# Table of Contents

- **Oral Presentations** *(in order of occurrence at the event)* ................................................................. 1
- **Poster Presentations** *(in alphabetical order by presenting author)* .................................................. 5
- **Index of Presenting Authors** ................................................................................................................. 46
- **Notes Pages** ........................................................................................................................................... 49
Melatonin Does Not Affect Nighttime Blood Pressure in African-Americans with Essential Hypertension: Results from Two Randomized Placebo-Controlled Clinical Trials (MAP-Trials)


Background: Melatonin has been shown to reduce nighttime blood pressure in Caucasians but these results have not been confirmed in African-Americans with nocturnal hypertension (HTN), who are at higher risk for development of cardiovascular events.

Methods: In a phase II, randomized, double blind, cross over design, 40 AA patients with essential HTN, on less than 3 drugs, were randomized to 4 weeks of controlled release (CR) melatonin or placebo at a daily dose of 8 mg PO at bedtime followed by 4 additional weeks of exposure to the other agent. Another overlapping group of 40 patients were exposed to 24 mg daily dose with the same design. Routine laboratory tests, overnight polysomnography (PSG) sleep studies, and 24h ambulatory blood pressure monitoring (ABPM) were performed at baseline and after each arm of treatment. Primary outcome was the changes in nighttime systolic (SBP) and diastolic (DBP). We also measured plasma p-selectin, e-selectin levels and urinary catecholamine and 6-sulfatoxymelatonin (marker of compliance) levels.

Results: 36 patients (90%) in each group completed the study. Average (SD) age was 50.42 (9.25) and 48.86 (9.88) years in the low and high dose studies respectively. There were more females than males in both studies (69.4% vs 30.6%). Compliance with medications was 96% in 8mg and 100% in the 24 mg studies. Melatonin (neither at 8mg nor at 24 mg daily dose) did not affect nighttime or daytime SBP, DBP, serum selectin and urinary catecholamine levels, or total sleep time.

Conclusions: In contrast with Caucasians, CR-melatonin at 8 mg or 24 mg daily dose did not have any significant effect on nighttime or daytime blood pressure in AAs with essential HTN when compared to placebo.

Lopinavir use and Human Papillomavirus (HPV) Infection in HIV-infected Women


BACKGROUND: Lopinavir, an HIV protease inhibitor (PI), inhibits HPV-mediated p53 degradation, and cervical application of lopinavir was associated with clearance of cervical dysplasia in a small clinical trial. It is unknown whether oral lopinavir use reduces HPV risk in HIV+ women.

METHODS: Specimens and data were obtained from 2793 HIV+ women enrolled in the Women's Interagency HIV Study in 1994/95 or 2002/03 at semiannual follow-up. During each visit, questionnaires were administered and cervicovaginal lavage (CVL) specimens for HPV DNA testing by MY09/MY11 PCR were obtained.

RESULTS: A total of 1291 HIV+ women receiving highly-active antiretroviral therapy (HAART) provided CVLs and were included in the analysis. Lopinavir use was reported by 233 (18%). Compared to non-users, lopinavir-users had a lower median CD4 count (298 vs 428 T-cells/mL; P<0.001) and were more likely to have plasma HIV viral load <4000 copies/mL (43% vs 26%, P<0.001). There was no difference between lopinavir-users and non-users in HPV DNA positivity (52% vs 45%; P=0.13). In multivariate GEE models studying women on effective HAART (HIV viral load <4000 copies/mL) adjusting for age, CD4, race/ethnicity, smoking, and number of recent sex partners, the HPV prevalence ratio for lopinavir-users vs non-users was not statistically significant (PR=1.25; 0.82-1.89; P=0.30).
CONCLUSIONS: These data reveal no reduction in HPV prevalence with oral lopinavir, suggesting oral and topical lopinavir use might have different impact. Additional analyses are pending to evaluate effect of LPV on HPV incidence and clearance. Future studies examining associations between HPV infection and cervical LPV drug concentrations are warranted.

9:00 am

Fatty Liver and Leaky Gut: A Deadly Duo
Rahman K, Thorn NE, Kumar P, Nusrat A, Parkos C, and Anania FA

Background: Non-alcoholic fatty liver disease (NAFLD) progresses to non-alcoholic steatohepatitis (NASH) in twenty percent of NAFLD patients. The exact mechanisms for disease progression are not entirely clear, although accumulating evidence suggests a role for intestinal barrier dysfunction in driving hepatic inflammation and disease progression. The AIM of the present study was to delineate the respective contribution of intestinal epithelial permeability to the pathogenesis of NASH in a mouse model of compromised intestinal epithelial permeability due to deletion of the tight junction protein, junctional adhesion molecule A (JAM-A-/-).

Methods: Male C57BL/6j (WT) or JAM-A-/- mice were fed either normal diet (ND) or a high fat, high cholesterol diet with 2% fructose water (HFCD). Intestinal epithelial permeability was assessed by in vivo FITC-Dextran permeability assay. Liver tissue injury and inflammation were assessed by histological, RT-qPCR, and flow cytometric analysis.

Results: Within 8 wks of HFCD feeding, JAM-A-/- mice developed steatosis, lobular inflammation, hepatocellular ballooning and fibrosis, which correlated with increased intestinal permeability and serum LPS levels. Only modest NASH-related histologic findings were observed in the HFCD-fed WT mice. Increased fibrosis in HFCD-fed JAM-A-/- mice correlated with increased α-smooth muscle actin (αSMA) expression. Flow cytometric analysis revealed increased intrahepatic macrophages, and recruitment of inflammatory monocytes in HFCD-fed JAM-A-/- mice. Taken together, our data indicate that rapid progression of liver injury in the HFCD-fed JAM-A-/- mice can be attributed to increased intestinal permeability resulting in enhanced translocation of bacterial products that drive hepatic inflammation.

10:15 am

Healthy HIV-infected Subjects Harbor HIV in Alveolar Macrophages, which can Impair Lung Function
Cribbs SK, Lennox J, Caliendo AM, Brown LA, Guidot DM.

Objective: Alveolar macrophages (AM) are specialized innate immune cells that reside in the alveolus, a separate compartment site compared to blood. AM can be infected by HIV-1, but reports quantifying HIV burden in AM are conflicting, and it is unclear what impact HIV infection has on AM function.

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We hypothesize that AM are an important reservoir for HIV, contributing to cell-cell spread of the virus within the lung and exhibiting abnormal immune function that contributes to the increased risk of severe lung infections.

Methods: We enrolled 22 subjects who underwent bronchoscopy and bronchoalveolar lavage. AM were isolated and HIV-1 RNA was quantified in the cells using the Abbott RealTime HIV-1 Assay. Proviral DNA was qualitatively measured using a modified version of the HIV-1 RNA assay. Phagocytosis was measured by incubating AM with FITC-labeled S. aureus and determining fluorescence with a Zeiss inverted microscope. Phagocytic index was calculated as (% positive cells x mean channel fluorescence)/100.

Summary of Results: 17 subjects had (+) proviral DNA and 7 had (-) proviral DNA in their AM. 94% in (+) proviral DNA vs. 100% (-) proviral DNA groups were on HAART. The median plasma viral load was 0 in both groups. HIV-1-infected subjects with (+) proviral DNA in their AM had a significantly lower AM phagocytic index compared to those with (-) proviral DNA in their AM [10.8 (IQR 5.1-31.9) vs. 64.9 (IQR 14.0-166.0), p=0.04].

Conclusions: Alveolar macrophages harbor HIV even in otherwise healthy subjects with undetectable plasma viral loads, representing a potential reservoir for the virus. In addition, HIV viral replication within these macrophages may impair phagocytosis and other immune functions, leading to an increased risk for lung infections.

10:30 am

Engineered Cell Therapy with Embryonic Stem Cell-Derived Cardiomyocytes Encapsulated in Injectable Nanomatrix Gel Enhanced Engraftment and Promoted Cardiac Repair in Experimental Myocardial Infarction
Ban K, Park HJ, Kim S, Andukuri A, Jun HW and Yoon YS

Background: A significant barrier to the therapeutic use of stem cells is poor cell engraftment in vivo. Here, we evaluated the therapeutic potential of cardiomyocytes (CM) derived from mouse embryonic stem cells (mESC) with injectable self-assembling peptide amphiphile nanomatrices that incorporates cell adhesive ligand (PA-RGDS) on experimental myocardial infarction (MI).

Methods and results: We first cultured rat CMs in PA-RGDS for 7 days and found that ~90% of the CMs survived, indicating that PA-RGDS supports the viability of CMs. Next, we intramyocardially injected mouse CMs with/without PA-RGDS. As results, we found that ~3 folds higher engraftment in the CM+PA-RGDS hearts suggesting that PA-RGDS significantly increased the retention of the injected CMs in the heart in vivo. We further investigated the therapeutic effects and long-term engraftment of mESC-CMs with PA-RGDS on MI in comparison with various control groups. Echocardiography demonstrated
that the CM-only and CM+PA-RGDS groups showed higher cardiac function at week 2. However, from week 3, higher cardiac function was only maintained in the CM+PA-RGDS group; this was sustained for 12 weeks. Confocal microscopic examination of the cardiac tissues harvested at 14 weeks demonstrated sustained engraftment and integration of mESC-CMs into the host myocardium and expressed representative CM proteins such as cardiac troponin T and a/b myosin heavy chain in the PA-RGDS group only.

Conclusions: This study for the first time demonstrated that PA-RGDS encapsulation can enhance survival of mESC-derived CMs and improve cardiac function post-MI. This nanomatrix gel-mediated stem cell therapy can be a novel option for treating MI.

10:45 am

Long-Term Effects of Metformin and Sitagliptin on Near-Normoglycemic Remission, β-Cell Function and Insulin Sensitivity in Obese African Americans with Hyperglycemic Crises
Anzola J, Duan W, Hudson M, Zhao L, Umpierrez GE, Smiley D

Most obese African American (AA) patients with new-onset diabetes (DM) presenting with hyperglycemic crises achieve near-normoglycemic remission during follow-up. The optimal treatment after stopping insulin is unclear; thus, this blinded RCT investigated if metformin (MTF) or sitagliptin (SIT) could delay hyperglycemic relapse and preserve β-cell function in AA patients with history of diabetic ketoacidosis (DKA) or severe hyperglycemia (HG, BG ≥ 400 mg/dL). A total of 48 newly-diagnosed AA patients in remission were randomized to MTF 1000mg/day (n=17), SIT 100 mg/day (n=16) or PBO (n=15). Modified oral glucose tolerance tests were performed at baseline, 3 months and every 6 months for up to 41 months while in remission to measure longitudinal changes in β-cell function (BCF) and insulin sensitivity (IS). Relapse was defined as fasting BG >130 mg/dl, random BG >180 mg/dl x2, and/or A1c ≥7.0%.

Compared to PBO, SIT and MTF significantly reduced the number of patients with hyperglycemic relapse (73% vs 25% vs 29% respectively, p=0.01) with a comparable remission period for SIT and MTF groups (median 589 vs. 472 days, p=0.97), both longer than placebo (p=0.03). Patients in remission had better markers of BCF during follow-up (p < 0.05) and similar levels of IS compared to those who failed without differences among treatment groups. Treatment with SIT resulted in higher indices of BCF (insulinenic index, C-peptide index), while the MTF group had better indices of IS (CISI, HOMA-IR).

In conclusion, SIT and MTF prevented hyperglycemia recurrence and prolonged the insulin-free remission period in obese AA patients with new-onset, hyperglycemic crises. This effect appears to correlate with improvements in β-cell function and/or insulin sensitivity.

11:00 am

Role of Intestinal Dysbiosis in the High Fat Diet-Induced Gastrointestinal Transit Delay in Mice
Nezami BG, Anitha M, Mwangi SM, Chassaing B, Vijay-Kumar M, Gewirtz A, and Srinivasan S

Background: We recently reported that high fat diet (HFD) in mice leads to delayed colonic motility. Here we investigated the role of gut microbiota in the pathogenesis of HFD-induced intestinal dysmotility and studied the impact of prebiotic oligofructose (OFS) in counterbalancing the dysbiosis. Methods: Eight week old male C57BL/6 mice were fed a regular diet (RD, 18% Kcal from fat) or HFD (60%) for 12 weeks. The effect of OFS on HFD-induced gastrointestinal motility changes was studied by adding OFS to the diets for 5 weeks. Serum and stool endotoxin levels were measured using Limulus Amebocyte Lysate and a specific TLR4 ligand reporter assay, respectively.

Results: Calculating geometric center showed that small intestinal transit was significantly slower in the HFD compared to RD (P<0.05) and distal gut transit measured by bead expulsion test was slower in the HFD (P<0.01). HFD feeding caused an increase in Firmicutes (3.6 fold, P<0.001), reduction in Bacteroidetes (33 fold, P<0.001) and an increase in Escherichia coli (36 fold, P<0.001). Serum endotoxin level (P<0.05) and stool endotoxin level (P<0.01) were increased in HFD fed mice. Adding OFS to HFD resulted in a significant decrease in Firmicutes and Escherichia coli, and increase in Bifidobacteria compared with HFD alone. Adding OFS to HFD also reduced serum endotoxin levels in mice, improved the number of colonic nitrergic neurons and increased small and distal gut transit (P<0.01).

Conclusions: HFD-induced delayed intestinal motility in mice is associated with dysbiosis. Manipulation of gut microbiota with OFS reduces endotoxemia and is associated with restoration of normal intestinal transit in HFD mice. We suggest that intestinal dysbiosis in HFD fed mice can contribute to the delayed intestinal motility.

2:00 pm

Panel of Seven Encapsulated and Nonencapsulated (iso)microRNAs in Human Samples that Predict Coronary Atherosclerosis Severity and Cardiac Events

Coronary Artery Disease (CAD) is a chronic inflammatory process that modifies microRNA (miRNA) abundance, intracellularly, in vascular and immune cells, and extracellularly, in plasma. Extracellular miRNAs are encapsulated in microvesicles (MV) or bound to proteins, and variations in miRNA profiles are promising as novel biomarkers of CAD severity. We hypothesized that CAD-associated variations in the miRNA profile are related to changes in the abundance of miRNA isoforms (isomiRs). IsomiR sequences are typically 1-3
neuton R MD, Kavtaradze N MD, Sher S MD, Ward C, Molina SA, Mitchell LA, Overgaard Tipton CM

Subset of Activated Naive B Cells Lupus Erythematosus Flares by Differentiation of a Novel Antibody Secreting Cells re Generated During Systemic rationale design of B cell-directed therapies for SLE. light into the pathogenesis of SLE and should contribute to the mutation and germinal center reactions. These findings shed B cells without further differenidation through somatic hypermutation and germinal center reactions. Strikingly, these naive cells displaying a high degree of clonality feed the ASC to autoantibodies. Unexpectedly, a novel subset of activated naïve cells, an original finding consistent memory and ASC. Moreover, clonally expanded ASC contain undergoing intraclonal diversification and differentiation into autoantibodies that contribute substantially to serum autoantibodies. Unexpectedly, a novel subset of activated naïve cells displaying a high degree of clonality feed the ASC to a greater degree than memory cells. These data support the development and clinical use of an isomiR biomarker panel to assess cardiovascular risk.

2:15 pm

Antibody Secreting Cells are Generated During Systemic Lupus Erythematosus Flares by Differentiation of a Novel Subset of Activated Naïve B Cells


Large expansions of antibody-secreting cells (ASC) are a hallmark of active systemic lupus erythematosus (SLE). Yet, their cellular origin, diversity, autoreactivity and contribution to serum autoantibodies remain unknown. We addressed these questions using Next Generation Sequencing coupled with serum antibody proteome and single cell monoclonal antibody analysis. During lupus flares, ASC display a highly diversified repertoire punctuated by large clones of SLE-specific VH-34 autoantibodies that contribute substantially to serum autoantibodies. Unexpectedly, a novel subset of activated naïve cells displaying a high degree of clonality feed the ASC to a greater degree than memory cells. Strikingly, these naïve cells persist in the circulation for several months while undergoing intraconal diversification and differentiation into memory and ASC. Moreover, clonally expanded ASC contain completely unmaturated antibodies of high autoreactivity also shared by activated naïve cells, an original finding consistent with direct differentiation outside the germinal centers. Together with measurements of anti-microbial ASC, our data indicate that selection of SLE-associated autoreactivities occur in the context of massive polyclonal activation with prolonged recruitment of activated naïve B cells. Our results provide the first evidence for the pathogenic autoreactive potential of naïve B cells without further differentiation through somatic hypermutation and germinal center reactions. These findings shed light into the pathogenesis of SLE and should contribute to the rationale of B cell-directed therapies for SLE.

3:15 pm

Tumor Necrosis Alpha Antagonism with Etanercept increases Circulating Endothelial Progenitor Cell Counts in Subjects with Psoriasis

Hayek S MD, Neuman R MD, Kavtaradze N MD, Sher S MD, Zhao L, Qunna Li, Waller E MD PhD, and Quyyumi A MD

Introduction: Psoriasis is independently associated with cardiovascular disease (CVD) and mortality, increased arterial stiffness and depressed circulating endothelial progenitor cell (PC) counts. TNF-α is central to the pathogenesis of psoriasis and is associated with endothelial dysfunction. Whether the TNF-α antagonist etanercept improve indices of endothelial function, arterial function and PC counts is unknown.

Methods: 21 subjects were enrolled in a double-blind, placebo-controlled, cross-over study. Subjects were randomized to receive subcutaneous injections of either etanercept 50 mg twice weekly or placebo for 12 weeks followed by a second 12-week period of the alternate treatment. Flow-mediated dilation, arterial wave analyses were performed and circulating PC counts measured.

Results: The cohort consisted of relatively young (40±11) bi-racial subjects (62% black) with mild psoriasis (median PASI 8) on systemic therapy and without known CVD. FMD (8.28 (5.25) vs. 8.77 (5.99) %, p=0.7), PWV (6.97 (1.42) vs. 7.24 (1.12) m/s, p=0.7) and AIx (19.9 (14.0) vs. 19.3 (13.4) %, p=0.9) remained unchanged post-etanercept compared to placebo. However, treatment with etanercept was associated with an increase CD34+/VEGFR2+ PC counts compared to placebo (0.026 (0.013[IQR]) vs [0.015(0.030[IQR])] cells/µL respectively, p=0.029).

Conclusion: Despite having negligible impact on signs of endothelial function and arterial stiffness, treatment with etanercept was associated with two-fold increase in endothelial PCs. Through improving the endogenous reparative capacity associated with PCs, treatment with etanercept may delay progression to vascular dysfunction. Long-term studies are required to define potential clinical benefits of early treatment with etanercept.

3:30 pm

Claudin-5 Increases Alveolar Permeability in Alcoholic Lung Syndrome by Destabilizing Claudin-18 / Zonula Occludens-1 Interactions


We found that alcohol abuse increases the severity of acute respiratory distress syndrome (ARDS) by impairing alveolar epithelial cell (AEC) tight junctions. In a rat model of chronic alcohol ingestion, decreased AEC barrier function was accompanied by increased cldn-5 and cldn-18 expression. Immunofluorescence of model type I AECs cultured on Transwell permeable supports showed that paracellular leak in cells from alcohol fed rats was accompanied by disrupted tight junction morphology. We then used Stochastic Optical
Reconstruction Microscopy (STORM) which increases the resolution of immunofluorescence to 20 nm. STORM revealed that alcohol caused a significant decrease in co-localization between AEC cldn-18 and ZO-1 along with increased co-localization between cldn-18 and cldn-5. Thus, cldn-5 binding to cldn-18 inhibits binding to ZO-1 which destabilizes tight junctions. We found that shRNA targeting to decrease cldn-5 expression improved AEC tight junction morphology and function. Conversely, transplanting cells to increase expression of YFP-tagged cldn-5 altered tight junction morphology and impaired barrier function. Thus, increased cldn-5 was necessary and sufficient to inhibit cldn-18 assembly and function. These data suggest that targeting cldn-5 may provide a therapeutic strategy to improve barrier function in ARDS.

**Poster Presentations**

In alphabetical order by presenting author.
Poster number listed above abstract.

Morning poster session 9:15 – 10:00 AM
Afternoon poster session 2:30 – 3:15 PM

### 40

**Active Tuberculosis Case Finding Among HIV Patients Using a WHO-recommended Screening Rule and Xpert MTB/RIF**

_Adelman MW, Tsegaye M, Kemper RR, Abeje TA, Tesfaye A, Asetfa A, Blumberg HM._

**Objective:** Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV) globally. The WHO recommends active TB case finding among PLHIV in high TB incidence areas, but TB diagnosis in resource-limited settings (RLS) is limited by low sensitivity of smear microscopy (standard of care). We evaluated the impact of implementing a TB screening algorithm combined with a rapid molecular diagnostic test (Xpert MTB/RIF) at an HIV clinic in Addis Ababa, Ethiopia.

**Design:** PLHIV were screened for TB with a WHO-recommended symptom-screen (cough, fever, night sweats, weight loss). Those with a positive screen (≥1 symptom) had sputum tested with smear microscopy, AFB culture, and Xpert.

**Results:** Of 828 PLHIV, 321 (39%) had a positive symptom screen. On multivariate analysis, PLHIV with an unscheduled visit (aOR 3.8, 95% CI 2.7-3.5), CD4 count <100 (aOR 3.1, 95% CI 1.6-5.9), past TB treatment (aOR 1.5, 95% CI 1.1-2.2), and not receiving anti-retroviral therapy [ART] (aOR 1.7, 95% CI 1.04-2.9) were more likely to have a positive symptom screen. Of those with a positive symptom screen, 217 provided sputum for diagnostic studies; 13 (6%) of 217 had pulmonary TB based on a positive Xpert and/or culture. CD4 count <100 was a risk factor for active TB disease (OR 4.9, 95% CI 1.5-16.3, p<.01). The sensitivity of AFB smear microscopy was 30%.

**Conclusion:** Nearly 40% of PLHIV at an Ethiopian clinic had a positive symptom screen and required TB diagnostic testing per WHO guidelines. Using culture and Xpert increased the yield of TB diagnosis given the poor sensitivity of smear microscopy. The large proportion of patients with a positive symptom screen suggests that the WHO-recommended algorithm is not feasible unless substantial resources are made available in RLS.

### 107

**The Role of Mitochondrial Reactive Oxygen Species in Hypoxia-induced Pulmonary Hypertension**

_Adesina SE, Hart CM, Sutliff RL_

Oxidative stress plays a critical role in pulmonary hypertension (PH) pathogenesis. The specific reactive oxygen species (ROS) responsible have not been defined, though mitochondrial ROS likely contribute. We hypothesize that mitochondrial O$_2^−$ and H$_2$O$_2$ promote PH pathogenesis.

Hypoxia effects on mitochondrial O$_2^−$ and H$_2$O$_2$ were measured using MitoPY1 and MitoSOX in human pulmonary arterial endothelial cells (HPAECs) exposed to normoxia (21% O$_2$) or hypoxia (1% O$_2$) for 72 hours. Mouse models with mitochondria-targeted SOD2 (TghSOD2) or catalase (mCAT) expression were used to modulate mitochondrial ROS. Control and transgenic mice were exposed to normoxia (21% O$_2$) or hypoxia (10% O$_2$) for 3 weeks. ROS levels (confocal microscopy and Amplex red assay), Nox mRNA levels (qRT-PCR), and proliferation and remodeling (α-SMA staining) were measured at the conclusion of the study.

Hypoxia exposed HPAECs had increased mitochondria-derived O$_2^−$ and H$_2$O$_2$ (p ≤ 0.5). Compared to control, mCAT expression prevented hypoxia-induced increases in lung H$_2$O$_2$, Nox2, Nox4, and PCNA mRNA, and α-SMA staining (p ≤ 0.5). Hypoxia-induced alterations in these markers were exacerbated in TghSOD2 lungs (p ≤ 0.5). These studies suggest that targeted attenuation of mitochondria-derived H$_2$O$_2$ attenuates pulmonary vascular derangements involved in PH pathogenesis.

### 45

**The Burden of Depression on Healthcare Utilization in a Population-Based Cohort of High-Risk Patients with Systemic Lupus Erythematosus**

_Aguire AJ, Bao G, Lin SS, Drenkard C._

Background: Systemic lupus erythematosus (SLE) is a chronic disease that predominantly affects black women. A common co-morbidity of SLE is depression, a debilitating disorder that affects 15-75% of SLE patients. Data from a mostly white SLE...
cohort suggests an association between depression and high emergency department (ED) use. We aimed to examine the relationship between depression and healthcare utilization in a predominantly black SLE cohort from the Southeastern US.

Methods: Georgians Organized Against Lupus (GOAL) is a population-based cohort of individuals with validated SLE from Atlanta, GA. Annual surveys furnish data on the demographics, disease outcomes and healthcare utilization of GOAL participants, of which 78% are black. We used data from the 2013-14 annual survey to examine the relationship between depression, as assessed by the 9-Item Patient Health Questionnaire (PHQ-9), and utilization of inpatient and ED resources in the past year.

Results: Among those participants with depression (PHQ-9 score ≥10), 57% had visited the ED, as compared to 42% of those with a score <10 (p=0.0014). Patients with and without depression had a mean of 1.5 ED visits and 1.0 ED visits, respectively (p=0.0003).

Conclusion: A greater proportion of depressed SLE patients had accessed ED resources for care. In addition, increasing depression severity was associated with gradually higher frequency of ED visits. Interestingly, we did not find an association between depression and hospitalization, suggesting that the reasons for increased ED visits did not meet inpatient admission criteria. Our data suggest the utility of depression screening modalities in the assessment of SLE patients and shed light on deficiencies in the care of depressed SLE patients.

21

Effects of a “Health Partner” Intervention on the Metabolic Syndrome
Wilson N, Al Mheid I, Cunningham L, Brigham K Martin GS, Gibbons G, Jones D, Vaccarino V and Quyyumi A

Introduction: The Metabolic Syndrome (MetS) is highly prevalent, afflicting a third of U.S. adults, and confers higher cardiovascular morbidity and mortality. While lifestyle modifications are the first-line of MetS treatment, sustained adherence is achieved by a minority of patients. We investigated the effects of a Health Partner (HP) intervention on MetS.

