Early Diagnosis in Pulmonary Arterial Hypertension: The Search for the Holy Grail

Idiopathic or heritable pulmonary arterial hypertension (I/H-PAH) in children is a progressive, incurable pulmonary vascular disease (1). In the last two decades, specific PAH-targeted therapies have emerged that were positively trialed for efficacy only in adults but are currently also used and recommended in children (2). Despite these therapies, however, the prognosis for a child who has received a diagnosis of PAH remains unfavorable, with an estimated 5-year transplant-free survival rate of around 60% (3). Early diagnosis and treatment of this disease have been associated with improved long-term survival. Therefore, screening patients at risk for developing PAH seems to be a rational approach to detect the disease early and improve outcomes (4, 5).

In this issue of the *Journal*, Sawada and colleagues (pp. 1397–1406) investigate the impact of a school ECG-based cardiovascular screening program on detecting I/H-PAH in a general population of Japanese schoolchildren (6). The authors, as well as the Japanese Pediatric Cardiac Society, have to be commended for this excellent and unique effort, as no such large-scale ECG screening program for pulmonary hypertension (PH) in children has ever been reported.

This Japanese ECG-based screening program also includes a questionnaire and physical examination, and the authors report that this program detected a unique subpopulation of pediatric patients with I/H-PAH who had only mild clinical symptoms (lower World Health Organization functional classification and longer 6-min-walk distance) without obvious right ventricular (RV) failure (lower plasma brain natriuretic peptide), but nevertheless established PH (mean pulmonary arterial pressure [mPAP] 61 ± 17 mm Hg and pulmonary vascular resistance index 18 ± 8 Wood units [WU] $\cdot$ m^2).

Initially, PAH is a clinically silent disease. Then, relatively late in its natural history, the PAP rises, at which point more than 60% of the small, distal pulmonary arteries have been obliterated. So, although the children identified by the screening program were considered to have no or only mild symptoms, with an mPAP of 61 mm Hg and a pulmonary vascular resistance index of 18 WU $\cdot$ m^2, their PAH may be detected earlier than without screening, but this is far from a true early diagnosis of PAH. One may speculate that the identified children, who had a more preserved RV function, were able to adapt well to the disease. Initial symptoms in pediatric I/H-PAH occur only after the RV fails to adapt to the increased afterload; furthermore, they are nonspecific and include symptoms such as fatigue and exertional dyspnea. Consequently, the delay between the onset of symptoms and a diagnosis of pediatric PAH is reported to be around 1.5 years (1).

So, does this early detection of a subset of children with I/H-PAH mean that the Japanese nationwide ECG-based screening of healthy children is a successful screening strategy for PH? This program was originally not designed for this specific purpose. Given the availability of PAH-targeted therapies and the concept that outcomes can be improved by earlier initiation of treatment, the identified children may have improved outcomes compared with those who presented with symptoms, which should be regarded a positive result of the program. In this respect, however, the results of the current study temper initial enthusiasm, as better outcomes could not be demonstrated (yet). This may be related to either the retrospective design of the study or the pulmonary hemodynamic profiles of the children, which indicated that they had advanced vascular disease similar to that observed in children not identified by the screening program (6).

In a screening program, the accuracy of the screening tool or strategy used is important. In PAH, once changes in the ECG are present, the RV has already adapted to the increased afterload—in particular, hypertrophy and dilatation, which are signs of relatively advanced disease. In other words, as discussed appropriately by the authors, an ECG alone will detect patients with significantly increased PAP and is unlikely to detect really early disease.

Moreover, the sensitivity of ECG for detecting RV hypertrophy is reported to be 40–60% depending on the criteria used, which increases the rate of false-negative results (7, 8). More importantly, although the specificity of ECG for detecting RV hypertrophy has been reported to be more than 90%, with an estimated incidence of pediatric I/H-PAH of 0.5–0.7 cases/million children/yr and a low prevalence, the posttest positive predictive value of the ECG for PAH will necessarily be low, as a simple function of Bayesian analysis (9, 10). This will result in a high number of false-positive results that will necessitate subsequent diagnostic workups (invasive or noninvasive). Unfortunately, the current study does not allow conclusions about the accuracy of screening in terms of the number of missed children with PAH (false negatives) or the number of patients with ECG abnormalities who turned out not to have PAH (false positives). These numbers are important to determine the cost effectiveness of the screening program and relate directly to the prevalence of the disease in the population. Therefore, most PAH screening programs that are currently being evaluated focus primarily on high-risk groups with an increased pretest probability for PH. These include individuals with the BMPRII mutation, systemic sclerosis, portal hypertension, or sickle cell disease, as well as preterm-born infants with bronchopulmonary dysplasia (5).

Once the PAH screening outcome is confirmed, several scenarios may be faced: *1)* PAH is definitely present and the patient is treated (a follow-up study should then prove that the diagnosis in an asymptomatic patient would lead to a better outcome); *2)* no signs of PAH are present, which raises the question of whether the patient should be rescreened, particularly in high-risk populations; and *3)* mPAP is abnormal but does not reach 25 mm Hg, which is currently required for a definite diagnosis and treatment. Because

normal PAP is considered to be 14.0 ± 3.3 mm Hg, at the 6th World Symposium on Pulmonary Hypertension held in Nice in 2018, a change in the definition of PAH was proposed that would decrease the lower limit of mPAP to 20 mm Hg and a pulmonary vascular resistance > 3 WU; however, no conclusion was made regarding whether patients with an mPAP between 20 and 25 mm Hg should be treated (11).

The ability to obtain an early diagnosis in PAH remains an important goal to be pursued. Sawada and colleagues have contributed to this quest by evaluating the performance of a large ECG-based screening program in healthy schoolchildren. Unfortunately, the studied screening program did not resolve this problem, and thus early diagnosis remains an important goal to pursue in children with PAH. ∎

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Smooth Muscle Cells: A Novel Site of P-Selectin Expression with Pathophysiological and Therapeutic Relevance in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a debilitating disease associated with increased pulmonary artery pressures, reduced lung function and exercise ability, and progressive right heart failure (1). Endothelial dysfunction, vasoconstriction, pulmonary vascular remodeling secondary to smooth muscle cell proliferation and hypertrophy, muscularization of precapillary arterioles, and distal vessel loss are among the key pathophysiological processes in PAH (2). Present pharmacologic interventions target primarily vasoconstriction and are, as such, able to slow down, but not reverse, disease progression. Hence, therapies that could reverse the proliferative phenotype of pulmonary vascular cells and, thus, improve RV function without causing adverse effects are highly desirable (3).

P-selectin expressed on activated endothelium and platelets promotes inflammation by serving as a ligand for PSGL-1 (P-selectin glycoprotein ligand-1) on leukocytes to mediate leukocyte rolling and leukocyte–platelet aggregation, respectively