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Moderator
Sessions Moderated by Ginny L. Bumgardner, M.D., Ph.D., Professor of Surgery, Division of Transplantation; Associate Dean for Research Education, The Ohio State University Medical Center

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Fibroblast MIR-21 Regulates MMP-2 Expression via a PTEN Mechanism in the Ischemia-Reperfused Heart


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PURPOSE/HYPOTHESIS: Matrix metalloproteinase 2 (MMP-2) has been shown to be closely associated with myocardiac ischemia, heart failure and cardiac mechanical dysfunction. However, the underlying mechanism of how MMP-2 is regulated during myocardiac ischemia remains ambiguous. Recently, cluster of short non-coding RNAs, which are known as microRNAs, have been shown to regulate cardiomyocyte hypertrophy and cardiac functions.

METHODS: Mouse model of myocardiac ischemia was achieved by left anterior descending coronary artery (LAD) ligation. Laser captured microscopy is used for RNA isolation in normal and infarct region. Localization of microRNA or protein interested was validated by in situ hybridization and immunocytohistochemistry. Expression of protein and both microRNA and mRNA were achieved by Western blot and quantitative real time PCR respectively. For in vitro study, isolated cardiac fibroblasts were subjected to transfection of miR-21 mimic, miR-21 inhibitor or pGL3-PTEN-3’-UTR luciferase reporter construct to validate the phosphatase and tension homologue (PTEN) as a direct target of miR-21.

RESULTS: Expression of miR-21, one of the crucial microRNAs in heart function, within the infracted region was up-regulated, as depicted by in situ hybridization and real-time PCR from RNA isolated from laser microdissected tissue. Immunohistochemistry revealed that the expression of vimentin, a fibroblast marker, was co-localized with miR-21 signal in infracted region. In isolated cardiac fibroblast, PTEN was observed to be a direct target of miR-21, as evidenced by immunoblotting and pGL3-PTEN-3’-UTR luciferase reporter assay. Transfection of miR-21 mimic elevated MMP-2 expression, which was further augmented by depletion of endogenous PTEN. These results were further supported by in vivo data indicating that the expression of PTEN and MMP-2 was suppressed and elevated respectively within the infracted region.

CONCLUSIONS: This work constitutes the first report indicating that in the infracted myocardium miR-21 serves as a key regulator of MMP-2 expression in a PTEN-dependent manner.
Atrial Fibrillation after Esophagectomy: A Marker of Increased Morbidity and Mortality


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INTRODUCTION: Atrial fibrillation (AF) occurs relatively infrequently in noncardiac surgery patients. However, it seems that AF occurs more frequently after esophagectomy, increasing ICU stay. We therefore sought to define the incidence and associated morbidities of AF after esophagectomy.

METHODS: Retrospective review of all patients who underwent esophagectomy at a single academic center. Patients with preexisting AF were excluded.

RESULTS: Between May 1996 and December 2007, 156 patients underwent esophagectomy. New onset AF complicated 32 (20.5%) of esophagectomy cases. Most AF occurred on postoperative day two, with 87.5% of new AF events occurring during the first three postoperative days. Pulmonary complications were more frequent in the AF group (59.4%) than in the non-AF (NAF) group (15.32%, P<0.01) and usually preceded or were concurrent with AF. Anastomotic leaks were also more common in the AF group (28.1%) than in NAF group (6.45%, P<0.01) and were identified 4 days after the onset of AF (95% CI, 1.1-7.3). Hospital mortality was higher in the AF group (21.9%) than in the NAF group (0%, P<0.01). Time to resolution of AF was not different between amiodarone, beta blocker, or diltiazem treatment. Age, gender, type of cancer, surgical approach, epidural analgesia, statins or NSAIDs, did not affect likelihood of developing AF.

CONCLUSION: After esophagectomy, new onset AF is strongly associated with anastomotic leaks, pulmonary complications, and increased mortality. While pulmonary complications occurred coincident with the onset of AF, anastomotic leaks were identified approximately four days later. Occurrence of AF after esophagectomy should prompt an aggressive search for anastomotic leak, in addition to management of the dysrhythmia. Prophylaxis for AF in esophagectomy could impair or delay diagnosis of anastomotic leak.
MiRNA-130b Targets DNA Methyltransferase 1 in Esophageal Adenocarcinoma

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BACKGROUND: MiRNAs are small, noncoding RNAs (~20-22 nucleotides) that regulate gene expression by interacting with the 3’ UTR of mRNA resulting in translational inhibition. The tumor suppressor gene, p16, is often lost in Barrett’s metaplasia and esophageal adenocarcinoma through hypermethylation by DNA methyltransferase 1 (DNMT1). MiR-130b has predicted complementarity to the 3’ UTR of DNMT1. We sought to determine if miR-130b exerts its effect through DNMT1 and if miR-130b is lost in human esophageal cancer.

