliferation and migration
10:30am	Gao	Syndecan-1 inhibits arterial smooth muscle cell proliferation through interference with PDGF-B production
10:45am	Numhom	Identification of differentially expressed genes in fibroblasts from deep dermal cones of the Duroc porcine model of fibroproliferative scarring
11:00am	Carter	Topical p38 MAPK inhibition attenuates full thickness burn wound inflammatory signaling
11:15am	Kohler	LPS upregulates cellular demand for Zn^{2+} in murine macrophages
11:30am	Shaligram	Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy perfusion for peritoneal surface malignancies: effective, but at what cost?
11:45am	Wassenaar	The safety of biologic mesh for laparoscopic repair of large, complicated hiatal hernias
12:00pm	Petersen	Resolution of respiratory symptoms following Heller myotomy for achalasia
12:15pm	FitzSullivan	Improved lung transplant outcomes with new bronchial anastomosis technique

3:30pm **HELEN & JOHN SCHILLING LECTURE – Hogness Auditorium, UW HSB**

A Salt and Battery: Ion Transport and the Injury Response

Jeffrey B. Matthews, M.D.
Dallas B. Phemister Professor of Surgery
Chairman, Department of Surgery
Dean for Clinical Affairs, Biological Sciences Division
The University of Chicago; Chicago, Illinois

A CRITICAL EVALUATION OF THE IMPACT OF LEAPFROG'S EVIDENCE-BASED HOSPITAL REFERRAL

Massarweh N, Pellegrini C, Symons R, Flum D

Background: Evidence-based hospital referral (EBHR) is a Leapfrog Group quality metric based primarily on hospital procedural volume. It has yet to be determined if EBHR has led to regionalized surgical care and whether it has improved patient outcome.

Methods: Before and after cohort study of 11,414 adults (1994-2007) who underwent pancreatic or esophageal resection or abdominal aortic aneurysm (AAA) repair in Washington state. Adjusted mortality, readmission, and complication rates were assessed before and after EBHR was introduced.

Results: Hospitals meeting an EBHR volume metric in any year ranged from 0-6. Comparing before and after 2001, the proportion of patients treated at hospitals meeting the EBHR volume metric for a given procedure increased for pancreatic (25.4% versus 50.2%, $p<0.001$) and esophageal resection (41.5% versus 59.2%, $p<0.001$), but was similar for AAA repair (16.3% versus 17.6%, $p=0.13$). In general, rates of adverse events were lower at hospitals meeting an EBHR volume metric. However, across Washington state, overall rates of mortality, readmission, and complications generally did not improve in the seven years after the introduction of the EBHR initiative. Outcomes at low volume centers did not improve.

Conclusions: Although a greater proportion of pancreatic/esophageal resections were performed at hospitals meeting a given EBHR volume metric in the seven years after Leapfrog began the EBHR initiative, this shift had a negligible impact on outcomes across Washington state. It remains to be determined why regionalization for AAA repair did not occur and why regionalization trends in pancreatic/esophageal surgery have not had the intended impact of improving overall safety outcomes.

ORGANIZATIONAL FACTORS THAT PROMOTE SUCCESSFUL IMPLEMENTATION OF THE WHO SURGICAL SAFETY CHECKLIST

Foster D, Arriaga A, Edmondson L, Singer S, Gawande A

Each year, dozens of promising innovations are introduced to improve health and health care. A substantial proportion of these are rigorously tested and found to have impressive results in pilot studies prior to their release. Despite such results, many fail to realize their potential in real-world use. The successful translation of knowledge from research to practice depends upon more than the quality of the process that produces an innovation or the results that can be achieved under optimal conditions. Real-world success requires that innovations are not only well-designed, but also well-implemented. Implementation is the process by which an adopting organization executes an innovation and supports its introduction and use. Although implementation is often overlooked, the success or failure of an innovation—and thus the relevance of the research upon which it is based—depends upon it.

For example, in 2008 the World Health Organization (WHO) conducted a pilot study of a Surgical Safety Checklist in eight hospitals around the world. Akin to the pre-flight checks required of pilots in the aviation industry, the WHO Checklist contains 19 critical items to be discussed before, during, and after surgery. All eight sites received careful instruction regarding the use of the Checklist including specific techniques for data collection and reporting. In the final analysis, Checklist use was associated with a reduction in 30-day mortality from 1.5% to 0.78%. Surgical site infections dropped from 20.5% to 13.5%, and emergent re-operation declined from 2.4% to 1.7%. However, no single item or combination of items on the Checklist could explain such dramatic results. The pilot study provided convincing evidence of benefit from using the Checklist, but it could not explain why the Checklist worked or how the environments into which it was introduced contributed to its effect.

The research groups of Dr. Sara Singer and Dr. Atul Gawande at the Harvard School of Public Health have combined their expertise in leadership and mixed qualitative and quantitative methods to study Checklist implementation at six hospitals in Washington state. Through interviews with implementation leaders (surgeons, anesthesiologists, and nurses) and surgeons actively using the Checklist in their operating rooms, a wide range of implementation strategies and practices has been identified. Analysis is currently underway to understand their impact on checklist acceptance, adherence, and subsequent outcomes. The specific factors that promote successful implementation (as well as plans for a larger study relating implementation practices to teamwork, Checklist process adherence and post-operative outcomes) will be presented at the Resident Research Symposium.

HEALTHCARE UTILIZATION AMONG SURGICALLY TREATED MEDICARE BENEFICIARIES WITH LUNG CANCER

Farjah F, Wood D, Varghese T, Massarweh N, Symons R, Flum D

Background: Markers of increased healthcare utilization are surrogates for adverse events, and one such metric—prolonged length of stay greater than 14 days (PLOS)—was recently endorsed as a provider-level performance measure.

