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Commentary

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Adult Congenital Heart Disease Related Pulmonary Arterial Hypertension: Novel Definitions and Therapeutic Trends

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Abstract

Adult congenital heart disease (ACHD) often leads to increased blood flow in the pulmonary circulation resulting in pulmonary arterial hypertension (PAH), which is associated with increased patient morbidity and mortality. According to the 2020 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, PAH is present when the mPAP is greater than 20 mmHg and PVR is greater than 3 WU (pre-capillary pulmonary hypertension). The most common classification of ACHD-PAH patients is in four groups depending on the defect type, shunt direction, and history of congenital heart disease surgical correction. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) showed that bosentan is effective in treating patients with Eisenmenger Syndrome, whereas the more recent Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity (MAESTRO) Study concluded that Macitentan has a neutral effect on the same population. Treatment of patients with ACHD-PAH should be individualized and carried out in specialized centers.

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Commentary

Adult congenital heart disease (ACHD) often leads to increased blood flow in the pulmonary circulation due to a blood shunt from an intracardiac defect or extracardiac communication. As a result, pulmonary arterial hypertension (PAH) often occurs in this setting increasing patient morbidity and mortality.

ACHD-related PAH (ACHD-PAH) has been traditionally characterized by increased mean pulmonary artery pressure (mPAP) combined with increased pulmonary vascular resistance (PVR). According to the 2020 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, PAH is present when the mPAP is greater than 20 mmHg (> 25mmHg in the 2015 ESC/ERS guidelines) and PVR is greater than 3 WU (pre-capillary pulmonary hypertension) [1,2]. This PVR cut-off has been chosen to differentiate patients with ACHD and PAH from those with ACHD and post-capillary pulmonary hypertension (PPH) which is usually due to systemic valve regurgitation. Patients with PAH are expected to improve with PAH-targeted treatments while this is not the case for patients with PPH. It is anticipated that due to the new PAH definition, more patients with ACHD and PAH will benefit from the earlier institution of PAH-specific medications.

The most common classification of ACHD-PAH patients is in four groups depending on the defect type, shunt direction, and history of congenital heart disease (CHD) surgical correction. Group A includes patients with Eisenmenger syndrome (ES) severely elevated PVR, right to left shunt, and cyanosis at rest. Group B consists of patients with large defects, moderately elevated PVR, and mainly left to right shunt. Group C includes patients with PAH and small cardiac defects that do not participate in the pathophysiology of PAH. Group D encompasses patients who display PAH after CHD surgical correction [2].

The survival of ACHD-PAH patients varies greatly and depends on PAH-specific therapy and the underlying structural heart disease. The COMPERA-CHD registry [3] confirmed previous observations that survival of ACHD-PAH patients is significantly better than those with primary PAH (76% vs. 54%) but also considerably reduced compared to congenital heart disease patients who do not have PAH despite the use of PAH-specific treatments.

ACHD-PAH management has been significantly improved upon the application of PAH-targeted treatments. Medications that inhibit the endothelin pathway, increase nitric oxide (NO) levels, and activate prostanoid receptors, reduce pulmonary artery pressures, and improve prognosis of these patients [4].

Of particular interest regarding ACHD-PAH treatment is that bosentan and macitentan, two medications acting on the same

receptors, ultimately gave conflicting results when given in patients with ES. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) [5] showed that bosentan is effective in treating ES patients, whereas the more recent Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity (MAESTRO) Study [6] concluded that Macitentan has a neutral effect on the same population. These contradictory results are possibly due to the different study designs. BREATHE-5 included patients with simple defects (atrial septal defect and ventricular septal defect) who did not receive PAH-targeted treatments as background therapy and there were no patients with Down syndrome. In contrast, in the MAESTRO study patient population was more heterogeneous including patients with Down syndrome (8.8%), complex defects (24.3%), and a significant proportion (27.4%) of study patients were treated with phosphodiesterase-5 inhibitors (PDE-5i). Patients in BREATHE-5 were in World Health Organization Functional Class (WHO FC) III while patients in MAESTRO were in WHO FC II and III. The primary endpoint in BREATHE-5 was oxygen saturation (a measure of safety) and the reduction of PVR (a measure of effectiveness). Improving exercise capacity by increasing 6 Minute Walk Distance (MWD) was a secondary endpoint for the study. In contrast to BREATHE-5, the MAESTRO study had exercise capacity and 6MWD as a primary endpoint. Macitentan reduced NT-proBNP and like Bosentan was able to decrease PVR in the hemodynamic sub-study.