METHODS: RNA was isolated from 61 resected esophageal adenocarcinomas and matched adjacent normal glandular epithelium. RNA was hybridized to miRNA microarray chips containing more than 700 human microRNA genes. Class comparison was used to identify differentially expressed miRNA between normal and malignant tissues. Flo-1 (human esophageal adenocarcinoma cell line) was transfected with precursor miR-130b. qRT-PCR and Western blot were undertaken to evaluate miR-130b and DNMT1 expression respectively, in vitro. Cell cycle was determined by FACS analysis.

RESULTS: MiR-130b was differentially underexpressed relative to adjacent normal mucosa in esophageal adenocarcinomas by microarray with 39 tumors showing little or no expression. qRT-PCR confirmed no expression of miR-130b in the Flo-1 cell line as well. MiR-130b overexpression following transfection was confirmed by qRT-PCR. DNMT1 expression was completely abrogated in Flo-1 cells when miR-130b was restored by transfection with precursor miRNA. In addition, an increase in apoptotic fraction was found in cells transfected with miR-130b by FACS analysis.

CONCLUSIONS: MiR-130b plays an important role in the epigenetic modification of esophageal adenocarcinomas by inhibiting DNMT1. Increased miR-130b expression in vitro results in an increased apoptotic fraction, perhaps by indirect restoration of p16 function.
Optimal Ganciclovir Prophylaxis to Prevent Cytomegalovirus Reactivation in Immunocompetent Hosts

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PURPOSE: Immunocompetent critically ill surgical patients can reactivate latent cytomegalovirus (CMV) and these patients have significantly higher morbidity and possibly mortality. Prevention of reactivation using therapeutic ganciclovir (GCV) in a murine CMV (MCMV) sepsis model reduces pulmonary fibrosis demonstrating that reactivation is pathogenic. Antiviral therapy is not innocuous, so before embarking on clinical trials to prevent CMV reactivation, we sought to determine the efficacy of several GCV treatment strategies.

METHODS: BALB/c mice latently infected with MCMV were subjected to sepsis, then randomized into one of five treatment groups. Seventy-one surviving mice received either therapeutic GCV (10 mg/kg/day X 21 days), short course therapeutic GCV (10 mg/kg/day X 7 days), low dose GCV (5 mg/kg/day X 21 days), delayed therapeutic GCV (10 mg/kg/day X 14 days, delayed 7 days), or placebo. Short course GCV and low dose regimens limit GCV exposure during prophylaxis, while delayed GCV simulates treatment after diagnosis. Pulmonary reactivation was confirmed by focused expansion assay, and histologic sections were evaluated for tissue fibrosis. Separate experiments evaluated the influence of GCV on early LPS induced pulmonary TNF expression using quantitative PCR 1, 3, and 7 days after treatment.

RESULTS: There was no significant difference in sepsis survival between groups (~60%), and all GCV regimens prevented MCMV reactivation significantly better than placebo (p<0.002). Therapeutic GCV had the lowest incidence of reactivation (1/12), and short course GCV showed similar reactivation rates (2/16). Both low dose and delayed GCV were associated with significant breakthrough reactivation (6/14 and 7/14 respectively). Therapeutic GCV had the lowest incidence of pulmonary fibrosis, and importantly all other regimens showed similar fibrosis to saline treatment. Delay of GCV therapy for 1 week after the onset of sepsis was associated with significantly worse fibrosis (p<0.05) than early therapy. GCV therapy did not seem to reduce early TNF expression.

CONCLUSIONS: Although short course therapeutic GCV is efficacious in preventing reactivation after sepsis, it is unclear if short course therapy will prevent pulmonary injury. Altogether, these results suggest that a treatment trial in humans should use therapeutic GCV initiated as early as possible to minimize CMV reactivation and associated pulmonary injury.
Enhanced Antitumor Activity of Interferon-Alpha in SOCS1-Deficient Mice Is Mediated by CD4+ and CD8+ T Cells

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HYPOTHESIS: Interferon-alpha (IFN-a) is used to treat melanoma tumors and is also important for the surveillance and destruction of tumor cells in normal tissues by the immune system. Proteins belonging to the suppressors of cytokine signaling (SOCS) family have been shown to regulate cytokine signal transduction in various cell types, but their role in modulating the response of immune cells to IFN- has not been fully explored. We hypothesized that SOCS1-deficient mice would have an enhanced responsiveness to the antitumor effects of IFN-a, possibly via the actions of CD4+ or CD8+ T cells.

