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Editorial

Evaluating a strategy of PAH therapy pre-treatment in patients with atrial septal defects and pulmonary arterial hypertension to permit safe repair ("treat-and-repair")

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Pulmonary arterial hypertension (PAH) associated with congenital heart disease (PAH-CHD) remains a major cause of morbidity and mortality in the growing adult congenital heart disease population. In the face of sustained progress, fewer patients are presenting with severe pulmonary vascular disease (PVD) and reversal of the shunt, cyanosis and multi-organ involvement, characteristic of Eisenmenger syndrome [1]. By contrast, patients with predominant systemic-pulmonary shunts and varying degrees of PAH are more commonly encountered. It is widely accepted that, in the absence of PVD, repair of a significant systemic-pulmonary shunt confers a clear benefit, improving or normalising life expectancy in young patients. The presence of preoperative PAH is, however, associated with atrial tachyarrhythmias, heart failure and mortality in the post-operative period [2]. Moreover, an adverse medium and long-term outcome has been described in patients with PAH after CHD repair, despite successful defect correction.

Disease targeted therapies are, nowadays, routinely used in PAH patients, including those with CHD, to reduce pulmonary vascular resistance (PVR), reduce morbidity and improve exercise capacity and quality of life [3]. The success of oral PAH therapies led to a dilemma being posed: [4] Can intracardiac communications, previously considered inoperable due to severe PAH, become amenable to surgery after successful treatment with vasodilators? This has come to be known as the "treat-and-repair" approach. Despite great interest by physicians around the world and numerous retrospective case series reported, the short and long-term consequences of the "treat-and-repair" approach remain unclear.

Evidence is hard to obtain in CHD, especially in sub-populations such as PAH-CHD. Multicentre registries are invaluable in this setting. In this issue of the *International Journal of Cardiology*, Bradley et al. present data on "treat-and-repair", focusing on patients with an atrial septal defect (ASD) and PAH precluding intervention [5]. In one of the largest cohorts of its kind, the investigators collected data on 69 adult patients from 9 North American centres, presenting over a 22-year period. Following PAH therapy, 19 patients underwent CHD repair, with an improvement in 6-minute walk test distance and echocardiographic parameters compared to those managed medically. After an average 7.2 years from repair, there was no significant survival difference between the 2 groups.

This study is a welcome initiative and provides some insight into the subject of "treat-and-repair", but like most registries, it leaves many questions unanswered. In the absence of randomisation or statistical adjustment (e.g. propensity score matching) to account for selection bias, differences between groups receiving intervention versus medical management are difficult to interpret. Indeed, deciding to repair the defect in a patient with clear evidence of PVD remains a complex decision. International PH and CHD guidelines provide haemodynamic cut-offs for deciding operability, based on limited evidence and expert consensus, but allow for a large "grey area" of uncertainty (Fig. 1). The recommended cut-offs have also changed over the years and differ between contemporary guidelines [6–8].

For "treat-and-repair" to enter clinical practice, we need selection criteria to identify patients in whom this strategy is likely to be safe and effective. It is generally accepted that cyanotic patients at the extreme end of the spectrum of PAH-CHD (Eisenmenger syndrome, Fig. 1), should not be offered repair, as they are likely to have irreversible PVD. Similarly, patients with PAH in the presence of a small (coincidental) defect should not be repaired, as the defect may act as a relief valve for the pressure-loaded right ventricle rather than being the cause of PAH. There remains a large population of patients with larger defects and raised PVR, in whom the decision to repair is influenced by haemodynamics (Fig. 1).

The population described by Bradley et al. had a wide range of pulmonary vascular resistances, from near-normal to over 15WU, in both the "treat-and-repair" and medical management groups. Patients who underwent repair had a greater average drop in PVR after PAH therapy compared to the unrepaired group. However, approximately half of the subsequently repaired patients had a PVR after PAH therapy above the cut-off of 4.6WU (equivalent to a PVRindexed 8WU$*$m^2), which would preclude closure according to current international guidelines, while many more remained within the "grey zone" (PVR > 2.3WU, PVRindexed>4WU$*$m^2) [7]. Moreover, 30% of the cohort that underwent repair were receiving intravenous prostanoid therapy, indicating the presence of severe PVD in many patients. It is, therefore, not