Methods and Results: 119 university employees with MetS (51±9 years, 59% women) were enrolled in a program that promotes clinical self-knowledge and healthier lifestyles at the Center for Health Discovery and Well Being. Baseline anthropometric, laboratory and vascular function measurements were used by the HP to generate an action plan that included strategies to improve dietary and exercise habits, and subjects were followed up to 2 years. Repeated measures ANOVA showed significant changes in waist circumference(p=0.007;baseline vs. 2 years: 103 vs. 98 cm), weight (p=0.004; 216±35 vs. 205±37 lbs), body fat percent(p=0.04; 39±7 vs. 38±8), fasting insulin levels (p=0.03; 11±8 vs. 7.9±10 μU/ml), low density lipoprotein (p=0.005; 115±31 vs. 105±29 mg/dl), as well as a reduction in carotid-femoral pulse wave velocity(p=0.02; 7.4±2 vs. 6.7±1 m/s), systolic(p=0.001; 131±18 vs. 126±14 mmHg) and diastolic blood pressure(p=0.006; 85±11.1 vs. 80±10).

Conclusion: A personalized, goal directed HP intervention improves abnormalities associated with MetS, including significant blood pressure improvements that accompanied decreased central arterial stiffness. These improvements were sustained after two years of follow-up. Whether HP intervention improves long-term outcomes and whether it is cost-effective needs further investigation.

66

Preoperative Echocardiography Predicts Right Ventricular Failure after Implantation of Left Ventricular Assist Devices: Interim Results from a Prospective Cohort Study

Introduction: Right ventricular failure (RVF) occurs in 20%-40% of contemporary, continuous-flow left ventricular assist device (LVAD) recipients. Preoperative clinical scores inadequately predict RVF risk.

Methods: Adult LVAD candidates without planned RV support are enrolled in an ongoing study. Primary endpoint is RVF by 90 days, defined by INTERMACS as need for (1) inotropes or pulmonary vasodilators any time past 7 days post-LVAD implant with concomitant high central venous pressure and low cardiac index or (2) need for mechanical RV support. The Michigan RVF score was used as the clinical score comparator.

Results: As of 3/2014, 41 patients have been enrolled (Table 1). Preoperative echocardiograms were performed a median of 4 days (1, 14) prior to implantation; 3 patients had inadequate echocardiographic windows for complete RV assessment (feasibility 92.7%). At 90 days, 15/38 patients (39.5%) developed RVF (2 deaths) and 3 (11.5%) died from other causes. Median duration of inotrope use was 7 days (5, 12); 7 patients (18.4%) required pulmonary vasodilators; 1 patient required mechanical RV support. Among echocardiographic parameters (Table 2), left ventricular (LV) diameters, RV global longitudinal strain, tricuspid regurgitation, and pulmonary acceleration were associated with RVF. Using backward logistic regression (P in 0.1, P out 0.05), a score derived from tricuspid regurgitation grade, LV systolic diameter, and RV global longitudinal strain had a C statistic of 0.88 (95%CI: 0.75-1.00; P<0.001) for RVF prediction. In comparison, the clinical score had C=0.63 (95%CI: 0.47-0.78; P=NS).
Conclusions: A preoperative echocardiographic score strongly predicts 90-day RVF after LVAD implantation and offers improved discrimination compared to a clinical score.

Guillain-Barre Syndrome and Lupus Nephritis: Simultaneous Presentation and Remission. A Case for Neuro-Renal Syndromes
Al-Khatib S, Guasch A

Inflammatory demyelinating polyneuropathies (IDP) have been reported in association with glomerulonephritis. The glomerular pathologies have mainly included minimal change disease (MCD), membranous nephropathy, or focal segmental glomerulosclerosis (FSGS). Our purpose is to emphasize the frequent association, common mechanisms and treatment in this neuro-renal syndrome. A 33 y.o male presented with lower extremity paralysis, anasarca, and a serum creatinine of 1.76 mg/dL. EMG was consistent with Guillain-Barre Syndrome. Positive serology included ANA, dsDNA, Anti-Smith, RNP IgG, SSA/RO. 24-hour urine had 19.3g proteinuria. Kidney biopsy revealed lupus nephritis (LN) IV & V. 5 days of plasmapheresis failed to improve symptoms. Pulse dose steroids and one dose of cytoxan administered. Next day patient's strength began to improve. Patient discharged with steroids and follow up. Patient received cytoxan monthly for 5 months, along with a steroid taper. Proteinuria and neurological symptoms resolved simultaneously, with renal function returning to baseline. We have a unique case of an IDP associated with LN not before described in the literature. Previously there has been an emphasis on MCD, FSGS and membranous nephropathy, suggesting a common etiology. Experimental disease models, evidence proving that INF2 mutation is responsible for cases of Charcot-Marie-Tooth with FSGS by disrupting distinctly diverse Schwann cells and podocytes, and cases of IDP with nephropathies showing a temporal existence with a positive response to immunosuppression for both the neuropathy and nephropathy are consistent with a common mechanism/antibody causing both pathologies. This association may lead to further research in this newly described area of neuro-renal syndromes.

A Multidisciplinary Approach is Successful in Improving Vascular Access Outcomes in an Underserved Dialysis Population in a Large Indigent-Care Public Hospital
Arshad Ali, Ravi R Rajani, Susan M Shafii and Vandana Niyyar

Background: The three basic kinds of vascular access for hemodialysis (HD) are an arteriovenous (AV) fistula, AV graft, and a central venous catheter (CVC). The Fistula First Catheter Last recommends an AVF prevalence rate of 68%. However, 80% of ESRD patients initiate HD with a CVC and 52% dialyze with a CVC at >90 days. In a retrospective review, we studied patient, physician and socioeconomic factors as they relate to a specific underserved and uninsured ESRD population at Grady Memorial Hospital—“the undocumented immigrants” who do not have legal access to the US medical system.

Methods: We conducted a retrospective review of the medical records from 11/01/2010 to 04/7/2014. A multipronged approach led by the renal fellows included detailed counseling, emphasizing compliance and involvement of their families. Social workers and interpreters were extensively involved to overcome the socio-economic, cultural and language barriers. Results: There were a total of 35 patients in this cohort on 04/07/2014. The average age was 47.8 +/- 13.9 years, with a male to female ratio of 1.2:1. They were predominantly Hispanic (74%), African (23%), & Asian (3%). The etiology of the renal failure was HTN (51%), Diabetes (31%), Glomerulonephritis (6%), HIVAN (3%) and Others (9%). All were initiated on HD with CVC. We found a 77% conversion rate of CVC to AV access, of which 33% were radiocephalic AVF, 37% brachiocephalic AVF, 26% brachio basilic AVF and 4% AVG. The average time of conversion from CVC to AV access was 6.3 months +/- 255 days.

Conclusions: This retrospective review indicates that it is possible to achieve optimal dialysis vascular access in an underserved and uninsured patient population by using a multidisciplinary approach. Renal physicians should take the lead and assume the role of team leaders.

Discovery-Based, High-Resolution Plasma Metabolomics Following a Vitamin D3 Intervention in Adult Patients with Cystic Fibrosis

We explored the impact of high-dose vitamin D3 supplementation on metabolism using high-resolution plasma metabolomics analysis. Methods: Subjects were 25 adults with CF who were hospitalized for acute pulmonary exacerbation and followed-up 3 months later as part of a double-blind, randomized, placebo-controlled trial. Subjects received a single, oral bolus dose of 250,000 IU vitamin D3 (n=12) or placebo (n=13). Plasma was analyzed using high-resolution liquid chromatography-mass spectrometry. Data was analyzed using an in-house pipeline that includes false discovery rate (FDR) analysis (FDR q=0.20) and hierarchical clustering analysis. A metabolite was defined as specific mass to charge ratio (m/z) with an associated retention time and ion intensity. Analyses compared metabolites that differed between the
treatment groups at 3 months and metabolites that differed between baseline and 3 months within the treatment groups. The METLIN Database was used to match m/z’s to known metabolites. Results: A total of 11,111 metabolites were detected. FDR analysis identified 12 metabolites that differed between the vitamin D3 and placebo groups at 3 months post-intervention, including vitamin D3 derivatives, sphingolipids, and several unmatched metabolites. Within the vitamin D3 group, 13 metabolites differed between baseline and 3 months, including several sulfur amino acid metabolites, membrane lipids, and other unmatched metabolites. Conclusion: Plasma metabolomics distinguished CF patients receiving high-dose vitamin D3 from those who received placebo. Vitamin D3 appeared to influence several pathways, including those involved in lipid membrane and sulfur amino acid metabolism. These data provide insight into potential extra-skeletal metabolic effects of vitamin D3 in adult CF.

1

Polymerase δ-Interacting Protein 2 Promotes Postischemic Neovascularization of the Mouse Hindlimb


Collateral vessel formation can functionally compensate for obstructive vascular lesions in patients with atherosclerosis. Neovascularization processes are triggered by fluid shear stress, hypoxia, growth factors, chemokines, proteases, and inflammation, as well as reactive oxygen species, in response to ischemia. Poldip2 is a multifunctional protein that regulates focal adhesion turnover and vascular smooth muscle cell migration and modifies extracellular matrix composition. We, therefore, tested the hypothesis that loss of Poldip2 impairs collateral formation. The mouse hindlimb ischemia model has been used to understand mechanisms involved in postnatal blood vessel formation. Poldip2-/- mice were subjected to femoral artery excision, and functional and morphological analysis of blood vessel formation was performed after injury. Heterozygous deletion of Poldip2 decreased the blood flow recovery and spontaneous running activity at 21 days after injury. H2O2 production, as well as the activity of matrix metalloproteinases-2 and -9, was reduced in these animals compared with Poldip2+/+ mice. Infiltration of macrophages in the peri-injury muscle was also decreased; however, macrophage phenotype was similar between genotypes. In addition, the formation of capillaries and arterioles was impaired, as was angiogenesis, in agreement with a decrease in proliferation observed in endothelial cells treated with siRNA against Poldip2. Finally, regression of newly formed vessels and apoptosis was more pronounced in Poldip2-/- mice. Together, these results suggest that Poldip2 promotes ischemia-induced collateral vessel formation via multiple mechanisms that likely involve ROS–dependent activation of matrix metalloproteinase activity, as well as enhanced vascular cell growth and survival.

CSF Biomarkers Correlate with Magnetic Resonance Spectroscopy Metabolites During Hiv Disease


Background: HIV-associated neurocognitive disorders (HAND) persist in the cART era. Persistent immune activation appears to contribute to the pathology of HAND and evidence exists that biomarkers of immune activation correlate with cerebral metabolites measured by magnetic resonance spectroscopy (MRS).

Methodology: Data from 91 participants were analyzed from five sites in the United States as part of the CHARTER study. MRS concentrations of N-acetylaspartate (NAA), choline (Cho), myo-inositol (MI), and creatine (Cr) were quantified using LCModel in frontal white matter (FWM), frontal gray matter (FGM), and basal ganglia (BG). CSF biomarkers were measured by immunoassay. Multivariable mixed effects models accounted for demographic and disease characteristics as well as proportion of relevant tissue volume within each voxel.

Results: Median values were: current CD4+ count 458/mm3, nadir CD4+ count 145/mm3, log10 HIV RNA 1.72 (plasma) and 1.7 (CSF). 26% were hepatitis C seropositive. Higher (↑) levels of MCP-1 and IP-10 were each associated with ↑levels of MI and Cr in FWM. A particularly strong association was found between ↑MCP-1 and ↑Cho in BG while a weaker association was found between ↑IP-10 and ↑NAA in FWM.

Conclusions: In this cross-sectional analysis of HIV infected individuals from multiple sites, two CSF indicators of monocyte chemotaxis (MCP-1) and antiviral immune responses (IP-10) were associated with cerebral metabolites reflecting energy metabolism, membrane remodeling, neuronal integrity, and glial proliferation. There was also an unexpected association between Cr and MRS metabolites that has not been reported in other studies.

Self-Reported Mobility Improvements after Dance Rehabilitation Correlate Minimally with Objectively Measured Mobility Improvement in Older Adults

Angel N, Bozzorg A, Hackney ME.

Adapted Tango (tango) has objectively improved older adults’ (OA) mobility and quality of life (QOL); however, it is unknown if self-reported improvement correlates to these objective changes. We evaluated relationships between objective and self-reported improvement in mobility domains (balance, walking, strength, endurance, and coordination) in OA after
Severely Elevated Growth Hormone Levels Impact Surgical Outcomes in Acromegaly-Emory University Experience

Anthony JR, Alwahab U, Kanakiya NK, Pimentel DM, Veledar E, Oyesiku NM, Ioachimescu AG

Objective: Transsphenoidal adenomectomy (TSA) is first-line treatment for acromegaly. While surgical cure is negatively influenced by cavernous sinus invasion (CSI), the impact of preoperative growth hormone (GH) levels is equivocal. Our aim is to determine the impact of preoperative GH levels on biochemical remission after TSA.

Methods: This is a retrospective case series of 79 consecutive acromegaly patients operated between 1994-2013. All had their first TSA at Emory, immunohistochemically confirmed GH adenomas, and follow-up >3 months. Remission was defined as normal IGF-1 in the absence of adjuvant therapy. We calculated Youden indices to determine the GH threshold to predict remission. We compared the 2 groups as defined by the GH threshold.

Results: Remission rate was 48.1% (38/79). Preoperative GH of 40ng/mL was the GH threshold for continued remission (sensitivity 97%, specificity 42%). Absence of CSI was the only predictor of remission in multivariate analysis. Preoperative GH, tumor diameter and preoperative IGF-1 predicted remission in univariate analysis.

Group A (GH>40) had 19 patients (9 men), age 43±13, median follow-up of 37.7 months (5.6-112.2). Tumor diameter was 2.7±1.0 cm, preop GH 136±176 and IGF-1 of 1032±301 ng/mL. Three patients (15%) had remission at 3 months, but 2 recurred within 2 years.

Group B (GH≤40) had 60 patients (25 men), age 47±13 median follow-up of 42.6 months (3-186.8). Tumor diameter was 1.6±1.0 cm, preop GH 11.1±9.8 and IGF-1 of 745±327. Thirty five patients (58%) had remission at 3 months with no recurrence during follow-up. Group A had larger, more invasive tumors, higher preoperative IGF1 levels and more residual tumors (p<0.05).

Conclusion: GH levels >40ng/mL negatively impact surgical remission after TSA in acromegaly.

5

Pleiotropic Manifestations of TSH-Secreting Pituitary Adenomas: Emory University Case Series

Azzalin A, Appin C, Puttnam R, Ritchie JC, Brat D, Oyesiku N, Ioachimescu A.

Background: TSH secreting pituitary adenomas are extremely rare. We present 3 cases plurihormonal TSH-omas from one pituitary center.

Clinical Cases:
1. A 46 year old man presented with atrial fibrillation. Labs remarkable for TSH of 3.57 (0.5-4.78 mcIU/mL), Free T4 of 2.8 (0.7-1.8 ng/dL), and glycoprotein hormone alpha-subunit (GSU)/TSH molar ratio of 3.6 (<1). MRI: 1x1 cm pituitary mass. He received octreotide followed by TSA and became euthyroid. Immunochemistry: positive for TSH, GH and PRL.

2. A 57 year old man found to have a pituitary mass (3.6x3.0 cm) during staging for lung adenocarcinoma. IGF-1 was elevated 861 (68-245ng/mL), with normal thyroid evaluation, GSU/TSH molar ratio 6.21. He was started on lanreotide with improvement of IGF-1. A year later, thyroid hormones were elevated with TSH 2.37mcU/mL. He underwent TSA and became euthyroid. Immunochemistry: positive for TSH, PRL and GH.

3. A 49 year old man presented with dizziness and sweating. TSH was 6.40 mcU/mL, FT4 2.1 pg/mL and GSU/TSH molar ratio 14.53. He underwent TSA for 1.9x1.5 cm pituitary mass. Presented 4 years later with tumor progression. Had TSH 7.11 mcU/mL, FT4 1.7 ng/dL, GSU/TSH molar ratio 6.19. He underwent repeat TSA and became euthyroid. Immunochemistry: positive for TSH, PRL, LH and FSH. All adenomas had positive immunoreactivity for pituitary transcription factor 1 (Pit-1).

Conclusion: Few plurihormonal TSH-omas are reported. New hyperthyroidism in a patient with acromegaly (case 2) is exceptionally rare. Our cases illustrate possible mechanisms of TSH-oma tumorigenesis, including Pit-1 overexpression, dedifferentiation between cell lines and development from precursor stem cells. Long-term surveillance is key as clinical and biochemical phenotype may change.
Effect of Pancreatic Mass Lesions on Pancreatic Duct Diameter

Aim: To evaluate the effect of pancreatic adenocarcinoma and neuroendocrine tumor on the pancreatic duct (PD) and thus provide descriptive information regarding pancreatic masses and offer predictive criteria to identify patients at high risk for a pancreatic mass.

Methods: Patients who underwent endoscopic ultrasound for pancreatic indications in a high volume academic center from 2011-2013 were identified. Patients who had biopsies that revealed adenocarcinoma or neuroendocrine tumors in the pancreas were identified and the PD size was ascertained from EUS, CT, or MRI.

Results: One hundred and thirty eight patients were identified with pancreatic adenocarcinoma or neuroendocrine tumors and a measured PD diameter for inclusion in the analysis. Of the 138 cases, 106 (76.8%) had a dilated PD at some location. There were 70 masses within the head and 61 (87.1%) of these had a dilated PD. Out of the 14 masses in the neck, 12 (85.7%) diluted the PD. There were 21, 13, and 20 cases in the body, tail, and uncinated process, respectively; of these, 17 (81.0%), 3 (23.1%), and 13 (65.0%) cases, respectively dilated the PD. Furthermore, out of all masses in the head, 56 (80.0%) had a dilated PD upstream of the mass. Eleven (76.6%) masses in the neck and 16 (76.2%) masses in the body had a dilated PD upstream.

Conclusion: Patients with pancreatic adenocarcinoma or neuroendocrine tumor are likely to have pancreatic ductal dilatation. Patients with risk factors for pancreatic malignancy and a dilated PD should have a complete evaluation for an obstructing mass lesion.

Proline-Rich Tyrosine Kinase 2 Regulates NF-kB and PPARγ to Promote Pulmonary Vascular Wall Cell Proliferation
Bijli KM, Kang B-Y, Adesina SE, Murphy TC, Kleinhenn JM, Sutliff RL, Hart CM

Hypoxia stimulates pulmonary hypertension (PH) in part by increasing the proliferation of pulmonary vascular wall cells via sustained activation of mitogen-activated protein kinase, ERK 1/2, nuclear factor-kappaB (NF-kb) and downregulation of peroxisome proliferator-activated receptor-gamma (PPARγ) levels. However the upstream signaling events that mediate NF-kb upregulation and PPARγ downregulation remain unknown. We examined the role of proline-rich tyrosine kinase 2 (Pyk2) in hypoxia-induced proliferation of human pulmonary artery smooth muscle cells (HPASMC). Exposure of HPASMC to hypoxia (1% O2) for 72 hours resulted in the activation of Pyk2. siRNA-mediated Pyk2 depletion or its pharmacological inhibition attenuated hypoxia-induced HPASMC proliferation. Pyk2 inhibition attenuated hypoxia-induced: 1) ERK 1/2 activation, 2) NF-kb transcriptional activity and 3) reductions in PPARγ mRNA levels and activity. Conversely, siRNA-mediated PPARγ depletion enhanced whereas PPARγ overexpression attenuated Pyk2 activation. Pyk2 levels were higher in pulmonary vascular tissues and lungs of hypoxic and smooth muscle-PPARγ knockout mice respectively compared to control mice. In human pulmonary artery endothelial cells, Pyk2 depletion caused: 1) reduced hypoxic NF-kb p65 activation and Nox4 protein expression and 2) restoration of PPARγ protein levels. Taken together these findings suggest that hypoxic Pyk2 signaling plays a central role in promoting proliferative phenotype of pulmonary vascular wall cells associated with PH pathobiology.

Epigenetic Regulation of Naive B Cell Activation in Systemic Lupus Erythematosus
Bilal EL, Scharer CD, Barwick BG, Jenks SA, Neary BE, Boss JM and Sanz I
Anastomosis Location Optimization

Patient-Specific Left Ventricle Assist Device (LVAD) increased immunoglobulin secretion. Marginal zone maturation, decreased IL-10 production, and are epigenetically poised for activation, which may explain increased CD86 levels, and the expression of IgG or IgA when analysis of several SLE patients. Further flow analysis of SLE consistent with low CD83 levels observed in RNA-Seq and flow CD83 gene was hypermethylated in SLE naïve B cells, which is well as in the transcriptional regulator Sin3a. Interestingly, the methylation in the B-cell activation genes CD83 and CD97 as analysis of SLE and HC naïve B cells also revealed differential hypomethylated when compared to HCs. Promoter-targeted analysis was utilized to determine DNA methylation differences of select genes in healthy control (HC) and SLE naïve B cells. Lastly, multidimensional flow analysis was conducted to determine B cell activation marker and immunoglobulin expression levels on SLE naïve B cells. Global DNA methylation analysis of SLE naïve B cells revealed several genes, including interferon-regulated genes, were hypomethylated when compared to HCs. Promoter-targeted analysis of SLE and HC naïve B cells also revealed differential methylation in the B-cell activation genes CD83 and CD97 as well as in the transcriptional regulator Sin3a. Interestingly, the CD83 gene was hypermethylated in SLE naïve B cells, which is consistent with low CD83 levels observed in RNA-Seq and flow analysis of several SLE patients. Further flow analysis of SLE naïve B cells revealed decreased CD21 and CD24 levels, increased CD86 levels, and the expression of IgG or IgA when compared to HCs. Our results suggest that SLE naïve B cells are epigenetically poised for activation, which may explain several lupus B cell characteristics including decreased marginal zone maturation, decreased IL-10 production, and increased immunoglobulin secretion.

Patient-Specific Left-Ventricle Assist Device (LVAD) Anastomosis Location Optimization

Bonilla-Alicea R, Taylor R, Veneziani A.

Continuous Flow Left Ventricle Assist Devices (CF-LVADS) aid the affected heart by mechanically pumping blood from the left ventricle and into the systemic circulation. CF-LVADS have become an alternative to heart transplantation since transplant demand is higher than donor heart supply. The goal of this research is to elucidate the relationship between the LVAD output graft attachment inclination and position and the resulting outflow hemodynamics to determine the optimum graft placement location in a patient-specific manner. A patient-specific aortic geometry was reconstructed from medical images (DICOM) using the level-set segmentation method. Computational Fluid Dynamic (CFD) modeling was used to simulate blood flow inside the aortic geometry under different inflow boundary conditions. The resulting hemodynamics under LVAD assist were compared with non-LVAD hemodynamics to objectively evaluate the effect of the LVAD on the resulting blood flow. Relevant hemodynamic parameters such as Supra-Aortic Volumetric Flow Splitting, Wall Shear Stress (WSS), Time-Averaged WSS (TAWSS) and Oscillatory Shear Index (OSI) were calculated for each of the cases being studied. The reduced diameter of the LVAD output graft combined with the physiologic volumetric flow rate creates a high-velocity jet that impinges on the aortic wall surface, resulting in increased dynamic pressure and velocity gradients in the aorta. Significant recirculation is introduced into the aorta, which traduces to increased WSS and OSI magnitudes when compared to physiologic operation. The non-physiologic hemodynamics created by LVADS may be a concern for Destination Therapy (DT) patients as the increased WSS and OSI magnitudes are associated with pro-inflammatory conditions.

100

Accuracy of the CMS-2728 to Identify Nursing Home Care in Older Incident End-Stage Renal Disease Patients

Bowling, CB, Zhang, R, Franch, H, Huang, Y, Mirk, A, McClellan, WM, Johnson II, TM, Kutner, N

Background: The Centers for Medicare & Medicaid Services (CMS) Medical Evidence Report Form (CMS-2728) is required for all end-stage renal disease (ESRD) patients initiating maintenance renal replacement therapy. In 2005, the CMS-2728 was revised to include data collection on nursing home (NH) institutionalization; however, the validity of this item has not been reported.

Methods: There were 27,913 patients ≥ 75 years of age with incident ESRD in 2006, which constituted our analysis cohort. We determined the accuracy of the CMS-2728 using a matched cohort that included the CMS Minimum Data Set (MDS) 2.0, often employed as a “gold standard” metric for identifying patients receiving NH care. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the CMS-2728 NH item. Additionally, we compared characteristics and mortality risk by CMS-2728 and MDS NH status agreement.

Results: The sensitivity, specificity, PPV and NPV of the CMS-2728 for NH status were 33%, 97%, 80% and 79%, respectively. The CMS-2728 NH indicator was associated with a greater need for assistance with daily activities. Compared to those without the MDS or CMS-2728 NH indicator (MDS no/CMS-2728 no), multivariable adjusted hazard ratios (95% CI) for mortality associated with NH status were 1.54 (1.46 – 1.63) for MDS yes/CMS-2728 yes, 1.47 (1.41 – 1.53) for MDS yes/CMS-2728 no, and 1.37 (1.24 – 1.51) for MDS no/CMS-2728 yes.

Conclusions: The CMS-2728 may underestimate NH institutionalization among older adults with incident ESRD, but identifies a group with increased risk for mortality. The potential for misclassification may have important ramifications for assessing prognosis, developing advanced care plans and providing coordinated care.
Does Adapted Tango Improve Motor-Cognitive Function, and Mobility in Older Adults in Senior Independent Living Communities?

Bozzorg A, Byers C, Butler G, Sweeney M, Rossbach L, Hackney ME

This study aimed to control for social interaction while determining adapted Argentine tango (tango) efficacy for improving mobility and motor-cognitive function in older adults. Secondary aims were to determine if former dance experience was associated with improvements and to evaluate the program for participant satisfaction, changes in depression and quality of life. 74 older adults (age: 59-95 years, non-white: 31%, female: 72%, >80 years: 73%) from independent living communities in an urban metro area participated. Participants were assigned to 20 sessions of 90-minute Tango (n=62) or Health Education (n=12) classes over 12 weeks. Mobility, motor-cognitive function, cognition and psychosocial function were evaluated pre- and post-intervention, and 3-months post-intervention. Two (groups) x three (times) repeated measures ANOVAs with post-hoc paired comparisons evaluated group differences after treatment. Forty-four Tango and ten Education participants completed 20 sessions. Significant interactions revealed Tango participants improved on mobility (p=0.006), and backward and fast gait speeds (p<0.001), compared to Education participants, who demonstrated improvements in depression (p=0.001) compared to Tango. Planned within-group comparisons revealed Tango participants improved in motor-cognitive function measured with a body position spatial memory task (p=0.028), whereas Education did not. Gains were maintained 3-months post-intervention. Adapted Tango, a multimodal exercise, may address motor-cognitive function involving spatial-cognition and gait deficits in older adults, with lasting gains. Improvements did not appear to be related to social interaction nor to previous dance experience.

Adjudicated Versus “Administrative” Heart Failure with Preserved Ejection Fraction


Introduction: The proportion of heart failure (HF) with preserved ejection fraction (HFpEF) is reported to be as high as 40%-60% based on administrative data, but these estimates have not been clinically validated.