Methods: A cohort study (1992-2005) aimed to describe increased healthcare utilization among 21,067 operated lung cancer patients using the Surveillance, Epidemiology, and End Results (SEER) Medicare database. Increased utilization was defined by PLOS, discharge to an institutional care facility (ICF), or readmission within 30 days.

Results: Twelve percent of patients had a PLOS, 13% were discharged to an ICF, and 15% were readmitted. In multivariate analyses, factors associated with a higher odds of PLOS, discharge to ICF, or readmission included age >80 years, increasing comorbidity index, not being married, and pneumonectomy (all $p<0.05$). Relative to patients living in the West, those in the Midwest or South had higher risk of PLOS and readmission but lower odds of discharge to ICF (all $p<0.05$). Adjusted rates of PLOS decreased significantly over time, whereas adjusted ICF and readmission rates increased (all $p<0.01$). Patients who required increased utilization had higher adjusted 2.5-year mortality rates compared to those who did not (PLOS: 42% versus 20%; ICF: 32% versus 20%; readmission: 33% versus 19%; all $p<0.001$).

Conclusions: Baseline health status and non-clinical factors were associated with increased utilization; non-uniform trends in utilization were observed over time; and increased utilization was associated with worse long-term outcomes. These findings have implications for quality improvement initiatives that measure increased healthcare utilization as a surrogate for provider performance.

BLUNT AORTIC INJURY: THE HARBORVIEW EXPERIENCE

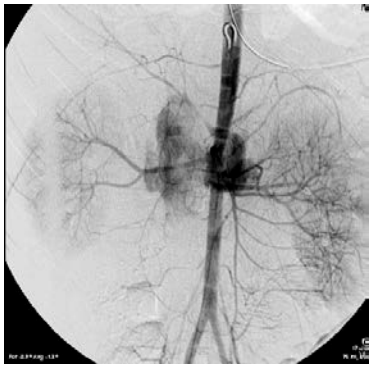
Quade S, Lundgren R, Starnes B

Background: Blunt aortic injury (BAI) occurs in approximately 0.3% of all trauma patients who survive to Emergency Department (ED) presentation. BAI remains a leading cause of trauma-related mortality despite improvements in pre-hospital care and automobile safety. Over the last decade, treatment has transitioned from open to endovascular repair based on case series demonstrating improved survival and reduced morbidity.

As the only Level 1 Trauma and Acute Care Center for a five state region, Harborview treats an unusually high number of patients with BAI. We sought to evaluate our experience over the last decade in treating patients who survived to presentation.

Methods: We identified all patients admitted with BAI from January 1, 1999 to December 31, 2008. Patients were analyzed based on type of aortic injury, aortic repair, associated injury severity, mortality, major morbidity, and length of stay. Injury severity was determined by Injury Severity Score (ISS) and type of injury by review of the imaging and operative notes.

Results: During the study period, 134 patients with BAI were treated at our institution. The average age of injury was 39, with 70% of patients having been in motor vehicle collisions. Seventy percent of injuries were at the aortic isthmus and 73% were pseudoaneurysms. Fifty-five patients received an open repair, 50 received endovascular repair, and 29 were managed non-operatively. The average length of stay was 24 days, typically related to other injuries. Seventy-three percent of patients survived. There were 29 procedure-related complications (28%): 16 in the open repair group and 13 in the endovascular repair group. Five percent of patients had late complications. Of the survivors, approximately 50% had at least one follow-up visit. Nine percent of patients in the endovascular repair group had new findings on follow-up imaging



Conclusions: This study represents one of the largest single-center experiences in caring for patients with BAI. Treatment at our institution has transitioned from open to endovascular repair as the mainstay of management. Over 2/3 of our patients are managed using this approach, and the associated mortality is low. As there is little follow-up on patients with endovascular repair, additional research is needed to determine long-term durability.

IDENTIFYING RISK FACTORS FOR PULMONARY EMBOLISM DIAGNOSED DURING THE INITIAL TRAUMA EVALUATION

Mandell K, Gunn M, McIntyre L, Jurkovich G, Cuschieri J

Introduction: Pulmonary embolism (PE) is a known cause of morbidity and mortality following trauma. Prior studies suggest an incidence of 0.2–1.0%. While some of these emboli are symptomatic, the incidence of asymptomatic PE is increasing as spiral CT scans are more widely employed. There is a known hypercoagulable state occuring at the moment of trauma and continuing after injury. Several studies have outlined risk factors for PE and thromboembolic events in trauma patients including: age >40, spinal cord injury, spine fracture, head injury, long bone fracture, pelvic fracture, venous injury, and transfusion. Timing of PE has also been examined, with as many as 30% occurring in the first week after injury and up to 15% in the first 48 hours. So far, only case reports exist of emboli diagnosed during the initial trauma evaluation. This study describes factors associated with the early (<24h) development of PE and hypercoagulable state following severe trauma.

Methods: Retrospective data were collected on all patients at Harborview Medical Center diagnosed with a PE following trauma between 2002 and 2007. We examined demographic data, timing of the PE in relation to time of injury, risk factors for thromboembolism, and outcome for all patients surviving >24 hours after injury. Patients with pulmonary emboli occurring within the first 24 hours were then compared to patients diagnosed later in their hospital course.

