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

Sunu B. Raharjo1, Noriaki Yuniadi2, Yoga Emoto3, Kazuhiko Nakayama3, Ganesja M. Harimurtia

1Department of Cardiology & Vascular Medicine, Faculty of Medicine, University of Indonesia/National Cardiovascular Center Harapan Kita, Jakarta, Indonesia
2Division of Clinical Pharmacy, Kobe Pharmaceutical University, Kobe, Japan
3Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan
E-mail address: sunu.b.raharjo@gmail.com (S.B. Raharjo)

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 therapeutic target for PH.


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

Aiko Ogawa4, Katsumasa Miyaji5, Hiromi Matsubara6
4Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan
5Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan
E-mail address: aiko-oky@umin.ac.jp (A. Ogawa)

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.