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REVIEW ARTICLES

Pulmonary Arterial Hypertension Associated With Congenital Heart Disease

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Summary:

The management of patients with congenital heart disease (CHD) and pulmonary arterial hypertension (PAH) has changed dramatically with the development of targeted therapy with selective pulmonary vasodilators.

It is important to develop evidence-based guidelines for the management of these patients, and to achieve this, a register of adult Bangladeshi patients with PAH associated with CHD should be established. At the World Symposium in Nice, France, in 2013, the consensus was reached that patients with a pulmonary resistance of < 4 Wood Units (WU)û0m2 have operable disease, and patients with a pulmonary resistanceof > 8 WUû0m2 have inoperable disease. However, these criteria are conservative. Some patients with a pulmonary resistance of > 8 WUû0m2 and a good response to a pulmonary vasodilator test have operable disease and a favorable clinical course long after repair of CHD. The criteria determining operability in patients with PAH associated with CHD in the era of pulmonary vasodilators should be established using data obtained from patient registers and/or multicenter studies. The optimal management of Eisenmenger syndrome should also be established using data obtained from patient registers. Prospective studies should be conducted to determine the life expectancy of patients with Eisenmenger syndrome in the era of targeted therapy. A relatively mild increase in pulmonary resistance may result in failure of a Fontan circulation. The effects of pulmonary vasodilators on the long-term prognosis of patients who have undergone the Fontan operation are still unclear. (Int Heart J 2015; 56: S1-S3).

Key words: Target therapy, Pulmonary vasodilator, Eisenmenger syndrome, Fontan operation, Pulmonary resistance.

The management of patients with congenital heart disease (CHD) and pulmonary arterial hypertension (PAH) has changed dramatically with the development of targeted therapy using selective pulmonary vasodilators.

Many studies have reported on the efficacy of targeted therapy for PAH associated with CHD(1) This special issue reviews recent clinical studies of patients with PAH associated with CHD, and various aspects of the pathophysiological mechanisms underlying this condition

Definition and Classification

In 2013, a new classification system for PAH associated with CHD was announced, based on the expert consensus reached at the World Symposium in Nice, France, in 2013 (TableI).(2) This classification system is useful when discussing patients with PAH associated with CHD. PAH is defined as a mean pulmonary arterial (PA) pressure of ≥25 mmHg in association with a PA wedge pressure or left atrial pressure of ≤ 15 mmHg.3) This definition applies regardless of the age of the patient, and is accepted in pediatricand adult medicine. As the systemic arterial pressure is lower in young children, especially in infants, a lower mean PA pressure such as 20 mmHg may also be a clinically significant risk factor for development of pulmonary hypertension as the patient grows. Even though a PA pressure of ≥25 mmHg is used to define pulmonary hypertension, the long-term prognosis of infants with a PA pressure of 20–25 mmHg should be carefully studied.

Pulmonary arterial resistance is calculated using the formula: (mean PA pressure in mmHg " left atrial pressure or PA wedge pressure in mmHg) / pulmonary flow in L/minute/m2. The units for pulmonary resistance are WUû0m2, with the WU multiplied (not divided) by the body surface area. A paper by Simonneau, *et al (*2) erroneously reported the units as WU/m2. It should also be noted that the left atrial or PA wedge pressure should be subtracted from the mean PA pressure. Sometimes "total pulmonary resistance" is reported as the mean PA pressure without subtracting the left atrial pressure. It is important

to use the same units when engaged in discussions about the operability of patients with PAH associated with CHD. Calculation of pulmonary resistance requires measurement of the mean PA pressure. In patients with pulmonary regurgitation, the PA diastolic pressure decreases and the PA systolic pressure increases because of the increased stroke volume. The effect of pulmonary regurgitation on the mean PA pressure has not been studied, and there is still uncertainty regarding the pulmonary resistance in patients with pulmonary regurgitation.

Prevalence of PAH Associated With CHD

Patient registers and guidelines for the management of PAH associated with CHD should be established for Bangladeshi patients, because there may be race-related and region-related differences in the clinical course of this condition.