Results: A total of 32,630 trauma patients were admitted during the 5-year period who survived >24 hours. Two hundred fifty-one (0.77%) had a diagnosis of PE during their course; 53 (21%) of these were diagnosed during initial trauma evaluation (within the first 24h). Factors associated with very early PE were female gender (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.4-5.6), obesity (OR 2.1, 95% CI 1.1-4.1), initially elevated base deficit (OR 1.1, 95% CI 1.0-1.2), and crush injury (OR 4.27, CI 1.7-10.6). No differences were noted in surrogates for coagulation (INR, units transfused). No differences between the two groups were noted in survival, time to death or discharge, ventilator days, or intensive care unit days.

Conclusions: Over 20% of pulmonary emboli were diagnosed on initial trauma evaluation (<24h). The diagnosis of PE was made on abdominal CT scans, which included lower chest or aortic contrast chest CT done as part of the trauma work-up in all but 7 patients. The majority of these appeared incidental, as morbidity and mortality were not significantly different between those diagnosed with PE on day 1 or later in their course. Risk factors associated with early PE included female gender, obesity, elevated base deficit, and crush injury. It is unclear whether findings of very early PE are due to actual timing of the PE or just the timing of diagnosis. This is because increases in CT scanning and awareness of the risk of PE have led to an overall increase in diagnosis of incidental PE, many of which would only come to attention if the patient became symptomatic. Because the significance of incidental PE is unknown, more studies are needed to delineate both its clinical significance as well as possible management strategies.

VEHICLE MISMATCH:
A NATIONAL ESTIMATE OF PREVENTABLE INJURIES

Mandell SP, Mack CD, Jurkovich, G, Bulger EM

Objective: The number of light truck vehicles (LTV) on U.S. roadways has been increasing. We sought to determine the relative risk (RR) of severe injury associated with LTV vs. passenger vehicle (PV) mismatch following U.S. motor vehicle collisions.

Methods: This is a retrospective cohort study with the primary outcome of moderately severe injury (Injury Severity Score (ISS) >8, Abbreviated Injury Score (AIS) >2). We searched the National Automotive Sampling System Crashworthiness Data System (NASS CDS) for occupants in frontal and side impact crashes from 1993-2007. Occupants in PVs struck by LTVs were compared to PV occupants struck by another PV. Poisson regression was used to estimate the relative risk of severe injury after adjusting for driver age, driver gender, and change in velocity during the crash (Δv). Because 21% of cases were missing Δv, multiple imputation by chained equations was used to estimate the missing values. NASS CDS weights were used to estimate the risk of severe injury nationally.

Results: PV occupants in frontal impact crashes with a LTV as the striking vehicle were at increased risk of severe injury compared to those struck by another PV (RR 1.37 95% confidence interval [CI] 1.09-1.73) (Table 1). A similar increased risk was observed in side impact crashes (RR 1.34 95% CI 1.12-1.62) (Table 2). Increased risk of injury was also identified in several body regions.

Conclusion: Motor vehicle mismatch crashes are associated with a significant increase in risk of severe injury for PV occupants in the United States.

Table 1. Frontal Impacts

PV-LTV vs. PV-PV	Crude RR 95% CI	Adjusted RR 95% CI
ISS >8	1.67 (1.34-2.08)	1.37 (1.09-1.73)
Thor AIS >2	1.92 (1.49-2.48)	1.40 (1.02-1.91)
Abd AIS >2	2.97 (1.65-5.37)	2.20 (1.23-3.93)
UE AIS >2	1.52 (1.16-1.99)	1.33 (1.04-1.71)
LE AIS >2	2.06 (1.64-2.59)	1.56 (1.25-1.95)

Table 2. Side Impacts

PV-PV vs. PV-LTV	Crude RR 95% CI	Adjusted RR 95% CI
ISS >8	1.83 (1.51-2.23)	1.34 (1.12-1.61)
Head AIS >2	2.25 (1.58-3.19)	1.52 (1.05-2.19)
Thor AIS >2	1.80 (1.33-2.43)	1.25 (0.96-1.62)

LE AIS >2	**1.66 (1.30-2.12)**	**1.06 (0.83-1.36)**

EARLY REINSTITUTION OF STATIN THERAPY IN CRITICALLY INJURED PATIENTS IS ASSOCIATED WITH A REDUCTION IN POST-INJURY DEVELOPMENT OF ORGAN FAILURE

Cheng A, Mandell K, Sterling J, Arbabi S, Jurkovich G,
Maier R, Cuschieri J

Background: Statins are effective lipid-lowering agents with pleiotropic effects, including anti-inflammatory properties, and have been shown to reduce the incidence of sepsis in patients with acute bacterial infections. The effect of statins in acutely injured patients, however, is unclear. Recently, pre-injury statin use was shown to be associated with improved survival in the elderly trauma patient, while a subsequent follow-up multi-center prospective cohort study by us suggested that statin use is associated with increased risk of post-injury multiple organ failure (MOF). To examine these divergent views, we focused on statin use in the early post-injury period. We hypothesized that pre-injury statin use is protective; however, its early discontinuation in the acute post-injury period may actually be detrimental.

Methods: Data were obtained from a single center prospective cohort study evaluating clinical outcomes in bluntly injured adults with hemorrhagic shock. Patients with traumatic brain injury and not surviving >48 hours were excluded. Patients with pre-injury statin (PIS) use and those with in-hospital reinstitution of statin (RS) therapy within 48 hours were identified. PIS and RS, in combination with other variables associated with the development of MOF, were placed in a stepwise multivariate logistic regression to identify independent predictors of MOF.

