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EFFECTS OF RENAL ARTERY STENTING ON KIDNEY FUNCTION AND BLOOD PRESSURE IN PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY DISEASE: OUR EXPERIENCE. K.K. Padigala, S.S. Pechitty, G.J. Frem, Memorial Medical Center, Johnstown, PA.

Purpose of Study: Earlier studies have shown that renal artery stent revascularization in the presence of atherosclerotic renal artery disease has a beneficial effect on blood pressure (BP) control and renal function, while some authors have reported that stent revascularization has minimal or no effect on kidney function. We did a retrospective chart review of the effect of stenting in our patient population with atherosclerotic renal artery stenosis. **Methods:** This study involved 18 patients who underwent stent placement for atherosclerotic renal artery stenosis between 1999 and 2004 in our facility. The most common indication for the procedure was a combination of uncontrolled hypertension requiring three or more medications and worsening renal function. Patients whose serum creatinine was greater than 4.0 mg/dL at the time of stenting were excluded from the study. Renal function was estimated by calculating the glomerular filtration rate (GFR) using the MDRD equation. BP and GFR were recorded just before the procedure and at regular 3-month interval follow-up visits at the outpatient clinic up to 1 year. Differences in GFR and BP at baseline and 1 year after the procedure were compared for statistical significance using the Wilcoxon matched pairs sign rank test. A p value < .05 was considered statistically significant. The institutional review board of our hospital approved the study protocol. **Results:** Mean age of our study population was 74 ± 14 years and 70% of patients also had diabetes mellitus type 2. At 1 year after the procedure mean systolic blood pressure decreased from 143 mm Hg at baseline to 131 m mHg (p = .05). Mean diastolic blood pressure decreased from 76 mm Hg to 67 mm Hg (p = .006) and the mean arterial pressure decreased from 98 mm Hg to 88 mm Hg (p = .0195). Further, the mean GFR decreased from 38.14 mL/min/1.73 sq.m to 35.16 mL/min/1.73 sq.m (p = .2634). **Conclusions:** Significant improvement was noted in the blood pressure variables in patients who were treated with stent deployment. There was a small but statistically nonsignificant decrease in GFR; perhaps improved blood flow and blood pressure control helped stabilize kidney function in the face of underlying diseases such as diabetes. Our findings support a clinically important and statistically significant decline in blood pressure following stenting of atherosclerotic renal artery stenosis. However, in contrast to some previous studies, no significant improvement was noted in the renal function.

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A RARE CASE OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS POSITIVE FOR BOTH ANTIGLOMERULAR BASEMENT MEMBRANE ANTIBODY AND PERINUCLEAR ANTINEUTROPHILIC CYTOPLASMIC ANTIBODY. A.J. Simpson, Emory University, Atlanta, GA.

The case presented is of a 50-year-old female with a chief complaint of weakness, nausea, and vomiting. She was found to be in acute renal failure with a creatinine of 10.0, and urinalysis showed dysmorphic red blood cells. Renal biopsy showed extensive glomerular crescents suggestive of rapidly progressive glomerulonephritis. Follow-up tests revealed that she was positive for both anti-GBM (glomerular basement membrane) antibodies and p-ANCA (antineutrophilic cytoplasmic antibody). She presented late in the disease process with very poor renal function, and despite aggressive treatment, she remained dialysis dependent 4 months after diagnosis. This patient represents a rare presentation of rapidly progressive glomerulonephritis with concomitant presence of both anti-GBM antibodies and p-ANCA. Anti-GBM or Goodpasture's sydrome is a rare disease, with only approximately 30% of these patients also being positive for ANCA, most commonly p-ANCA. Alternatively, about 5% of patients positive for p-ANCA are anti-GBM positive. The significance of recognizing these patients with this presentation lies in the clinical outcome. Patients with pure anti-GBM rarely recover from severe renal disease, whereas up to 75% of those with ANCA-associated vasculitis can recover renal function even when presenting with acute renal failure that requires dialysis. Patients who are positive for both antibodies have survival and renal recovery rates much more similar to anti-GBM disease than ANCA-associated vasculitis. As a result, these patients benefit from more aggressive treatment than is standard for ANCA-associated vasculitis alone. Therefore, it may be prudent to test patients diagnosed with either disease for the other antibody to guide therapy and outcome.