Methods: We evaluated 1752 consecutive patients who received outpatient care during the first quarter of 2012 for an encounter ICD-9 code of 402.X1, 404.X1, 404.X3, or 428.XX. Medical records were reviewed for HF symptoms, signs, and treatment; last reported ejection fraction (EF); all previous EF documentations; and special causes of HF (congenital heart disease or specific cardiomyopathies). We classified confirmed HF cases not due to special causes into 3 mutually exclusive categories: (1) HFpEF: current EF >40% without any previous EF ≤40%; (2) HF with recovered EF (HFrecEF): current EF >40% but previous EF ≤40%; and (3) HF with reduced EF (HFrEF): current EF ≤40%.

Results: HF was confirmed in 1652 cases (94.3%). Among these, 321 had HFpEF (19.4%; 95%CI 17.6-21.4); 268 had HFrecEF (16.2%; 95%CI 14.5-18.1); and 992 had HFrEF (60.0%; 95%CI 57.7-62.4); the remaining 71 cases (4.3%) had HF due to special causes. In comparison, the proportion of HFpEF on the basis of ICD codes and last EF without further adjudication would have been 39.0%. Patient characteristics are summarized in Table 1. Patients with HFpEF were significantly older and had more women than other groups. After 2 years of follow up, age- and gender-adjusted mortality was 10.2% in HFrEF, 8.6% in HFpEF, and 4.4% in HFrecEF patients (stratified log-rank P=0.005).

Conclusions: The proportion of clinically verified HFpEF is considerably lower compared to estimates from administrative data. Many patients with preserved EF actually represent HFrecEF, which has a more favorable prognosis.

Increased Mechanical Strain with Hypertension Leads to Inflammation of the Aorta

Caesar C, Lyle AN, Taylor WR

It is known that elevated mechanical strain in disease states, such as hypertension, leads to vascular inflammation. However the underlying mechanisms modulating this process are still largely unexplored. In this study, we used in-vivo and in-vitro approaches to determine if mechanical strain increases osteopontin (OPN), a pro-inflammatory protein, in a hydrogen peroxide (H2O2) and NADPH oxidase dependent manner. Utilizing two mouse models of hypertension, induced by angiotensin-II (AngII) or norepinephrine (NE) infusion, we found blood pressure was significantly increased. Aortic OPN mRNA and protein was also increased in both the AngII and NE treated groups. However, in AngII treated aortas of transgenic mice that overexpress catalase, a H2O2 scavenger, in vascular smooth muscle cells, we found a decrease in hypertension-induced OPN expression compared to wild type littermate controls.

In-vitro studies using rat aortic smooth muscle cells (RASMs) that were cyclically strained showed a 3 fold (p<0.001) increase in OPN mRNA and 5 fold (p<0.001) increase in OPN protein. H2O2 levels were also increased 4 fold (p<0.05). RASMs strained in the presence of catalase exhibited blunted OPN protein compared to untreated, strained RASMs (72.6% decrease, p<0.05). Finally, RASMs strained in the presence of non-specific NADPH oxidase inhibitors, DPI and apocynin, showed a significant decrease in strain-induced OPN protein compared to untreated, strained RASMs (77.6% decrease, p<0.01 and 43.8% decrease, p<0.05, respectively).

These results suggest that mechanical strain, as experienced by the vascular wall under hypertensive conditions, leads to increases in osteopontin via an NADPH oxidase and ROS-dependent pathway.
Randomized Controlled Trial of Intensive versus Conservative Glucose Control in Patients Undergoing Coronary Artery Bypass Graft Surgery (GIUCO-CABG)

Cardona SD, Pasquel FJ, Smiley DD, Farrokhii FF, Newton CA, Unigwe OM, Peng L, Halkos ME, Puskas JD, Guyton RA, Thourani VH, Umierrez GE.

This randomized controlled trial aimed to determine whether intensive glucose control (intensive, BG target: 100-140 mg/dl) reduces perioperative complications compared to conservative glucose control (conservative, BG target: 141-180 mg/dl) in hyperglycemic patients undergoing CABG. After ICU care, subjects were transitioned to the same treatment regimen targeting BG<140 mg/dl before meals during the hospital stay and 90 days post discharge.

The primary outcome was differences in a composite score of hospital complications including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute renal failure, and major cardiovascular events. A total of 302 patients were randomized to intensive (n=151) or conservative (n=151) glucose control following a computerized insulin infusion algorithm. The groups were well balanced. The mean ICU daily BG was 132±14 mg/dl (IQR 124-139) in the intensive group and 154±20 mg/dl (IQR 142-164) in the conservative group (p=0.09), or hospital length of stay (11.4±11 vs. 9.5±6 days, p=0.13). In the ICU, a BG <70 mg/dl occurred in 8% and 2% of the intensive and conservative groups (p=0.03), with no BG <40 mg/dl. After ICU care, there were no differences between intensive and conservative groups in mean daily BG (143±28 mg/dl and 141±29 mg/dl), patients with hypoglycemia (0.99; <40 mg/dl: 1% vs. 3%, p=0.68), or hospital readmissions (18% vs. 20%, p=0.62).

In summary, intensive control targeting a BG of 100-140 mg/dl in the ICU did not reduce perioperative complications, mortality or hospital length of stay compared to a less strict glucose target of 141-180 mg/dl in hyperglycemic patients undergoing CABG surgery.

PPARγ Attenuates Hypoxia-Induced Hypertrophic Transcriptional Pathways in the Right Ventricle

Carthan KA, Kang BY, Kleinhenz J, Sutliff R, and Hart CM.

Rationale: Pulmonary hypertension (PH) is characterized by increased pulmonary vascular pressures and resistance which promote right ventricular hypertrophy (RVH). The pathways that lead to RVH in PH have yet to be defined. Previous evidence demonstrates that activation of NFAT and NF-kB mediate RVH. PPARγ ligands, like pioglitazone, attenuate hypoxia-induced PH and RVH. Therefore, we hypothesized that pioglitazone inhibits NFAT and NF-kB activation to attenuate hypoxia-induced RVH.

Methods: Male, 8-12 week old C57BL/6J and NFAT-luciferase mice were exposed to normoxia (21% O₂) or hypoxia (10% O₂) for 21 days and gavaged with pioglitazone (10 mg/kg/d), or vehicle the final 10 days. NFAT activation, NFATc2 protein, and NF-kB/p65 protein levels from nuclear and cytosolic fractions were measured. Wheat germ agglutinin staining was employed to assess cardiomyocyte hypertrophy in the right ventricle (RV) and left ventricle (LV).

Results: Treatment with pioglitazone attenuated hypoxia-induced increases in RVH, right ventricular systolic pressure (RVSP), NFATc2 and NF-kB activation, RV NFAT luciferase activity, and cardiomyocyte size. Despite increased LV NFAT luciferase activity, hypoxia did not induce LV hypertrophy (LVH).

Conclusions: Treatment with pioglitazone attenuated hypoxia-induced activation of transcriptional pathways in the RV, including NFAT and NF-kB and reduced RVH and cardiomyocyte hypertrophy. Activation of NFAT in the LV was not associated with LVH. These studies suggest differential transcriptional regulation of hypertrophy in the RV and LV and identify PPARγ as a potential therapeutic target to prevent RVH.

Characterization of Reactivity in an Expanded Autoreactive VH4-34 Clones in SLE

Chida AS, Tipton C, Jenks S, Deshpande P, Wang Y, Hartson L and Sanz I.

SLE is a systemic autoimmune disease characterized by production of a range of autoantibodies. Antibodies expressing the 9G4 idiotype, encoded by the framework-1 hydrophilic patch of VH4-34, provide a unique model to understand the participation of different autoantigens in SLE pathogenesis. 9G4 are highly reactive against several lupus antigens: nuclear antigens (ANA), apoptotic cells, dsDNA and binding to B cells (BCB). Furthermore repertoire analysis, demonstrates that VH4-34 B cell clones are expanded and persist over a period of months in multiple B cell subsets. To compare the specificity of these clones with previously described reactivities, we cloned immunoglobulin heavy and light chains from sorted single cells 9G4+ plasma blast (PB) and expressed them as monoclonal antibodies (mAb). 11 mAb matched expanded PB clones detected by high throughput repertoire analysis during a flare 5 months earlier. These antibodies were from 5 different clones and some of which had undergone or going somatic hyper mutation (SMH). Strikingly, VH4-34 antibody that lacked SMH was found to be reactive against multiple lupus antigens including ANA, dsDNA, BCB, Chromatin, and Ro. This data suggest blood PB in SLE are either relatively long lived or the product of ongoing differentiation from a long lived precursor. Indicating that tolerance defects in SLE can result in polyreactive autoreactivity even in the absence of ongoing selection through SHM. The expansion and reactivity of VH4-34 clones is evidence of their role in SLE pathogenesis and the binding properties and antigen selection of 9G4 antibodies in different B cell compartments are presently being examined by antigen microarrays.
Non-Viral Direct Reprogramming of Fibroblasts into a Three Dimensional Vascularized Cardiomiimetic Tissue


Several muscle-specific miRNAs are involved in cardiac development and differentiation. Accordingly, we hypothesized that these muscle-specific miRNAs could reprogram fibroblasts into various cardiac cell types. Mouse tail-tip fibroblasts were transfected with miR-1a-2-5p, miR-208a-3p, miR-208b-3p, miR-208b-5p or miR-499-5p. qRT-PCR analyses showed that miR-208b-3p most highly induced mRNA expression of cardiomyocyte (CM)-, endothelial cells (ECs)-, smooth muscle cells (SMC)-marker genes. A combined treatment of ascorbic acid (AA) and BMP4 with miRNAs enhanced reprogramming efficiency and maturation, as evidenced by spontaneous contractions of reprogrammed CM (rCMs) and formation of vascular network by reprogrammed-ECs (rECs) and -SMCs (rSMCs). Ten days after the treatment, a substantial amount of extracellular matrix was deposited, leading to formation of a tissue-like patch referred to as cardiomiimetic tissue (CMT). We transplanted CMT labeled with CM-Dil or generated from fibroblasts of GFP transgenic mice onto the apex of the mouse heart. At week 4, histologic examination of the heart sections showed robust engraftment and retention of CMT-derived cells. Systemic perfusion of BLS-1 lectin at week 4 revealed formation of functional blood vessels by rECs alone or together with host ECs. In addition, rCMs formed mass-like structures and showed clear striations and GJA1 expression. In conclusion, we for the first time demonstrated that a combined treatment of a specific miRNA mimic, AA, and BMP4 is able to reprogram postnatal fibroblasts into functional CM, EC- and SMCs-like cells, induce formation of ECMs, and generate a cardiac-tissue like structure. This novel tissue reprogramming can serve as a platform for cell therapy, disease modeling and drug development.

Radiofrequency Ablation Lesion Monitoring Using Imbedded Micro-Electrodes versus Standard Bipolar Electrograms

Clermont, EC, Lloyd MS

One obstacle to effective and safe radiofrequency ablation is lack of accurate identification of ablated tissue. One surrogate commonly used to determine an ablated site is bipolar electrogram voltage, but this measure is crude and can detect adjacent, non-involved tissue which impairs accuracy. The present study examined an ablation catheter with finely-spaced pin “micro-electrodes” to determine if their reduced distance from the center of ablation would more accurately measure regional voltage and thus serve as a more reliable gauge of effective lesion formation.

We analyzed electrograms during atrial flutter ablations and compared bipolar voltages of conventional catheter tip bipoles versus those measured via the micro-electrodes. A total of 14 ablated sites and 8 non-ablated sites in typical atrial flutter ablation procedures were assessed. An effectively ablated site was defined as lack of local capture at a pacing energy of 10 mA and 2 ms.

The average bipolar voltage for the effectively ablated sites was $0.09 \pm 0.06$ mV for the micro-electrodes and $0.16 \pm 0.12$ mV for the conventional bipoles ($P=0.004$). In contrast, there was no significant difference among the mean voltages for the non-ablated sites where average micro-electrode measurements were $0.38 \pm 0.24$ mV versus $0.46 \pm 0.33$ mV for the standard configuration ($P=0.4$).

In conclusion, imbedded micro-electrodes within an ablation catheter have similar voltages to standard measured bipoles in non-ablated tissue, but have significantly lower voltages in sites of ablated cardiac tissue. These findings suggest utilization of micro-electrodes for such procedures could reduce ablation times and avoid unnecessary delivery of radiofrequency to appropriately treated cardiac tissue.

Mycophenolate Mofetil for the Treatment of Membranous Lupus Nephritis

Cobb J, Navarrete J

Background: Most of the research examining the treatment of pure membranous lupus nephritis (LN) occurred before mycophenolate mofetil (MMF) was readily available. We are reporting the clinical characteristics and response rates of our pure membranous LN patients treated with MMF in comparison to other treatments.

Methods: Retrospective chart review from 2005-2013. We analyzed data comparing LN class V patients treated with MMF in comparison to other therapy options (cytoxan, calcineurin inhibitors, prednisone alone, imuran, and rituxan).

Results: There were 36 patients with membranous LN without any proliferative changes. 35 patients identified as being of black race. 35:1 female to male ratio. MMF treated patients (n=15) and other therapies group (n=21). Comparison of MMF treated patients to other therapies initial mean serum creatinine 0.78 mg/dL vs. 1.3 mg/dL, $p=.08$. Comparison of MMF treated patients to other therapies final mean serum creatinine 1 mg/dL vs. 1.88 mg/dL, $p=.10$. Comparison of MMF treated patients to other therapies initial mean serum albumin 2.45 g/dL vs. 2.42 g/dL, $p=.94$. Comparison of MMF treated patients to other therapies final mean serum albumin 3.32 g/dL vs. 2.97 g/dL, $p=.34$. Initial mean urine protein levels in MMF treated patients 3.52 g/24 hours and 3 g/24 hours in the other therapies patients, p=0.62. Final mean urine protein levels in MMF treated group 1.35 g/24 hours and 1.25 g/24 hours in the other therapies group, p=.90.

Conclusions: We did not observe differences in final mean serum creatinine, albumin, and urine protein levels in our patients treated with MMF in comparison to other therapies.
More data is needed but MMF seems to be a viable treatment option for pure membranous lupus nephritis.

101

Pre-ESRD Care and Mortality in Incident ESRD Patients with Multiple Myeloma
Cobb J, Plantinga L, McClellan WM

BACKGROUND: The relationship between mortality and pre-ESRD care in incident ESRD patients with multiple myeloma (MM) has not been examined. We hypothesized that pre-ESRD care would be more prevalent among MM-ESRD patients compared to other ESRD patients and that receipt of that care would be associated with lower mortality.

METHODS: Among 439,206 incident U.S. hemodialysis patients with a primary attributed cause of renal failure (ESRD) due to MM (6/1/05-5/31/09) identified using the US Renal Data System, odds ratios for reported pre-ESRD care by ESRD due to MM (n=4561) vs. other causes (n=434,645) were obtained.

RESULTS: MM-ESRD patients were less likely to have any pre-dialysis nephrology care [34.8% vs. 58.5%, adjusted OR =0.38, 95% CI, 0.34-0.43] compared to patients with ESRD due to other causes. MM-ESRD patients were also more likely to have catheters on first dialysis (91.8% vs. 75.6% respectively, adjusted OR=4.16, 95% CI, 3.54-4.86). Incident MM-ESRD patients having any pre-dialysis nephrologist care and receiving pre-dialysis care greater than 6 months had a statistically significant reduction in 1 year mortality (fully adjusted HR for death 0.89, CI 0.82-0.97 and 0.88, CI 0.80-0.96 respectively). The use of a catheter for dialysis access led to a 1.6 fold increase in one year mortality in incident MM-ESRD patients (fully adjusted HR for death 1.55, CI 1.32-1.83).

CONCLUSIONS: MM-ESRD patients were less likely to have any pre-dialysis nephrology care and were more likely to use catheters on first dialysis. However, pre-dialysis care is independently associated with reduced mortality in these patients. These results suggest that pre-ESRD care should be prioritized in MM patients approaching ESRD.

41

A Longitudinal Approach to Looking at Retention in Care and Viral Suppression Across the HIV Care Continuum
Colasanti J, del Rio C, Armstrong WS

Background: Currently published HIV care continua are cross-sectional snapshots of the HIV care process. We examine retention in care and viral suppression in a clinic cohort over 36 months.

Methods: A retrospective cohort study with 36 month follow-up was conducted on patients who enrolled at the Infectious Diseases Center of the Grady Health system (IDP) in the year 2010. Retention for each 12 month period was defined as attending at least 2 provider visits separated by ≥ 90 days. Viral suppression was defined as the last viral load of a 12 month period being < 1000 copies/mL. Chi-square tests were performed to evaluate the difference in rates of short-term and long-term retention and viral suppression.

Results: 650 patients were enrolled in 2010 (78.2% male; 82.5% Black; 55% men who have sex with men) with a mean age (SD) of 39 years-old (10.6). The percent of patients retained for 12, 24 and 36 months were 77.4%, 48.8% and 38.2% respectively while those achieving viral suppression were 68.3%, 45.5%, and 36.9%. Retention and viral suppression for any single 12 month period were 80.3% and 76.3% respectively. The proportion of patients retained and virally suppressed in a single 12 month time period was statistically significantly greater (p<0.001) than those achieving the same benchmarks at 24 and 36 months.

Discussion: A great majority of patients in our cohort were able to achieve both retention and viral suppression at a single point in time, however long-term (24 and 36 month) retention and viral suppression were suboptimal. Our data suggest that the current HIV care continuum model may portray falsely optimistic retention and viral suppression rates.

47

Impact of Multiple Central Lines on Central Line-associated Bloodstream Infection (CLABSI) Rates
Couk J, Chernetsky Tejedor S, Steinberg JP, Jacob JT

Background: CLABSI rates are leading causes of healthcare associated infections and inter-institutional comparison of CLABSI rates are used for pay-for-performance measures. The CDC definition of CLABSI has a denominator of one line-day if one if one or more central lines are present on a given day. This method may be unfavorable to institutions with high patient acuity. We compared the effect of using the standard denominator to one that uses the actual number of lines.

Methods: CLABSI rates were calculated for all adults in two 500-bed hospitals from 12/1/2009 to 6/30/2011 using standard CDC definitions. Two denominators for CLABSI rates were used, 1) the standard CDC method and 2) a modified method counting n central lines in one patient in one day as n central line-days. CLABSI rates were determined for ICUs and non-ICU wards.

Results: Among 15,843 hospital admissions there were 238 CLABSI (82 in ICUs; 156 in wards). Using the CDC method, there were 142,840 central-line days (52,776 in ICUs; 90,064 in wards). The modified method identified 166,562 central line-days (70,122 in ICUs; 96,440 in wards). In ICUs, 37% of admissions contributing line-days had more than one central line compared to 11% of admissions to non-ICU wards. Use of the modified denominator compared to the standard denominator reduced the CLABSI rate per 1000 central-line days by 25% in ICUs (1.55 vs. 1.17) but only 6% (1.62 vs. 1.73) for non-ICU wards.
Conclusions:
By counting more than one central line per patient day, CLABSI rates in ICUs decreased by 25%; the decrease in rates outside the ICU was more modest. These results suggest that institutions with high acuity of patient care may be at a disadvantage for inter-institutional CLABSI comparisons when using the current methodology.

42
Understanding Early Humoral Responses to HIV Infection
Deshpande P, Sanz I

It is important to understand primary B cells responses to design a successful vaccine against HIV infection. Previous studies have demonstrated that a subset of broadly neutralizing antibodies (BNAs) to HIV cross-react with autoantigens indicating that self tolerance might curtail the development of protective HIV-reactive B cells. To characterize the early processes we profiled serial PBMC samples from acute HIV patients for the newly classified subset called activated naive B cells (IgD+CD27+MTG+CD38lowCD24-CD21-) using flow cytometry. We also looked at PBMCs from patients with high and low levels of BNA activities for comparison. We found that acute HIV and high BNA activity patients have enhanced frequency of activated naive B cells that appear to decrease as the infection progresses. Serial sera from acute were examined for anti-HIV-specific antibody responses, total immunoglobulin and autoantibody levels (9G4 and G6/G8 antibodies are inherently self-reactive and are found in SLE and RA respectively) using ELISA. We found that anti-HIVgp160-specific responses detected by IgG and 9G4 decrease while those detected by IgM and G8 respectively increase or remain unchanged during the course of infection. To understand the selection of antibodies during primary response, acute HIV samples were sorted for different subsets for deep sequencing of antibody repertoire using high throughput MiSeq platform. Our results indicate the presence of IgG and IgA subclasses in the activated naive B cell fraction. Overall our results demonstrate that primary HIV infections elicit robust short-lived B cell responses that are non-sustainable either due to the disruption of germinal centers and/or commencement of ARV therapy hampering the development of long-term protective responses.

48
Transfusion of Storage-Aged Blood Significantly Impairs Endothelial Function in Anemic Compared to Healthy Patients
Hayek S, Dua K, Razazi P, Pouassi C, Neuman R, Ashram K, Sher S, Roback J, Quyyumi A

Introduction: Recent studies have suggested that transfusions of storage-aged RBCs (saRBC) are associated with worse clinical outcomes as compared to fresh RBC (fRBC) transfusions. One potential underlying mechanism is the impairment of NO-mediated vasodilation following saRBC transfusion. However, this effect has not been identified in human recipients.

Methods: In a randomized, cross-over design study, twelve healthy subjects (mean age 34±12, 36% female) and six anemic outpatients (age 61±17, 17% female, 53 with myelodysplastic syndrome and 53 with acute myelogenous leukemia) received either saRBC (>14 days) or fRBC (<14 days) transfusion followed by the alternate blood storage age on a follow-up visit. Endothelial function was assessed using flow-mediated dilation (FMD) of the brachial artery prior to, 1 hour post, and 24 hours post-transfusion.

Results: At baseline there were no significant differences in FMD between healthy and anemic subjects (6.4±5.7 % versus 7.6±5.8 %, p=0.7). When transfused with saRBC, there was a significant decrease in FMD in the anemic compared to healthy subjects (3.5±4.0% versus 7.9±4.2%, p=0.030). There were no significant changes in FMD in either group when transfused with fRBC (7.1±3.5% in healthy versus 7.7±3.5% in anemic subjects, p=0.7).

Conclusion: Transfusion of saRBC significantly impairs endothelial function in anemic but not healthy subjects. The impact of saRBC is thus highly dependent on recipient factors. Further studies in larger sample of patients is warranted to fully characterize this effect.

Role of NADPH Oxidase 1 in Actin Cytoskeleton Remodeling During PDGF-Induced Migration
Duran CG, Verma K, and San Martin A

During atherosclerosis and postangioplasty restenosis, the release of growth factors such as platelet derived growth factor (PDGF) results in the migration of vascular smooth muscle cells (VSMCs) into the intima. It was previously shown that NADPH oxidase 1 (Nox1) is indispensable for neointima formation and migration of VSMCs. The specific signaling cascades by which Nox1 mediates migration are unclear, but several studies have linked Nox1 to regulation of the actin cytoskeleton. Here we demonstrate that Nox1 plays a role in regulating transient PDGF-induced f-actin rich structures called circular dorsal ruffles (CDRs). The function of CDRs is not well understood, but previous studies have demonstrated that they are important for directional migration. In mouse embryonic fibroblasts (MEFs), CDRs form within 5 min following PDGF stimulation and subsequently resolve by 20 min post stimulation. However, a significantly greater percentage of Nox1KO MEFs generate CDRs compared to WT cells at 5 and 10 min after PDGF stimulation (52% vs 43%, and 43% vs 32% respectively). In addition, Nox1KO MEFs display ~40% reduction in migration in a transwell migration assay. We have previously shown that Nox1 deficient cells have a lower amount of active cofilin, an actin depolymerizing protein; overexpression of cofilin corrects the migration deficit in these cells. We now show that overexpression of cofilin also rescues the CDR phenotype found in Nox1KO cells (36% vs 27% for LV-GFP infected KO vs WT cells, and 28% vs 27% for LV-cofilin infected cells). In total, our work demonstrates the critical role of Nox1 in PDGF-induced actin remodeling and migration, and for the first time links cofilin activity to the generation CDRs.
Metformin Use and Assessment of Vitamin B12 Status among Older Veterans

Elliott JL, Kancherla V, Patel BB, Holland NW, Johnson TMI, Phillips LS, Oakley GP, Vaughan CP

Metformin may lead to reduced levels of serum B12, yet guidelines are silent regarding B12 monitoring. We sought to determine whether older diabetic veterans on long-term metformin therapy are more likely to have a subsequent evaluation of vitamin B12 level compared to controls without diabetes or metformin therapy. Patients at the Atlanta VA from 2002 – 2012 were included in a matched cohort study. Cases had an ICD-9 diagnosis for diabetes. Cases also had a metformin prescription (≥ 500mg/day) refilled for more than 6 months. Controls were patients without diabetes and not on metformin during the same period. Controls were pair-matched to cases by age, sex, race, and number of years treated at VA. Conditional logistic regression was used to estimate crude and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). Participants include 3,213 cases (mean age 59.4 years, range 50 – 98, 97.9% male, 64.6% non-Hispanic white, 60% treated at VA for 7-10 years) and 3,213 matched controls. Overall, 25% cases and 39% controls had at least 1 serum vitamin B12 lab assessment (p<0.0001). Mean index serum B-12 concentrations were significantly lower in the case group, compared to controls (441.8 pg/dL vs. 498.2 pg/dL, respectively; p<0.0001) with 37% of cases below 300 pg/dL compared to controls (441.8 pg/dL vs. 498.2 pg/dL, respectively; p<0.0001). The estimated aOR for not having a subsequent vitamin B12 evaluation among cases compared to controls was 2.36 (95% CI=1.44, 3.89) among multivitamin users, and 1.22 (95% CI=1.05, 1.41) among non-multivitamin users. This study suggests older veterans on metformin are more likely to show laboratory evidence of B12 deficiency, yet are less likely to have testing.

Survey of Quality Improvement and Patient Safety Efforts in Continuing Medical Education Activities at Emory School of Medicine

Evans, ME, Murphy, DJ, Berry, AJ

Quality Improvement (QI) is becoming an increasingly important aspect of healthcare delivery. Learning From Defects (LFD) is a structured approach geared toward improving quality and patient safety following a clinical or operational event that adversely affects patient care. It is comprised of the following steps: explaining what happened, reviewing the factors that contributed to the incident, describing efforts that will be made to prevent the incident from happening again, designating a team to implement these efforts, and following up to determine if desired improvements have been made. Continuing medical education (CME) activities provide a unique venue for implementing LFD in both an educational and practical manner. However, it is not known how commonly CME activities utilize this or any other model of QI. Our objective was to determine which methods, if any, are currently being employed by CME activities at Emory SOM with the goal of improving quality and patient safety. CME course directors completed our 10-question survey that inquired about their use of specific aspects of the Learning From Defects model, and gauged their opinion regarding its utility in their conferences.
prevention. The Emory TravelWell Center (TW) is a member of the Global TravEpiNet (GTEN), a national surveillance network of clinics created to improve traveler health. We describe travelers seen at TW for pre-travel consultations, with particular attention to vaccination acceptance.