Results: In all, 648 patients were evaluated over 5 years. Fifty-nine (9.1%) of these patients had received PIS. PIS patients were older and had higher body mass index (BMI) scores than the patients who did not receive statins. PIS use was not associated with any improvement in outcome, including a reduction in MOF. Among the patients with PIS, 24 (40.6%) were not restarted on their statins within 48 hours. These patients were found to have an increased risk of morbidity and mortality when compared to the 35 (59.4%) patients who were restarted on their statin therapy within 48 hours of their injury. The adjusted odds ratio calculated from using step-wise logistic regression analysis for patients who were not restarted on statin therapy was 10.5 times more likely to be associated with the development of MOF than those patients who had their statin restarted (95% confidence interval: 1.33-83.63).

Conclusion: Pre-injury statin therapy in critically injured patients who discontinue their statins early after the time of injury is significantly associated with an increased risk for post-injury MOF. Thus, patients with pre-injury statin use should be restarted soon after injury to avoid withdrawal-associated morbidity and mortality.

	Statin Restarted	Statin Not Restarted	p value
Max MOF score	4.6	7.6	0.0001
MOF (%)	5	22	0.0001
Infection	14	16	0.3409
SSI	7	4	0.7467
BSI	2	6	0.0335
VAP	7	11	0.0343
ICU LOS	12.9	18.8	0.1394
HOS LOS	27.0	33.7	0.3013
Ventilator days	8.4	16.5	0.0198
Mortality	4	10	0.0073

PLASMA LEVELS OF NON-ESTERIFIED FATTY ACIDS PREDICT THE DEVELOPMENT OF MULTIPLE ORGAN DISORDER SYNDROME IN TRAUMA PATIENTS

Sakr S, Knutson S, Wilson C, Hennessy L, Arbabi S,
O'Keefe GE, Cuschieri J

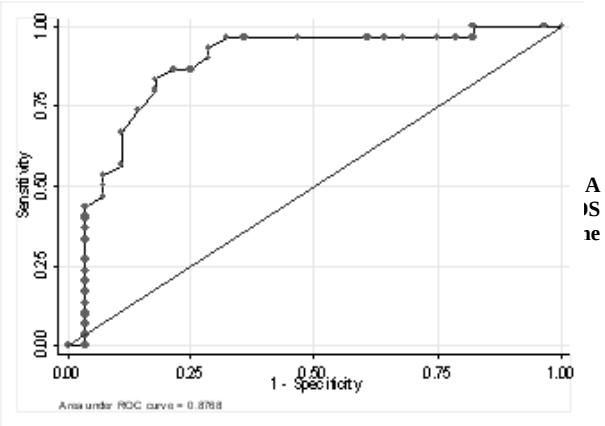
Background: Non-esterified fatty acids (NEFAs) are mobilized in critically ill patients. Their high levels are associated with dysregulated inflammatory states. During other illnesses, this dysregulated immune state associated with NEFA levels is thought to lead to the development of acute respiratory distress syndrome (ARDS) and multiple organ disorder syndrome (MODS). The relationship between NEFA levels and trauma has not been previously investigated. Thus, we set out to determine the role of plasma NEFA levels in predicting outcomes in a population of severely injured trauma patients.

Methods: Fifty-eight severely injured patients admitted to Harborview Medical Center were evaluated. Clinical and outcome variables were prospectively collected. Additionally, blood samples were collected 24 hours post-injury, and plasma was isolated and frozen for further analysis. NEFA levels were measured by an enzymatic assay. A plasma NEFA level was determined for the subsequent development of MODS by developing a receiver operating characteristics curve (ROC) and defining the optimal NEFA level using the Youden index. Outcomes based on NEFA levels were assessed by a step-wise regression model.

Results: A ROC was generated for plasma NEFA levels and MODS development, with a NEFA level of 380 mmol/L having the highest sensitivity and specificity (Figure). NEFA levels were associated with both the development of ARDS (odds ratio [OR] 4.8, 95% confidence interval [CI]: 1.1-21.8) and MODS (OR 8.98, 95% CI: 1.98-40.7) after adjusting for age, sex, injury severity, blood transfusions, and body mass index (BMI). A NEFA level >380 mmol/L was associated with increased intensive care unit length of stay (8.5 ± 3.4 versus 10.8 ± 4.7, p=0.03), and reduced ventilator free days (21.9 ± 3.4 versus 19.2 ± 3.8, p=0.05). No difference was seen in the rate of nosocomial infection, mortality or glucose levels.

Conclusions: The plasma NEFA is a key mediator involved in alterations of innate and adaptive immunity. Elevated plasma NEFA levels following injury appear to correlate with the development of ARDS and MODS. This measurement may be useful as a biomarker for prognosis and serve to identify patients at higher risk of adverse outcome who would benefit from novel therapeutic interventions.

ROC of NEFA levels and



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SMOOTH MUSCLE α-ACTIN: AN INHIBITOR OF PROLIFERATION AND MIGRATION

Grabski A, D'Souza T, Caylor J, Reidy M, Clowes A, Daum G

Background: The failure of surgical procedures intended to restore blood flow has been attributed to restenosis, an event associated with aberrant smooth muscle cell (SMC) behavior. In response to vascular injury, SMCs become activated and undergo a process termed phenotypic modulation, whereby normally quiescent and contractile SMCs begin to proliferate and migrate. This coincides with decreased expression of a set of SMC phenotypic marker genes, including smooth muscle α-actin (SMA). While known for decades, little is known about whether expression of SMA maintains SMCs in an inactive quiescent state. Using a mouse model of arterial injury, we have shown that expression of SMA is markedly decreased 2 days after injury. Importantly, we found that SMA is re-expressed 7 days after injury only in arteries which do not form lesions, and intimal SMC proliferation is negatively correlated with SMA expression. Therefore, we hypothesized that the re-expression of SMA after injury inhibits SMC proliferation and possibly migration. The clinical relevance of this hypothesis is underlined by a recent study demonstrating that mutations in SMA are associated with the premature onset of coronary artery disease and ischemic strokes. We have recently found that sphingosine 1-phosphate (S1P) and its receptor sphingosine 1-phosphate 2 (S1P2R) promote expression of SMA, which is regulated by the transcription factor serum response factor (SRF) and its cofactors of the myocardin related transcription factor family (myocardin, MRTF-A and MRTF-B). Recent studies have established that cardiac and SMC-specific cofactor myocardin are essential for the expression of SMA during differentiation of SMCs. The purpose of this study was to test the hypothesis that SMA is an inhibitor of SMC proliferation and migration, and that myocardin is required for S1P-induced SMA expression.

