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Treatment of pulmonary arterial hypertension in Eisenmenger's Syndrome : practice makes (almost) perfect

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Pulmonary arterial hypertension (PAH) associated with congenital heart diseases (CHD) is a rare[1], severely debilitating condition[2] associated with a high morbidity and mortality[3,4]. Although the incidence remains unknown, the prevalence of PAH-CHD ranges between 1.6 to 12.5 cases per million[1,2]. Survival is generally considered better than other forms of PAH, although patients with corrected shunts appear to evolve similarly than idiopathic PAH[4]. The Eisenmenger Syndrome (ES) was named by Paul Wood after the description of what remains one of the first evidence of PAH by Viktor Eisenmenger almost 120 years ago[5]. This syndrome is the combination of a large cardiac defect, pulmonary hypertension, cyanosis and polycythaemia. In addition, the ES is a unique form of PAH as it is frequently associated with end-organ damage and associated conditions such as iron deficiency[1,2].

The management of PAH has been redefined recently, implementing in practice the accumulating evidence favouring a combination strategy, either initial or sequential[1]. However, the data supporting such strategy in PAH associated with CHD and in particular the ES is very thin. In fact, the population of PAH-CHD (mostly corrected shunts) included in randomized controlled trials (RCT) testing monotherapy and combinations does not exceed 15 and 10 % respectively[1]. Unsurprisingly but sadly, patients with ES have been consistently excluded from many trials. To date, there is only one multicentre RCT that has been performed in this condition[6]. It demonstrated that the endothelin receptor antagonist (ERA) bosentan could safely be administered in this population, as it didn't cause further hypoxemia (the primary objective of this safety study). In addition, treatment with bosentan was associated with a decrease in pulmonary vascular resistance (PVR) even in the presence of already severely disturbed hemodynamics. Other small trials with the phosphodiesterase type-5 inhibitors (PDE5-i) sildenafil (n=10)[7] and tadalafil (n=16)[8] reported favourable functional and haemodynamic effects in patients with ES. In contrast, no RCT has yet tested the effects of sequential combination therapy in this unique population.

In PAH as in other rare diseases, it is generally accepted that well-kept registries, based on clinical practice, may provide important evidence; the latter may even be more informative than a RCT exposed to recruitment issues[9-11]. In this issue of the journal, the study performed by Sebastien Hascoët and colleagues rightfully illustrate this paradigm. The authors thoroughly describe the characteristics and outcome of 69 patients with ES treated with PAH therapies and followed in two centres in France[12]. They demonstrate a significant reduction in median values of pulmonary vascular resistance (PVRi, - 5.1 WU/m^2, $p<0.0001$), which was associated with a significant improvement in cardiac index (CI, + 0.4 L/min/m^2, $p<0.0001$) and exercise capacity by 6-minute walking test (6MWT, +49 m, $p<0.0003$). Hemodynamic improvement (decrease in PVR and transpulmonary gradient, and increase in CI), was observed in 68.0% of patients, although this benefit was not present after a median of 4.9 years. In addition, the authors also documented outcome and sought to identify predictors of outcome. One third of the patients were dead, transplanted or awaiting transplant after 7 years and half experienced these events after 15 years. Both haemodynamic response and superior vena cava O_2 saturation were found to independently predict outcome.