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Advances in PH Journal

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Reviews

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A total of 69 abstracts were presented during the poster sessions at the Conference.The winning abstracts in Basic Science and Clinical Science werepresented as oral abstracts during the scientific sessions and are included in this issue of Advances.

BASIC SCIENCE: Loss of apelin signaling impairs nitric oxide synthesis and exacerbates pulmonary hypertension

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Background: Apelin is a peptide ligandfor APJ, a G-protein coupled receptor highly expressed in the vascular wall. Althoughboth apelin and APJ are highly expressed in the pulmonary vasculature, their function in this vascular bed is unknown. Given the known vasodilatory and vasculoprotective roles of this pathway,we hypothesized that its disruption would lead to worsening of the vascular remodeling that occurs in pulmonary hypertension.

Methods: Apelin deficient (KO) micewere used to assess right ventricular systolic pressures after 3 weeks of hypoxia.Lungs were perfused with contrast agent(Microfil), and imaged using microcomputedtomography (CT) imaging. NOlevels were measured in the serum and lungs were evaluated for expression ofendothelial nitric oxide synthase (eNOS)and KLF2 using quantitative real-timepolymerase chain reaction (RT-PCR) andwestern blots.

Results: We found that apelin nullmice developed more severe pulmonary hypertension in response to hypoxia compared to wildtype mice (34.1 vs. 28.3 mmHg, p 0.001). Micro-computed tomographyof the lungs demonstrated significant vascular abnormalities in the hypoxia-treated apelin null mice, including marked pruning of the smaller vessels (Figure). Apelin null mice had a significant reduction of serum nitric oxide(NO) levels. This was associated with a decrease in pulmonary endothelialnitric oxide synthase (eNOS) expression, in conjunction with a decreasein expression of KLF2, a known transcriptional regulator of eNOS. In vitroknockdown of apelin mRNA in pulmonaryartery endothelial cells led to amarked decrease in eNOS and KLF2 transcript levels. Moreover, serum apelinlevels from patients with pulmonaryhypertension were significantly lowerthan those in healthy controls (1.25 vs.0.89 ng/mL, p 0.037).

Conclusions: These data demonstratethat disruption of apelin signaling can exacerbate pulmonary hypertension, secondaryto vascular remodeling in the context of decreased expression of KLF2 and eNOS, and identify this pathway as a potentially important therapeutic target for treatment of this refractory human disease.

BASIC SCIENCE: Inflammatory Response in Pulmonary Hypertension MathewRajammaMD

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We have previously shown that monocrotaline (MCT)-induced pulmonary hypertension (PH) is associated with an early and progressive IL-6 mRNA upregulation, IL-6 bioactivity, loss of endothelial caveolin-1 and reciprocal PY-STAT3 activation. PY-STAT3 is activated by IL-6, and caveolin-1 suppresses PY-STAT3 activation. Caveolin-1, an important immunomodulator, inhibits cell proliferation and participates in apoptosis. Anti-inflammatory treatment instituted early inhibits IL-6 upregulation, rescues caveolin-1, inhibits PY-STAT3 activation and attenuates PH. Our main purpose was to investigate whether inflammation played any role in hypoxia-induced PH in rats and to compare and contrast with the MCT model.

Male Sprague-Dawley rats (150-175 g) were subjected to hypobaric (1/2 atmospheric) hypoxia or given a single sc injection of MCT (60 mg/kg). Hemodynamic data, the expression of caveolin-1and PY-STAT3 in the lungs were examined at 48h, 1 and 2 wks.

PH and RVH were observed at 2 wks post-MCT and at 1and 2 wks of hypoxia. PY-STAT3 activation occurred in both models before the onset of PH and was progressive. The MCT model revealed progressive loss of caveolin-1; whereas in the hypoxia model, caveolin-1 expression was not altered.

MCT-induced PH is associated with disruption of endothelial caveolin-1 and reciprocal activation of PY-STAT3. In contrast, the hypoxia model exhibited PY-STAT3 activation without concomitant loss of caveolin-1. Importantly, these dissimilar models of PH show hyper-activation of PY-STAT3 before the onset of PH, indicating a role of inflammatory response to injury in the pathogenesis of PH. Since caveolin-1 suppresses PY-STAT3 activation; the significant PY-STAT3 activation in the hypoxia model may be indicative of caveolin-1 dysfunction. Thus, the disruption or dysfunction of endothelial caveolin-1 may promote inflammatory response and cell proliferation, contributing to PH.

CLINICAL SCIENCE: Pericardial Effusions in Patients with Pulmonary Arterial Hypertension: Long-term Prognosis and Treatment Outcomes FenstadEricMD

FenstadE LeR SinakL Maradit-KremersH AmmashN VillarragaH OhJ FrantzR McCullyR McGoonM KaneG Mayo Clinic Division of Cardiovascular Disease, Department of Internal Medicine, Rochester, MN, USA

Reports to date have suggested that pericardial effusion is an uncommon and unfavorable

sign in patients with Pulmonary Arterial Hypertension. The long-term significance of effusion size and patient characteristics remains unclear and the safety of pericardiocentesis in this patient population has been questioned.

