Fundamental Insight into Pulmonary Vascular Disease: Perspectives from Pediatric PAH in Japan

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Abstract

In Japan, we have a unique experience with pulmonary arterial hypertension (PAH): mandatory electrocardiography (ECG) screening in apparently healthy school children and lung biopsy study in infants with congenital heart disease and atypical PAH. Our recent nationwide survey demonstrated that the school ECG screening in Japan detects a substantial pediatric IPAH population that is associated with already established PH but without apparent right heart failure; early treatment in PAH patients was associated with better outcomes. Our lung biopsy study in small infants with atypical CHD-PAH in a single institute showed that microscopic respiratory disease was associated with the development of severe PH, which is unexplained by CHD but is reversible in acute vasodilator testing. We presented some experimental data supporting the benefit in initiating early treatment in PAH and targeting at-risk population from the perinatal period.

Keywords

Pulmonary hypertension · Electrocardiogram · Lung biopsy · Lifelong cardiology · Congenital heart disease

Pulmonary arterial hypertension (PAH) is a progressive and fatal disorder characterized by occlusive vascular disease (PVD), including intimal hyperplasia and plexiform lesions in small pulmonary arteries. Since PAH still remains an incurable disease, it is required to explore the pathobiological mechanisms, which may confer new therapeutic targets and strategies. In Japan, we have a unique experience with

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T. Nakanishi et al. (eds.), *Molecular Mechanism of Congenital Heart Disease and Pulmonary Hypertension*, https://doi.org/10.1007/978-981-15-1185-1_22

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PAH: mandatory electrocardiography (ECG) screening in apparently healthy school children and lung biopsy study in infants with congenital heart disease and atypical PAH. In this presentation, recent clinical and experimental data are presented on the basis of lessons from PAH in Japan.

22.1 Early Detection and Early Treatment of PAH: Mechanistic Insights

For the early detection of cardiovascular diseases, a school ECG screening has been executed for all the first graders in elementary, middle and high schools in Japan. Our recent nationwide survey demonstrated that the school ECG screening in Japan detects a substantial pediatric IPAH population that is associated with already established PH but without apparent right heart failure; early treatment in PAH patients was associated with better outcomes. In exploring the pathobiological basis of these findings, experimental studies using a human PAH-like rat model produced by Sugen/hypoxia (SuHx) treatment were performed. Animal studies showed that early but not late treatment reversed occlusive PVD, which was associated with increased apoptosis and suppressed anti-apoptotic molecule survivin expression in α -SMA cells in the intima. Further studies using SuHx models and human samples showed α -SMA cells in the intima were immature SMC-like cells although the origin of such cells remains to be explored; microarray analysis indicated distinct gene expression profiles in the early treatment.

22.2 Pathological Basis of Atypical CHD-PAH: Clinical and Mechanistic Implications

Some patients with Eisenmenger syndrome experience no obvious heart failure due to systemic pulmonary shunting in infancy, which is unexplained. Although a complex interplay of epithelial-endothelial cells is required for lung morphogenesis, its clinical relevance is unclear. Our lung biopsy study in small infants with atypical CHD-PAH showed that microscopic respiratory disease was associated with the development of severe PH, which is unexplained by CHD but is reversible in acute vasodilator testing. Such lung disease could be related to high functional PVR in infancy and late irreversible PAH unless CHD is timely repaired.

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