Methods: GTEN data for travelers seen at TW for pre-travel consultations between January 2009 and July 2014 were analyzed with descriptive statistics. Variables reviewed included age, sex, destination, medical problems, vaccination history, vaccines given, medications prescribed, and recommended vaccines that were declined.

Results: During the study period, there were 5,102 pre-travel visits. Travelers had a median age of 43 years (range 0-89), and 52.2% were male. The majority of travelers cited leisure (n=2,313; 45.3%) or business (n=1,973; 38.7%) as reasons for travel. Most (82.0%) had itineraries inclusive of countries ranked low or medium in the 2011 UN Human Development Index, and the highest frequency destinations were India (14.8%), China (6.0%), and South Africa (5.7%). Malaria prophylaxis was prescribed in 65.5% of encounters. The percentage of travelers declining recommended vaccinations was highest for influenza vaccine (n=786; 15.4%).

Discussion: Travelers seen at TW had high-risk itineraries, with malaria endemicity in over two-thirds of destinations. However, influenza vaccine acceptance was suboptimal, particularly considering that influenza is the most common vaccine-preventable disease in travelers. Further analysis of GTEN data could describe characteristics of those who decline vaccinations and inform education strategies to improve acceptance.

74

A Chimeric Plasmodium Vivax CSP Vaccine Candidate Induces a Multifunctional T Cell Response


Plasmodium vivax accounted for 50% of the malaria cases occurring outside sub-Saharan Africa. Vector control measures are not effective against hypnozoites, a dormant stage form responsible for relapse infections, thus an effective vaccine is essential for P. vivax control and eradication. A well characterized vaccine candidate is the circumsporozoite protein (CSP). Anti-CSP antibodies inhibit the invasion of hepatocytes by sporozoites in vitro. Cellular immune responses against CSP have also been correlated with protection. However, previous CSP-based vaccines have shown limited success inducing cellular immunity. Based on our reported strategy to develop chimeric P. yoelii proteins to enhance cellular reactivity, we designed and tested for immunogenicity in mice, a chimeric protein based on the P. vivax CSP. In this engineered protein, regions of the PvCSP predicted to contain T cell epitopes were genetically fused to an immunodominant B cell epitope derived from the amino terminal region I and to repeat sequences representing the two types of PvCSP repeats. The chimeric protein, known as PvrMRC-CSP, induced high frequencies of PvrMRC-CSP-specific multifunctional CD4+ and CD8+ T cells producing interleukin-2 (IL-2), gamma interferon (IFN-y) and tumor necrosis factor alpha (TNF-a) simultaneously. The ability of PvrMRC-CSP to produce multifunctional T cells is encouraging, since these cells are strongly related with protection in humans. To our knowledge this is the first time that a recombinant protein based on P. vivax CSP is able to induce a cellular response of this quality. Interestingly, PvrMRC-CSP was also recognized by naturally acquired antibodies derived from individuals living in malaria endemic areas. These features make PvrMRC-CSP a promising vaccine candidate.
An Integrated Service Delivery Model to Identify Persons Living with HIV and to Provide LINKage to HIV Treatment and Care in Prioritized Neighborhoods

Frew PM, Archibald M, Schamel JT, Saint-Victor DS, Fox E, Holstad MM

Objective: We examined the impact of Project LINK HIV prevention service delivery and linkage-to-care in Atlanta census tracts with high HIV prevalence rates.

Methods: We explored multilevel factors influencing Project LINK service utilization through combined geospatial-survey analyses inclusive of descriptive, associative, and HLM methodologies. Using random-intercept models adjusting for baseline effect differences among participants from different zip codes, we examined HIV service availability, local prevention and clinical support services, and HIV educational options.

Results: Survey participants (N=547) included mostly African American (88.8%) and middle aged 40-59 persons (63.7%). Many neighborhood-level effects were observed with both intention to obtain HIV testing and counseling and to refer others to LINK services, including availability of neighborhood HIV support organizations, population composition, socioeconomic status, and HIV prevalence rates. Positive attitudes towards the LINK initiative resulted in greater intention for ongoing HIV testing (p<0.01) and HIV care referral (p<0.01). Transgender persons also indicated greater likelihood of referring others to LINK (p<0.05).

Conclusions: Project LINK reached the intended audience, prompting greater intention to engage in HIV testing, care, and referral to community partner organizations serving those in the selected neighborhoods. This study highlights important socioecological effects of a geographically-focused coalition effort to improve HIV testing and subsequent referral to care for persons who may not be engaged in routine HIV prevention and treatment.

Pulmonary Artery Systolic Pressure Independently Predicts All-Cause Mortality in Patients with Coronary Artery Disease Irrespective of a Diagnosis of Heart Failure


Background: Elevated pulmonary artery systolic pressure (PASP) is associated with a worse outcome in heart failure (HF), but the prognostic role of PASP in patients with coronary artery disease (CAD) remains unknown.

Methods: 863 patients with known or suspected CAD (age: 64±13 years, 62% male) enrolled in the Emory Cardiovascular Biobank were followed for a median 455 days for all-cause death. Transthoracic echocardiographic parameters included measurement of left ventricular ejection fraction (LVEF, range: 5-80%) and diastolic function parameters. Youden's index from the receiver operating curve analysis was used to determine the best cutoff for PASP (cutoff=43 mmHg).

Results: 88 (10%) subjects died during follow-up. PASP correlated with left ventricular ejection fraction (LVEF, N=644, r=-0.20, p<0.0001), C-reactive protein (CRP, N=539, r=0.12, p=0.004), and mitral valve inflow E/A ratio (N=359, r=0.32, p<0.0001), mitral valve deceleration time (N=260, r=-0.16, p=0.007), and left atrial size (LAs, N=694, r=-0.25, p=0.0001). High PASP predicted incident mortality in a model adjusted for age, gender, diabetes, hypertension, dyslipidemia, smoking, glomerular filtration rate, CRP, heart failure, Gensini angiographic severity score, as well as aspirin, statin, beta-blocker, and angiotensin converting enzyme-inhibitor use (HR: 3.3, p=0.000001). The association of PASP with death was independent of LVEF (HR=3.2, p=0.00002). Thus, high PASP also predicted mortality in subjects with LVEF>50% and no history of HF (HR: 4.7, p=0.004).

Conclusion: High PASP >43 mmHg is an independent predictor of mortality in patients with CAD even in those without HF. Whether high PASP predicts future development of HF and hospitalization for HF needs to be investigated.

Sleep Hygiene and Sleep Quality in Veteran Caregiving Dyads

Griffiths PC, Paul S, Harrill A, Liu D

This study addresses sleep hygiene and sleep quality in caregiving dyads—a topic that has important implications for the quality of life for older Veterans and their family caregivers (CG). Data are from phase one of a three phase study which examined sleep patterns in a sample of Veterans over the age of 60 who require assistance from a cohabitating caregiver (CG).

Caregiving can extend over many years and becomes increasingly more demanding as the health and independence of care recipients decline. Sleep quality can be compromised in caregivers. Poor sleep can contribute to falls, medication errors, daytime drowsiness and institutionalization of the care-receiver. In caregiving dyads, the sleep of one care-partner can adversely affect the sleep of the other thereby exacerbating the problem for both members of the dyad. Actigraphy was used over seven nights to objectively measure sleep in 62 Veteran Caregiving Dyads (124 individuals). Daily journals were used to record sleep hygiene practices and to identify the nature and types of sleep disturbance. Dyadic concordance was assessed for sleep hygiene factors, subjective and objective sleep quality. Socio-demographic, health characteristics and descriptive analyses of the sleep hygiene practices for “good” versus “poor” sleepers and Care- Receivers versus Caregivers are compared and contrasted to elucidate potential intervention targets. Results are discussed in terms of the implications for assessment of sleep hygiene factors (which are amenable to intervention) in addition to standardized measures of sleep quality or sleepiness.
Nano-Hydroxyapatite Stimulates Sustained Changes in Gene Expression in Differentiating Osteoblasts
Ha SW, Beck GR

The use of nanotechnology is particularly well suited for the generation of novel biomaterials. Nano-biomaterials can be used as scaffolds, coating for implants, or drug delivery. Nano-biomaterials are particularly well suited for medical applications associated with the skeletal and dentition. These tissues consist mainly of Hydroxyapatite (HA) which makes up 60-70% of the skeleton and 80-90% of tooth enamel. Synthetic hydroxyapatite (HAp) (Ca10(PO4)6(OH)2) has generated interest for use in skeletal and orthopaedic repair. Nano-sized hydroxyapatite (Nano-HAp), which can be altered in size, shape, and composition to enhance biologic effects, is now being investigated as biomaterial in skeletal applications. Nano-HAp is also generated endogenously by osteoblasts in the form of matrix vesicles as the initiator of bone formation in the skeleton as well as in pathological vascular calcification, although the origins are not fully understood. A critical yet poorly understood aspect of nano-biomaterials is the interface with, and effect on, biological systems, whether locally or systemically.

Here we investigated whether Nano-HAp (ellipsoid 50nm x 100nm) could be used to modify osteoblast lineage determination and differentiation. We investigated the cellular and molecular response and identified dramatic, sustained changes in gene expression. The results identified a specific coordinated program involved in the long-term regulation of genomic output with most genes known to be involved in the coordinated program involved in the long-term regulation of changes in gene expression. The results identified a specific and molecular response and identified dramatic, sustained determination and differentiation. We investigated the cellular and molecular response.

Satellite Cells are the Major Source of the Receptor for Advanced Glycation End Products and Play a Role in Collateral Growth

Coronary and peripheral artery disease are growing health concerns that can lead to impaired blood flow and tissue ischemia, though growth of collateral vessels can help to restore blood flow and improve outcomes. Collateral formation is a complex process that involves cytokine signaling, inflammatory cells, cell proliferation and migration, and matrix remodeling. One factor that is associated with negative effects on collateral growth is the receptor for advanced glycation end products (RAGE); however, the cellular source and the mechanism of its regulation is not fully understood. The goal of this study was to determine if RAGE is increased in the ischemic regions and to investigate the mechanism regulating its expression using both in vivo and in vitro systems. Following ligation of the femoral artery in the hind limb ischemia (HLI) model, RAGE expression as quantified by qRT-PCR was increased 12.2 ± 3.9 fold in the ischemic versus non-ischemic leg at day 5. However, the infusion of PEG-Catalase to decrease hydrogen peroxide (H2O2) significantly blunted the increase (1.4 ± 0.5, n=6, p=0.0007). These results suggest that RAGE expression is mediated by H2O2 and is present even in non-diabetic tissue. In situ hybridization revealed that satellite cells are the source of RAGE in leg. A primary cell line of satellite cells was established and stimulation with exogenous H2O2 showed a 2.3 ± 0.3 fold increase in RAGE expression at 4 hours as quantified by qRT-PCR. Furthermore, cultured satellite cells also have a 4.0 ± 1.9 fold increase in MCP-1 at 4 hours and osteopontin was increased 4.5 ± 2.0 fold at 18 hours. Thus in addition to being a major source of RAGE in the ischemic limb, satellite cells may also serve as a novel source of factors regulating collateral growth.

Circulating Progenitor Cell Profile of Patients with Peripheral Arterial Disease
Hayek S MD, Al Mheid I MD, Awad M MD, Yadalam A, Anoka N MD, Khan A MD, Sher S MD, Li Q MS, Waller E MD PhD, Quyyumi A MD

Introduction: Bone marrow-derived circulating progenitor cells (PC) are involved in vascular repair and regeneration, and disturbances in the number and mobilization of PCs are thought to contribute to the pathogenesis of cardiovascular disease (CVD). Whether peripheral arterial disease (PAD) is associated with specific changes in PCs is unknown.

Methods: Eighty-two patients with PAD (mean ABI 0.62±0.13) recruited at outpatient clinics of Emory University Hospital and the Atlanta VA Medical Center were matched to 82 controls by age (63±7), gender (92% male), race (49% white), BMI (30±7), diabetes mellitus (39%), smoking (49%), hypertension (35%), HDL (43±12) and LDL (91±29) using propensity score matching with a tolerance of 0.3. Circulating PC counts enriched for CD45med were measured by flow cytometry and compared using the Mann-Whitney U Test.

Results: Patients with PAD had significantly lower endothelial (CD34+/VEGFR2+) PCs compared to controls (0.047 (0.046, IQR) versus 0.195 (0.204, IQR) cells/µL respectively, p<0.001), but higher hematopoietic (CD34+/CD133+) PCs (1.27 (0.82, IQR) versus 1.03 (0.82, IQR) cells/µL, p=0.004). There were no statistically significant differences in total CD34+/CD45med (2.52 (1.3, IQR) versus 2.38 (1.88, IQR) cells/µL p=0.3, and CD34+/CXCR4+ cells (1.26 (0.76, IQR) versus 1.27 (1.12, IQR) cells/µL p=0.6. There was no correlation between ABI and PC counts.

Conclusion: Patients with PAD had significantly depressed endothelial PC counts. Whether decreased endothelial PC counts heralds disease progression or predicts outcomes requires further investigation.
Purinergic Signaling is Enhanced in the Absence of UT-A1 and UT-A3
Himmel NJ, Rogers RT, Redd SK, Blount MA

The extracellular nucleotide ATP is an important paracrine regulator of renal tubular transport of water and urea. P2Y2, the predominant P2Y receptor expressed in the medullary collecting duct, mediates the action of ATP and thus, is important for urinary concentration. To investigate the role of purinergic signaling in the absence of urea transport in the collecting duct, we housed wild type (WT) and UT-A1/A3 null (KO) mice in metabolic cages to monitor urine output. Not only did we confirm that KO mice are polyuric, we also observed that urinary cAMP was lower (WT: 3100 ± 467 vs KO: 699.3 ± 95 pmol/ml/creatinine) despite elevated circulating AVP (WT: 8.3 ± 1 vs KO: 28.4 ± 5 pg/ml) in KO mice. Because P2Y2 regulates AVP-stimulated transport by damping cAMP synthesis, we hypothesized that, similar to other animal models of AVP-resistant polyuria, purinergic signaling is increased in the KO mice. In fact, urinary levels of ATP are higher in KO (21.34 ± 5.3 nM/creatinine) compared to WT (5.6 ± 3.5 nM/creatinine) mice and purinergic-mediated prostanoid (PGE2) production was elevated (WT: 12.4 ± 2.5 vs KO: 32.7 ± 7.1 pg/ml/creatinine). The mRNA expression of P2Y2 was not significantly different in the inner medullas of WT and KO mice which, given the resistance of the KO mouse collecting duct to AVP, was to be expected. Collectively, our data suggest that the reduction in medullary osmolality due to the lack of UT-A1 and UT-A3 induces an AVP-resistant polyuria that is exacerbated by elevated purinergic signaling.

MicroRNA-182 targets FoxO3 and attenuates glucocorticoid-induced atrophic signaling in muscle

Skeletal muscle atrophy occurs in response to a variety of conditions including diabetes, chronic kidney disease, cancer, mechanical ventilation, and HIV/AIDS. Previous studies have demonstrated that activation of the Forkhead box O (FoxO) transcription factors results in skeletal muscle atrophy in patients, animals and cultured cells. The FoxO proteins cause muscle wasting by increasing the expression of components of the ubiquitin-proteasome and autophagy-lysosome proteolytic systems. To identify potential modulators of the atrophy process, an in silico target scan analysis of known microRNAs (miRs) was performed, and miR-182 was predicted to target the FoxO mRNAs. To test whether miR-182 regulates expression of the FoxOs, C2C12 myotubes were transfected with miR-182 and levels of FoxO1 and FoxO3 proteins were evaluated. miR-182 reduced the amount of FoxO3 but not FoxO1. Treatment of C2C12 myotubes with dexamethasone (1 µM, 6 hr) to induce muscle atrophy decreased miR-182 expression by 63% (P<0.05). Transfection of miR-182 into myotubes prevented the glucocorticoid-induced upregulation of multiple FoxO3 target mRNAs including MAFbx/Atrogin-1, ATG12, Cathepsin L, and LC3. To determine if miR-182 is altered in an in vivo model of muscle atrophy, miR-182 was measured in the gastrocnemius muscle of rats with acute diabetes (3 d) induced by streptozotocin. miR-182 was decreased 44% (P<0.05) by diabetes. These data identify miR-182 as a new and important regulator of FoxO3-mediated signaling during muscle atrophy induced by catabolic disease states.

Antigen Specific and Nonspecific Activation of IgG Memory Cells in SLE Blood
Ichikawa HT, Sanz I.

Systemic Lupus Erythematous (SLE) is a systemic autoimmune disease characterized by autoreactive antibodies in the serum. Abnormal expansion of circulating antibody secreting cells (ASC) has been reported to correlate with disease activity. Previously, we demonstrated polyclonality of ASC in SLE blood. Polyclonal activation of class switched IgG memory cell pool was suggested by detectable levels of anti-flu and anti-tetanus IgG ASC in SLE blood without vaccination. In this paper, we sought for the relationship between IgG switched memory cell activation and IgG ASC for typical SLE ASC (anti-dsDNA; n=40, anti-Sm; n = 40 and anti-Ro ASC; n = 38). METHODS: IgG ASC and IgG memory cells were detected by ELISPOT from SLE blood and seven-day PBL culture (+IL-2 and R848), respectively. RESULTS: First, polyclonal activation of IgG switched memory cells in SLE blood was confirmed by demonstrating that the frequencies of anti-flu IgG memory cells and ASC were comparable regardless of disease activities and ASC expansion levels. Second, for SLE typical ASC, we found the appearance of IgG ASC for anti-dsDNA, anti-Ro and anti-Sm correlate with the IgG memory cell frequencies. However, there were a few in anti-dsDNA IgG ASC that were found at over 100 times higher frequencies than that of anti-dsDNA IgG memory cell. CONCLUSION: Based on the correlation of frequencies, SLE typical IgG ASC are more likely depending on antigen nonspecific polyclonal activation of IgG memory cells but certain antigens (e.g. dsDNA) contribute to further clonal expansion of the corresponding IgG ASC.
Phenotypic and functional characterization of an expanded IgD-CD27- memory B cells subset in systemic lupus erythematosus

Jenks SA, Patel A, Dale GA, and Sanz I

SLE patients have perturbations in B cell subsets including a large expansion of IgD-CD27- B cells (DN) in patients with active disease. Related cell populations have been characterized as anergic in other conditions such as HIV and RA but little is known about the function and phenotype of DN in SLE. The purpose of this study to clarify the function of DN B cells in SLE by using to flow cytometry and gene expression studies to define phenotypic characteristics that distinguish SLE DN from other B cell subsets. We found that the DN population in both HCD and SLE patients was heterogeneous for expression of the B cell follicle homing receptor CXCR5. In a large cohort of SLE patients, CXCR5- DN (DNCX- ) were the dominant population in patients with expanded numbers of DN but only a minor population in HCD or SLE patients without DN expansion. Further phenotypic analysis by flow cytometry and RNA sequencing show that DNCX- also lack expression of common B cell lineage markers such as CD24 and CD21 but express high levels of CD19 and the dendritic cell marker CD11c. DNCX- do not express the Fc receptor homolog FCRL4, a marker of exhaustion in HIV B cells. DNCX- gene expression was also characterized by increased expression of gene related to antigen presentation (HLA-DR, CD86), Toll like receptor and pathogen sensing (TLR-2, TBK1), and inflammation (IRF-7). Functionally, DNCX- were not anergic, as proximal B cell receptor signaling was intact and they responded robustly to TLR7. These data are consistent with a model in which DNCX serve as a link between innate and specific immune responses during infection. In SLE patients the normal regulatory mechanisms that limit this response may fail leading to self perpetuating cycles of inflammation and self reactivity.

Identification of Circulating CD4+ T Follicular Helper Cell (TFH) Response after Smallpox Vaccination


Background: Since smallpox eradication and halting of vaccinations the population is susceptible to smallpox, a bioterrorism threat. IMVAMUNE derived from the Modified Vaccinia Ankara strain is safer than prior smallpox vaccines. The interplay of plasmablasts and memory B cells (MBC) in the generation and maintenance of seroprotection needs to be better understood. TFH are germinal center T cells involved in generating antibody (Ab) responses and express molecules that provide critical help to differentiation and maturation of B cells. A study of influenza vaccination demonstrated that blood TFH cells are antigen-specific, induce MBC to differentiate into plasma cells, and correlate with specific Ab titers. An ongoing smallpox vaccination trial provides a unique opportunity to study the role of blood TFH cells in shaping both naïve and MBC responses.

Methods: Twenty participants received the vaccine at days 1 and 29. Phenotypic characterization of circulating TFH cells by flow cytometric methods will be correlated with serologic measurements of immune response (ELISA titers and plaque reduction neutralization titer PRNT50). Functional characterization of circulating TFH cells by ex vivo stimulation of PBMC with IMVAMUNE and staining for cytokine expression (IL-2, IL-10, IL-21, INF-y, CD154) will be done.

Results: Circulating TFH cells (ICOS+CXCR3+CXCR5+CD4+ cells) increased 8 days post first vaccine. A smaller increase was seen after the booster dose. Circulating TFH levels returned to prevaccination levels at day 57.

Conclusion: Circulating TFH cell levels increased after immunization with IMVAMUNE. Correlation with PRNT50 and ELISA titers, and further characterization of circulating TFH cell function, are underway.

PPARγ Activation Reduces Hypoxia-Induced Endothelin-1 Expression Through Upregulation of miR-98

Kang BY, Park KK, Kleinhenz JM, Murphy TC, Green DE, Bijli KM, Yeligar SM, Carthan KA, Searles CD, Sutliff RL, and Hart CM.

Rationale: Endothelin-1 (ET-1) plays a critical role in endothelial dysfunction and contributes to the pathogenesis of pulmonary hypertension (PH). We hypothesized that PPARγ stimulates microRNAs that inhibit ET-1 and pulmonary artery endothelial cell (PAEC) proliferation.

Objective: To clarify molecular mechanisms by which PPARγ regulates ET-1 expression in vitro and in vivo.
Methods and Results: In PAEC isolated from patients with pulmonary arterial hypertension, miR-98 expression was reduced, and ET-1 protein levels and proliferation were increased. Similarly, hypoxia reduced miR-98 and increased ET-1 levels and proliferation in vitro. In vivo, hypoxia reduced miR-98 expression and increased ET-1 and proliferating cell nuclear antigen (PCNA) levels in mouse lung, derangements that were aggravated by treatment with the vascular endothelial growth factor receptor antagonist, Sugen5416. Reporter assays confirmed that miR-98 binds directly to the ET-1 3′-untranslated region. Compared to littermate control mice, miR-98 levels were reduced and ET-1 and PCNA expression were increased in lungs from endothelial-targeted PPARγ knockout mice, whereas miR-98 levels were increased and ET-1 and PCNA expression were reduced in lungs from endothelial-targeted PPARγ overexpression mice. Gain or loss of PPARγ function in PAEC in vitro confirmed that alterations in PPARγ were sufficient to regulate miR-98, ET-1, and PCNA expression. Finally PPARγ activation with rosiglitazone regimens that were aggravated by treatment with the vascular endothelial nuclear antigen (PCNA) levels in mouse lung, derangements that were predominant in white. The mean plasma 25(OH)D concentration was 17.5 ± 6.1 ng/mL at baseline. At 5 days, subjects randomized to vitamin D3 had higher mean plasma 25(OH)D compared to the placebo group (39.1 vs. 19.1 ng/mL, p<0.001). However, plasma 25(OH)D concentrations returned to near baseline at 90 and 365 days in the vitamin D3 group and remained unchanged in the placebo group. PTH and calcium concentrations were unrelated to changes in 25(OH)D levels and were similar between groups over time.

Discussion/Conclusions: A 250,000 IU dose of vitamin D3 given in November resulted in a robust increase in plasma 25(OH)D after 5 days but was unable to sustain this increase after 90 days. A larger or more frequent dosing regimen may be needed for long-term sufficiency in this population.

22

Amplified Drug Resistance and Association with Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis
Kempker RR, Kipiani M, Mirskhulava V, Magee MJ, Tukvadze N, Blumberg HM.

Background: Given a scarcity of existing data, we sought to measure rates of amplified drug resistance (ADR) and its effect on clinical outcomes among multidrug-resistant tuberculosis (MDR-TB) patients.

Methods: A retrospective study of patients receiving treatment for MDR-TB in Tbilisi, Georgia. Drug susceptibility testing (DST) for second-line drugs (SLDs) was performed at baseline and after 3 and 6 months and every 3rd month thereafter if cultures were positive. ADR was defined by any SLD that went from susceptible on baseline DST to resistant on follow-up DST. Risk factors for ADR and the association of ADR with poor outcomes (default, treatment failure, or death) were assessed.

Results: 135 of 152 patients followed during the study period were included (11 excluded with XDR; 6 with ≤3 months follow-up). Of the 135 patients, 17 (13%) developed ADR at a mean of 215 days after starting MDR-TB treatment. ADR was seen similarly to ofloxacin (10/123, 9%) and either capreomycin or kanamycin (11/105, 10%). In multivariate analysis, the presence of cavitary disease (aOR 5.1, 95%CI 1.5-16.9), resistance to ≥ 6 drugs (aOR 4.8, 95% CI 1.4-16.7), and a four-month positive acid-fast bacillus (AFB) sputum smear (aOR 7.5, 95%CI 1.4-39.2) were significantly associated with ADR. Risk of poor treatment outcome was significantly higher among patients with ADR (87%, 3 death, 4 failure, 6 default) compared to patients without ADR (37%, 4 death, 1 failure, 36 default), p <0.01. ADR (aOR 5.7, 95%CI 1.11-29.4) was significantly associated with a poor treatment outcome in multivariate analysis.

Conclusions: Risk of ADR was high among patients being treated for MDR-TB and ADR was significantly associated with poor treatment outcomes. Methods to better prevent and manage ADR are needed.

23

Intra Cavitary Penetration of Levofloxacin among Patients with Multidrug-resistant Tuberculosis
Background: We hypothesized that failure of second-line drugs (SLD) drugs to adequately penetrate pulmonary cavities may be a factor in poor treatment outcomes among MDR-TB patients.

