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Session 8: Pulmonary Hypertension

The evolving paradigm of pulmonary arterial hypertension and the evolving role of endothelin-1

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Pulmonary arterial hypertension (PAH) remains a devastating illness, with an average survival that is still less than 5 years. Our understanding of PAH has evolved from considering it a disease of vasoconstriction, to recognizing that disordered cellular proliferation and resulting physical obstruction of the microvascular lumen are the principal causes of the increased pulmonary microvascular resistance. In parallel, insights gained from less frequent types of PAH, such as the heritable form of idiopathic PAH and PAH associated with Hereditary Hemorrhagic Telangiectasia, have highlighted the importance of disordered growth factor signalling in the origin and pathogenesis of the disease, particularly by members of the transforming growth factor β superfamily, including bone morphogenic proteins. Moreover, it has become clear that the endothelial cell is central to the disorder, in terms of abnormal cell signalling, mediators and proliferation. Emergence of apoptosis-resistant endothelial clones and change to a neoplastic phenotype are hallmarks of PAH. Endothelial-derived mediators normally help maintain vascular heath. Abundant locally-produced prostacyclin and nitric oxide, and low levels of edothelin-1 normally preserve vascular patency. This balance is reversed in PAH, with low levels of prostacyclin and nitric oxide, and excess production of endothelin-1. Therapeutic blockade of endothelin-1 has resulted in clinical benefit for thousands of patients with PAH, who have had improvement in functional capacity and fewer clinical deteriorations. Each generation of endothelin antagonists improves on this track record. However, none of these agents is curative, and the potential reasons will be discussed. There is tremendous crosstalk between mediator systems in the vascular wall. With regard to endothelin-1, this is an area that requires further exploration, in order to understand the triggers for increased endothelin-1 levels and how to control them in PAH. Recent evidence suggests important interactions between the bone morphogenic protein and endothelin-1 systems, which deserve more study. The ultimate goal would be to suppress endothelin-1 synthesis and eliminate its contribution to the progression of this disorder.

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Balloon pulmonary angioplasty as a treatment option for chronic thromboembolic pulmonary hypertension

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Although pulmonary endarterectomy (PEA) can sufficiently decrease pulmonary arterial pressure (PAP) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), not all patients can undergo PEA because of technical limitations. Several drugs such as endothelin receptor antagonist to treat pulmonary hypertension have been used to manage these patients, but sufficient decrease of PAP cannot be achieved. Balloon catheter would easily reach to surgically inaccessible lesions and therefore, we hypothesized that balloon pulmonary angioplasty (BPA) would be an effective treatment option for inoperable patients with CTEPH. We have treated 162 inoperable patients with CTEPH (WHO functional class III or IV despite full medical treatment, mean age 62 years old) with BPA. Mean PAP significantly decreased after BPA (from 44.9 to 24.0 mm Hg ($P < 0.001$)). Forty patients developed severe reperfusion pulmonary injury after BPA and 5 of them died during hospitalization. Additional 3 patients died during follow-up period and 3-year survival rate was 94.4%. Sixty-four out of 132 patients have been followed up for more than one year after BPA. Decrease of mean PAP was maintained (21.9 mm Hg). Thus, BPA would be an effective therapeutic option in these patients who have otherwise no proven treatment.

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Adipose-derived regenerative cells therapy improves monocrotaline induced rat pulmonary arterial hypertension with suppressing endothelin-1 though an anti-inflammatory mechanism

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Introduction pulmonary arterial hypertension (PAH) is characterized by functional and structural changes in the pulmonary vasculature, and despite the progress of pharmacotherapy, the prognosis of patients with advanced PAH remains poor. Adipose-derived regenerative cell (ADRC) therapy has recently emerged as a novel therapy for ailments of various organs by promoting cell regeneration at site of pathology. In this study, we investigated the efficacy of ADRCs therapy on PAH using monocrotaline (MCT)-induced PAH rat model, and explored underlying mechanisms.