Methods: Mouse SMCs were prepared from uninjured carotid arteries and maintained in 10% fetal bovine serum. SMCs were transfected with either a small interfering RNA (siRNA) construct targeting SMA or a non-specific scrambled control (SCR) using the Amaxa electroporation method. Growth of SMA or SCR siRNA transfected SMCs in 10% fetal bovine serum was measured by the MTT colorimetric assay over 6 days. Migration of SMA or SCR siRNA transfected SMCs towards 20ng/mL platelet-derived growth factor subunit B (PDGF-BB) was determined using a microchemotaxis chamber. For cofactor studies, SMCs were treated with myocardin, MRTF-A, MRTF-B or SCR siRNA. Effects of siRNA gene knock-down were measured by real-time quantitative polymerase chain reaction (PCR) or Western blotting.

Results: Transfection with SMA siRNA, unlike SCR siRNA, resulted in an average of 80% knock-down of the SMA protein, which persisted for 7-10 days. After 6 days of growth in 10% serum, there was a 15-fold increase in SMCs transfected with SMA siRNA compared to a 7-fold increase in SMCs transfected with SCR siRNA. In response to 20ng/mL PDGF-BB, SMCs transfected with SMA siRNA migrated 40% more than SMCs transfected with SCR siRNA. Regarding SMA expression, S1P induced SMA expression by 10-fold over quiescent SMCs. In contrast to previously published studies establishing myocardin as the SRF co-factor required for SMA induction, we have found that MRTF-B is the critical transcription cofactor required for S1P-induced SMA expression.

Conclusions: These studies clearly demonstrate that decreased SMA expression increases SMC proliferation and migration. In addition, we have identified S1P as a positive regulator of SMA expression through MRTF-B transcriptional regulation. Studies are ongoing to determine if MRTF-B is the SRF co-factor which might regulate re-expression of SMA after injury.

SYNDECAN-1 INHIBITS ARTERIAL SMOOTH MUSCLE CELL PROLIFERATION THROUGH INTERFERENCE WITH PDGF-B PRODUCTION

Gao L, Fukai N, Chen L, Kenagy R, Daum G, Clowes A

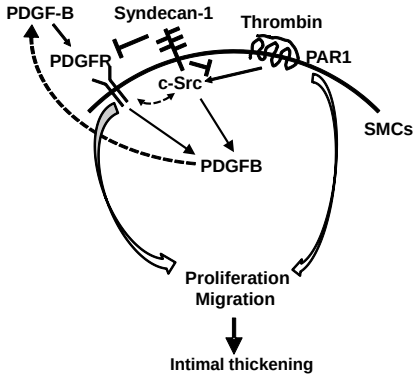
Background: Arterial injury induces smooth muscle cell (SMC) proliferation, migration, and intimal accumulation of cells and extracellular matrix, which contribute to stenosis following reconstruction. These processes can be suppressed by the administration of the glycosaminoglycans heparin and heparan sulfate, but little is known about the role of endogenous heparan sulfate proteoglycans including syndecan-1 in the vessel wall. We have previously shown that syndecan-1-null mice form large lesions after carotid artery ligation, and that SMCs isolated from syndecan-1-null mice proliferate more and migrate faster than those from the wild-type animals in response to growth factors. The addition of soluble syndecan-1 ectodomains inhibits growth factor mediated SMC proliferation and migration. All these findings indicate that syndecan-1 is an inhibitor of intimal formation.

Purpose: To investigate the molecular mechanisms by which syndecan-1 inhibits vascular smooth muscle cell proliferation.

Methods: Smooth muscle cells isolated from wild-type and syndecan-1-null mice were evaluated for growth and platelet-derived growth factor (PDGF) production in response to thrombin stimulation. Pharmacological inhibitors of receptor and non-receptor tyrosine kinases were employed to evaluate their contribution to thrombin-induced PDGF-B expression. Small interfering RNA (siRNA) assays were used to study the roles of PDGF-B and PDGFR-β in thrombin-induced SMC proliferation.

Results: Cultured SMCs from syndecan-1-null mice show a significantly increased growth and production of PDGF-B in response to thrombin. Inhibition of PDGFR kinase activity partially blocks thrombin induced PDGF-B expression while Src kinases inhibitor decreases thrombin-induced PDGF-BB expression in the null cells to the wild type level. siRNA knock down of PDGF-B suppresses thrombin-mediated cell proliferation in syndecan-1-null SMCs.

Conclusions: These results suggest the possibility that syndecan-1 may limit SMC proliferation in injured arteries by suppressing SMC activation at least partially through regulation of injury-induced PDGF-B production.



IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES IN FIBROBLASTS FROM DEEP DERMAL CONES OF THE DUROC PORCINE MODEL OF FIBROPROLIFERATIVE SCARRING

Numhom S, Zhu K, Carrougher G, Hocking A, Klein M, Gibran N, Engrav L

Introduction: Hypertrophic scarring is a major devastating problem after burn injury. The molecular etiology of this process remains unknown. Hypertrophic scarring only occurs on those body parts where the skin contains dermal cones with a fat dome. The Duroc porcine model of fibroproliferative scarring has been validated for clinical, histological, immunohistochemical and molecular similarity to human hypertrophic scar, and Duroc skin also possesses dermal cones. Numerous studies of fibroblasts in hypertrophic scarring have been performed over the past decades, but the fibroblasts associated with dermal cones have not been studied. The identification of differentially expressed genes in dermal cone fibroblasts from deep wounds compared to shallow wounds may reveal insights into the pathophysiology of fibroproliferative scarring.

Methods: Shallow and deep wounds were created on the backs of Duroc pigs and biopsied 5 months after wounding. Fibroblasts were isolated and cultured from the deep dermal cones of the scars. Total RNA from third passage fibroblasts was extracted, amplified and hybridized to the Affymetrix Porcine Genechip®. The expression of genes in deep wound fibroblasts relative to shallow wound fibroblasts was considered to be significantly over or under-expressed if the fold change was >1.4 and the ratios were significantly changed ($p<0.1$) with paired t-test comparisons. We next developed directed graphical networks with functional genomics using Ingenuity® Pathways Analysis.

Results: We identified 284 differentially expressed genes; 116 were over-expressed and 168 were under-expressed. Ingenuity® Pathways Analysis revealed the network of genes associated with connective tissue development and disorders. (Table)

Functions	Expression	Molecules in Network
Connective tissue disorders, Connective tissue development	Over-expressed	AGT, COL6A1, LPIN1, LSS, PCSK1, PER1, PIR
	Under-expressed	CRYZ, DYNLL2, ETV5, GLS, HNRNPA3, HNRNPA2B1, MYEF2, MYO5A, PCNT, STK11, SUB1, SUZ12, SYNE2

Conclusion: We identified candidate genes that may be involved in the pathophysiology of fibroproliferative scarring and a directed graphical network. This network may now be integrated with traditional laboratory reductionist methods.

TOPICAL p38 MAPK INHIBITION ATTENUATES FULL THICKNESS BURN WOUND INFLAMMATORY SIGNALING

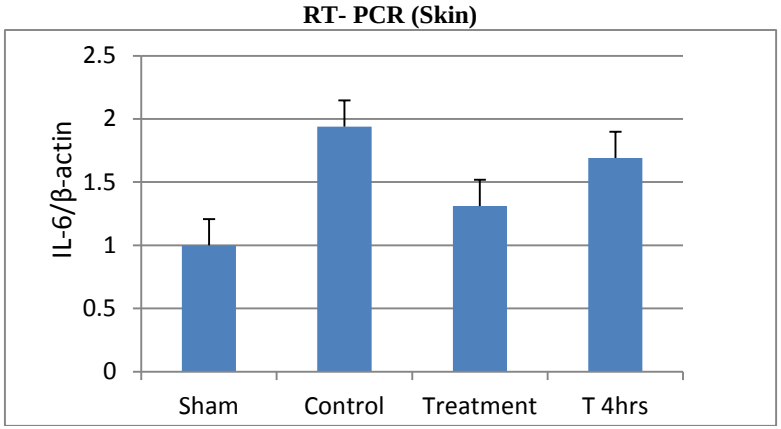
Carter D, Warsen A, Hemmila M, Cuschieri J, and Arbabi S

Background: Inflammatory signaling pathways, such as the p38 mitogen-activated protein kinase (MAPK) pathway, play a central role in host responses to injury. We demonstrated that topical p38 MAPK inhibition reduced expression of inflammatory mediators in the burn wound, leading to improved end-organ function and survival. In our previous studies, topical p38 MAPK inhibitors effectively attenuated inflammatory signaling in a partial thickness scald burn model. However, full-thickness burn wounds may act as a barrier to topical immunomodulators. In this study, we evaluated the efficacy of immediate and delayed topical p38 MAPK inhibition on full thickness burns.

Methods: Mice received sham or 40% total body surface area (TBSA) full thickness burn injuries and were treated with a topical p38 MAPK inhibitor (treatment) or vehicle immediately or 4 hours after thermal injury. All animals were sacrificed at 12 or 24 hours after injury. Skin and lungs were harvested and analyzed by the enzyme-linked immunosorbant assay (ELISA) for cytokine expression. In addition, real-time reverse transcription polymerase chain reaction (RT-PCR) was used to evaluate for interleukin (IL)-6 mRNA expression.

Results: Topical p38 MAPK inhibitor attenuated dermal IL-6 and macrophage inflammatory protein (MIP)-2 expression. IL-6 mRNA expression confirmed these results (graph).

Conclusion: Topical p38 MAPK inhibitors are potent in reducing burn wound inflammatory signaling. This effect is retained with burns of varying thickness and with delayed application of the inhibitor. These preliminary studies demonstrate that inhibition of p38 MAPK may attenuate burn-induced inflammatory responses. This topical treatment is easy to apply and can be initiated early post-injury.



LPS UPREGULATES CELLULAR DEMAND FOR Zn^{2+} IN MURINE MACROPHAGES

Kohler J, Blass A, Williams M, Faldetta K, Kelly E, Soybel D

Introduction: In response to injury, local infection, or systemic sepsis, zinc (Zn^{2+}) is required for optimal activation and function of the innate immune response. The activated macrophage is essential in this response, both through its role as a professional phagocyte and its release of inflammatory mediators. In this study, we used an *in vitro* model of macrophage activation to test the hypothesis that cellular demand for Zn^{2+} is increased in response to bacterial endotoxin (lipopolysaccharide [LPS]). An additional goal was to explore the pathways by which that demand is satisfied.