METHODS: SOCS1-deficient (-/-) or control mice on a C57BL/6 background were injected i.p. with the murine melanoma cell line JB/MS on day 0. Mice then received daily injections of either PBS or IFN-A/D (2x10^4 U/day) i.p. for 30 days. Mice in antibody depletion experiments were given rat anti-mouse CD4, rat anti-mouse CD8, or purified rat control IgG (100 ug i.p.) in order to deplete immune cells. For flow cytometry experiments, freshly isolated splenocytes were stained with CD80 or appropriate isotype control antibodies and fixed in formalin prior to analysis. Flow cytometry was used to test for the expression of CD4, CD25, and foxp3 on immune suppressive regulatory T-cells. Log-rank Kaplan-Meier survival curves were used to evaluate survival.

RESULTS: Control mice injected with IFN-A/D had a mean survival of 18 days (range 16-20 days) compared to PBS treated mice with a mean survival of 13 days (range 12-16 days) (p=0.005). The antitumor effects of IFN-A/D therapy were significantly enhanced in SOCS1 -/- mice as 75% of these mice were cured of their tumors, whereas all PBS treated mice died at 13-16 days (p=0.004). Depletion of CD8+ T-cells markedly inhibited the antitumor effects of IFN-A/D in SOCS1 -/- mice (p=0.002). Similarly, SOCS1 -/- IFN-A/D treated mice depleted of CD4+ T-cells resulted in 17-26 day survival versus 100% cure rate for control mice (p < 0.001). SOCS1 -/- mice treated with IFN-A/D showed a trend towards increased numbers of CD4/CD25/foxp3 T-regulatory cells compared to PBS treated mice (2.6% vs. 1.6% total splenocytes). Finally, splenocytes from SOCS1 -/- mice treated with IFN-A/D showed a trend towards decreased expression of the co-stimulatory molecule CD80 (5.7% vs. 8.7% total splenocytes).

CONCLUSIONS: SOCS1 -/- mice have a CD4 and CD8 dependent increase in survival in response to IFN-A/D. Additionally there is an increase in the number of T-regulatory cells and a decrease in expression of the co-stimulatory molecule CD80. Modulation of SOCS1 in patients with melanoma receiving IFN-a could lead to an increase in survival.
The Role of Screening Duplex Scans in Trauma Patients upon Transfer to Inpatient Rehabilitation

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PURPOSE/HYPOTHESIS: Trauma patients have an elevated risk of deep vein thrombosis (DVT). Acceptance of trauma patients to our affiliated inpatient rehabilitation center often requires screening duplex in asymptomatic patients which often leads to delay in transfer and unnecessary costs. We assessed the value of screening duplex ultrasounds for deep vein thrombosis in patients discharged from our institution to an inpatient rehabilitation center and identified risk factors which may correlate with positive duplex scans.

METHODS: A retrospective analysis of 306 patients admitted through our Level 1 Trauma Center who were accepted to an affiliated inpatient rehabilitation center over a 2 year period was performed to evaluate the importance of DVT prophylaxis, assess our institution’s incidence of trauma related DVT, and assess which categories of trauma patients are most susceptible to developing DVTs upon transfer to a rehabilitation center.

RESULTS: Of the 306 patients studied, 159 (51%) received screening duplexes. Of the 159 patients that received screening duplexes 15 developed DVTs while in the hospital, which correlates to an incidence of 9%. 93% of patients received prophylaxis by sequential compression devices or pharmaceutical means. A change in management upon transfer to a rehabilitation center after diagnosis of DVT was undertaken in 87% of patients. No change in management was necessary in the other 13% due to previously placed IVC filters. Of the patients with positive duplex scans 20% (3/15) had lower extremity fractures, 20% (3/15) had pelvic fractures and 33% (5/15) had spinal fractures. None of the patients had associated venous injuries. Of the patients with positive duplex scans, 40% (6/15) had no associated lower extremity, pelvic or spinal fractures.