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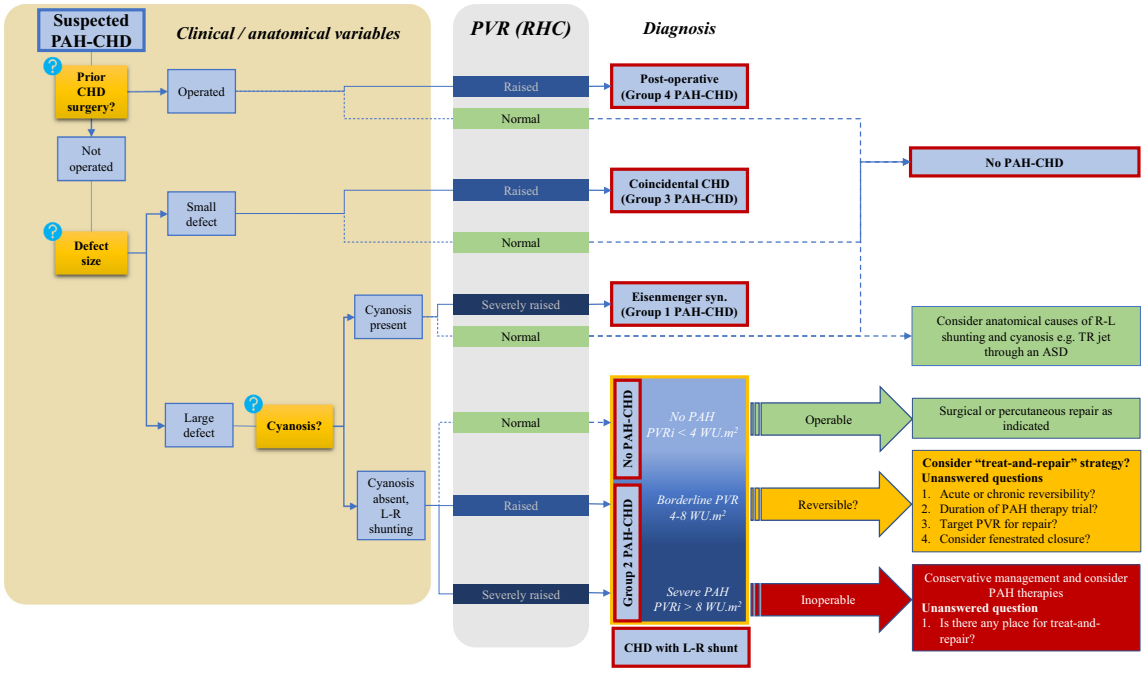

Fig. 1. Algorithm describing the diagnostic pathway for the 4 types of pulmonary arterial hypertension in congenital heart disease (PAH-CHD). Initially, clinical and anatomical variables are used to separate groups 1, 3 and 4 PAH-CHD. For patients with ongoing left-right shunts, pulmonary vascular resistance is then used to differentiate into those who do not have pulmonary arterial hypertension and those with group 2 PAH-CHD. According to the international guidelines, there is a significant area of uncertainty (rightmost yellow box). This is where a "treat-and-repair" strategy may be considered. Abbreviations: ASD = atrial septal defect; CHD = congenital heart disease; L-R = left-to-right heart; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension in congenital heart disease; PVR(i) = pulmonary vascular resistance (indexed); R-L = right-to-left heart; RHC = right heart catheterization; TR = tricuspid regurgitation.

surprising that the vast majority of patients needed to stay on PAH therapy after repair.

The concept of "safe repair" of a defect in PAH-CHD patients eludes us. With advances in intervention and surgery, combined with expert perioperative care, many PAH-CHD patients may survive to hospital discharge. The difficulty in drawing conclusions from the "treat-to-repair" literature to date is, in part, due to the fact that mechanisms behind PVD in patients with pre-tricuspid shunts, such as ASDs, are incompletely understood. Compared to PAH associated with post-tricuspid shunts, PAH associated with pre-tricuspid shunts occurs later in life and is rare [9]. Increased pulmonary blood flow is thought to be a necessary, but not sufficient component for the development of PAH. The process also requires a genetic predisposition or additional contributory factors that allow the activation of a cascade of mediators and result in vasoconstriction and vascular remodelling. Patients with sizable ASDs typically present with right ventricular dilatation. If PVD develops, however, the right ventricle is subjected to an additional (pressure) load, which may result in right ventricular hypertrophy, further dilatation, progressive dysfunction and reduction in the shunt. In these patients, closing the defect will abolish the volume load and may lead to a decrease in right ventricular size, but will not abolish the pressure load and long-term impact of PVD on prognosis.

Despite reassuring signals in the short-to-medium-term, the long-term consequences of a "treat-and-repair" strategy are yet to be proven in patients with PAH and systemic-pulmonary shunts. At present, the decision to follow a "treat-and-repair" approach should be made on an individual basis after comprehensive, multidisciplinary evaluation in a specialist PAH-CHD centre with appropriate patient consent, explaining the significant uncertainty behind this approach. For now, the old adage holds: "I can close it" does not mean "I should close it" [10].

Declaration of Competing Interest

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