Single center cohort study of all patients first seen with Group 1 PAH at a specialty PH center between 1995 and 2006. All patients had echocardiograms. Pericardiocentesis was performed under echocardiographic guidance with moderate conscious sedation in a monitored inpatient setting for those who received intervention.

Of 577 patients, 26% (150 patients) had pericardial effusion on echocardiography. The majority of effusions (128 of 150) were small (<1 cm in size). Moderate or greater effusions were present in 22 patients (9.3%) with evidence of hemodynamic compromise in 14 patients requiring pericardiocentesis. After adjusting for age, sex, functional class, and six minute walk distance, two factors independently associated with the presence of pericardial effusion were collagen vascular disease (OR 3.71; 2.05, 6.87) and right atrial pressure (OR 1.83 per 5 mm Hg; 1.33, 2.54). Median survival for patients with ? moderate effusion, mild effusion, and no effusion was 12 months, 36 months, and 69 months respectively ($p<0.001$). The degree of the pericardial effusion was most predictive of poor outcome in patients with collagen vascular disease associated PAH. Twelve of 14 patients undergoing pericardiocentesis had collagen vascular disease. Treated pericardial effusions were large (832 ± 512) and generally serous. Survival at 48 hours was 100% and associated with clinical improvement in 13/14. Repeat pericardiocentesis was required in three patients.

The incidence of any pericardial effusion on echocardiogram is low in patients with PAH. Effusions are typically small, occur in the setting of connective tissue disease, and are associated with elevated right atrial pressure. However, even small pericardial effusions are independently associated with poor survival. Rarely do pericardial effusions cause tamponade but when present can be safely drained with echo-guided pericardiocentesis in a monitored inpatient setting.

CLINICAL SCIENCE: Unrecognized Glucose Intolerance is Common in Pulmonary Arterial Hypertension

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Background: Diabetes mellitus is a well established risk factor for systemic vascular disease, but the relationship of glucose intolerance and diabetes mellitus with pulmonary vascular disease is not known. Previous studies have suggested insulin resistance is common in pulmonary arterial hypertension (PAH); and the metabolic syndrome, which includes insulin resistance, is common in pulmonary venous hypertension. Glycosylated hemoglobin(HbA1c) is emerging as a preferred test for the diagnosis of diabetes mellitus(DM). We have found that elevations in HbA1c are common in PAH; however the relationship of elevated HbA1c with PAH severity and functional assessment is unknown. We hypothesized that glucose intolerance evidenced by a HbA1c 6.0%is common in PAH and is associated with more

severe disease.

Methods: We prospectively measured HbA1c in patients with PAH diagnosed by right heart catheterization who were seen over a six-month period at our Pulmonary Vascular Center. Detailed demographic, functional, and hemodynamic data were collected at enrollment and subsequent visits and recorded in a database. Data are presented as mean standard deviation.

Results: 51 patients with PAH wereevaluated, 10 patients had known DM. 41patients without history of diabetes had HbA1c collected (mean age 52 14, female 31, IPAH 26). The mean HbA1c was 6.0 0.6%. 23 PAH patients(56%) had unrecognized glucose intolerance(HbA1c 6.0%) denoting high risk for DM, 6 (15%) had unrecognized DM(HbA1c 6.5%). Age and body mass index (BMI) were not different in PAH patients with glucose intolerance or DM and those with normal HbA1c (age 55 10 vs 49 18 yrs, p 0.24; BMI 29.9 9 vs 28.5 7 kg/m2, p 0.6). Right heart catheterization data, C-reactive protein,and brain natriuretic peptide levels were not different between groups. Glucose intolerance was common in patients with NYHA Class III heart failure (n 13/18). Mean six-minute walk distance (6MWD)for PAH patients with HbA1c 6.0% was significantly lower (Figure).

Conclusions: Unrecognized glucose intolerance and diabetes mellitus are common in PAH patients and higher HbA1c correlates with worse six-minute walk distance. Further studies are needed to discern if dysregulated glucoseor insulin resistance play a role in PAH pathogenesis or are a feature of more severe disease.

Comments

Related Resources

- MIF in Hypoxic Pulmonary Vascular Remodeling and Cell Proliferation
- WHO Group III: PH Owing to Lung Disease and/or Hypoxia
- Molecular and Hemodynamic Determinants of Right Ventricular Response to Pulmonary Hypertension
- Future Perspectives for the Treatment of Pulmonary Arterial Hypertension
- Inflammation in Pulmonary Hypertension: How Immunobiology Provides the Missing Link Between These Conditions

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