Methods: We conducted a clinical pharmacokinetic study to measure levofloxacin (LEVO) concentrations among MDR-TB patients undergoing adjunctive surgery in Tbilisi, Georgia. All patients had serum collected at 0, 1, 4, and 8 hours as well as at time of cavity removal, and levofloxacin concentrations were measured using high performance liquid chromatography (HPLC). Microdialysis was performed using a no-net flux method (0.5, 2, 20, and 30 μg/ml) on ex vivo tissue after resection and a HPLC method with mass spectroscopy detection (HPLC-MS/MS) was used to quantify levofloxacin concentrations in the dialysate. Non-compartmental analysis was used to obtain pharmacokinetic parameters.

Results: 11 patients had surgery performed. Most were male (91%); with median age 33 years, body mass index 23.0 kg/m2, and CrCl 115.2 ml/min. LEVO doses were 750mg (9, 81%) and 1000mg (2, 17%). Median total LEVO serum Cmax was 5.9 μg/ml (range 1.1-12.3 μg/ml); three patients had Cmax <1.8 μg/ml (normal 8-12). Median free LEVO concentration at time of resection was 5.2 μg/ml while median intra-cavitary concentration was 4.4 μg/ml (range 0.46-9.59 μg/ml); mean cavitary/serum LEVO ratio was 1.33. There was no significant difference between serum and cavitary LEVO concentrations (p=0.39).

Conclusions: We found a wide range of serum LEVO concentrations and good penetration of LEVO into cavitary lesions among a cohort of chronic MDR-TB patients undergoing surgery. Given high tissue penetration, optimizing serum LEVO concentrations should be a priority among patients with cavitary MDR-TB.

2

Smooth Muscle-Targeted Overexpression of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) Disrupts Vascular Wall Structure and Function
Kleinhenz JM, Murphy TC, Pokutta-Paskaleva AP, Gleason RL, Lyle AN, Taylor WR, Blount MA, Yang Q, Sutliff RL, Hart CM.

Objective: To clarify the role of PPARγ in vascular smooth muscle cells, a mouse model with tamoxifen-inducible, smooth muscle cell-targeted PPARγ overexpression (smPPARγOE) was generated and characterized.

Approach & Results: smPPARγOE attenuated contractile responses in aortic rings, increased aortic compliance, caused aortic dilatation, reduced mean arterial pressure and pressor responses to angiotensin II administration. Molecular characterization revealed that compared to littermate control mice, aortas from smPPARγOE mice expressed lower levels of contractile proteins and increased levels of adipocyte-specific transcripts. Morphological analysis demonstrated increased lipid deposition in the vascular media and in smooth muscle of extravascular tissues. Adenoviral-mediated PPARγ overexpression in human aortic smooth muscle cells or treatment of mouse aortic smooth muscle cells isolated from smPPARγOE with tamoxifen in vitro stimulated increased adipocyte markers and lipid uptake.

Conclusions: Smooth muscle-targeted PPARγ overexpression disrupts vascular wall structure and function in part by driving medial smooth muscle cell to adipocyte transdifferentiation. These results emphasize that PPARγ activity plays an influential role in vascular smooth muscle cell phenotype and function.

Adiponectin Agonist ADP355 Attenuates Ccl4-Mediated Liver Fibrosis: Therapeutic Implications by Multiple Molecular Mechanisms in Vivo and In Vitro
Kumar P, Smith T, Rahman K, Thorn NE, Anania FA.

Adiponectin is known to possess anti-fibrogenic properties; however clinical testing of such a large peptide that circulates in high concentrations would be cost prohibitive. Recently adiponectin-like small synthetic peptide agonists were beneficial in the treatment of breast cancer in mice. The AIM of the present work was to study ADP355 a synthetic peptide, employing both in vivo and in vitro approaches to determine its efficacy as an anti-fibrotic agent; and, identify whether AP-1 transcriptional activation. In vivo experiments—adult C57B6/j male mice were gavaged with CCl4 thrice weekly for six weeks. A gold nanoparticle-ADP355 conjugate was administered to the experimental mice. Liver injury was assessed by serum biochemistry, histology and immunoblot. In vitro experiments—rat hepatitis stellate cells or human HSC cell line were transiently transfected with MMP-1 promoter deletion constructs. Mice gavaged with CCl4 and injected with ADP355 nanoparticle conjugates had significantly lower transaminases levels than mice treated with gold nanoparticles alone. Sirius Red staining was significantly reduced in CCl4-gavaged ADP355 treated mice. Key markers of fibrogenesis—α-SMA, TGFβ1, CTGF, TIMP-1—were markedly attenuated at mRNA and protein levels. These studies were corroborated by ex vivo immunohistochemical liver staining. Conversely liver lysates from ADP355 treated mice increased phosphorylation of both AMPK and eNOS while Akt phosphorylation was attenuated. Adiponectin/ADP355 treatment, of transiently transfected HSCs did increase MMP-1 promoter activation four-fold; however the deletion mutant at -275 bp upstream from the start site abolished this effect. These findings suggest ADP355 is a potent anti-fibrotic agent.

South Asian Immigrants Have Similar Indices of Vascular Function Compared to African Americans

Introduction: South Asian (SA) immigrants have been found to have a higher all-cause mortality rate and associated chronic...
diseases such as obesity, hyperlipidemia, coronary artery disease and diabetes mellitus compared to the native population. Whether SA have worse subclinical indices of vascular function compared to African Americans (AA) is unknown.

Methods: 728 SA subjects (mean age 50±12, 53% male, BMI 26±5 kg/m² and LDL 107±31 mg/dL) were enrolled in a community health fair setting, with a subset of 194 who underwent carotid intima-media thickness (IMT) measurements, and 619 arterial pulse wave analysis. One hundred and sixty AA subjects (mean age 47±10, 14% male, BMI 32±7, LDL 111±34) enrolled as part of the Center for Health Discovery also underwent IMT and pulse wave analysis. Measurements were compared.

Results: The SA subjects were older and had lower BMI compared to the AA group (p<0.001). Unadjusted measurements show SA have significantly higher IMT measurements (0.80±0.24 versus 0.66±0.15 mm, p<0.0001) and augmentation index corrected at HR of 75 bpm (AIX75) (27±10% versus 23±10%, p<0.0001) compared to AA respectively. Pulse wave velocity was however similar in SA and AA subjects (7.0±2.0 versus 7.5±1.5 m/s, p=0.2). In multivariate analysis adjusting for age, gender, BMI and LDL, the correlations of IMT (B=-0.181, p=0.182) and AIX75 (B=-0.061, p=0.207) with race were no longer significant.

Conclusion: SA subjects have indices of vascular function similar to AA. Whether cardiovascular outcomes in SA are different and whether they would benefit from specific therapies warrant further investigation.

Baseline Levels of Influenza-Specific Memory B- and T-Cells Modulate Human Immune Responses to a Swine Variant Influenza A/H3N2 Vaccine

A swine variant of Influenza A/H3N2 (H3N2v) has recently caused increased disease in the US, primarily among children who are exposed to pigs and have little pre-existing immunity against this virus. Recent seasonal influenza vaccines do not substantially improve sero-protection against this virus, however a substantial proportion of adolescents and young adults have cross-reactive antibody against H3N2v due to past exposures to antigenically related influenza viruses.

Here we report the results from a clinical study with antibody, CD4+ T cell, plasmablast and memory B cell responses in 25 healthy adults immunized at the Hope Clinic of the Emory Vaccine Center with 2 doses of monovalent inactivated influenza A/H3N2v vaccine. As expected, prior to immunization we were able to detect H3N2v-specific IgG-secreting memory B cells (MBC) and CD4 T cells in the majority of adults examined. After vaccination, we confirmed the rapid transient appearance in blood of plasmablasts (day 8) dominated by IgG-switched B cells. Analysis of the immunoglobulin heavy chain genes has thus far revealed a pauci-clonal response and high levels of somatic hypermutation Interestingly, MBC level at baseline positively correlated with post-vaccination Ab response whereas baseline CD4 T cell response negatively correlated with post-vaccination CD4 and Ab responses. We found recent seasonal vaccination in the preceding two years did not influence the Ab response to the H3N2v vaccine.

These results demonstrated that assessment of baseline biomarkers may predict immunological outcome of influenza vaccination. The data reveal mechanisms responsible for variable immune responses following vaccination or natural infection.

Pendrin Localizes to the Adrenal Medulla where it Modulates Catecholamine Release

Pendrin is an aldosterone-sensitive, Na+-independent Cl-/HCO3- exchanger expressed in intercalated cells within the renal cortex where it modulates blood pressure. Since pendrin gene ablation stimulates the release of renin, but not aldosterone, we hypothesized that pendrin is expressed in the adrenal gland and modulates adrenal function. Thus, we examined rat and mouse adrenal pendrin mRNA and protein abundance by PCR, immunoblot and immunohistochemistry and examined adrenal responses in wild type and pendrin null mice. Pendrin protein was detected in adrenal lysates from wild type, but not pendrin null mice. In both mice and rats, we observed pendrin mRNA and protein in the adrenal medulla but not in the adrenal cortex. Since the adrenal medulla produces catecholamines, further experiments examined plasma epinephrine responses to 5 and 20 min of immobilization stress in wild type and pendrin null mice. Basal epinephrine concentration was similar in wild type and pendrin null mice. Immobilization stress increased epinephrine in both groups, but responses were ~50% higher in pendrin null vs wild type after either 5 or 20 min of immobilization stress (20 min: KO, 1562 ± 263, n=4, vs WT, 1041 ± 129 pg/ml, n=6, P < 0.05). We conclude that pendrin is expressed in the adrenal medulla where it may blunt stress-induced epinephrine release.

Direct Reprogramming of Human Dermal Fibroblasts into Endothelial Cells Using Single Transcription Factor

As endothelial cells (ECs) are a key element of vasculature and are indispensable for repairing injured or ischemic tissues, generation of ECs is important and many approaches have been developed. Direct conversion or reprogramming of postnatal cells to desired cell types using lineage- or cell type-specific transcription factors (TFs) has gained a great attention for regenerative medicine, because it is advantageous given that the cells do not have to revert to the preliminary cell stages
of either iPSCs or progenitor cells—both of which entail tumorigenic potentials. Hence, the time to reach the target cells is noticeably shortened, and the expense, significantly reduced. Several studies recently showed generation of ECs from fibroblasts with the pluripotency factors or from amniotic fluid cells with a combination of EC transcription factors (TFs). However, no studies have shown direct reprogramming of human postnatal cells into ECs. Here, we investigated to reprogram human dermal fibroblast (HDF) to ECs with EC TFs. We utilized various combinations of seven EC TFs to transduce HDFs and found that the ETV2 alone best induced endothelial features. KDR+ cells which were sorted at day 7 from ETV2-transduced HDFs showed endothelial characteristics and thus were referred to as reprogrammed ECs (rECs). These rECs displayed a cobble-stone morphology, formed tubular structures, took up acetylated-LDL, and bound lectin. More importantly, the rECs contributed to vessel formation in vivo as demonstrated animal disease models. This is the first demonstration that a single EC transcription factor, ETV2, is able to reprogram human postnatal cells, HDFs directly to functional ECs, which could be useful in the areas of cell-based therapy and drug discovery.

82

Modulation of Neutrophil Activity Using Encapsulated Mesenchymal Stem Cells for Cardiac Ischemia-Reperfusion
Zemskova MA, Taylor WR, Levit RD

Introduction: Myocardial infarctions are often treated with reperfusion therapy. Myocardium is damaged due to ischemia-reperfusion (IR) first by cell loss during hypoxia and later due to the harmful effects of reperfusion. Neutrophils play a central role in reperfusion damage by producing oxygen radicals and amplifying the inflammatory cascade. In bone marrow, mesenchymal stem cells (MSCs) establish an anti-inflammatory environment. We hypothesize that MSCs can exert an anti-inflammatory effect on neutrophils via paracrine effect.

Methods: Neutrophils were isolated from the peripheral blood of healthy donors. Human bone marrow derived MSCs were encapsulated in alginate to prevent direct interaction as a method to isolate their paracrine effect. Reactive oxygen species production (ROS), degranulation and migratory activity of the neutrophils were measured.

Results: Neutrophils treated with encapsulated MSCs showed decreased production of hydrogen peroxide and superoxide as measured by Amplex Red Assay and CellROX Assay compared to non-treated controls.

Conclusion and future directions: MSCs may be a good cell based therapy to treat IR due to their anti-inflammatory effects. The effect on neutrophil degranulation, migration and survival are currently under investigation in vivo and in vitro.

85

Gut Microbiota Plays a Pivotal Role in the Bone Loss Induced By Sex Steroid Deficiency

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Postmenopausal osteoporosis results, in part, from the chronic inflammatory state caused by sex-steroid deficiency. One of the involved mechanisms is increased production of TNF by activated T cells but the nature of the antigens (Ags) driving T cell activation is unknown. The intestine contains trillions of microbes known as the microbiota. The microbiota is crucial for the induction, training, and function of the host immune system, contributes to inflammatory processes, and regulates bone mass accrual. To determine the role of microbiota to the bone loss of sex-steroid deficiency, germ-free (GF) mice and mice housed in standard conditions (control mice) were treated with vehicle or Leuprolide, a GN-RH agonist that blocks sex-steroid production mimicking ovariectomy, at 375 µg/month for 10 weeks starting at 10 weeks of age. uCT analysis at sacrifice revealed that GF mice had a higher trabecular bone volume (BV/TV), and cortical bone volume (CT.Vo) in the distal femur and the spine, as compared to controls. Demonstrating a role for gut microbiota, Leuprolide caused a greater bone loss in control mice than in GF mice. The difference in Leuprolide-induced loss of bone volume between control and GF mice was ~27 % in the femoral metaphysis. Moreover, Leuprolide increased the frequency of TNF+CD4+ and TNF+CD8+ T cells in the BM in control mice but not in the BM of GF mice. In summary these findings demonstrate that gut microbiota plays a significant role in inducing bone loss and increasing bone turnover in sex-steroid deficient mice by providing the Ags required for BM T cell expansion and increased TNF production. We suggest that the composition of gut microbiota may be involved in regulating the magnitude of bone loss experienced by postmenopausal women.

103

Role of Sympathetic Nervous System Overactivation in Intradialytic Hypertension
Lin A, DaCosta D, Park J

End-stage renal disease (ESRD) patients with a paradoxical increase in blood pressure (BP) during hemodialysis, defined as intradialytic hypertension (IDH), are at significantly higher risk of cardiovascular events and mortality. The mechanisms underlying IDH are unknown, and the role of abnormal sympathetic nervous system (SNS) responses remains unexplored. We hypothesized that ESRD patients prone to IDH have an overactivation of SNS activity during hemodialysis that is mediated by oversensitization of the cardiopulmonary baroreceptors, resulting in exaggerated reflex increases in central SNS output in response to volume removal during hemodialysis.

ESRD patients with and without IDH were compared. Intraneural recordings of SNS activity directed to muscle (MSNA) using microneurography, continuous electrocardiography and beat-to-beat arterial BP were
measured at baseline, and during orthostatic stress induced via lower body negative pressure (LBNP). LBNP was applied at low doses (< -20 mm Hg), which isolates the cardiopulmonary baroreflex, and at high doses (> -30 mm Hg), which simulates orthostatic stress from volume removal during hemodialysis. We observed a greater increase in MSNA during both low dose and high dose LBNP in IDH prone patients compared to controls. We also observed a greater SBP response during orthostatic stress induced by LBNP at doses > -10 mm Hg. ESRD patients with IDH have an exaggerated pressor response to orthostatic stress. IDH patients had a greater MSNA response during both low-dose and high-dose LBNP, suggesting that SNS overactivation underlies the exaggerated pressor response during orthostatic stress, and that the exaggerated SNS response may be mediated by oversensitization of the cardiopulmonary baroreflex.

55

Racial Differences in Preemptive Referral For Kidney Transplant Evaluation
Lovasik BP, Basu M, Schrager J, Pastan S, Patzer RE

Background: Racial disparities exist in access to kidney transplantation, but little is known about disparities in access to preemptive referral for kidney transplant evaluation (PRKTx), or referral prior to initiating dialysis, since referral is not measured in national surveillance data.

Methods: KTx center-level data for 4,914 end-stage renal disease patients referred to Emory Transplant Center for KTx evaluation from 2005-2010 were linked with United States Renal Data System data and 2009 Census American Community Survey poverty data. Logistic regression models were used to examine the association between race and PRKTx.

Results: Of 4,914 referred patients, 934 (19.0%) were preemptively referred, including 32.0% of white but only 13.0% of black patients (p<0.0001). Among all referred patients, 1,977 (40.2%) were waitlisted (62.8% PRKTx vs. 34.9% referred after dialysis start). In crude analyses, white patients were over 2 times more likely to be PRKTx (OR=3.13; 95% CI: 2.70-3.70). After adjusting for clinical, demographic, and socioeconomic factors, white patients were significantly more likely to receive a PRKTx than black patients (OR=2.39; 95% CI: 2.02-2.84).

Conclusions: Preemptive referral for KTx evaluation is associated with improved access to waitlisting and both deceased and living donor KTx. Racial differences in PRKTx exist even after accounting for differences in demographic, clinical, and socioeconomic characteristics. Interventions that promote early access to care prior to ESRD among African Americans may reduce disparities in access to transplant.

Geographic Determinants of Low Pre-ESRD Nephrology Care in the United States
Lovasik BP, Hao H, Pastan S, Chang H, Patzer RE

Background: Pre-ESRD nephrology care is crucial for optimizing clinical outcomes for patients with ESRD. Geographic variation of pre-ESRD nephrology care coverage has not been studied nationally.

Methods: A marginal mixed generalized estimating equation model was used to estimate the association of the proportion of patients within a facility who received pre-ESRD nephrology care and facility-level neighborhood characteristics among 5,387 dialysis facilities across the US. SaTScan testing was utilized to detect geographic clusters of dialysis facilities with low pre-ESRD nephrology care.

Results: Dialysis facilities in the lowest quintile of pre-ESRD nephrology care were geographically clustered in 5 distinct areas (P<0.05), including San Francisco, Los Angeles, Chicago, Miami, and Baltimore and along the corridors of Mississippi and Ohio River. (Figure 1) Facilities in the lowest quintile of pre-ESRD nephrology care were more likely to be located in inner cities compared to those in the highest quintile (45.8% vs 21.8%, OR=1.88, P=0.014). Lowest quintile facilities were significantly more likely to be in high-poverty neighborhoods (24.2% vs. 16.6%, OR=1.96, P=0.030). The proportion of racial minorities within a neighborhood was not associated with pre-ESRD nephrology care rates (P=0.929).

Conclusions: The proportion of patients receiving access to pre-ESRD nephrology care within a facility varies by geographic region. Policy makers and ESRD Networks should target these low-pre-ESRD facilities and regions to improve access to nephrologist care with interventions and specific pilot programs aimed at improving patient outcomes. Further examination of what factors make geographic regions better or worse at providing pre-ESRD nephrology care is warranted.

3

The Role of Human Osteopontin Isoforms in Collateral Formation
Lyle AN, Harirforoosh S, Joseph G, Weiss D, Taylor WR

Coronary and peripheral artery diseases lead to impaired blood flow and ischemia. The development of new collaterals in response to ischemia involves cytokines, inflammation, cell proliferation and migration, and arteriogenesis with vascular smooth muscle cells (VSMCs). Our work has shown that osteopontin (OPN), an inflammatory protein, is required for collateral formation. Humans express three OPN isoforms (a, b, and c) and the roles of each in collateral formation and cell migration remain undefined. To investigate the differential effects of human OPN isoforms on collateral formation, we used a murine model of hind limb ischemia on OPN-/- mice. Mice received intramuscular injections of 2x108 infectious lentivirus particles for OPNa or OPNc. OPNa rescued collateral formation, as measured by perfusion, while OPNc significantly
increased perfusion over OPNa and WT animals. To determine if the impaired migration of OPN-/- VSMCs could be rescued, OPN a, b, or c conditioned media was used in a Boyden Chamber Assay. OPNb had no effect on migration, whereas OPNa and OPNc increased basal migration. Only OPNc enhanced PDGF-induced migration. Migration requires dynamic focal adhesion (FA) turnover. FAK phosphorylation at Y397 occurs downstream of αvβ3 and CD44 receptor activation and is needed for FA assembly. To investigate if OPN isoforms differentially activate FAK via αvβ3 or CD44, VSMCs were stimulated with OPN a, b, or c ± receptor blocking antibody. OPN c and b increased Y397FAK, whereas OPNa did not. Our data demonstrate a functional difference in OPN isoforms on collateral formation, VSMC migration and signaling. Understanding the mechanisms underlying OPN isoform-mediated collateral formation may lead to new therapeutic approaches to treat ischemic pathologies.

86

Comparison of Route and Immunocompromised Status in Patients Receiving Fecal Microbiota Transplantation for Clostridium Difficile

Mandalia AB, Ward A, Kraft CS, Dhere T.

Background: Fecal microbiota transplantation (FMT) has revolutionized the treatment of Clostridium difficile infection (CDI). Our study assesses differences in response rates in the following subgroups: route of FMT delivery and immunocompromised (IC) status.

Methods: This is a retrospective chart review of patients receiving FMT from Dec. 2012 to Dec. 2013. Eligible patients include those with 2 or more relapses of CDI, who did not respond to treatment, and/or have failed a vancomycin taper. Patients are IC if they are immunosuppressed due to a medical condition, hematopoietic stem cell transplant patients, or on current or recent (<3 month) immunosuppressant therapy. Response to FMT is defined as cessation of diarrhea and/or a negative C. difficile PCR at 4 weeks. Student's t-test was performed between groups and p-values <0.05 were considered significant.

Results: Out of 37 FMTs attempted, 36 were performed in 30 patients. Data was available for 31 FMT performed in 24 patients. 18 (75%) patients responded after one FMT. Five (20.8%) responded after a second FMT. One (4.2%) responded after a third FMT. A comparison of FMT using the upper gastrointestinal (UGI) tract (n=8) versus colonoscopy (n=23) demonstrated response rates of 62.5% and 87%, respectively, with no significant difference. A comparison of FMT in IC (n=11) versus immunocompetent (n=20) demonstrated response rates of 75% and 81.8%, respectively, with no significant difference. One patient, a hematopoietic stem cell transplant recipient, was found to have chronic graft-versus-host disease of the terminal ileum, and FMT was not performed.

Conclusion: No significant differences in response were seen when comparing UGI tract versus colonoscopy of FMT delivery as well IC versus immunocompetent patients.

CD31+ T Cell Depletion Independently Predicts Diastolic Dysfunction in Women with Signs and Symptoms of Ischemia Without Obstructive Coronary Artery Disease: Results from the NHLBI-Sponsored Women Ischemia Syndrome Evaluation (WISE)


Background: The pathophysiology of diastolic dysfunction (DD) is incompletely understood and therapeutic strategies are limited. Recent evidence suggests that endothelial dysfunction plays a role in the development of diastolic dysfunction. CD31+ T cells have neoangiogenic qualities and their decrease is associated with endothelial dysfunction. We evaluated the association between CD31+ T cells and diastolic function in women with signs and symptoms of myocardial ischemia and no obstructive CAD by angiography.

Methods: 141 women with normal systolic function enrolled in the WISE from 2009-2012 were studied. Left ventricular end diastolic pressure (LVEDP) was measured, and CD31+ T cell counts and their frequency were measured in blood using flow cytometry. Cine cardiac MRI was performed to measure diastolic filling parameters (peak filling rate [PFR] and time to peak filling rate [tPFR]).

Results: Mean age was 54±10 years, BMI was 31±9; 41% had hypertension, 13% diabetes, 11% hyperlipidemia, and 3% were smokers. PFR correlated with age (r=0.23, p=0.006), cardiac mass (r=-0.17, p=0.048) and CD31+ T cell count and frequency (r=0.22, p=0.010 and r=0.20, p=0.016). CD31+ T cells correlated negatively with age (r=0.25, p=0.004). After adjusting for age, race, smoking, hypertension, diabetes, hyperlipidemia, and body mass index, CD31+ T cell count and frequency were independent predictors of PFR (β=0.26, p=0.041 and β=0.33, p=0.007, respectively), but were not related to the tPFR and LVEDP.

Conclusion: In women with ischemia without obstructive CAD, lower numbers of CD31+ T cells were independently associated with DD. Further prospective studies are warranted to investigate the role of CD31+ T cells in the pathophysiology of DD and related adverse outcomes.

Liver Injury and Inflammation Leads to Profound Hepatic Natural Killer Cell Dysfunction and Predisposes the Liver to Metastatic Disease

Mendel JB, Tedesco D, Price A, Grakoui A.

Comprising 30-50% of human and 5-20% of mouse hepatic lymphocytes, NK cells play a major role in regulating hepatic immune homeostasis. Their ability to respond to infected and neoplastic cells in an antigen independent manner has led to investigations into the use of NK cells as a therapeutic option for liver fibrosis and cancer. A complex integration of genetic
and environmental signaling molecules regulate expression of inhibitory and activating receptors that control NK cell function. Alterations of the NK cell repertoire have been reported to contribute to the pathology of viral infections, liver fibrosis, and cancer. As such, I sought to define the effects of hepatic injury and inflammation on NK cell function.

Analysis of NK cell function after liver injury revealed significantly reduced cytotoxic potential. Furthermore, we observed a significant decrease in IFN-γ and TNF-α production when NK cells were stimulated with PMA/ionomycin directly ex vivo. To demonstrate the in vivo consequences of the observed compartmental defect in NK cell function, mice were injected with the NK cell dependent melanoma cell line, B16. Mice that received a single dose of a hepatotoxic drug three days prior to B16 challenge had more metastatic lesions compared to control animals. These data demonstrate that hepatic injury and inflammation leads to hypofunctional NK cells with consequent failure to prevent tumor metastasis. Understanding the mechanisms leading to NK dysfunction secondary to inflammation from hepatitis and acute injury may help reveal novel pathways to prevent tumor metastasis and development of hepatocellular carcinoma.

89

Cross-talk Between Connexin 43 and CFTR in ER Quality Control
Molina SA, McCarty, N and Koval MH

An endoplasmic reticulum (ER) resident chaperone, ERp29, was previously identified to promote the quality control of cystic fibrosis transmembrane conductance regulator protein (CFTR). ERp29 also regulates the trafficking and oligomerization of a gap junction protein, connexin43 (Cx43). The ERp29/Cx43 complex regulates Cx43 oligomerization in the ER allowing for the formation hexameric hemichannels only in the TGN. Here we examined the ability of HeLa cells stably expressing Cx43 to form Cx43 membrane channels in the presence of the wild type and the most common mutant form of CFTR, ΔF508, in order to assess chaperone cross-talk. CFTR expression is controlled by a TetOn system where CFTR mRNA and protein expression is regulated to mRNA and protein levels observed in primary airway cells. With a TetOn expression system we are able to probe cellular stress conditions in the presence and absence of transiently expressed CFTR. We assessed ER stress by using a luciferase-based transcription factor assay, qRT-PCR for ER stress markers and chaperones, and we also analyzed the effect of Δ508-CFTR on gap junction intracellular communication via dye transfer studies. Mutant ΔF508-CFTR can induce trafficking errors through ERp29 leading to decreased Cx43 protein trafficking and increased overall cellular sensitization to ER stress in a HeLa cell model which mimics cystic fibrosis airway cell protein expression levels.