Methods: Real-time fluorescence imaging: Cultured RAW 267.7 macrophages were plated on glass coverslips. Fluorescence was monitored using the fluorescent zinc reporter FluoZin™-3 AM (Molecular Probes®). Cells were imaged during exposure to zinc-supplemented (50 µM) Ringer's solution with or without LPS pre-treatment (100 ng/ml, one hour), and results were normalized to baseline values. **Zinc transporter expression:** RAW cells and isolated murine splenic macrophages were exposed to LPS (50 or 100 ng/ml) for 4 hours, then processed for semi-quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) against the 24 known members of two critical zinc transporter families, the Zip family (which transfers Zn^{2+} into the cytoplasm from both extracellular and intracellular pools) and the ZnT family (which exports Zn^{2+} from the cytoplasm to subcellular compartments or to the extracellular space). **Statistical analysis:** Results were analyzed using t-tests and the Mann-Whitney rank-sum test for non-parametric data, as appropriate.

Results: Increased demand for zinc: Cells exposed to LPS immediately showed an increased rate of Zn^{2+} uptake. After five minutes' exposure to zinc-supplemented Ringer's solution, macrophages pre-treated with LPS demonstrated a 248% increase in signal from baseline, compared to a 182% increase in control cells (n=32 cells in 6 paired experiments, $p<0.05$). **Upregulation of intracellular Zn^{2+} importers:** LPS caused increased transcription of two known Zn^{2+} import (Zip) proteins, Zip 1 and Zip 14. In cultured macrophages, Zip 1 mRNA was increased almost 3-fold versus control (relative quantification [RQ] 2.71, standard error [SE] 0.25, n=5, $p<0.001$), and Zip 14 mRNA was increased 4.75 times (SE 0.33, n=5, $p<0.001$). In primary splenic macrophages, Zip 1 was increased 5.52-fold (SE 1.34, n=3, $p=0.01$), while Zip 14 was increased 7.5-fold (SE 1.16, n=3, $p<0.001$). In contrast, no changes were seen in the ZnT zinc exporter family.

Conclusions: LPS induces a profound response in the macrophage, increasing demand for free Zn^{2+} from extracellular sources. To meet the increased demand, two known Zn^{2+} importers are upregulated. Zip 1 likely imports Zn^{2+} to the cytoplasm from the extracellular space, while the intracellular location of Zip 14 suggests activation of processes that transfer Zn^{2+} into the cytoplasm from intracellular pools such as the phagosome, endoplasmic reticulum, or Golgi apparatus. These transporters may provide targets for treatment of illness, injury, and surgical wound healing.

CYTOREDUCTIVE SURGERY AND INTRAPERITONEAL HYPERTHERMIC CHEMOTHERAPY PERFUSION FOR PERITONEAL SURFACE MALIGNANCIES: EFFECTIVE, BUT AT WHAT COST?

Shaligram A, Mann L, Mann G

Background: Peritoneal carcinomatosis is seldom curable. Maximal cytoreductive surgery (CS) combined with intraperitoneal hyperthermic chemotherapy perfusion (IPHC) has been used in efforts to improve oncologic outcomes, but it is an aggressive therapy associated with high complication rates.

Purpose: To review the oncologic outcomes, morbidity, and mortality associated with CS/IPHC performed by a single surgeon at the University of Washington Medical Center.

Methods: After obtaining Institutional Review Board approval, retrospective chart review was performed. Fifty consecutive patients undergoing 53 CS/IPHC (mitomycin C or cisplatin) treatments from June 2002 to May 2009 were included in the study. Charts were reviewed for patient, tumor and treatment factors. Morbidity was analyzed and graded; mortality and oncologic outcomes were assessed.

Results: Median age was 57 (range 24-76), with 36 female patients. The most frequent pathological diagnosis was appendiceal neoplasm (62%), followed by colorectal cancer (16%), mesothelioma (14%), and other (8%). The median peritoneal carcinomatosis index was 12 (range 0-36 of a possible 39). Complete gross cytoreduction was achieved in 91% of operations. Perioperative mortality was 8%. Almost half of all patients had some complication: major in 21%, and minor in 28%. Eleven percent developed an intra-abdominal abscess requiring drainage, and eight percent developed an enterocutaneous fistula requiring parenteral nutrition and/or surgical repair. Median survival was 25 months.

Conclusion: CS/IPHC for peritoneal carcinomatosis has a significant morbidity and mortality. Durable responses are possible; therefore, CS/IPHC should be considered for select patients after careful consideration of risks.

THE SAFETY OF BIOLOGIC MESH FOR LAPAROSCOPIC REPAIR OF LARGE, COMPLICATED HIATAL HERNIAS

Wassenaar E, Shebrain S, Sinan H, Martin V, Pellegrini C, Oelschlager B

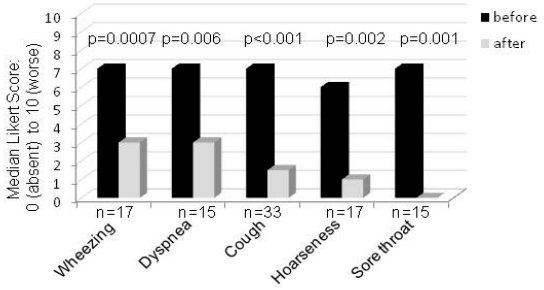
Objective: Laparoscopic repair of large, complicated hiatal hernias is associated with a high risk of recurrence. Biologic mesh decreases recurrence and prevents complications associated with synthetic mesh; but its safety profile has not yet been fully determined. To answer this question we analyzed the outcomes of biologic mesh used to repair these "high risk" hiatal hernias.