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NOVEL MECHANISM OF PROSTAGLANDIN E_2–MEDIATED ENDOTHELIAL CELL BARRIER ENHANCEMENT: ROLE OF EPCR, $S1P_1$ RECEPTOR, EPAC, RAP1, AF-6, AND PROFILIN. P.A. Singleton,* S. Dore,# J.G.N. Garcia,* *Department of Medicine, The University of Chicago, Chicago, IL; #Department of Anesthesiology, Johns Hopkins University, Baltimore, MD.

Prostaglandin E_2 (PGE_2) is an important tissue-specific autocrine inflammatory mediator. In lung, unlike other tissues, PGE_2 exerts an anti-inflammatory, tissue-reparative, and endothelial cell (EC) barrier protective response, which can have therapeutic potential in various pulmonary diseases. Therefore, we examined the mechanism of PGE_2-induced pulmonary EC barrier regulation. Addition of PGE_2 (100 nM, 5–30 minutes) to EC induced recruitment of EP2 and EP3 receptor (E prostanoid receptor subtypes), EPCR (endothelial cell protein C receptor), $S1P_1$ receptor, Epac (cAMP-activated Rap1 exchange factor), Rap1 (small GTP binding protein), AF-6 (scaffolding protein that binds activated Rap1 and profilin), and profilin (actin polymerizing cytoskeletal protein) to caveolin-enriched microdomains (lipid rafts). Silencing EP2 (but not EP3), EPCR (siRNA) or inhibiting adenylyl cyclase activity (2′,5′-dideoxy-3′-ATP) attenuated PGE_2-induced recruitment of Epac and Rap1 to EC lipid rafts. Silencing $S1P_1$ receptor inhibited PGE_2-induced AF-6 and profilin recruitment to EC lipid rafts. Finally, inhibiting lipid raft formation (methyl-β-cyclodextrin), inhibiting adenylyl cyclase activity, or silencing EP2, EPCR, $S1P_1$ receptor, Epac, Rap1, AF-6, or profilin attenuated PGE_2-induced increased EC barrier function. Taken together, these data suggest that PGE_2 ligation of EP2 receptor induces EPCR and $S1P_1$ receptor signaling required for Epac, Rap1, AF-6, and profilin recruitment to lipid rafts during pulmonary EC barrier enhancement.

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ADRENOCEPTOR BLOCKERS AND FOCAL VENTRICULAR TACHYCARDIA DURING CORONARY ARTERY OCCLUSION. D. Xing, T. Staley, J. Martins, Internal Medicine, University of Iowa and VAMC, Iowa City, IA.