What is striking about the MAESTRO study is that patients in the placebo group significantly improved 6MWD in a similar way to the Macitentan group. Indeed, the study was largely neutral due to the impressive performance of the placebo group. A similar improvement in the exercise capacity of the placebo group was not observed in BREATHE-5. It is difficult to attribute this improvement only to PVR reduction. Other factors such as patients' training may explain the difference. There are also questions about the suitability of 6MWD as a measure of exercise capacity in patients with Down syndrome because patients' cooperation may in some cases be particularly difficult. Overall, in cases of endothelin inhibitor administration, bosentan should be preferred in ACHD-PAH based on the results from BREATHE-5. In small studies, ACHD-PAH patients received oral or inhaled prostanoid pulmonary vasodilators in addition to background treatment for PAH. It seems that the non-parenteral administration of prostanoids in patients with ACHD-PAH and ES is well tolerated and may delay disease progression, but the effectiveness of the combination requires further studies [7,8].

Treatment of patients with ACHD-PAH depends on their clinical classification. Patients with PAH and small hemodynamically insignificant intracardiac or extracardiac defects or those who develop PAH after CHD surgical correction should be treated as patients with primary PAH. ES patients should receive PAH-specific treatment if they have symptoms and their functional class is greater than II. Endothelin inhibitors are the preferred treatment as they have the most robust studies in ACHD-PAH patients. In cases of clinical deterioration, arrhythmias, decrease in oxygen saturation, right ventricular dysfunction, increase in natriuretic peptides, and a decrease in their exercise capacity, PDE-5i should be added to the regimen. Treatment with prostacyclin or prostacyclin analogs is reserved for WHO FC IV patients. Patients with large cardiac defects, predominantly left to right shunt and moderately elevated PVR, should be treated as patients with ES when they are considered inoperable or to proceed to surgical correction otherwise [4] (Figure 1).

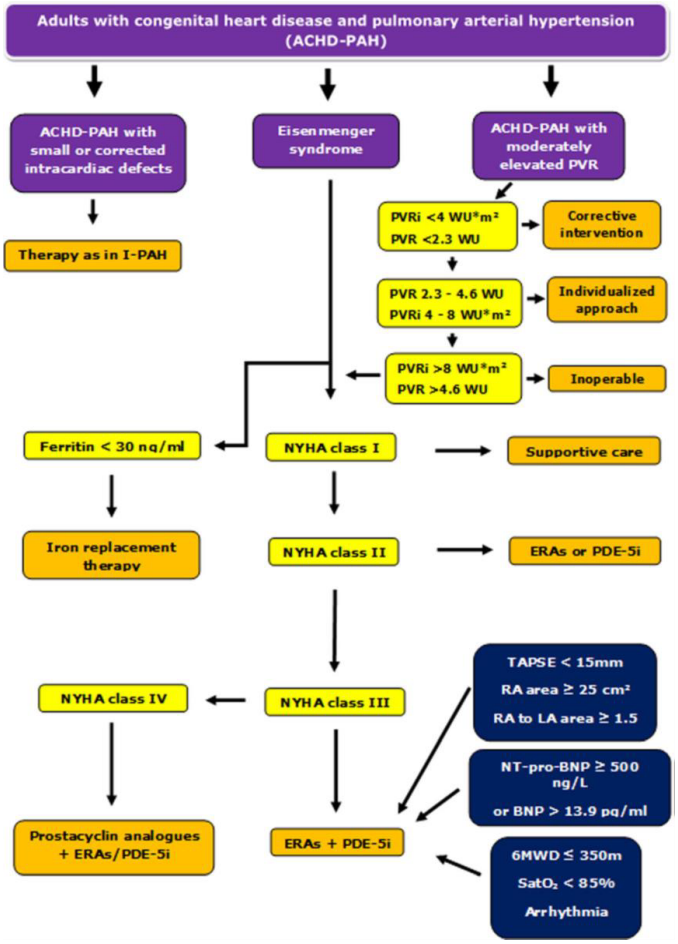

Figure 1: Treatment algorithm of adult congenital heart disease (ACHD) related pulmonary arterial hypertension (ACHD-PAH). Bosentan should be preferred over other endothelin inhibitors.

Note: Source of image (With permission from Papamichalis M, et al. Heart Fail Rev. 2020;25(5):773-94.)

CHD complicated by PAH is associated with increased morbidity and mortality and should be aggressively addressed. As this patient group is extremely heterogeneous, treatment should be individualized and carried out in specialized centers.

Conflict of Interests Statement

The authors declare no conflict or competing interest with respect to the authorship and publication of this article. The authors have no financial relationship with any organization.

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