16

Insulin Stimulated Glucose Uptake is Defective in the Cystic Fibrosis Affected Human Airway

Molina SA, Hansen JM, Prince CZ, Moriarty HK, Infield DT, Stauffer B, Hunt WR, Ziady AG, Koval M and McCarty N

Cystic fibrosis (CF) is one of the most commonly inherited diseases in Caucasians. Accelerated lung decline is known to occur in disease states such as diabetes, CF, and CF related diabetes (CFRD). This includes pulmonary exacerbations, progressive fibrosis of the lung, recurring bacterial infections, and accompanied by a precipitous decline in lung function. The airway is lined by a complicated pseudostratified epithelium that contains multiple cell types which function to work together to prevent infection and maintain a physical barrier between the sterile serous compartment of the lung and the non-sterile hostile air environment of the airway. We sought to understand the basic questions of how fluctuations in plasma glucose regulation and insulin responses affect the glucose barrier. We asked if this natural glucose flux was disrupted in disease states such as cystic fibrosis and CFRD by assessing glucose uptake experiments. We questioned whether insulin-stimulated glucose uptake in the airway could be a possible mechanism for ASL glucose clearance resulting from increased post-prandial glucose flux into the airway. We analyzed Glut4 translocation with confocal microscopy. In this process, we also characterized the NuLi-1 normal airway primary cell line and compared this to the age, sex and genotype matched CuFi-5 cells. We found that primary normal human bronchial epithelial cells (NhBECs) increase glucose uptake in response to insulin and that CFTR ΔF508-affected CFhBECs do not respond to insulin treatment. Confocal imaging revealed dynamic Glut4 transporter movement with insulin stimulation in NhBECs and defective Glut4 translocation in CFhBECs. In addition, we found that primary hBECs apically express the insulin receptor.

30

Transforming growth factor Beta 1-induced epigenetic modification of Thy-1 in primary lung fibroblasts
Neveu W, Mills S, Sueblinvong V.

Rationale: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease that increases with age. Although the causative mechanisms remain poorly understood, there is data implicating transforming growth factor β1 (TGFβ1) in its pathogenesis. We identified in senescent mice a pro-fibrotic lung phenotype with an increase in the number of fibroblasts negative for Thy-1, a protein associated with fibrosis. Given that loss of Thy-1 expression by methylation leads to a fibrotic phenotype in fibroblasts, we evaluated whether TGFβ1 epigenetically regulates Thy-1 differentially in lung fibroblasts with age.

Methods: Lung fibroblasts harvested from young (3 month) and old (24 month) mice were treated with TGFβ1 ± the DNA methyltransferase (DNMT) inhibitor 5-AZA for 72 hrs and analyzed for Thy-1 gene expression by quantitative RT-PCR. DNMT gene expression in cells at baseline and following TGFβ1 treatment was also determined.

Results: TGFβ1 decreased Thy-1 expression in fibroblasts from young mice. In contrast, TGFβ1 plus 5-AZA had minimal impact
on Thy-1 expression. Lung fibroblasts from old mice express higher levels of TGFβ1 and lower levels of Thy-1 at baseline. Treatment of these cells with 5-AZA increased Thy-1 expression. No significant difference was observed in DNMT expression in response to TGFβ1 in fibroblasts from young or old mice, which is in agreement with studies showing dissociation between DNMT mRNA levels and protein activity.

Conclusions: TGFβ1 induces Thy-1 methylation in lung fibroblasts, and the decreased expression of Thy-1 in fibroblasts from old mice may be a consequence of elevated TGFβ1 and activation of the DNMT pathway. Future studies to determine how Thy-1 is regulated as fibroblasts age may identify therapeutic targets in IPF.

43

Hepatitis B Outcome in Coinfected HIV-HBV Individuals in the Tenofovir/Emtricitabine Era
Nguyen D, Nguyen ML, Chu K, and Osborn M

Background: Hepatitis B is an important public health issue with the HIV epidemic. In the USA, HBV-HIV represent 6-10% of people living with HIV/AIDS. We report our experience with HBV-HBV coinfected patients.

Methods: Of 1011 naive HIV patients enrolled at IDP from 06/2004 to 12/2011, those with HBsAg+ were studied. Demographics, antiretroviral treatment and HBV and HIV markers were abstracted. p<0.05 was considered significant.

Results: There were 89HBsAg+ patients. Of those, 76(86%) were male, 73(82%) black, and 58(65%) men having sex with men or bisexuals. The age at HIV diagnosis was 34.4 years. The majority 82 (92%) had a positive HBsAg at enrollment and 5 became positive during follow up. The baseline CD4 count was 87.16+/-123 cells/mL. Among the 63(70%) with HBV VL at baseline, 12(20%) had undetectable viral load (ULV) and 32(51%) had high VL (> 1 million). Among those, 48(55.2%) had an ULV at the last visit, and 7(8%) developed immunity with HBsAb+; 7(33%) of 22 became HBsAb+;6 of the 7 were on truvada (TVD)and 1 on FTC-containing regimen. Among those who had HBV UVL 83% were on TVD, and 10% on a 3TC or FTC-containing regimen. Among the 5 patients who acquired HBV after enrollment, all were male and 3 received HBV immunization.

Conclusion: In our clinic, half of HBV-HIV patients on ART had UVL HBV and 8% developed HBV immunity. Further studies with more uniform HBV markers are needed in HBV-HIV individuals. Greater efforts are needed to immunize susceptible HIV+patients with HBV vaccine.

8

Spectrum of Kaposi’s Sarcoma Encountered Among HIV-Infected Patients in an Inner-City Hospital in the Established Antiretroviral Era
Nguyen ML, Zeng C, Adamski M, Mosunjac M and Gunthel C

Background: The incidence of Kaposi sarcoma, an AIDS-defining cancer has dramatically decreased in US in the combined antiretroviral therapy (cART) era. We present our experience with KS encountered among admitted patients in an inner-city hospital over a 3-year period.

Methods: Grady Memorial Hospital hospital records were queried for discharge diagnosis that included KS from October 2010 to October 2013. Demographic data and HIV markers were collected.

Results: There were 43 patients admitted with active KS during the 3-year period, with the majority being male (97%) and African (81%). At KS diagnosis (dx), the median age was 37 (range: 19-62), the median CD4 count was 11(range: 1-462) and 1/3 was on ART. The most commonly involved organs are skin, gastrointestinal tract, lungs and lymph nodes. The median time of HIV dx to KS dx was 2 years (range: 0-26 years). Half of the patients had a concomitant or recent (within past 6 months) opportunistic infection (PCP(n=14), toxoplasma encephalitis(n=4), CMV retinitis/colitis(n=2), or cryptococcosis(n=2)). Of note, a third had coinfection with a viral hepatitis: 11(26%) had chronic active hepatitis B and 3 (7%) had active hepatitis C. A third had a poor KS prognostic index. 26 patients received chemotherapy for KS. The median follow up from KS diagnosis was 343 days (14-2234). 14(33%) died within one year of KS diagnosis.

Conclusion: In our hospital, 1/3 patients with HIV-associated KS had poor outcome despite wide availability of cART and chemotherapy. Vigilance to get patients into care and start ART earlier will help improve KS survival.

56

Patient Acuity Scores to Prevent Rapid Responses

In the last 10 years patient safety committees nationwide have focused on creating taskforces such as rapid response teams (RRTs) that can intervene on patients that start to decompensate prior to a code. Internal medicine does not have a widely accepted scale to grade the severity of illness. The Duke Hospitalists adapted a previously used scale by Dr. Edelson et al (2011) and used it prospectively to determine if there was a correlation in the presenting acuity of illness and the number of RRTs in the first 24 hours and to see if there would be a decrease from year to year. The differences in mean severity score by occurrence of a rapid response (RRT) in multiple categories were examined using analysis of variance (ANOVA). There were significant differences in mean acuity score between patients who experienced an RRT at any time and those who did not, patients who experienced an RRT within 12 and 24 hours of admission and those who did not, patients who experienced an RRT and patients who underwent an unplanned transfer and those who did not (all p’s<0.007). All of the level seven scores that had a rapid response were transferred to the critical care unit as well as 79% of the level six scores. There were no significant differences in the number
of rapid responses between 2012 and 2013. A high patient acuity score has been shown to correlate with rapid responses and transfers to higher level of care within the first 24 hours. Patients that had a RRT had a higher score with a trend towards increasing transfer rates with elevated scores. Using this scoring system did not lead to a lower amount of RRTs in comparing years, however it could be used for selective monitoring to prevent sentinel events.

57

**Pure Proliferative Lupus Nephritis versus Mixed Proliferative Lupus Nephritis: A Comparison of Demographic and Clinical Characteristics**

Osikoya OA, Adedinsewo DA, Enofe N, Odewole OA, Navarrete JE, Cobb J, Oommen AA, Ilori TO

Introduction: Lupus Nephritis (LN) is an important manifestation of Systemic Lupus Erythematosus. Although divided into six classes (I to VI), LN can occur as a mixture of two classes. We aim to compare the baseline clinical characteristics of patients with pure and mixed proliferative LN in a university hospital.

Methods: Retrospective review of kidney biopsy pathology reports and medical records of LN patients from January 2000 to December 2011. Records were obtained electronically from the hospital's central clinical data warehouse using ICD9 codes (710.0, 583.8) and validated by matching with a renal biopsy database from pathology. Only confirmed biopsies by a hospital provider were included in this analysis (n=167). Descriptive, Chi-square, standard parametric and non-parametric analyses, were performed to evaluate the differences in baseline clinical characteristics between patients with mixed and pure proliferative LN. Data analysis was done using SAS® 9.3 statistical software and α = 0.05.

Results: In comparing the two groups: pure vs. mixed proliferative LN, there were no significant differences in age (mean (SD) =35.9(13.0) vs. 32.3(9.4), p=0.27), gender (females (n%)= 46(86.8%) vs.35(81.4), p=0.58) or race (Non-Hispanic Black (n%)= 32(76.2) vs. 33(82.5), p=0.59) across both groups. Differences in patients with eGFR <60ml/min at baseline (n %) = 27(50.9) vs. 20(46.5), p=0.69) and mean 24hr urine protein (mean (SD) 3.6 (3.1) vs. 3.2 (3.0), p=0.68) were also not statistically significant across the two groups.

Conclusion: There were no significant differences between the pure and mixed proliferative LN patients across all demographic and clinical variables examined at baseline.

58

**Diabetes Care in Long-Term Care Facilities: A Randomized Controlled Study**


Managing hyperglycemia and diabetes is challenging in geriatric patients in long-term care (LTC) facilities. This pilot trial at two LTC facilities enrolled patients with type 2 diabetes (T2DM) that had hyperglycemia (BG >180 mg/dL or two BG >150 mg/dL and A1C >7.5%) on diet and/or oral antidiabetic drugs (OADs). Patients were randomized to receive basal insulin (glargine, starting dose 0.1 U/kg/day) plus sliding scale insulin (glulisine) before meals for BG >200 mg/dL or to continue OAD plus SSI (regular) before meals for BG >200 mg/dL for 26 weeks. Primary endpoints were differences in glycemic control as measured by mean fasting and daily BG, HbA1c levels, and hypoglycemia between groups. A total of 75 patients were recruited in each group (age: 79±8 yr, BMI: 30.1±6.5 kg/m2, duration of DM: 8.2 ±5.1 yrs). During the study period, the mean fasting BG in the basal group was similar compared to the OAD group (130±26 vs. 123±23, p=0.12); however, there were no differences in the rate of complications, daily mean BG, HbA1c at 3 and 6 months, frequency of hypoglycemia, number of emergency room visits, hospitalizations or mortality between treatment groups (all p=NS). In summary, the results of this randomized pilot study indicate that patients with T2DM in long-term care facilities achieved and maintained similar glycemic control when treated with either basal insulin or OAD plus insulin supplements.

58

**Relationship of Sociodemographic and Disease Factors with Loss to Follow-Up and Appointment Noncompliance in Indigent Patients with Systemic Lupus Erythematosus**

Pham A, Bao G, Lim SS, Drenkard C

Background: The relationship of noncompliance with sociodemographic and disease factors has been poorly identified in Systemic Lupus Erythematosus (SLE). We investigate the impact of organ damage, health status, and depression on non-compliance with medical care in a predominantly indigent Black cohort.

Methods: We selected a sample of indigent SLE patients from the Grady Lupus Clinic to examine loss to follow-up (LTF) and appointment noncompliance. LTF was defined as no GLC visits for 12 months, and appointment noncompliance was calculated as 1 minus the rate of accomplished GLC visits within 12 months. Predictors were assessed with validated self-administered tools. Logistic regression and multi-way ANOVA analyzed associations of sociodemographic and disease factors with outcomes.

Results: The cohort encompassed 127 patients (94% non-white, 91% females, and 73% live below the poverty line). While depression increased the risk of LTF, longer disease duration and poverty were found to be protective. The adjusted appointment noncompliance rate was higher in those with severe disease activity (34%; 95%CI 19-48%), compared to those with mild disease activity (18%; 95%CI 1-35%), p-value 0.058. In contrast, patients with organ damage have lower appointment noncompliance (22%; 95%CI 8-26%) than those without organ damage (33%; 95%CI 16-50%), but the difference is not statistically significant (p 0.083).

Conclusion: Barriers to optimizing SLE outcomes include noncompliance defined as loss to follow-up and appointment noncompliance. Our data recognizes lower compliance in...
patients with depression, shorter disease duration, higher income, and higher self-reported disease activity. Targeted intervention can be tailored with these factors in mind.

104

Insurance Status and U.S. Region Associated with Placement of Permanent Vascular Access in Hemodialysis Patients with End-Stage Renal Disease Secondary to Lupus Nephritis

Plantinga L, Drenkard C, Patzer R, Pastan S, Lim SS, McClellan W

Prior data suggest sociodemographic and regional variability in quality of end-stage renal disease (ESRD) care among lupus patients. We aimed to describe permanent vascular access (PVA) placement among hemodialysis (HD) patients with ESRD secondary to lupus nephritis (LN-ESRD) and to examine whether placement differs by sociodemographics and across U.S. regions. Among 5562 incident U.S. HD patients with LN-ESRD initiating treatment 7/05-9/11, we estimated associations of PVA placement (arteriovenous fistula or graft used or in place on first dialysis, vs. temporary catheter only) with race/ethnicity, insurance, and region using national surveillance data (United States Renal Data System), with logistic regression models adjusting for potential confounders. Fewer than one-quarter (24.4%) of incident HD patients with LN-ESRD patients had a PVA placed, compared to 36.0% of other ESRD patients. Hispanic LN-ESRD patients were 15% less likely than their white counterparts to have a PVA but the association was not statistically significant (OR=0.85; 95% CI, 0.69-1.05). Having no (vs. private) insurance was associated with 38% lower likelihood of PVA among LN-ESRD patients (OR=0.62; 95% CI, 0.49-0.79). There was substantial, statistically significant Network-level variation, with adjusted probabilities of PVA placement ranging from <0.20 (Midwest, Southern California) to >0.30 (Northwest, New England). Most LN-ESRD patients are not initiating HD with a PVA, and those who are Hispanic or uninsured or who live in the Midwest or Southern California at the start of ESRD may be even less likely to have PVA. Targeted interventions to increase PVA placement among LN-ESRD patients are warranted to prevent potential morbidity and mortality associated with temporary catheters.

105

Catheters for Hemodialysis Access May Be Associated With Increased Risk of Poor Outcomes in Patients Transplanted Early

Plantinga L, Patzer R, McClellan W, Pastan S

Clinical guidelines recommend placement of a permanent vascular access (PVA) in all incident hemodialysis (HD) patients, but providers may rely on temporary catheters when patients are expected to receive a kidney transplant imminent. Whether this practice is associated with increased risk of poor outcomes is unknown. Using United States Renal Data System data, we examined mortality, hospitalizations, and transplant failure in 8617 U.S. incident HD patients (7/05-5/11) aged 18-69 who received a transplant within 1 year of HD start. Follow-up was defined from HD start (mortality, hospitalizations; median, 3.5 years) or transplant (transplant failure; median, 2.7 years) to death or end of follow-up (9/11). We used Cox proportional hazards and Poisson models with adjustment for age, sex, and race to estimate hazard ratios (HRs) and incidence rate ratios (IRRs) for catheter use vs. PVA (fistula/graft) used or in place at start of HD. Overall, 4861 (56.4%) started HD with a catheter. Catheter use was associated with 16% and 53% increased all-cause and infectious mortality risk among these patients, respectively, although the associations were not statistically significant (HR=1.16, 95% CI, 0.97-1.39; and HR=1.53, 95% CI, 0.86-2.71). Catheter use was associated with a modestly (5%) increased hospitalization rate (IRR=1.05, 95% CI, 1.01-1.08). Finally, transplant failure was 16% more likely among those recipients starting with a catheter (HR=1.16, 95% CI, 1.01-1.32). More than half of patients who receive a transplant within 1 year of starting HD do not have PVA in place. Providers should weigh potential modestly increased risks of mortality and morbidity in shared decision making regarding vascular access for HD patients who are likely to receive a transplant early.

59

Pre-Hospital Identification of Patients with Severe Sepsis: Development and Validation of a Novel Risk Prediction Score


The purpose of this study was to derive and validate a predictive model and clinical risk prediction score for pre-hospital severe sepsis (PreSS). This was a retrospective cohort study of adult, non-trauma, non-arrest, ‘at-risk’ patients transported by a single EMS system to a large public hospital 2011-2012. Of 555 patients who met inclusion criteria, 65% (n=360) were admitted to the hospital, and 14% (n=75) were admitted for SS with an in-hospital mortality of 34% (n=23). The following were predictors of SS: age modeled in tertiles with age 18-49 as the reference [age 40-59 (OR 4.28, p=0.026); age >=60 (OR 2.19 p=0.26)]; transport from nursing home (OR 4.73 p<0.001), 911 complaint category of ‘sick person’ (OR 3.04 p=0.003), hot tactile temperature (OR 2.90, p=0.007), SBP (OR 0.96, p=0.002), and O2 (OR 0.95 p=0.009). Area under the receiver operating characteristic curve was 0.842 (derivation cohort) and 0.820 (validation cohort). Using a sensitive cut point, sensitivity was 91% and specificity 34% (derivation cohort), and 78% and 26% (validation cohort). There was high correlation between the model and PreSS score (Pearson R = 0.907, p<0.0001). PreSS score sensitivity was 86%, and specificity was 47%. This study demonstrates that a simple, reliable pre-hospital severe sepsis screening tool can be developed, but further validation is needed prior to widespread clinical use.
Predictors of Mortality in End Stage Renal Disease Patients with Infective Endocarditis

Powell RE, Steinberg JP, Jacob JT

Background: Patients undergoing dialysis for end stage renal disease are at increased risk for infective endocarditis (IE), but the predictors of mortality from IE in this population are unclear.

Methods: Chronic dialysis patients with IE from 1990 to 2012 in 2 academic medical centers were retrospectively identified using ICD-9 codes and validated using the modified Duke criteria and chart review. Outcome was tracked until death or loss to follow up. Categorical variables were compared using chi-square and continuous variables with the t-test or Fisher's exact test. Logistic regression was used to predict 30-day mortality.

Results: Over 23 years, there were 258 patients with IE, 50.4% female with a median age of 55 years. Mortality rates were 24.2% in the hospital, 27.9% at 30 days, 57.0% at 1 year, and 75.8% at 3 years. Altered mental status at admission (55.1% vs 23.5%, p<0.001), embolic stroke (36.1% vs 27.4%, p<0.001), vegetation > 1.5 cm (70.0% vs 46.8%, p<0.001), thrombocytopenia (34.6% vs 15.8%, p=0.004), and age >65 (40.3% vs 24.7%, p=0.01) were more common in patients who died at 30 days compared to those who survived, while valve replacement surgery (15.3% vs 30.7%, p=0.01) and infection with enterococci (6.9% vs 19.9%, p=0.01) were less common. Age >65 (OR 7.41, 95% CI 2.15 – 25.5), embolic stroke (OR 4.32, 95% CI 1.17 – 15.9), vegetation >1.5 cm (OR 4.80, 95% CI 1.40 – 16.4), and thrombocytopenia (OR 5.15, 95% CI 1.44 – 18.4) independently predicted 30-day mortality, while valve surgery (OR 0.21, 95% CI 0.05 – 0.88) and infection with enterococci (OR 0.04, 95% CI 0.004 – 0.31) were protective.

Conclusions: Dialysis patients with endocarditis have high mortality. Surgery is associated with relatively lower risk of mortality.

Docosahexaenoic Acid Attenuates Palmitate-Induced Unfolded Protein Response in C2C12 Myotubes


Accumulation of saturated fatty acids in skeletal muscle results in dysregulation of protein metabolism and muscle atrophy. In cultured myotubes, the saturated fatty acid palmitate (PA) stimulates protein degradation and decreases cell size, while co-treatment with the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA) prevents the response. PA can also induce endoplasmic reticulum stress and activate the unfolded protein response (UPR) in myotubes, leading to decreased protein translation. This study tests whether DHA protects against palmitate-induced endoplasmic reticulum stress and activation of the UPR in muscle cells. C2C12 myotubes were treated with 500μM PA and/or 100μM DHA for 24h and protein markers of the UPR were evaluated by western analysis. PA induced activation of PKR-like endoplasmic reticulum kinase (PERK), as indicated by an increased phospho-PERK:total PERK ratio. PA also induced phosphorylation of (i.e. inactivated) eukaryotic initiation factor 2α (eIF2α) and increased the level of Nrf2 protein which controls the expression of several genes whose proteins are involved in proteolysis. Co-treatment with DHA attenuated the effects of PA on PERK and restored Nrf2 to the control level; however, eIF2α phosphorylation was similar in myotubes treated with PA and PA+DHA. Notably, PA activated ATF4 and a downstream mediator, CHOP, both of which control the expression of several autophagy-related genes and other proteins that regulate caspase proteases. DHA restored ATF4 and CHOP to control levels. These results indicate that DHA attenuates the effects of PA on activation of the UPR but does not restore global protein synthesis. This suggests that DHA maintains myotube diameter primarily by inhibiting palmitate-induced protein degradation.
Risk of Recurrent Clostridium Difficile Infection: Impact of Diagnostics and Treatment
Reddy SC, Almendares OM, Baughman W, Lessa FC, Farley MM.

Introduction: In the setting of expanded use of molecular diagnostics and new treatment options, understanding the epidemiology of recurrent C. difficile infections (CDI) is important.

Methods: We used active laboratory- and population-based surveillance data in metro Atlanta to identify a cohort of patients aged ≥ 18 years who developed an initial CDI (iCDI) from January 2010-September 2013. iCDI was defined as the 1st C. difficile-positive specimen by either molecular or toxin assay during the study period. Patients were excluded from cohort if a prior CDI was identified from September-December 2009. Each iCDI patient was followed up for at least 3 months for recurrent CDI (rCDI), defined as a C. difficile-positive specimen >14 days from a previous positive test. Cox regression model was used on a random sample of iCDI patients stratified by age and gender to determine adjusted hazard ratios (HR) for recurrence based on iCDI treatment.

Results: Of 11,945 iCDI cases identified, 22.0% developed a 1st recurrence, 7.0% developed a 2nd recurrence, and 2.8% developed 3rd recurrences. Diagnosis was made using a molecular assay in 49% of iCDI, 54% 1st, 57% 2nd and 61% of 3rd recurrences. The risk for a subsequent CDI was higher in those with one recurrence compared to those without any recurrences (HR 1.56, p<0.01). Of the 1,814 sampled cases, controlling for age, gender and diagnostic method, rCDI rates were similar in those treated with either metronidazole or vancomycin alone (p=0.13).

Conclusions: Almost a quarter of iCDI cases developed recurrent disease while a small proportion develop multiple recurrences. Additional studies are needed to further evaluate the link between more sensitive diagnostics and initial therapeutic choices with risk of CDI recurrence.

Heel/Toe Clearance and Variability Ascending and Descending Stairs in Older Adults with Mono Versus Multifocal Intraocular Lenses
Rezvan A, Hall CD, Hackney ME.

Intraocular lenses (IOLs) have been developed that provide both distance and near refraction (multifocal IOLs), which are rapidly becoming the standard implant for cataract surgery. Multifocal glasses increase variability of toe clearance of older adults when navigating stairs and increase fall risk; however, little is known about biomechanics of stair navigation in individuals with multifocal IOLs. This study aimed to compare the minimum heel and toe clearance and variability, while ascending and descending stairs, of individuals with bilateral, conventional monofocal IOLs versus multifocal IOLs. Twenty-three individuals participated. Eight participants with multifocal IOLs (4 men, 4 women; Age M= 66.5 years, SD= 6.26) and 15 participants with monofocal IOLs (All men, Age M = 69.9 years, SD = 6.9) underwent demographic, visual, and mobility measures. Motion analysis was used to calculate heel/toe clearance on stairs. Repeated measures analysis of variance (ANOVA) determined effects of multifocal and monofocal IOLs on minimum heel/toe clearance, and variability. Appropriate post-hoc pairwise comparisons were used (alpha < 0.05). No significant differences were found between the monofocal and multifocal groups on minimum clearance or variability. Foot clearance differed while ascending versus descending stairs: the first step up onto the stair had the greatest clearance; whereas, the final step down to the floor had the greatest clearance. Biomechanics of stair navigation are similar in multifocal and monofocal IOL users, suggesting no additional fall risk with the implantation of multifocal IOLs; however, larger samples are necessary for definitive recommendations.

Effects of Parathyroid Hormone Treatment on Skin Allograft Rejection in Mice
Reott M, Espinosa J, Allan K, Pacifici R

Parathyroid hormone (PTH) is involved with balancing calcium and phosphorus levels, making it especially important to monitor in both bone homeostasis and renal health. Additionally, changes in PTH levels in relation to hyperparathyroidism before and after organ transplantation are known and have been investigated for some time. Recent studies have also shown the importance of PTH in its effects on the immune system, which may suggest a role of PTH in the immunological processes involved in transplant tolerance and rejection. The results from our current investigation show that treatment with PTH both delayed rejection of mouse skin allografts as well as decreased the number of allograft rejections overall compared to the vehicle treatment control group. Interestingly, both continuous PTH treatment (cPTH) and intermittent PTH treatment (iPTH) were similarly effective in decreasing rejection in the recipient mice; even though these two treatments often provoke opposite osteoimmunologic responses. The results of the current study suggest there is an immunologic function of this hormone which is affecting the skin graft, and that administration of PTH may provide for an increase in allograft transplant tolerance.