CONCLUSIONS: These results suggest that standard use of screening lower extremity duplex scans in trauma patients requiring inpatient rehabilitation is a useful modality. Almost 10% of the patients that received duplex scans were found to have DVT’s and of those 87 percent had a change in their management as a result of these findings. Additionally, 60% of the patients with positive lower extremity duplex scans had lower extremity, pelvic or spinal fractures.
Changes in SICU Practice Improve Antibiotic Utilization for Ventilator-Associated Pneumonia

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PURPOSE/HYPOTHESIS: We have previously presented data regarding bronchoalveolar lavage and antibiotic selection for ventilator-associated pneumonia (VAP) from July-October 2005 in medical and surgical intensive care units. We have now examined all patients who had BALs performed from July-October 2008. We hypothesized that antibiotic use in the surgical intensive care unit (SICU) has improved in the interim due to a number of changes implemented since 2005. These include division of the SICU team into two rounding teams, addition of a second attending critical care specialist, presence of a dedicated pharmacist on SICU team rounds, an increased emphasis on antibiotic stewardship, an increase from two to four SICU fellows, and addition of nurse practitioners.

METHODS: Data were obtained with IRB approval for all patients undergoing BAL for initial suspicion of VAP in ICUs at our tertiary care institution in July-October of 2005 (n=187) and 2008 (n=186). Patients with other indications for BAL were excluded. BAL, blood, and urine culture results; length of stay; mortality data; and antibiotic use were recorded.

RESULTS: In the SICU initiation of appropriate empiric broad-spectrum antibiotics for treatment of VAP increased from 41.8 to 60% between the 2005 and 2008 periods (p=0.013). Use of inadequate narrow-spectrum antibiotics was stable (27.6 to 32%, p>0.05). The proportion of patients with VAP who did not receive antibiotics declined over the period from 30.6 to 8% (p<0.0002). Appropriate de-escalation of antibiotics based on culture-sensitive information improved from 52.0% in 2005 to 81.1% in 2008 (p<0.0002). Mortality was 27.6% in 2005 vs. 26.7% in 2008 (p > 0.05).

For comparison, MICU VAP mortality was 36.2% in 2005 and 30.2% in 2008 (p > 0.05) while MICU antibiotic initiation and tapering rates were stable over that time.

CONCLUSIONS: Multiple changes in SICU practice resulted in improved antibiotic initiation and de-escalation. While these changes may have unmeasured benefits with regard to patient outcomes and antibiotic resistance, in-hospital mortality was unchanged despite improved practices.
Palliative Resections for Stage IV Gastric Cancer: 16 Years of Experience with 69 Patients

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INTRODUCTION: Gastric cancer carries a poor prognosis worldwide with most patients presenting with incurable disease. Patients often present with severe symptomology which is only potentially remedied surgically. As such, palliative gastrectomy is commonly offered yet there is a paucity of data in the literature reporting its benefit. We sought to evaluate our experience with palliative gastrectomy in patients with advanced gastric cancer.

METHODS: We retrospectively reviewed gastric cancer patients treated at our institution between 1992 and 2008. Demographics, treatment, and outcome data were collected. Groups were compared with contingency table analysis (chi-squared and Fisher’s exact test where appropriate) and two-sample Student’s t-test for continuous variables. Kaplan-Meier survival curves were created and compared by log-rank analysis.

RESULTS: There were 218 stage IV gastric cancer patients during the 16 years of the study, of whom 69 underwent palliative resection. Of the 69 resections, 35 (50%) were male with mean age of 59.2 +/- 14.3. Of the 69 resections, 42 (61%) patients presented with intractable pain, 23 (34%) with nausea and vomiting and 12 (17%) with hemorrhage. 39 patients (56%) underwent total gastrectomy, 27 (39%) subtotal gastrectomy and 3 patients underwent a hemigastrectomy with en bloc pancreaticoduodenectomy. Mean blood loss was 484 ml (range: 50 - 1200 ml), similar among the types of procedures. Perioperative complication rate was 19% and perioperative (30-day) mortality rate was 7.2%. 35 patients (67%) had resolution of their symptoms; 20 (53%) of these patients underwent total and 13 (37%) subtotal gastrectomy (p=0.09). Symptoms resolved in 71% of patients presenting with pain, 58% presenting with nausea and vomiting and 43% in patients presenting with hemorrhage. Median survival was 8.7 months vs. 5.2 months for the non-resection group (p=0.069), with 33.7% surviving 12 months and 18% surviving 24 months. There was no significant difference in survival between total and subtotal resection (11.4 vs. 7.5 months, p=0.4). Resolution of symptoms did not influence survival (p=0.3).

