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Possible Role of Soluble St2 in Pulmonary Artery Hypertension

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Abstract

Pulmonary Artery Hypertension (PAH) is characterized an increased risk of premature death due to elevated pulmonary artery pressure / vascular resistance associated with right ventricle heart failure and multi organ dysfunction. PAH is frequently corresponded to clinical signs and symptoms of right side heart failure including decreased exercise tolerance, dyspnea, and edema. The current clinical guidelines recommended to use appropriate questionnaires, clinical status, hemodynamic features and parameters of cardiopulmonary exercise test to assay the PAH severity and prognosis. However, there are several limitations regarding implementation of these recommendations in routine practice including affordability of these methods, their cost, requires performing in specific laboratories or centers with high experienced teams. The aim of the editorial is to summarize knowledge regarding risk stratification in patients with established PAH based on monitoring of the levels of Soluble Suppression of Tumorigenicity (sST2) in blood. In has been suggested that sST2 can be seized upon simple tools for précised risk stratification in PAH.

Keywords: Pulmonary artery hypertension; Soluble ST2; Stratification; Risk; Prognosis

Introduction

The Pulmonary Arterial Hypertension (PAH) is steadily progressive maladaptive disorder with high risk of premature death [1]. According to current clinical statement PAH is defined as elevated mean pulmonary artery pressure ≥ 25 mm Hg at rest with simultaneously evidence of the presence of pre-capillary hypertension measured during right heart catheterization procedure [2]. Early diagnosis of the disease and exact prognostic stratification, especially in individuals at higher risk of PAH developing (chronic heart failure, connective tissue diseases, chronic obstructive pulmonary disease, congenital heart disease), remain challenging [3,4]. Questionnaires, standardized spirometry, exercise tolerance test, and cardiopulmonary test are recommended to justify stage of the disease and assay a risk of poor clinical outcomes [3,5].

Traditional parameters of pulmonary function test and exercise tolerance test have serious limitations (variability of repeated measures, lowered reproducibility of peak expiratory flow with standardized expiratory maneuvers) to be only methods of risk stratification, but they are widely affordable in routine clinical practice [3]. Consequently, the parameters of cardiopulmonary exercise test allow estimating the PAH severity and prognosis, but the method is quiet cost, requires performing in specific laboratories or centers with high experienced teams [6]. In this context, biological markers can be seized upon simple tools for précised risk stratification in PAH [7]. The aim of the editorial is to summarize knowledge regarding biomarker-based risk stratification in patients with established PAH.

Molecular targets for biomarker identification in PAH

The pathophysiological mechanisms of the development of PAH strongly relate to the primary conditions triggered the disease, although many of these innate factors remain uncertain. There is large body of evidence that there are three core signaling pathways mediating vascular remodeling and actively promote PAH development, i.e. NO-dependent mechanisms, endothelial signaling and prostacyclin pathway [7]. The inflammation and hypoxia are able to regulate extracellular matrix deposition and media wall thickness through over-expression of C-Jun-N-terminal kinase (JNK)-1 leading vascular remodeling and decreasing availability of NO via activation of its degradation by free radicals and other components of oxidative stress [8,9]. On the other hand, inflammatory cytokines (tumor necrosis factor alpha, interleukin-2, interleukin-6), Hypoxia Inducible Factor (HIF)-alpha, chemokine CXCR12, and prostacyclin acting through up-expression of vascular endothelial growth factor-1 and Transforming Growth Factor Beta 1 (TGF-1beta) genes coordinate neovascualogenesis, increase expression of inducible

NOs and regulate proliferative response through multiple mechanisms including mediation of mobbing, proliferation, differentiation and survival of endothelial progenitor cells [10,11].

Additionally, HIF-alpha directly inhibits key enzymes of Krebs' cycle, blocks aerobic glycolysis, induces mitochondrial dysfunction and thereby leads to dysmetabolic state including a deficiency of JNK-2. Finally, deficiency of JNK-2 expression in lung interacts with decreasing eNOs, lowered NO production, increased tissue and circulation poles of both angiotensin-II and endothelin-1, with regulate blood pressure control and play a pivotal role in structural alteration of small- and medium-sized pulmonary arteries. Moreover, there is evidence that JNK-2-dependent mechanisms coordinate TGF-1beta expression for synthesis and secretion of VEGF-1 by endothelial cells and mononuclears [12]. Indeed, JNK2 conveys Src/phosphotidylinositol 3-kinase and promotes vascular reparation via differentiation of endothelial progenitor cells. Additionally, endothelin-1, serotonin, hydrogen peroxide, and interleukin-6 caused significant increases ERK1/2-dependent phosphorylation in calpain activity that triggers vascular wall cell proliferation, perivascular fibrosis, and increased vascular resistance [13].

Finally, increased pulmonary vascular resistance and pulmonary pressure lead to pressure overload of right heart and induce right ventricular heart failure, progression of which worse lung perfusion, exacerbates chronic hypoxia, triggers of myocardial injury and biomechanical abnormalities and close up a pathological circle [14]. Taken together, vascular remodeling, vasoconstriction, low-grade inflammation, cardiac biomechanical and oxidative stresses, lowered availability of NO, are promising biomarkers that could have predictive value in risk stratification in PAH patients. It has been suggested that pathological processes like vascular injury, inflammation, fibrosis, cell death, and can be reflected by fluctuation of the levels of soluble suppression of tumorigenicity in peripheral blood.

Soluble ST2

Soluble Suppression of Tumorigenicity (sST2) belongs to the receptor of the interleukin-1 receptor family than cooperates with interleukin-33 and thereby exerts anti-proliferative and anti-inflammatory activities [15]. Elevated sST2 levels were found in acute coronary syndrome, myocardial infarction, PAH, and HF and they predicted all-cause death and CV mortality [16]. The levels of sST2 appear to relate to systolic and mean PAP, pulmonary vascular resistance, Right Ventricle (RV) EF, cardiac index, RV fractional area change and clinical exacerbation of PAH [17,18]. Meta-analysis provided by Luk KS et al. [19] has been reported that elevated levels of sST2 independently associated with severity and poor clinical outcomes in PAH patients. At the same time, single measured biomarker did not predict clinical outcomes in low-to-moderate-risk PAH patients. A multiple biomarker risk score including combination of renin, NT-proBNP, MR-proANP and sST2 was better for CV risk stratification to any single biomarker for accurately screening PAH patients at low, intermediate and high risk of death [20].

Consequently, sST2 can sufficiently improve the predictive model of PAH-related outcomes and it is promising biomarker for risk re-classification [21]. Moreover, some patients suspected idiopathic / inherited PAH could be differentiated from other individuals, in which elevated level of mean pulmonary blood pressure was increased due to other causes including antiretrovirus therapy, anticancer chemotherapy, and recurrent pulmonary thromboembolism [22]. However, large clinical studies are required to elucidate the predictive role of sST2 in patients with PAH. In conclusion, sST2 could be promising biomarker for risk stratification in PAH and probably a component of multiple biomarker-guided PAH therapy.

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