ZBTB46 is a Shear Stress Sensitive Transcription Factor in Endothelial Cells Contributing to Endothelial Cell Quiescence
Rezvan A, Sun H, Kim CW, Kumar S, Jo H.

Background: ZBTB46, also known as zDC or BTBD4, is a member of the BTB-ZF protein family which comprises a diverse group of transcription factors. Recently, Zbtb46 was identified as a transcription factor specific to classical dendritic cells among immune cells and responsible for keeping them in a quiescent state. Interestingly, endothelial cells (ECs) also...
express ZBTB46, however the role of ZBTB46 in ECs has not been studied. EC activation in areas of disturbed flow is a critical step in initiation of atherosclerosis, leading to heart attacks and stroke.

Hypothesis: ZBTB46 is expressed in quiescent ECs under laminar shear conditions and is down-regulated by disturbed flow, affecting EC gene expression, and leading to EC activation.

Methods: We used the mouse partial carotid ligation model to assess ZBTB46 shear responsiveness in vivo and a cone and plate cell culture model to assess shear responsiveness in vitro. We measured endothelial cell mRNA using qPCR and protein via western blot. We used immunofluorescence to show localization of ZBTB46 in the arterial wall. We performed a gene array comparing EC gene expression in ZBTB46 KO mice compared to WT control.

Results: ZBTB46 is expressed in both human and mouse ECs. ZBTB46 is down-regulated (50-70%) under disturbed flow conditions after 48 hours both in vivo and in vitro. ZBTB46 KO leads to significant gene expression changes in ECs (>150 genes changed >1.5 fold). Pathway analysis suggests an anti-inflammatory role for ZBTB46 in ECs, potentially through inhibition of NFkB. Conclusion: ZBTB46 is expressed and regulated by shears stress in ECs, and contributes to EC quiescence. Targeted manipulation of ZBTB46 expression may have therapeutic potential in conditions such as atherosclerosis or organ transplants.

32

Circulating miR-146a Shows Positive Correlation with Arterial Stiffness and Negative Correlation with Aerobic Exercise Capacity among Healthy Adults

Rooney K, Al Mheid I, Ghasemzadeh N, Jo H, Quyyumi AA, Searles CD, Rezvan A

Background: miR-146a is a micro-RNA expressed in many cell types, with increased expression in inflammation via TLR activation, leading to negative feedback regulation of inflammatory pathways. miR-146a is associated with atherosclerosis, AAA, and ischemic stroke. Circulating miR-146a (c-miR-146a) levels are higher in hyperglycemia, hyperlipidemia and acute coronary syndrome. c-miR-146a levels change variably in response to exercise in healthy individuals. We hypothesized that c-miR-146a is associated with sub-clinical vascular disease and explored its relationship with measures of arterial stiffness and cardiopulmonary fitness.

Methods: In 39 healthy volunteers, 56% male, aged 46.5±11 years, we performed qPCR for serum miR-146a levels (normalized to miR-346). Arterial stiffness was assessed by carotid-femoral pulse wave velocity (PWV) and cardiopulmonary fitness by peak oxygen uptake at maximal exercise. We used Spearman’s correlation in univariate analysis and after multivariate correction for age, gender and BMI.

Results: Mean PWV was 6.78±1.03 m/s, %pPVO2 110.7±31.7 and relative c-miR-146a expression 0.39±0.29. There was a strong correlation between increasing PWV (r=0.451, p=0.006) and decreasing %pPVO2 (r=-0.277, p=0.044) with higher c-miR-146 expression. After multivariate adjustment for age, gender and BMI, c-miR-146a expression correlated independently with PWV (β=0.43; p=0.013) and %pPVO2 (β=-0.336, p=0.024).

Conclusion: In healthy subjects, higher c-miR-146a levels are associated with increased arterial stiffness and reduced cardiopulmonary fitness. Circulating miR-146a levels may be used as a biomarker for subclinical vascular disease and whether at this stage it is mechanistically involved in disease or is a consequence of inflammation needs further study.

80

T Cell Expressed CD40L Potentiates the Bone Anabolic Effect of Intermittent PTH Treatment


T cells are known to potentiate the bone anabolic activity of intermittent parathyroid hormone (iPTH) treatment. One of the involved mechanisms is increased T cell secretion of Wnt10b, a potent osteogenic Wnt ligand that activates Wnt signaling in stromal cells (SCs). However, additional mechanisms might play a role, including direct interactions between surface receptors expressed by T cells and SCs. Here we show that iPTH failed to promote SC proliferation and differentiation into osteoblasts (OBs) and activate Wnt signaling in SCs in mice with a global or T cell-specific deletion of the T cell costimulatory molecule CD40 ligand (CD40L). Attesting to the relevance of T cell expressed CD40L, iPTH induced a blunted increase in bone formation and indices of trabecular bone volume and structure in CD40L− mice and mice with a T cell-specific deletion of CD40L. Therefore, expression of the T cell surface receptor CD40L is required for iPTH to exert its full bone anabolic activity.

60

Screening for Chronic Hepatitis C in the Birth Cohort in a Large Urban Primary Care Center

Miller L, Fluker S, Lundberg K, Rollin F, Park B, Quairoli K, Spaulding A

Background: The CDC and USPSTF recommend one-time hepatitis C virus (HCV) testing for all patients born between 1945 and 1965 (birth cohort). This program was implemented in the Primary Care Center (PCC) at Grady Memorial Hospital (Atlanta, GA), a large urban teaching hospital. We trained internal medicine residents to implement HCV screening and linked HCV positive patients to onsite care at the Grady Liver Clinic or with their PCPs.

Methods: The first phase was an educational intervention for all 147 internal medicine residents in the PCC. Project faculty sent an email to residents describing the importance of HCV screening, and then followed up with 1-on-1 education for all PCC residents during which a screening reminder was added to the residents’ electronic medical record note templates. Residents then screened appropriate birth cohort patients.
Colonic Polyptide Detection Rates Before and After Documentation of Colonoscopic Withdrawal Time
Sangha TS, Hao JH, Robinson C, Jiang QW, Yang Z, Cai Q.

Background: Previous studies associated colonoscopy withdrawal time greater than 6 minutes with increased adenoma detection. However, it is still hotly debated whether the screening colonoscopy confer any protection from right-sided colorectal cancer. The aim of this study is to determine if there is an inherent benefit to recording withdrawal times as a quality improvement measure and detecting of polyps in the right-sided colon.

Methods: A retrospective study was performed, involving a total of 1866 patient screening colonoscopies between October 2009 and June 2012. Patients with clinically significant family history were excluded.

Results: Of these 1866 patients, 971 colonoscopies had withdrawal times recorded. Bowel preparation was moderate to excellent for all screened patients. The data demonstrated an increased detection of right sided polyps (p value 0.000) with withdrawal times greater than 11 minutes and increased detection rate of sessile, semi-pedunculated and pedunculated polyps after versus before withdrawal time documentation.

Conclusion: We conclude that polyp detection rate is increased after withdrawal time documentation and longer withdrawal times, especially longer than 11 minutes, are associated with an increased detection of polyps in the right sided colon.

Novel Polymer-Based Strategy for Delivery of Mesenchymal Stem Cells for Cardiac Regeneration

Approximately 1.2 million Americans suffer from heart attacks each year. Following myocardial injury, 1 in 3 will develop congestive heart failure within 5 years as a result of compromised cardiac function. The delivery of mesenchymal stem cells (MSCs) to regenerate damaged heart tissue is a new frontier in cardiovascular therapy. MSCs are an ideal candidate for therapy as they secrete beneficial paracrine factors that recruit progenitor cells, promote angiogenesis, and limit inflammation and formation of scar tissue. These current limitations of MSC therapy may be largely attributable to poor distribution of these cells across areas of ischemia as well as their inability to be retained within the cardiac tissue after delivery. Our strategy facilitates a uniform distribution of encapsulated MSCs to the cardiac tissue and increases retention of the encapsulated MSCs by capturing them within terminal capillaries of the heart.

To determine the optimal size and number of PEG microparticles for delivery, we used the Langendorff isolated heart setup with a heart rat. Initial infusion with fluorescently tagged MSCs showed an even distribution of cells across the rat myocardium after aortie infusion by Langendorff setup. Microparticles ranged from 50 µm to 150 µm in diameter. The MSCs showed good viability up to 24 hrs after encapsulation. Up to 60,000 microparticles could be infused while preserving contractility of the heart. Histological sections post infusion with microparticles alone showed localization of the microparticles in blood vessels ranging from 10 µm to 70 µm.

Associations between Neighborhood Characteristics and Inflammation: The Morehouse and Emory Team Up To Eliminate Health Disparities (META-Health) Study
Shen J, Morris AA, Bidulescu A, Dunbar SB, Vaccarino V, Gibbons GW, Sperling LS, Quyyumi AA

Background: Inflammatory pathways may contribute to neighborhood effects on cardiovascular disease risk. We aimed to examine the association between neighborhood characteristics and inflammatory mediators relevant to cardiovascular pathophysiology: interleukin-6 (IL-6), tumor necrosis factors-α (TNFα) and C-reactive protein (CRP).

Methods: Subjects were 580 men and women between 30-90 years of age. Neighborhood environment, walkability, and cohesion were assessed using validated questionnaires. Plasma concentrations of IL-6, TNFα, and CRP were measured from blood samples.

Results: Participants from neighborhoods in the lowest (worst) tertile of environment had higher concentrations of IL-6 (p = 0.002), TNFα (p = 0.025), and CRP (p = 0.023) compared to those in the highest tertile. Those from neighborhoods in the lowest tertile of walkability had higher concentrations of CRP (p = 0.008) but demonstrated no difference in IL-6 (p = 0.22) or TNFα (p = 0.57). Conversely, participants from the lowest tertile of cohesion had higher concentrations of IL-6 (p = 0.003) and TNFα (p = 0.011), but demonstrated no difference in CRP (p = 0.24). In multivariate analysis including age, sex, race, smoking, education, income, body mass index, history of hypertension, diabetes, and dyslipidemia, the relationship during continuity visits. The project coordinator abstracted charts and contacted all HCV antibody positive patients and linked them to an educational session followed by a physician visit in the Liver Clinic or their PCP. The patients who screened positive were also sent for confirmatory testing.

Results: In the first year, 147 residents (100%) had received the educational intervention, and 2439 patients were screened for HCV. Of those, 190 (7.8%) were HCV antibody positive, and 149 of the 190 (78%) were tested for HCV RNA. Of these patients, 104 (70%) were RNA positive, confirming chronic HCV infection. Finally, 96% of the 104 patients with confirmed chronic HCV infection attended a linkage visit, either with their PCP or the Grady Liver Clinic. This project demonstrated that implementing the new HCV screening guidelines was feasible in a teaching hospital and yielded an unexpectedly high prevalence of HCV infection.
between neighborhood environment and IL-6 (B = -0.09, p = 0.045) and CRP (B = -0.11, p = 0.022) but not TNFα (B = -0.05, p = 0.30) persisted as did the relationship between neighborhood cohesion and IL-6 (B = -0.09, p = 0.040).

Conclusions: Subjects from neighborhoods with the worst environments, walkability, and cohesion had higher levels of systemic inflammation independent of socio-demographic and cardiovascular risk factors.

61

Low Neighborhood Cohesion is Associated with Poor Sleep Quality: The Morehouse and Emory Partnership To Eliminate Cardiovascular Health Disparities (META-Health) Study

Shen J, Morris AA, Bidulescu A, Dunbar SB, Vaccarino V, Gibbons GH, Sperling LS, Bliwise DL, Quyyumi AA

Background: There is growing evidence supporting the effect of neighborhood environments on health. Neighborhood social cohesion represents physical and emotional resources individuals can access via membership in a community and can affect sleep quality. Sleep quality is important for cognitive function, metabolism, weight, mood, immune function and cardiovascular health. We hypothesize that low neighborhood cohesion has an adverse effect on sleep quality.

Methods: We administered the Pittsburgh Sleep Quality Index (PSQI) to 570 participants (age 50.8 ± 9.3 years, 49.6% African-American, 63% female) enrolled in the Morehouse-Emory Partnership to Eliminate Cardiovascular Health Disparities (META-Health) Study. Poor sleep quality was defined as a total PSQI score ≥5. Neighborhood data was collected via validated questionnaires. Low cohesion was defined as a score <15 (median). Anthropometric data including weight and height were also collected. Depression was measured using the Beck Depression Index (BDI).

Results: In this community based population, 48.9% of participants were classified as having poor sleep quality and 40.7% came from low cohesion neighborhoods. The odds of having bad sleep quality was 1.68 times (95% CI = 1.09-2.58; p = 0.019) higher among participants from neighborhoods with low cohesion compared to those from neighborhoods with high cohesion adjusting for age, gender, race, education, household income, neighborhood noise, body mass index and depression.

Conclusions: Subjects from neighborhoods with low cohesion are more likely to have poor sleep quality independent of socio-demographic and psychological risk factors.

39

Characteristics, Treatments, and Outcomes of Hospitalized Heart Failure Patients Stratified by Etiologies of Non-Ischemic Cardiomyopathy: Insights from the American Heart Association Get With the Guidelines National Program

Shore S, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA,

Eapen ZJ, Hernandez AF, Yancy CW, Fonarow GC

Background: Over third of patients with heart failure (HF) have non-ischemic cardiomyopathy (NICM). Whether characteristics, treatments, and in-hospital outcomes of hospitalized HF patients differ by specific NICM etiologies is unclear.

Methods and Results: We analyzed data on 58,058 NICM patients hospitalized with HF from 319 U.S. hospitals participating in Get with the Guidelines-HF between 2005-2013. Characteristics, treatments, and in-hospital outcomes were assessed by NICM etiology. Regression techniques adjusted for site and patient-level characteristics were used to examine the association between NICM etiology and in hospital clinical outcomes. Overall, median age was 72 years, 59.7% were white, and 56.6% were women. Hypertensive (n=28,141; 48.5%) and idiopathic (n=17,808; 30.7%) cardiomyopathies accounted for the vast majority of patients with NICM. Postpartum (n=209; 0.4%), viral (n=447; 0.8%), chemotherapy (n=72; 1.2%), substance abuse (n=2,653; 4.6%), familial (n=556; 1.0%) and other (n=7,523; 13.0%) etiologies were far less frequent. There were no significant differences in baseline characteristics between those with hypertensive NICM compared to idiopathic NICM with respect to age (73 vs. 73 years), sex (58.7% vs. 57.8% males), and EF (47% vs. 43%).

Risk-adjusted quality of care measures provided to eligible patients did not vary by etiology. While unadjusted in-hospital mortality differed, after risk adjustment, only hypertensive cardiomyopathy had a lower mortality rate compared with idiopathic NICM (adjusted OR 0.83; 95% CI 0.71-0.97).

Conclusions: Characteristics of patients hospitalized with HF with NICM vary substantially by etiology. Both risk-adjusted quality of care and in-hospital outcomes did not significantly differ by specific etiology.

63

Site-Level Variation and Associated Strategies for Improving Adherence to Newer Anticoagulants: Insights from the National Veterans Health Administration System


Background: Unlike warfarin newer oral anticoagulants (NOAC) like dabigatran donot require frequent blood work and dose titration. However medication adherence in NOAC use is critical and reduced adherence is associated with adverse outcomes. We aimed to identify site-level practices associated with higher adherence to dabigatran.

Methods: All veteran health administration (VHA) sites with >20 atrial fibrillation patients on dabigatran between 2010-2012 were included. After purposive and snowball sampling, 47 pharmacists from 41 eligible sites participated in our qualitative inquiry. Patient adherence to dabigatran was defined by proportion of days covered (ratio of days supplied by prescription to follow-up duration) >80%.
Results: We observed site-level variation in patient adherence to dabigatran across sites with median proportion of adherent patients of 74% (IQR 66% - 80%). Review of practices across the participating sites showed that rigorous patient selection was performed at 31 sites, pharmacist-led education was provided at 30 sites and pharmacist-led monitoring performed at 28 sites. Provision of intensive pharmacist-led education (OR 1.57; 95% CI 1.08 – 2.26) and pharmacist-led adverse event monitoring (OR 1.89; 95% CI 1.40 – 2.66) were associated with improved odds of patient adherence. Additionally, longer duration of monitoring and providing more intensive care to non-adherent patients in collaboration with the physician provider improved odds for adherence.

Conclusion: Pharmacist-led initiatives were associated with higher odds of patient adherence to NOACs/dabigatran. These findings highlight the need for developing standardized quality measures for NOAC management and motivate the use of existing anticoagulation infrastructure for NOAC management.

Nrf2 and PU.1 are Coordinately Regulated in the Alveolar Macrophage
Staliteh B, Fan X, Guidot DM

In the alveolar macrophage, Nrf2 and PU.1 are the two transcription factors that drive cellular defenses against oxidative stress and immune-mediated injury, respectively. Recent data suggesting that Nrf2 and PU.1 may bind DNA in an interactive fashion led us to design a series of experiments to determine whether they are coordinately regulated in the alveolar macrophage. In parallel experiments, we transfected RNA silencing vectors to either Nrf2 or PU.1 into NR8383 cells (a rat alveolar macrophage cell line). After 24 hours, we quantified the gene expression of both targets using RT-PCR. At 48 hours, we assessed the effect of silencing RNA to Nrf2 on PU.1 protein expression via Western blotting. In addition, we used sulforaphane (SFP, a potent stimulator of Nrf2 activity) and assessed the effect on PU.1 gene and protein expression using RT-PCR and Western blotting, respectively. Transfection of alveolar macrophages with silencing RNA to Nrf2 resulted in a significant decrease in gene expression of PU.1 at mRNA level at 24 hours and a significant decrease in PU.1 protein expression at 48 hours. Transfection of silencing RNA to PU.1 resulted in a significant decrease in gene expression of both PU.1 and Nrf2 at 24 hours. Treatment with SFP significantly increased gene and protein expression of NQO1 (a downstream effector of Nrf2) but decreased gene and protein expression of Nrf2 and PU.1. These data provide further evidence of linkage between Nrf2 and PU.1, but further experiments are necessary to determine the source and implication of their linkage.

Nuclear Over-Expression of Thioredoxin-1 (Trx1) Protects Against Alcohol-Induced Lung Fibroblast-Myofibroblast Transdifferentiation
Sueblinvong V, Mills ST, Guidot DM

BACKGROUND: Previously we determined that alcohol-induced TGFβ1, suppresses Nrf2-activation of the anti-oxidant response element (ARE) in lung fibroblasts and the consequent oxidative stress induces more TGFβ1. We also identified that alcohol inhibits Nrf2 nuclear binding through suppression of Trx1, which maintains Nrf2 in a reduced and active state. We hypothesized that overexpression of Trx1 in the nucleus would attenuate alcohol-induced fibroblast-myofibroblast transdifferentiation.

METHODS: Mouse primary lung fibroblast (PLF) were transfected with either a nuclear-localized (NLS) or a nuclear export (NES) Trx1 vector and cultured with alcohol. α-smooth muscle actin (α-SMA) gene and protein expression were determined at 24 and 72 hours. In parallel, mice over-expressing Trx1 in the nucleus (NLSTg) and litter mate controls were fed alcohol in water for 8 wks prior to intratracheal bleomycin instillation; they were sacrificed 14 days later and lung was analyzed for Col1A1, TGFβ1, Nrf2 and glutathione-s-transferase (GST) gene expression.

RESULTS: Nuclear Trx1 overexpression decreased alcohol-induced α-SMA expression in vitro. In parallel, although Trx1 nuclear over-expression had no effect on Nrf2 expression, it increased GST expression and decreased Col1A1 and TGFβ1 expression in vivo.

CONCLUSIONS: Nuclear overexpression of Trx1 attenuated alcohol-induced fibroblast-myofibroblast transdifferentiation in vitro and decreased alcohol-induced TGFβ1 and collagen expression in the lung in vivo. These effects were associated with enhanced Nrf2-ARE activity as reflected by increased GST expression. Taken together, these findings provide new insights into how alcohol promotes fibrotic disrepair and renders the lung susceptible to injury during acute inflammatory stresses.

Association of High Dietary Saturated Fat Intake and Uncontrolled Diabetes with Constipation: Evidence from the National Health and Nutrition Examination Survey (NHANES)
Taba Taba Vakili S, Ghazi Nezami B, Shetty A, Chetty VK, Srinivasan S

Background: Constipation is highly prevalent affecting 14% of the population and 31.2% of diabetic patients. We recently reported that mice fed a diet high in fat had higher incidence of constipation compared to Regular diet. The aim of this study was to assess if a diet high in saturated fat (HSFD) is associated with higher risk of constipation in humans. Methods: Analyses were based on data from 6,207 adults from the 2005–2008 cycles of the National Health and Nutrition Examination Surveys (NHANES) who completed the bowel frequency questionnaire and had the relevant data related to diabetes. Constipation was defined as stool frequency less than 3 times per week. Multivariable logistic regression analysis was used to calculate prevalence odds ratio (POR) estimates. Statistical analyses were performed using RStudio software version 0.98.501(Boston, MA).
Results: The prevalence of constipation was 3.1%. After multivariate adjustment high saturated fat remained a predictor of constipation. POR for HSFD causing constipation was much higher in females and non-Hispanic blacks. In diabetics > 65 years, HSFD consumption increased POR for constipation significantly and those with poor glycemic control had a higher POR. Constipation was the greatest in females with uncontrolled diabetes on HSFD.

Conclusions: To our knowledge, this is the first time that HSFD is reported to increase the odds of constipation especially in uncontrolled diabetic females as well as non-Hispanic blacks. Clinical recommendations to treat constipation with adjusting dietary fat intake may increase patient satisfaction, and decrease health-care costs.

95

Glial Cell Line-Derived Neurotrophic Factor (GDNF) induces Liver Defatting - A Novel Strategy to Enable Transplantation of Steatotic Livers

Tabla Tabla Vakil Si, Kailar R, Rahman K, Mwangi SM, Anania FA, Srinivasan S

Introduction: Macrovesicular steatosis of >30% of hepatocytes increases the risk for primary graft dysfunction and is present in almost 50% of livers for transplantation. Previous studies have attempted defatting livers with a cocktail of defatting agents. We have previously shown that Glial Cell Line-Derived Neurotrophic Factor (GDNF) can protect against high-fat diet-induced hepatic steatosis in mice. We investigated if GDNF can cause liver defat steatotic livers making them amenable for transplantation.

Materials and Methods: C57BL/6J male mice were fed on RD or HFD for 8 weeks with resultant steatosis in the HFD-fed mice. Mice were euthanized and livers from each group were perfused at a rate of 50ml/h for 4 h with: Vehicle buffer, GDNF (100ng/ml) or known positive control defatting cocktail. Following perfusion livers were sectioned and stained with Oil Red-O and total fat content percentage was quantified using morphometry.

Results: HFD fed mice had higher mean fat content (32.95±1.45%) compared to RD (13.27±1.32%). In the steatotic livers, GDNF resulted in a significant (78%) reduction in steatosis (7.26±1.56% mean difference, n=5, P<0.01) compared to vehicle infusion. This reduction was as effective as the positive control cocktail (6.2±1.65% mean difference compared to vehicle, n=3, P<0.01). There was no effect of perfusion of any agents in the non-steatotic livers.

Conclusion: Our studies demonstrate a novel role for GDNF in liver defatting prior to transplantation. GDNF could be used to clear excess lipid storage in fatty livers providing a new means to recondition donor livers considered unacceptable for transplantation.

A Novel Imaging Approach for the Detection of Subclinical Bacterial Infections involving Medical Devices


Background: Infection of implantable medical devices is a significant clinical entity that poses a diagnostic challenge. We have developed a novel approach to specifically detect bacteria using fluorescent and PET imaging probes. In bacteria unlike mammalian cells, maltotetraose is taken up as a major energy source. We developed a maltotetraose-based fluorescent dye imaging probe (MDP) and a F-18 imaging probe (FMH), and determined their utility in detecting detect bacterial device infections.

Methods: SD rats were implanted with mock-ups of medical devices and divided into 3 groups. Infection rats were injected with 1 X 10^9 Staphylococcus aureus around the mock-ups, and turpentine rats were injected with 20ml of oil of turpentine to induce non-infectious inflammation. Two days later, MDP or FMH were injected intravenously and the animals were scanned with a fluorescent imaging device or PET imaging.

Results: By physical exam, the infected rats had no obvious signs of infection. In fluorescent imaging, MDP accumulated in the infected area 1 hour after injection and persisted for over 24 hours. In control and turpentine rats, there was no accumulation of MDP. In PET imaging, the accumulation of FMH around the infected device was significantly increased 30 minutes after injection. Histology confirmed that the control and turpentine rats had no evidence of bacterial infiltration at the site of implant whereas infected animals had abundant deposition of bacteria.

Conclusion: MDP and FMH are potentially useful for the specific diagnosis of bacterial infections of implanted medical devices. This strategy could be expanded to not only other sites of bacterial infections but could also be modified for the “theranostics” and novel anti-bacterial agents.

96

Impact of Preadolescent Malnutrition on Heart Growth

Tan L, Torres RA, Tejada T, Husain A, Naqvi N.

We have recently shown that a precisely timed burst of cardiomyocyte (CM) proliferation during preadolescence, elicited by a thyroid hormone (T3) surge, adds ~500,000 CMs (~40% increase in CM number) to the mouse heart between postnatal (P)15–P18 (Naqvi et al., 2014). This finding has therapeutic implications for congenital and acquired heart diseases (Palpant & Murry, 2014). We reasoned that factors influencing T3 levels during this period would have lasting impact on heart function by affecting the final CM population number (CPN). We hypothesize that preadolescent nutritional status critically influences the maturational heart growth by regulating preadolescent T3 levels.
Immediately after birth we divide the mice in an “optimal nutrition” (ON) and a “restricted nutrition” (RN) group. ON group had 4 pups and RN group 2 pups with the dam.

We show that preadolescent malnutrition results in 2-fold decreased serum T3 levels. Furthermore, preadolescent malnutrition results in blunted growth of the heart as evident from the body weight corrected heart growth in the RN group. To show that heart growth in the ON group is dependent on T3 we treated mice in the ON group with an inhibitor of thyroid hormone biosynthesis, propylthiouracil (PTU). PTU treatment of the ON group resulted in significantly reduced heart-to-body weight ratios at P14, P15 and P18 compared to vehicle treated ON group. We also find that P15–P18 CM hyperplastic burst is completely blocked with reduction in T3 levels resulting in significantly reduced CPN. Collectively, these studies suggest that early postnatal nutrition critically impacts heart growth by regulating preadolescent T3 levels.