CONCLUSIONS: This study represents the largest single-institution reported experience with palliative gastrectomy. Palliative resection in the face of stage IV gastric cancer is useful in select patients, with an acceptable perioperative mortality rate. Two-thirds of patients undergoing resection have their symptoms improve. Total gastrectomy seems to lead to better symptoms relief, compared to partial or subtotal gastrectomy. As expected, there is no significant survival benefit in the patients that undergo resection.
Toxic Epidermal Necrolysis Syndrome and SCORTEN: Ohio State University Medical Center Experience

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PURPOSE/HYPOTHESIS: Toxic epidermal necrolysis syndrome (TENS) is a rare, life-threatening disease of mucocutaneous desquamation often resulting from adverse drug reaction. SCORTEN is a severity-of-illness score that was developed to predict the mortality of patients affected with TENS within the first 24 hours of presentation. The purpose of this study is to retrospectively review the outcomes; particularly mortality, of patients with TENS treated at OSUMC, and compare them to those expected according to SCORTEN predictions. Recently, TENS patients have been managed at burn centers with improved patient outcomes.

METHODS: This is a retrospective chart review of all patients, age 18 or greater, admitted to OSUMC between January 2004 and October 2008, with the diagnosis of TENS/SJS. Data collected included late transfer to burn center, outcome, mortality, withdrawal of medication, lab data, complications, and risk factors. The SCORTEN equation was calculated for each patient to predict mortality. The accuracy of the SCORTEN mortality predictors was analyzed for the OSUMC patients with TENS/SJS.

RESULTS: On analysis of patients treated after establishment of the Burn Center, it was found that the SCORTEN equation was indeed predictive of mortality (r = 0.585) in patients diagnosed with TENS/SJS. Those patients managed by the burn service were found to have significantly greater epidermal detachment (p = 0.022). TENS patients treated by the burn service had no significant difference in length of stay or mortality, and actually had a significantly decreased length of ICU stay compared to TENS patients treated during the same time period by other services (mean 6d vs. 15.8d, p = 0.029).

CONCLUSIONS: The accuracy of the SCORTEN mortality predictors was validated in the patients with TENS/SJS treated at OSUMC. Despite establishment of the OSU Burn Center in February 2006, the majority of patients with TENS/SJS are being managed by various medical services. The patients treated by the burn service had significantly greater epidermal detachment. In spite of this, patients treated by the burn service had no difference in length of stay or mortality, and actually had a shorter ICU stay. These results reconfirm the benefits of the involvement of the burn service in the care of patients with TENS/SJS.
Occult Cytomegalovirus Infection in Vivarium-Housed Mice

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PURPOSE/HYPOTHESIS: Cytomegalovirus (CMV) is a beta herpes virus that is spread by oral ingestion that infects ~60-90% of the human population. Recently we have shown that murine CMV (MCMV) infection can influence murine transplant graft acceptance. During these studies, we also determined that “naïve” mice housed in the vivarium can acquire occult CMV infections. The purpose of this study was to determine a vector for this transmission. Because MCMV is endemic in wild mice, and there are wild mice in Wiseman, we hypothesized that vivarium-housed mice contract MCMV from wild mice. This hypothesis requires a method of contact, and because our mice are housed with micro-isolator lids, we hypothesized further that CMV might be introduced by chow contaminated by wild mice.

METHODS: We used mouse tissue from our previous epidemiologic studies as well as two wild mice caught in Wiseman hall. In addition, chow was obtained from several vivarium sources, as well as from outside “noncontaminated” sources. DNA were extracted from lung and salivary glands, and several MCMV genes were amplified by nested PCR. These amplicons were sequenced using PCR gel isolation, and the results were compared using the Bioedit sequencing alignment editor program.

RESULTS: Tissues of from both wild mice and vivarium-housed mice were confirmed to be MCMV positive. Similarly, all mouse chow samples were positive for MCMV DNA. Sequencing of MCMV DNA from vivarium mice showed significant differences from wild mice. Similarly vivarium mice MCMV DNA was significantly different from chow isolated MCMV DNA. Finally, MCMV DNA amplified from mouse chow appeared most similar to wild mouse MCMV DNA. Importantly, MCMV DNA amplified from vivarium-housed mice were compared to published wild and laboratory MCMV strains and were found to be most similar to two lab strains, Smith and Dm157 MCMV. Amplification and sequencing of the m157 gene suggests that the occult infected mice have Smith MCMV.