Methods male Wistar rats were divided into the control, MCT, and MCT with ADRCs transfusion (M/A) group. Seven million ADRCs were transfused by intravenous injection at day 7. PAH was evaluated by measuring acceleration time (AT) and deceleration (Dct) of PA flow using echocardiography. At day 28, pathological changes in pulmonary vessels were assessed. The expression of genes associated with PAH was analyzed at day 14 by real time RT-PCR. Results Echocardiography showed that ADRCs therapy inhibited the development of PAH at day 28

(AT: MCT 20.4 vs. M/A 24.0, Dct: MCT 1474.0 vs. M/A 898.6, $p < 0.005$). By histological analysis, pulmonary vascular remodeling induced by MCT was also inhibited (vessel wall thickness: MCT 0.44 vs. M/A 0.31, $p < 0.001$). MCT treatment increased mRNA levels of endothelin (ET) receptor-A, ET receptor-B, ET-1 and transforming growth factor (TGF)-beta in the lung. ADRCs therapy suppressed these increased mRNA ($p < 0.05$).

Conclusion ADRC therapy inhibited the development of PAH by reversing the changes in ET expression and inflammatory cytokines. These findings suggest that ADRC therapy may open a novel strategy to treat PAH.

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Role of bradykinin and endothelin-converting enzyme-1 in pulmonary hypertension

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Pulmonary hypertension (PH) is an unremitting disease defined by a progressive increase in pulmonary vascular resistance leading to right-sided heart failure. Using ECE1 knockout mice (ECE1 +/−) we demonstrated here that heterozygous deficiency of ECE1 protects mice against PH, RV hypertrophy, and pulmonary vascular remodeling on 3 weeks of exposure to hypoxia. We also observed that chronic hypoxia-induced PH is not only associated with increased levels of systemic and pulmonary endothelin-1, but also associated with diminished level of bradykinin (BK) peptide in lung. Genetic inactivation of ECE1 did not affect ET-1 levels but prevented the degradation of BK in lungs during hypoxia-induced PH. The clinical relevance of the data was indicated by our observation that the level of plasma BK in the pulmonary vein (PV) of patients with pulmonary hypertension due to atrial septal defect (ASD-PH) is significantly lower than in ASD patients without pulmonary hypertension (ASD-PH: 14.0 ± 7.2 ng/mL; ASD-noPH: 24.3 ± 20.8 ng/mL; $p < 0.05$). Furthermore, plasma BK level in PV has significant correlation with some hemodynamic parameters in this patient group (i.e. the pulmonary cardiac output, the ratio of pulmonary/systemic cardiac output and the systemic vascular resistance). Together, these data show that inhibition of ECE1 is protective against the development pulmonary hypertension through the preservation of bradykinin action. This study also showed that bradykinin level was diminished in PH and was correlated significantly with some hemodynamic parameters in mice and patients with PH, indicating BK as a promising therapeutical target for PH.

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Long-Term Survival in Japanese Patients with Idiopathic/Heritable Pulmonary Arterial Hypertension

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Background: Idiopathic/heritable pulmonary arterial hypertension (I/HPAH) is reported to have a poor prognosis despite the available therapeutic options. Although there are reports on survival of patients from Western countries, there is a shortage of data from Asia.

Methods: A retrospective chart review was performed on 56 patients with I/HPAH. Survival analysis was conducted by using Kaplan- Meier method and differences between parameters measured at baseline and after treatment were tested by the paired t-test. Results: There are 41 females (73%) and 15 males (27%) included in this study. The mean age was 32 ± 17 years old at the time of diagnosis. Mean survival time from diagnosis was 14.5 ± 0.8 years (95% CI, 12.9-16.2 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 100, 96, 96, 96 and 78%. In patients who underwent follow-up right heart catheterization at least 3 months later from the first catheterization at our hospital, WHO functional class improved from 3 to 2 ($P < 0.01$), and mean pulmonary arterial pressure was decreased from 63.2 ± 15.0 to 34.8 ± 10.3 mmHg ($P < 0.01$). Cardiac index was improved from 2.3 ± 0.8 to 3.5 ± 0.9 L/min/m2 ($P < 0.01$). At follow-up, 98% of patients were on PAH-targeted drugs: prostacyclin analogue ($n = 52$, 93%), endothelin receptor antagonists ($n = 38$, 68%), and phosphodiesterase type 5 inhibitors ($n = 29$, 52%). Forty-two patients (75%) were treated with combination therapy.

Conclusions: The study revealed a better survival of Japanese patients with I/HPAH than ever reported. Hemodynamic parameters were significantly improved. It might be caused by the difference of ethnicity or high prescription rates of targeted drugs used to treat I/HPAH.

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