87

Fecal Microbiota Transplant for Clostridium Difficile Disease in Older Adults


Fecal microbiota transplantation (FMT) is an emerging treatment for Clostridium difficile infection (CDI), but there is concern that older adults may experience an increased risk of adverse events (AEs). We conducted a single-center retrospective series on the use of FMT in older adults with CDI. Data was collected from clinical records for patients treated via FMT at Emory University beginning in July 2012. All FMT recipients treated at this center who were 65 years of age or older at the date of FMT were included in the study. Outcomes included (i) rates of CDI cure following FMT, (ii) serious adverse events (SAEs) such as death or hospitalization following FMT, and (iii) AEs related or unrelated to FMT. We included 31 older adults with recurrent CDI who received FMT an average of 9 months prior to followup (range 2-24 months). 20 of 31 individuals (65%) experienced an immediate and lasting resolution of CDI following FMT. 8 of 31 study members (26%) reported experiencing bowel habits of varying irregularity following FMT, all of which were controllable with over-the-counter treatments. Three documented treatment failures were observed in the study cohort (9%), including one patient who continued to suffer from CDI despite FMT and two patients who suffered CDI relapses after initial recoveries following FMT, all of whom had died. 5 deaths total occurred in the cohort group (16%), following FMT by an average of 128 days, all for reasons unrelated to FMT. 5 other cohort members suffered SAEs requiring hospitalization in the follow-up period, one of which was connected to FMT. The most common AE reported was subjective worsening of arthritis. We therefore conclude that FMT is a safe and effective treatment option for older adults with recurrent CDI.

19

Viral Hepatic Insulin Gene Transfer Ameliorates Hyperglycemia in STZ-Diabetic Pigs

Thule PM, Jia DJ, Nalli S, Campbell AG, Paveglio SA, Olson DE

Assessing the effects of hepatic gene transfer in pigs should provide a better indication of human responses to gene therapy than rodent studies. However, obtaining robust gene transfer into pig liver has been difficult, requiring partial hepectomy and ex vivo transfection, hepatic circulatory isolation, or segmental hepatic catheterization. Adenoviral (Ad) gene transfer in pigs is complicated by an expanded mononuclear phagocyte system (MPS) in pulmonary and hepatic beds that sequester virus and, upon activation, induces circulatory collapse. In contrast to rodents, adeno-associated viral (AAV) vectors fail to transduce hepatocytes in unprepared swine. We performed a series of experiments in pigs to determine if MPS depletion, with or without blockade and splenectomy, enhances Ad or AAV mediate hepatic gene transfer. We administered increasing doses of recombinant Ad or AAV to swine (10-20kg body weight) with or without MPS depletion induced by gadolinium chloride (GdCl3) or liposome encapsulated clodronate (Lipo-CI) infusion. Most Lipo-CI pigs also received MPS blockade with poly-inosinic acid (pi). MPS depletion with GdCl3 reduced pulmonary sequestration of Ad, and increased circulatory persistence and hepatic vector uptake, but failed to protect against Ad induced circulatory collapse. In contrast, Lipo-CI pretreatment alone prevented circulatory collapse when Ad were administered above a reported lethal threshold (3.5x1011Vp/kg). Lipo-CI treatment combined with pi mediated MPS blockade permitted survival, and diffuse hepatocyte transduction (0.5-5%) as determined by green fluorescent protein microscopy. Following Lipo-CI, pi treatment and splenectomy we obtained hepatic transduction with AAV. Using a metabolically responsive, liver specific insulin transgene hep...
Mitochondria are dynamic organelles that continually move through the cytoskeleton undergoing fusion and fission, two highly regulated processes that control mitochondrial morphology and ensure mitochondrial function, integrity and oxidative damage repair. These dynamics are involved in the regulation of energy production and important cellular processes such as proliferation. Recently, it was shown that the polymerase delta interacting protein 2 (Poldip2), which participates in vascular smooth muscle cell (VSMC) cytoskeleton remodeling, regulates cell cycle progression. In this work we hypothesize that Poldip2 controls mitochondrial dynamics by a cytoskeleton-dependent mechanism. Using confocal microscopy to evaluate the mitochondrial network, we found that when we downregulate Poldip2 using siRNA in human VSMCs, mitochondrial volume increases (52±0.1% vs. siControl, p<0.001) while mitochondrial number decreases (72±0.1%, p=0.02), consistent with a hyper-fused phenotype. Regarding the mechanism, we found that the silencing of Poldip2 upregulates Mgarp, a protein responsible for mitochondrial movement along the cytoskeleton, by 240%. This raises the possibility that Mgarp is a Poldip2 effector. Indeed, we found that Mgarp silencing reverses siPoldip2-induced mitochondrial fission. In order to evaluate the consequences of the Poldip2-mediated regulation of mitochondrial morphology, we use a Seahorse analyzer and found that siPoldip2 decreases mitochondrial ATP production (7.4±0.8 to 5.3±0.5 pmol/min/ug protein, p=0.04). Altogether, we demonstrated that Poldip2 controls mitochondrial morphology and ATP production by an Mgarp-dependent mechanism. Additionally, our data suggest that energy depletion and deficient mitochondrial fission affect cell cycle progression in VSMCs.

91

Polymerase Delta Interacting Protein 2 Regulates Mitochondrial Morphology and Energy Production in Vascular Smooth Muscles Cells
Torres G, Benavides G, Lassegue B, Darley-Usmar V, San Martín A.

Vascular smooth muscle cells (VSMCs), are subjected to different types of mechanical forces within the vessel wall which causes cytoskeletal reorganization. However, it remains incompletely understood how these mechanical forces are transduced. Cofilin, a protein that controls actin dynamics, is activated by Slingshot phosphatase-dependent Serine 3 dephosphorylation by redox dependent mechanisms. Nox4, which is a main source of O2- and H2O2 in the vessel wall, localizes in association with the cytoskeleton. Therefore, we hypothesize that the Nox4-mediated activation of cofilin is required for cytoskeletal reorganization after mechanical stimulation. Indeed, we observed that mechanical stretch induces cofilin dephosphorylation/activation (1 vs. 0.7±0.1 relative arbitrary units) and that it is blunted in Nox4 deficient cells (1 vs. 1.2±0.4 relative arbitrary units). More importantly, stretch-induced cytoskeletal alignment observed in wild type cells (18±3 vs.77±1 cell alignment (CA) p<0.001) is inhibited in cells where Nox4 (76±5 vs. 31±8 CA p<0.001) or cofilin activity has been downregulated (83±2 vs.17±4 CA p<0.0001). Finally, in order to confirm that cofilin is being activated by a Nox4-dependent pathway, we assess the ability of the phospho-deficient and constitutive active form cofilin S3A to reverse the phenotype of Nox4 deficient cells. Indeed, Cofilin S3A is capable to restitute the response to mechanical stimulation in Nox4 deficient cells (21±4 vs 64±4 CA p<0.0001). Our results demonstrate that cofilin is activated after stretch by a Nox4 dependent mechanism and that this pathway is required for mechanical stimulation-induced cytoskeleton reorganization.

64

Nox4-Dependent Cofilin Activation is Required for VSMC Cytoskeletal Reorganization after Mechanical Stimulation
Valdivia A, Montenegro MF, and San Martín A.

Evaluating an Electronic Health-Record Medication Ordering Clinical Decision Support Tool: Needs and Barriers to Use

EQUIPPED is a multi-site quality improvement initiative targeting Veterans Affairs Emergency Department (ED) providers to enhance geriatric prescribing. Interventions include provider education, academic detailing, and an electronic clinical decision support (CDS) tool. It is known that alignment of CDS tools with target-user needs and preferences ultimately determines adoption, routine use, and sustainability. ED provider interviews at the first implementation site were conducted to inform iterative user-centric CDS development pre-implementation at subsequent EQUIPPED sites. Interviews were conducted to identify perceived needs and barriers pertinent to CDS use among both ED staff (n=5 out of 16) and fee-based providers (n=7 out of approx. 44) and to evaluate barriers to use and preferences among staff providers directed to access the CDS tool. Interviews were analyzed with NVivo 10. Overall, providers identified 3 preferences and barriers at the level of process (user attitudes, beliefs, perceptions about
tool) and 2 at the level of access (user-tool interface). For instance, provider inertia (e.g., resistance to change) and user-interface limitations (e.g., limited integration with other aspects of the electronic record) were noted as significant barriers to use by the majority of those interviewed. Providers who both were directed to use the CDS tool (n=5) and who used the tool more than once (n=2) requested a dual alphabetical-categorical organization structure and pop-up patient creatinine clearance levels to enhance accessibility. These needs and barriers can be addressed to optimize the alignment between the CDS delivery and user-interface with ED provider needs and preferences, to ensure user-centricity and enhanced use at subsequent sites.

97

The Association of Vitamin D with Incident Urinary Incontinence in Older Adults

Vaughan CP, Tangpricha V, Goode PS, Burgio KL, Allman RM, Redden D, Granstaff S, Markland AD

Background: Urinary incontinence (UI) is highly prevalent among older adults and has been associated with vitamin D deficiency in cross-sectional analyses.

Methods: The UAB Study of Aging is a prospective cohort study of community-dwelling older adults. Analysis of 25-hydroxyvitamin D (25(OH)D) levels was performed on stored sera. UI was assessed every 6 months. The association between incident UI and vitamin D status was evaluated using multivariable logistic regression models adjusted for gender and ethnicity.

Results: Of 350 participants (175 male, 147 black, mean age 73.6 ± 5.8), 54% (189/350) were vitamin D deficient (25(OH)D < 20 ng/mL) and 78.9% (276/350) were vitamin D insufficient (25(OH)D < 30 ng/mL). Among the 187 subjects with no UI at baseline, 57.2% (107/187) were vitamin D deficient and 81% (152/187) were vitamin D insufficient. For these 187 subjects, the mean baseline 25(OH)D level was 20.5 ng/mL ± 9.7. Mean length of follow-up was 34.5 months (range 6 - 42). 175 of the 187 subjects had follow-up evaluation for incident UI over 42 months and incident UI occurred in 37% (65/175). Cumulative incident UI at 42 months was associated with vitamin D deficiency at baseline (aOR = 2.21 [0.93 – 5.21], p = .036), but there was no association between baseline vitamin D deficiency and incident UI (aOR = 1.18 [0.60 – 2.31], p=.638).

Conclusions: These results provide preliminary evidence of an association between vitamin D and incident UI in older adults. Intervention studies targeting a vitamin D insufficient (< 30 ng/mL) population are a next step in evaluating the potential of vitamin D to impact UI.

20

Association of Glycemic Control, Inflammatory Markers and Peri-Operative Complications in Patients undergoing CABG


Peri-operative hyperglycemia and diabetes (DM) are associated with increased inflammation and higher rates of hospital complications. We analyzed the association between glucose control, peri-operative complications and the inflammatory state in patients with DM and without history of DM (noDM) undergoing CABG. Markers of oxidative stress and inflammation included C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), cortisol (C), 2′,7′-dichlorofluorescin (DCF) and thiobarbituric acid-reactive substances (TBAR) were measured peri-operatively (preop, 3, 5 & 30 days postop).

Patients were randomized to intensive (BG 100-140 mg/dl, n=151) and conservative (BG 141-180 mg/dl, n=151) glucose control. 152 patients had DM. Mean ICU daily glucose levels were 132±14 mg/dl for the intensive and 154±16 mg/dl (P<0.001) for the conservative group. Preop CRP (p=0.002) and TNF-α (p=0.015) were higher in DM vs. noDM. Preop C levels were similar between DM and noDM groups; however, in the postop period, C levels were lower in DM vs. noDM (p=0.012). Day 3 TNF-α (p=0.025) and day 30 TNF-α levels were higher in DM vs. noDM (p=0.034). Preop and postop IL-6 levels were increased in patients with complications vs no-complications (Preop;p<0.05; postop;p<0.001). Postop C and DCF levels were higher in patients with complications vs. no-complications (p<0.05). TBAR levels were similar in DM vs. noDM and in complications vs. no-complications.

We observed no differences in hospital complications or inflammatory/oxidative stress markers between intensive and conservative glucose control. Patients with DM or with complications had higher glucose and inflammatory/oxidative stress marker levels compared to those without DM and complications.

92

Does Autophagosome-Proteolysis Contribute to CKD-Induced Muscle Atrophy?

Su Z, Hassounah F, and Wang X

We hypothesized that proteolysis through autophagosomes may contribute to the muscle wasting of CKD. We examined whether autophagosome activity contributes to CKD-induced muscle atrophy; and since we have shown that exercise increases the IGF-1 pathway, we asked whether exercise ameliorates CKD muscle wasting by blunting autophagosome activity.

In 25 g mice, we induced CKD by subtotal nephrectomy and examined the effect of resistant exercise (i.e., overloading of hindlimb plantaris muscles by removing gastrocnemius and soleus muscles) on muscle atrophy. mRNA expression of 4 markers of the autophagy-lysosomal proteolysis pathway in isolated plantaris muscles were measured to assess autophagosome activity. The markers were microtubule-associated protein 1A/1B-light chain 3 II (LC3 II, indicates autophagosome number), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3, indexes autophagosome formation), Vps34 (class III PI 3-kinase, a regulator of autophagic sequestration) and P62 (induction of reduced
autophagosome clearance). CKD increased the mRNA expression of the 4 markers (P<0.05) and exercise reversed this back to levels in control mice. Protein levels of Bnip3, LC3-II and Beclin-1 (an upstream regulator of autophagic sequestration) were increased in muscle from CKD mice vs controls. Exercise reversed these increases in autophagosome protein markers.

We conclude that autophagosome-mediated proteolysis contributes to CKD-induced muscle atrophy. Exercise slows the development of muscle atrophy by up-regulating the IGF-1 signaling pathway in part by inhibiting autophagy-lysosomal proteolysis pathway in CKD.

81

Hyperresponsiveness of B cells in Systemic Lupus Erythematosus patients to IL-10

Wang X, Jenks S, Deshpande P, Sanz I

Systemic lupus erythematosus (SLE) is characterized by expanded antibody secreting cells (ASCs), the production of autoantibodies, and for abnormalities in the cytokine milieu of SLE patients, such as IL-10. IL-10 can promote B cell activation and differentiation. However, the role of IL-10 in ASC differentiation in SLE patients is not clear. The objective of this study was to determine the effects of IL-10 on ASC differentiation in SLE, as compared to healthy control donors (HCD). We demonstrated that addition of IL-10 only weakly enhanced ASCs differentiation in HCD; in contrast, SLE patients had on average 1.6 fold more ASCs when IL-10 was included and this was significantly higher than HCD (p<0.004). The enhanced ASCs with IL-10 in SLE were also confirmed by ELISPOT assay, including total IgG and IgG against influenza antigen, and autoantigen specific antibodies including VH4-34 9G4+ antibodies and anti-Ro antibody, indicating a polyclonal activation of SLE B cells in response to IL-10 treatment. ASCs consist of two subpopulations, CD138- ASC and more mature CD138+ ASCs. After stimulation, a higher proportion of ASCs were CD138+ ASCs in SLE patients as compared to HCD, and IL-10 enhanced the proportion of both CD138- (1.6 fold) and CD138+ (1.7 fold). In contrast in HCD, IL-10 treatment modestly increased the proportion of CD138- ASC (1.1 fold) but substantially decreased the proportion of CD138+ ASCs (40% decrease). By using the sorted B cell subsets, we further demonstrated that CD27+ and CD27- switched memory cells, and not naive B cells, are the main population for the expanded ASCs following IL-10 treatment. In summary, the selective enhancement of ASC differentiation in SLE patients clarifies how elevated levels of IL-10 contribute to autoimmunity in SLE.

65

Race Differences in Hemodynamic Responses to Acute Mental Stress and the Role of Depressive Symptoms


Introduction: Increased hemodynamic responses to psychological stress have been associated with adverse cardiovascular outcomes. African Americans (AA) have worse cardiovascular outcomes than other ethnicities and heightened hemodynamic responses may be related. We hypothesized that AA would have significantly increased hemodynamic reactivity to mental stress as compared to Non-African Americans (NAA). Methods: We evaluated 574 patients (163 AA with CAD, who underwent a standardized mental stress challenge. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained during a resting period, a speaking task, and a recovery period, and rate-pressure product (RPP= SBP x HR) was calculated. Hemodynamic reactivity was evaluated as the difference in RPP at rest and during mental stress. Depressive symptoms were measured with the Beck Depression Inventory-II. Results: As compared to NAA, AA patients were younger, had lower education and income, and higher prevalence of diabetes, obesity, hypertension, current smoking, and depressive symptoms. Throughout stress, AA patients had higher SBP and DBP. However, hemodynamic reactivity was significantly lower in AA (RPP 3114 vs 3620, p< 0.02). Adjusting for baseline RPP, age, gender and smoking did not substantially alter the association. However, after adjusting for depressive symptoms, the association was attenuated by 23% (p=0.16). In the final model, baseline RPP, depressive symptoms and BMI were significantly associated with a lower RPP response to mental stress (p<0.01). Conclusions: AA patients with CAD, compared with NAA, have persistently elevated blood pressure throughout mental stress, but tend to have lower hemodynamic reactivity to stress. Depressive symptoms may play a role.

71

Co-localization and Fluorescence Resonance Energy Transfer (FRET) Demonstrate Interaction between the Sodium Chloride Cotransporter (NCC) and the Epithelial Sodium Channel (ENaC)

Wynne BM, Mattheyses AL, Al-Khalili O, Abinash M, Mallick R, Eaton DC and Hoover RS

Regulation of systemic blood pressure occurs predominately via renal maintenance of sodium and water balance. The sodium chloride cotransporter (NCC) and the epithelial sodium channel (ENaC), are both primary mechanisms for sodium reabsorption and have been found to be expressed apically in the late distal convoluted tubule (DCT2). Hyperactivity of sodium reabsorption by either protein can produce increases in blood pressure. Classically, these transporters have been thought to work independently of each other. However, regulatory systems such as aldosterone and angiotensin II for both NCC and ENaC contain appreciable overlap. We hypothesized that NCC and ENaC may be co-localized intracellularly, as well as interacting with each other. COS-7 cells were co-transfected with vectors containing either: GFP-tagged NCC and/or mCherry-tagged subunits of ENaC α, β or γ. Co-localization and FRET acceptor photobleaching (Emory ICI Core) experiments were then performed. Transfection of COS-7 cells with GFP-tagged NCC and mCherry-tagged ENaC (α, β or γ) revealed significant intracellular co-localization.
Furthermore, using FRET in dual transfected NCC+EnaC α, β or γ cells, we observed a significant increase (p<0.05, ANOVA) in EGFP fluorescence following mCherry photobleaching. Cells co-transfected with NCC and EnaC α or β exhibited more than a 23% increase in EGFP fluorescence, as compared to NCC+mCherry vector only expressing (9.1% ± 1.9) cells. These novel data suggest an intimate association and interaction between NCC and α and β subunits of EnaC, which may influence our understanding of salt transport in the distal nephron.

**4 Long-Term Outcomes of Patients with Peripheral Arterial Disease Treated with Granulocyte-Monocyte Stimulating Factor**


**Introduction:** Subjects with peripheral arterial disease (PAD) and intermittent claudication treated with a short course of granulocyte-monocyte stimulating factor (GM-CSF) have exhibited improvement in peak walking times (PWT) without a significant increase in adverse events at 6 months post-therapy. The long-term effectiveness and safety of GM-CSF in patients with PAD is unknown.

**Methods:** 159 patients who received a 4 week course of either placebo or GM-CSF as part of the GPAD-2 study were contacted and their medical records reviewed. Seventy-two had PAD and 36 were randomized to GM-CSF and 32 to placebo. There were a total of 8 deaths, 3 (1.9%) in the placebo group and 5 (3.2%) in the GM-CSF group (p<0.001). Twenty-five (39.1%) of patients who received GM-CSF and 32 (46.4%) were re-hospitalized, p=0.5. There were no statistically significant differences in the composite outcome of death-myocardial infarction-lower extremity revascularization (17.0% with GM-CSF, 11.9% with placebo, p=0.3). In the GM-CSF group the changes in PWT (-47±158 seconds, p=0.3) and ABI (-0.07±0.25, p=0.4) were not statistically significant, while time to claudication decreased (-83±116 seconds, p=0.04).

**Conclusion:** A 4 week course of GM-CSF may be associated with adverse outcomes at long-term follow-up. Improvements in walking time were not sustained. Studies with longer treatment courses of GM-CSF are warranted to determine whether such therapy is effective and safe in patients with PAD.

**34 TREM-1 Accentuates Lung Injury by Inducing Mir-155 and Mir-147 in Macrophages**

**Yuan Z, Panchal D, Syed M, Joo M, Colonna M, Sadikot RT**

Acute respiratory distress syndrome (ARDS) is a group of heterogeneous diseases with poor prognosis. Triggering receptors expressed on myeloid cells (TREMs) are a family of immunoglobulin cell surface receptors expressed on myeloid cells which are emerging as potent amplifiers of TLR initiated inflammatory responses however little is known about the mechanisms by which TREM-1 accentuates the inflammatory response. Since the activation of TREM-1 leads to production of multiple pro-inflammatory cytokines we hypothesized that TREM-1 may mediate its effect through regulation of miRNAs. Immunohistochemistry performed on human lungs from patients with ARDS showed an increased expression of TREM-1. Our studies showed that TREM-1+ mice have an enhanced survival compared to wild type mice after administration of lethal doses of LPS. Bronchoalveolar lavage from TREM-1+ mice showed significantly decreased expression of key inflammatory mediators including IL-1β, TNF-α, IL-6, MIP-2 and KC compared to wild type mice. To define the mechanisms by which TREM-1 accentuates TLR induced inflammatory responses.

**TREM-1 Accentuates Lung Injury by Inducing Mir-155 and Mir-147 in Macrophages**
response we performed microarray analysis for miRNA from TREM-1⁻/⁻ and wild type macrophages. TREM-1⁻/⁻ macrophages showed a significantly lower expression of miR-155 and miR-147 which regulate the expression of multiple pro-inflammatory cytokines. These data for the first time show that TREM-1 regulates the expression of miRNAs which can modulate the production of pro-inflammatory cytokines. Our studies provide a new paradigm for understanding the contribution of TREM-1 in lung inflammation and will lay the ground work for developing future human therapies that will have a significant impact on treatment of devastating diseases such as ARDS.

Oral presentations are located in the front of the abstract book in the order in which they will occur at the event.
<table>
<thead>
<tr>
<th>Author</th>
<th>Poster</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelman, M</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Adesina, S</td>
<td>107</td>
<td>5</td>
</tr>
<tr>
<td>Aguirre, A</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Al Mheid, I</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Al-Anbari, R</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>Al-Khatib, S</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>Ali, A</td>
<td>98</td>
<td>7</td>
</tr>
<tr>
<td>Alvarez, J</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Amanso, A</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Anderson, A</td>
<td>67</td>
<td>8</td>
</tr>
<tr>
<td>Angel, N</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Anthony, J</td>
<td>46</td>
<td>9</td>
</tr>
<tr>
<td>Azzalin, A</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Baxi, A</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Bijili, K</td>
<td>108,109</td>
<td>10</td>
</tr>
<tr>
<td>Blalock, E</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Bonilla-Alicea, R</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>Bowling, B</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>Bozzorg, A</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Burkman, G</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Caesar, C</td>
<td>72</td>
<td>12</td>
</tr>
<tr>
<td>Cardona, S</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Carthan, K</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Chida, A</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>Cho, J</td>
<td>116</td>
<td>14</td>
</tr>
<tr>
<td>Clermont, E</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td>Cobb, J</td>
<td>101, 102</td>
<td>14,15</td>
</tr>
<tr>
<td>Colasanti, J</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Couk, J</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Deshpande, P</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>Dua, K</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td>Duran, C</td>
<td>69</td>
<td>16</td>
</tr>
<tr>
<td>Elliott, J</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Evans, M</td>
<td>49</td>
<td>17</td>
</tr>
<tr>
<td>Fairley, J</td>
<td>50, 51</td>
<td>17</td>
</tr>
<tr>
<td>Farooq, K</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Fonseca, J</td>
<td>74</td>
<td>18</td>
</tr>
<tr>
<td>Frew, P</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>Ghasemzadeh, N</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>Griffiths, P</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Ha, S</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Hansen, L</td>
<td>88</td>
<td>20</td>
</tr>
<tr>
<td>Hayek, S</td>
<td>117</td>
<td>20</td>
</tr>
<tr>
<td>Himmel, N</td>
<td>110</td>
<td>21</td>
</tr>
<tr>
<td>Hudson, M</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Ichikawa, HT</td>
<td>75</td>
<td>21</td>
</tr>
<tr>
<td>Iffrig, E</td>
<td>70</td>
<td>21</td>
</tr>
<tr>
<td>Jenks, S</td>
<td>76</td>
<td>22</td>
</tr>
<tr>
<td>Kabhani, S</td>
<td>77</td>
<td>22</td>
</tr>
<tr>
<td>Kang, B</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Kearns, M</td>
<td>94</td>
<td>23</td>
</tr>
<tr>
<td>Kempker, R</td>
<td>22, 23</td>
<td>23</td>
</tr>
<tr>
<td>Kleinhenz, J</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Kumar, P</td>
<td>29</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Poster</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar, S</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>Lai, L</td>
<td>78</td>
<td>25</td>
</tr>
<tr>
<td>Lazo-Fernandez, Y</td>
<td>111</td>
<td>25</td>
</tr>
<tr>
<td>Lee, S</td>
<td>118</td>
<td>25</td>
</tr>
<tr>
<td>Levit, R</td>
<td>82</td>
<td>26</td>
</tr>
<tr>
<td>Li, J</td>
<td>85</td>
<td>26</td>
</tr>
<tr>
<td>Lin, A</td>
<td>103</td>
<td>26</td>
</tr>
<tr>
<td>Lovasik, B</td>
<td>54, 55</td>
<td>27</td>
</tr>
<tr>
<td>Lyle, A</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Mandalia, A</td>
<td>86</td>
<td>28</td>
</tr>
<tr>
<td>Mekonnen, G</td>
<td>112</td>
<td>28</td>
</tr>
<tr>
<td>Mendel, J</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Molina, S</td>
<td>16, 89</td>
<td>29</td>
</tr>
<tr>
<td>Neveu, W</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Nguyen, D</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>Nguyen, ML</td>
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