CONCLUSIONS: These data confirm that vivarium-housed mice can develop occult MCMV infections that are not detectable by traditional screening. Because DNA in mouse chow and wild mice is different from vivarium-housed mice, we conclude that this is not the vector of transmission. Others have reported that low titer infections with other viruses can elicit virus specific T-cells, without detectable serum antibody responses, and we are currently performing experiments to determine if this can happen with MCMV.
Intra-Operative Fluorescence Vascular Angiography in the Design and Management of Microvascular Free Tissue Transfer

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PURPOSE/HYPOTHESIS: The use of perforator flaps has increased the need for sensitive pre-, intra-, and postoperative flap vascularity assessment. Conventional imaging techniques have failed to resolve vascular anatomy with the accuracy necessary to improve outcomes. We have employed emerging imaging techniques that allow for real time dynamic, intra-operative identification of not only vascular anatomy but flap perfusion.

METHODS: Laser-assisted intra-operative indocyanine green fluorescent-dye angiography (LA-ICGA) using two different commercial imaging systems was performed on 29 microvascular free tissue transfer cases in a prospective fashion. Fluorescence imaging was used to define flap vascular anatomy pre and post anastomosis in all cases.

RESULTS: All flaps were successfully imaged. Images obtained after tissue transfer confirmed patent anastomosis and tissue perfusion in all cases. In this series we had no flap failures or operative re-explorations. In one case the information obtained from imaging prior to flap elevation was used to alter skin paddle design to incorporate perforators that would otherwise have been excluded.

CONCLUSIONS: This technique represents a novel method for evaluating flap vascularity in a variety of flap types. Real time assessment may allow for more accurate flap design and has the potential to accurately identify the site of thrombosis and blood flow compromise. Future studies will evaluate the potential for this technique to guide flap design and to evaluate perfusion and microsurgical anastomoses. This technique may reduce the occurrence of complications and improve overall clinical outcomes.
Surgical Clinical Correlates: Implementation of a First-Year Medical School Program

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PURPOSE/HYPOTHESIS: Medical students state the need for a clinically oriented anatomy class so to maximize their learning experience. We hypothesize that first year medical students who take the Surgical Clinical Correlates in Anatomy program perform better than their peers in their anatomy course, their surgical clerkships and ultimately choose surgical residencies.

METHODS: We designed and recently implemented this elective program for the first year medical students. It consisted of General Surgical Knowledge, Orthopedic Surgery, Plastic Surgery, Urology, Cardiothoracic Surgery, General Surgery, Vascular Surgery and ENT sessions. Each session had defined learning objectives and interactive cadaveric operations led by attending surgeons. The program was elective and had 25 participants randomly selected from 93 volunteers. A questionnaire was provided before and after the program to all first year medical students. The medical students will be followed for their entire medical school career.

RESULTS: Based on our questionnaires, 24/25 students felt that the Surgical Clinical Correlates in Anatomy program was helpful and would recommend it to others. 23/25 students thought that the class should be continued. A dependent t-test revealed that opinions of surgeons had significantly improved for the entire first year medical school class (0.105 to 0.133). ANOVA showed there was a significantly greater increase in positive opinions for participants in Surgical Clinical Correlates when compared to the rest of the class (-0.72 for participants and -0.12 for nonparticipants). There was no significant change in negative opinions overall. Analysis of the first year anatomy scores showed that our participants averaged 87.7%, those that volunteered for the class but were not chosen to participate averaged 86.9%, and the rest of the class averaged 85.9%. Our data showed a significant decreased interest in surgery for the entire first year class when matched pre and post-evaluations were compared. We will comparatively analyze clinical surgical rotation scores and residency matches.

CONCLUSIONS: A need exists among medical students to develop a clinically correlated anatomy program that will maximize their learning experience, improve their performance and allow them to make more informed career choices. The recent implementation of this Surgical Clinical Correlates in Anatomy program fulfills this need.
Safe Alternative Transgastric Peritoneal Access in Humans:
NOTES

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OBJECTIVE(S): Diagnostic transgastric endoscopic peritoneoscopy (DTEP) has been used as a tool to evaluate the abdomen via a natural orifice. Visualization of the abdominal wall is excellent after transgastric endoscopic access. We present our experience with transgastric endoscopic peritoneoscopy (TEP) to access the peritoneum, visualize the abdominal wall, direct trocar placement and perform adhesiolysis without laparoscopic visualization in patients undergoing laparoscopic roux-en-y gastric bypass procedures (LSRYGB).