Operability

At the World Symposium in Nice, consensus was reached that patients with a pulmonary resistance of < 4 WUû0m2 have operable disease, and patients with a pulmonary resistance of > 8 WUû0m2 have inoperable disease (Table II). 2) However, these criteria are rather conservative. In 1991, a study conducted at our institute found that patients with an atrial septal defect (ASD) and pulmonary resistance of < 14 WUû0m2 had operable disease (6) However, the follow-up period after ASD repair was only 3–5 years in the majority of patients in that study, and longer follow-up may have revealed poor outcomes in patients with very high pulmonary resistance. Nevertheless,We believe that some patients with a pulmonary resistance of > 8 WUû0m2 who have a good response to an acute pulmonary vasodilator test have operable disease and can achieve a good clinical outcome long after the repair of CHD. In some countries, adult patients with ASD and high pulmonary resistance are treated aggressively with intravenous epoprostenol, and if the pulmonary resistance decreases, they undergo percutaneous ASD closure. Before the availability of targeted therapy, surgical treatment of patients with CHD and PAH was thought to result in worsening of long-term PAH(7) However, several pulmonary vasodilators are now available, and many patients receive combination vasodilator therapy. Repair of CHD can be performed in patients with borderline PAH who have a reasonable response to an acute vasodilator test performed by experts, but closure of cardiac defects should still be considered with great care in patients with severe PAH. . In a study , l patients who underwent closure of a ventricular septal defect and had a PA systolic pressure

Table-I

*Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease**

1. Eisenmenger syndrome
2. Left-to-right shunts
   - Correctable#
   - Noncorrectable
3. Pulmonary arterial hypertension with coincidental congenital heart disease
4. Postoperative pulmonary arterial hypertension

*5th World Symposium on Pulmonary Hypertension, Nice, 2013. #Correctable with surgery or intravascular nonsurgical procedure. Reproduced in a modified format from Simonneau, *et al*. J Am Coll Cardiol 2013; 62: D34-41.(2) with permission from Elsevier.

Table-II

Criteria for Closing Cardiac Shunts in Patients With Pulmonary Arterial Hypertension Associated with Congenital Heart Defects

PVRi ,WU/m2	PVR,WU	Correctable#
< 4	< 2.3	Yes
> 8	> 4.6	No
4–8	2.3–4.6	Individual patient evaluation in tertiary centers

of > 50 mmHg in the intensive care unit immediately after the procedure died during the follow-up period (8). Although that study was conducted before the availability of targeted therapy, the results suggest that PAH may progress in patients with a PA pressure of > 50 mmHg. It is still unknown where catheter closure of an ASD or ventricular septal defect is feasible when patients have a PA pressure of > 50 mmHg immediately after the procedure, now that targeted therapy is available. The long-term prognosis after closure of an ASD or ventricular septal defect in patients with PAH who receive targeted therapy has not yet been elucidated.

Management of ES

The guidelines recommend anticoagulant therapy for the management of idiopathic PAH, but not ES. We previously reported that platelets are activated in patients with cyanotic CHD.(9) The use of anticoagulant and/or antiplatelet drugs in patients with ES is controversial, but these drugs have been used with increasing frequency over recent years. Further large-scale studies are needed to determine outcomes in patients receiving such treatment. In patients with ES, targeted therapy used to be indicated only for functional class III/IV, but the indications have now been expanded to include functional class II. It is still unclear whether targeted therapy improves the prognosis of patients with functional class I, and a clinical trial with long-term follow- up may be necessary to investigate this.

Prognosis of Patients With ES

The reported life expectancy of patients with ES is about 50 years. However, this reflects the life expectancy of patients who did not receive targeted therapy. Prospective studies should be conducted to determine the life expectancy of these patients in the era of targeted therapy. Such studies require the establishment of patient registers.

Fontan Circulation and PAH

In some patients who have undergone the Fontan operation, long-term central venous pressure and PA pressure increase to > 15 mmHg and cardiac output remains low (1.5–2.5 L/minute/m2), resulting in increased pulmonary resistance of > 2.5 WUû0m2. Pulmonary resistance of > 2.5 WUû0m2 may not be high in patients with a biventricular circulation, but is high in patients with a univentricular circulation. A relatively mild increase in pulmonary resistance may result in low cardiac output, protein losing enteropathy, dilated right atrium, pulmonary thromboembolism, and arrhythmia in patients who have undergone the Fontan operation. The effects of pulmonary vasodilators.

on the long-term prognosis of these patients have not yet been elucidated.

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