Background: Ventricular tachycardia (VT) of focal endocardial and Purkinje origin occurs in humans. Pharmacological blockade of adrenoceptors on endocardial tissues may selectively prevent the induction of focal VT. We tested the hypothesis that alpha adrenoceptor blocker WB4101(WB), beta-1 receptor blocker metoprolol (Met), and beta-2 receptor blocker ICI 118,511(ICI) prevent the induction of focal ischemic VT and evaluated possible mechanisms. **Methods:** Fifty alpha chloralose anesthetized dogs with 1 to 4 hours of coronary artery occlusion (CAO) were involved. Twenty-three multipolar plunge electrodes were placed in and surrounding the risk zone of anterior descending coronary artery. three-dimensional activation mapping off-line helped to identify the origin of VT. If VT was reproducibly induced, WB (0.3 μg/kg, IV), Met (1 mg/kg), or ICI (0.2 mg/kg, IV) was given. The effects of blockers on delayed afterdepolarizations (DADs) and triggered activity (TA) recorded from endocardium and Purkinje tissue excised from the focal origin of VT were studied in vitro by standard microelectrode techniques. **Results:** Eleven dogs were given WB; two had VTs blocked with the same or more extrastimuli. Twelve dogs were received ICI; only 3 had VT blocked, which were no different compared to focal endocardial or Purkinje VT in dogs with saline treatment, of which 1 of 12 had apparent block (p = ns). However, 7 of 15 dogs given Met had focal VT blocked, which was different from the saline treated (p < .05). Of tissues at the origin of VT, excised and studied in vitro, all foci showed DADs and TA with ISO, which were were blocked by WB (10^{-7} M, in 2 of 6, p = ns), ICI (10^{-7} M, in 0 of 4, p = ns) and Met (10^{-7} M, in 6 of 8, p < .05 vs control). **Conclusions:** Pharmacological blockade of beta-1 adrenoceptor in acute ischemia selectively prevents induction of focal VT due to DADs and TA but alpha adrenoceptor and beta-2 receptor blockade does not.

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LYSOPHOSPHATIDIC ACID INDUCES INTERLEUKIN-13 RECEPTOR α2 EXPRESSION AND SECRETION AND DOWN-REGULATES INTERLEUKIN-13 SIGNALING IN HUMAN BRONCHIAL EPITHELIAL PRIMARY CELLS. Y. Zhao,[1] D. He,[1] J. Zhao,[1] E.W. Spannhake,[2] A. Leff,[1] V. Natarajan,[1] [1]Department of Medicine, The University of Chicago, Chicago, IL; [2]Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

Rationale: IL-13, a Th2 cytokine, plays pivotal role in pathogenesis of bronchial asthma by inducing airway hyperresponsiveness (AHR), mucus hyperproduction, and submucosal thickness. IL-13 mediates airway responses via IL-13 receptor α1 and IL-4 receptor. Recent studies show that a decoy receptor for IL-13, namely IL-13 receptor α2 (IL-13R α2), mitigates IL-13 signaling and function. However, the mechanism(s) of regulation of IL-13R α2 generation and its role in IL-13 signal transduction is not clear. This study provides evidence for regulation of IL-13R α2 production and secretion and IL-13-dependent STAT6 signaling by lysophosphatidic acid (LPA) in human primary bronchial epithelial cells (HBEpCs). **Methods/Results:** LPA (1 μM) treatment of HBEpCs, in a time-dependent fashion, increased IL-13R α2 gene expression without altering the mRNA levels of IL-13 R α1 and IL-4 R. Furthermore, LPA (1 μM) stimulated secretion of IL-13 R α2 into the cell culture medium as evidenced by Western blotting with anti-IL-13 Rα2 antibody. Pretreatment with PTx (100 ng/mL, 3 hours), or JNK inhibitor, or c-jun siRNA attenuated LPA-induced IL-13R α2 secretion. Overexpression of phospholipase D (PLD) 1 or 2 catalytically inactive mutants or pretreatment with 1-butanol, but not 3-butanol, attenuated LPA-induced IL-13R α2 secretion as well as phosphorylation of JNK. Pretreatment of HBEpCs with 1 μM of LPA for 6 hours attenuated IL-13-induced phosphorylation of STAT6 but not the IL-4-induced phosphorylation of STAT6. In addition, replacement of media from LPA- (1 μM, 6 hours) challenged cells with fresh media or transfection with IL-13R α2 siRNA reverted IL-13-induced phosphorylation of STAT6. **Conclusions:** We show here that LPA induces IL-13R α2 expression and secretion via PLD and JNK/AP-1 signaling and that pretreatment with LPA down-regulates IL-13 signaling in HBEpCs. These data suggest a novel mechanism of regulation of IL-13R α2 and IL-13 signaling that may be of physiological relevance to asthma and airway remodeling.

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