METHODS: Forty patients scheduled to undergo LSRYGB for the treatment of morbid obesity participated in the study. There are two arms to the study. The initial 20 patients underwent preinsufflation of the abdomen prior to TEP. The second 20 had no preinsufflation. Ten patients in each arm had no history of abdominal operations. The other 10 have had previous intra abdominal procedures. TEP was performed through a gastrotomy created using an orally placed therapeutic gastroscope without laparoscopic visualization to guide access. Adhesions are visualized, evaluated and in some cases taken down endoscopically prior to trocar placement. The gastrotomy is used for EEA anvil placement in the LSRYGB. Aspirates of the stomach and post-gastrotomy peritoneal cavity were collected and sent to a third party (PACE Analytical) for bacterial analysis. Diagnostic findings, operative times and clinical course were recorded.

RESULTS: The average time for completion of the endoscopic intervention was 19 min. Three patients had limited visualization due to significant intra abdominal adhesions (2) and omental fat (1). Three of the 20 who had no previous surgeries and 17 of 20 with a history of intra abdominal interventions had adhesions visualized endoscopically. Endoscopic adhesiolysis was performed in one and four patients in these groups respectively. Six occult umbilical hernias, one inguinal hernia and one hiatal hernia were noted on endoscopic exploration. There were no complications related to intubation of the stomach, creation of the gastrotomy, or endoscopic exploration of the abdomen. The bacterial load within the peritoneum after DTEP was markedly lower than the amount found in gastric aspirates (p-value < 0.001). In 23% of the cases there were identical species isolated in the stomach and peritoneal aspirates. No clinically significant infectious complications occurred secondary to NOTES.

CONCLUSIONS: TEP is a safe and accurate means to access the peritoneum visualize the abdominal wall, perform adhesiolysis and direct trocar placement in the morbidly obese without laparoscopic guidance. There is no clinically significant risk of infection posed by DTEP. Safe and reliable gastric closure remains the sole limitation to its clinical use outside of a protocol necessitating a gastrotomy.
Glutathione Disulfide Induces Neural Cell Death via a 12-Lipoxygenase Pathway

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PURPOSE/HYPOTHESIS: Reduced glutathione (GSH) is an ubiquitous low molecular weight intracellular thiol present in all aerobic cells in millimolar concentrations. Under conditions of oxidative stress, large amounts of GSH are rapidly oxidized to GSSG. Thus, elevated GSSG/GSH ratio is often used as a marker of oxidative stress. Over the years, GSSG has been viewed as a metabolic waste-product. Cell death is often associated with high GSSG levels. Such results are interpreted as evidence for oxidative stress without addressing any potential functional significance of GSSG in the death process. We hypothesized that under specific conditions, GSSG functionally participates in signaling for cell death.

METHODS: Mechanisms that trigger the oxidation of GSH to GSSG in a cell such as exposure to ROS or to ROS-generating cytokines also induce numerous other cellular responses. Thus, it is challenging to dissect which of those responses actually contributed to the death process. To address this complication, we raised cellular GSSG content by microinjection. Control cells were microinjected with either the corresponding reduced form GSH or the vehicle (PBS).

RESULTS: GSSG, but not GSH, caused cell death at pathophysiologically relevant concentrations. GSSG-induced death of the neural cells was protected in the presence of the 12-lipoxygenase inhibitor alpha-tocotrienol or BL15. Previous work from our laboratory has identified 12-lipoxygenase as a key executioner of neural cell death relevant to stroke. Results of this study indicate that GSSG induces 12-lipoxygenase dependent death of neural cells. Furthermore, GSSG-dependent glutathionylation of 12-lipoxygenase is a critical player in neural cell death. We tested our hypothesis by using glutaredoxin, a deglutathionylating enzyme in mammalian cells, and noted that glutaredoxin transfected neural cells were protected against glutamate challenge. To test the significance of our findings in vitro, GSSG was stereotaxically injected to the brain in vivo and MRI was performed to quantify tissue lesion.

CONCLUSIONS: Findings of this study lead to question the significance of GSSG in such processes. From the standpoint of novel therapeutic approaches, strategies directed at improving or arresting cellular GSSG clearance may be effective in minimizing oxidative stress related tissue injury or potentiating the killing of tumor cells, respectively.
Transoral Incisionless Fundoplication for GERD: Early North American Results

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INTRODUCTION: The most recent FDA-approved endolumenal device to treat gastroesophageal reflux disease (GERD) is the Esophyx (EndoGastric Solutions, Inc., Redmond, WA, USA) transoral incisionless fundoplication (TIF). This device deploys full-thickness serosa to serosa fasteners into the gastric wall to form an interrupted suture line at the base of the gastroesophageal junction, thus recreating the gastroesophageal valve. The goal of this current study is to demonstrate safety and efficacy of translumenal incisionless fundoplication with a selected patient population.