Methods: All patients (n=125) who had biologic mesh (Surgisis®, Cook Medical, Inc.) implanted and who had a minimum follow-up of 6 months were included in this study. We recorded all complications and sent all patients a standardized symptom questionnaire.

Results: Median follow-up was 37 months (range 6-103 months). Repairs were performed for paraesophageal hernia in 86 (69%), large sliding hiatal hernia with obesity in 6 (5%) and redo Nissen fundoplication in 33 patients (26%). There were no immediate complications related to the mesh. Thirty-day mortality was nil.

Completed questionnaires were collected from 49 patients (40%). Three patients (5%) developed a symptomatic recurrent hiatal hernia; one required reoperation. No patient has had an erosion, stricture, or complication directly related to the mesh.

Conclusions: There were no immediate or long-term complications associated with the mesh. The use of biologic mesh for laparoscopic repair of large, complicated hiatal hernias appears safe.



RESOLUTION OF RESPIRATORY SYMPTOMS FOLLOWING HELLER MYOTOMY FOR ACHALASIA

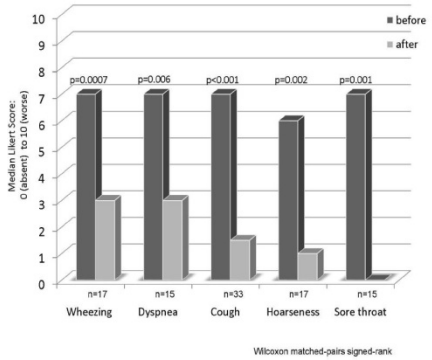
Petersen R, Khandelwal S, Tatum R, Sinan H, Aaronson D,
Martin A, Pellegrini C, Oelschlager B

Introduction: Some patients with achalasia complain of respiratory symptoms. In this study we sought to define the prevalence, the pathogenesis and the effect of Heller myotomy on these symptoms.

Methods: We studied the course of 111 patients with achalasia who underwent Heller myotomy between 1994 and 2008 and who agreed to participate in this study. All patients completed a questionnaire postoperatively assessing the preoperative and postoperative prevalence and severity of symptoms using visual analog scales. Patients reporting respiratory symptoms (dyspnea, hoarseness, cough, wheezing, or sore throat) occurring at least once per week prior to myotomy, and/or history of asthma or pneumonia, were included for analysis.

Results: All patients presented with dysphagia as their primary complaint, and 63/111 (57%) reported respiratory disease or symptoms prior to surgery. They all underwent Heller myotomy and 51/63 (81%) had, in addition, an antireflux procedure (Dor or Toupet fundoplication). After a median follow-up of 71 months (range: 9-186 months), 55/63 (87%) patients experienced durable improvement in their dysphagia. The frequency and severity (Figure) of all respiratory symptoms decreased significantly. Twenty-four of the 29 patients (82%) who reported a history of pneumonia prior to surgery did not experience recurrent episodes after Heller myotomy.

Conclusions: This study shows that achalasia is associated with a relatively high prevalence of respiratory symptoms and disease. As esophageal emptying improves, evidenced by resolution of dysphagia, respiratory problems disappear as well suggesting that they were caused by aspiration of retained food and secretions. The substantial improvement of respiratory symptoms and disease after Heller myotomy, which was heretofore not appreciated, is yet another benefit of surgical therapy for this disease.



IMPROVED LUNG TRANSPLANT OUTCOMES WITH NEW BRONCHIAL ANASTOMOSIS TECHNIQUE

FitzSullivan E, Farjah F, Gilbert E, Keech JC, Mulligan MS

Background: Lung transplantation is an effective treatment option for select patients with end-stage pulmonary disease. Nevertheless, successful transplantation continues to be challenged by the occurrence of airway complications in up to 17% of lung transplant recipients. In the majority of centers, a single running suture line creates the anastamosis between the recipient's native main bronchi and the donor's main bronchi, leaving a cuff of two donor bronchial rings intact. However, this cuff of tissue is susceptible to ischemia, leading to formation of an anastomotic stricture that requires additional instrumentation to treat. This ultimately impairs lung function and long-term outcomes.

Hypothesis: We hypothesized that minimizing the donor tissue cuff (performing the anastomosis more distally), using a running suture through the membranous bronchi and interrupted figure-of-eights through the cartilaginous bronchi, would lead to fewer anastomotic complications and improve lung function.

Methods: We conducted a retrospective chart review of a single surgeon over an 8-year period. Recipient characteristics measured included age, gender, indication for transplantation, use of cardiopulmonary bypass, ischemia time, and transfusion requirement. Donor characteristics measured included age, gender, challenge PaO2, presence of an infiltrate, bronchial culture, and cause of death. Outcomes measured included length of mechanical ventilation, evidence of grade 3 graft dysfunction, development of pneumonia, cellular rejection, humoral rejection, anastomotic complications and their required management, as well as mortality. Pulmonary function was assessed using standard pulmonary function tests and compared to baseline measurements.

Results: There were 306 lung transplants performed during this time period, with 165 performed using the traditional single suture technique and 141 performed using the new technique. The two treatment groups did not have any significant difference in recipient or donor characteristics. However, there was an overwhelming decline in the number of anastomotic complications in recipients who received the new technique (<1% versus 9%). Additionally, those recipients who received the new technique demonstrated significantly better post-transplant lung function, both short- and long-term.

Conclusions: Minimizing the length of donor bronchi and using the combination of running and figure-of-eight sutures for the bronchial anastomosis reduces airway complications and improves lung function. The improvement in lung function may partially be due to the improved ability to both diagnose and treat distal airway disease.