METHODS: Twenty six patients with chronic GERD underwent Esophyx fundoplication between September 2007 and February 2009. Eight patients were excluded from the post operative assessment. Five of the ten patients were lost to follow up. Two patients asked to be removed. One patient passed away from a self-inflicted drug overdose. Prospective data in the form of validated questionnaires were used. The GERD-Health Related Quality of Life instrument (GERD-HRQL) and the Anvari score along with proton pump inhibitor (PPI) use was collected at three months and compared to baseline scores. Exclusion criteria included American society of Anesthesia Index (ASA) >3, Body Mass Index (BMI) >40 kg/m2, hiatal hernia > 2 cm and the diagnosis of an esophageal motility disorder or any complicating gastroesophageal pathology.

RESULTS: There were 10 males and 16 females with mean overall age of 45 years. Median BMI was 28 (20-38). Mean valve circumference was 217 degrees and valve length was 2.7 cm Mean procedure time was 65 minutes and mean length of stay was one day (range 0-6). The mean Anvari and GERD-HRQL (Velanovich) score improved significantly by 47% (34 to 16, \( p=0.004 \)) and 64% (22 to 8, \( p=0.004 \)) respectively. Sixty-nine percent of patients were still taking antireflux medications and 32% of patients were entirely satisfied with the procedure. There were two adverse postoperative events involving bleeding at the GE junction requiring repeat endoscopy and cauterization. Three patients (12%) had persistent symptoms requiring Nissen fundoplication.

CONCLUSION: The Esophyx transoral incisionless fundoplication appears to be safe and effective for the treatment of GERD. Our early North American results show significant improvement in quality of life and overall symptoms. Further studies with more objective data such as post procedure pH monitoring and endoscopic neo-valve assessment are needed to help determine overall effectiveness.
Characterization of the Therapeutic Potential for Supplemental Oxygen Therapy in Acute Ischemic Stroke

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PURPOSE/HYPOTHESIS: In terms of consumption, the brain’s demand for oxygen is among the highest of all organs underscoring the significance of characterizing oxygen-sensitive mechanisms in acute ischemic stroke (AIS) pathology. To date, the significance of targeting AIS-caused focal hypoxia management remains unclear. Despite the support of numerous case reports and small animal research, the three clinical pilot studies that probed the efficacy of hyperbaric oxygen to treat AIS reported insignificant, or potentially harmful, outcomes. We hypothesize that conflicting outcomes reported in literature stem from a limited window of benefit for supplemental oxygen therapy to treat AIS. The objectives of this study were twofold: (1) to define the therapeutic window of opportunity for supplemental oxygen by employing normobaric and hyperbaric oxygen at the onset of ischemia or at reperfusion in a rodent model of middle cerebral artery occlusion (MCAO); and (2) to employ high density transcriptome screening towards uncovering oxygen-sensitive molecular mechanisms implicated in AIS.

METHODS: Transient MCAO in rodents was employed to delineate the therapeutic potential of normobaric and hyperbaric oxygen during occlusion (NBO, HBO) versus normobaric and hyperbaric oxygen at reperfusion (rNBO, rHBO). Stroke lesion volumes were quantified using 4.7T magnetic resonance imaging at 48h along with histochemical assessment of oxidative stress and neurodegeneration. Unbiased query of oxygen responsive gene networks in stroke-affected tissue was performed using GeneChip™. Verification of gene candidates was achieved by real-time PCR from laser captured neurons in stroke affected region of the brain.

RESULTS: NBO and HBO attenuated, while rNBO and rHBO exacerbated, AIS-associated lesion volume, oxidative stress and neurodegeneration. NBO was sufficient to correct penumbral tissue pO₂ during AIS. Directed microarray analysis revealed oxygen-sensitive gene networks related to blood-brain barrier integrity, glutamate metabolism, and apoptosis.

CONCLUSIONS: AIS presents a temporal window of opportunity to minimize brain tissue damage using supplemental oxygen therapy. Findings of this study provide key information relevant to the successful design of clinical trials aimed at testing the effects of supplemental oxygen in stroke affected patients.