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EDITORIAL

Tetralogy of Fallot, pulmonary valve replacement, and right ventricular volumes: are we chasing the right target?

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This editorial refers to 'Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot'†, by J.P. Bokma *et al.*, on page 829.

Tetralogy of Fallot (TOF) is the most common cyanotic heart defect (CHD), accounting for 3–5% of all infants born with a CHD.[1] Survival prospects without intervention are bleak, and <25% of unoperated patients survive to adulthood.[2] With the advent of surgical palliation and particularly with intracardiac repair operations, the fate of babies born with TOF has changed dramatically, and survival to adulthood is now the rule.[3] Milestones in the treatment of TOF are illustrated in *Figure 1*. Adult survivors are, however, not cured, and many are left with residual haemodynamic lesions, with severe pulmonary regurgitation (PR) being the most prevalent, found in more than half of all patients. A landmark paper published by Gatzoulis and colleagues in the year 2000 has found an association between significant PR and the risk of sudden death and sustained ventricular tachycardia.[4] Based on this observation, growing interest has arisen in whether alleviating PR by pulmonary valve replacement (PVR) may decrease the risk of adverse outcomes.

In this issue of the journal, Bokma and colleagues report their data on remodelling of right ventricular (RV) volumes after PVR in young adults with repaired TOF as measured by cardiac magnetic resonance (CMR) imaging.[5] They demonstrate that early RV remodelling after valve replacement is maintained after a median follow-up of 6.3 years in patients who did not require redo valve replacement (7/106 underwent redo PVR during follow-up and were excluded from analysis). Almost a third of patients within the study cohort were found to have significant obstruction or regurgitation of the prosthetic valve conduit or had moderate or severe tricuspid valve regurgitation at last follow-up. Pre-operative RV end-systolic volume was the single best predictor of optimal post-operative remodelling (defined as RV end-diastolic volume <108 mL/m^2 and RV ejection fraction >48%). This optimal remodelling was observed in 22% of the study population. In the second part of their paper, the authors analysed adverse clinical outcomes (sustained ventricular arrhythmias, death, or heart failure) in 106 patients who had pre-operative CMR studies. Adverse events were observed in a high proportion of patients (17%). Pre-operative end-systolic RV volumes of >95 mL/m^2 were identified to have a strong association with adverse clinical endpoints.

The study by Bokma and colleagues is in line with a number of studies that have been published over the last few years addressing RV remodelling after PVR.[6–8] Based on these and other studies, the following concepts have gained increasing popularity in the adult congenital heart disease community: (i) PR in adults with repaired tetralogy of Fallot leads to progressive RV dilatation and progressive RV dysfunction; (ii) RV dilatation is one of the main risk factors for adverse cardiovascular events; and (iii) timely prosthetic PVR with subsequent decrease in RV volumes decreases the risk of adverse events and improves long-term outcomes.

At many centres, decision-making regarding PVR in patients with significant PR is mainly based on CMR measures of RV volumes, often using fixed volumetric thresholds, even in asymptomatic patients.[6–8]

The rapidly growing enthusiasm for prosthetic PVR in patients with repaired TOF over the past decade is impressively demonstrated by an analysis of the Pediatric Health Information Systems database which demonstrated that the annual number of PVRs performed in patients >10 years old with repaired TOF at the 35 contributing US centres more than tripled between 2004 and 2012.[9]

Although the concept of using RV volumes for decision-making for PVR is widely used, its evidence base regarding its impact on

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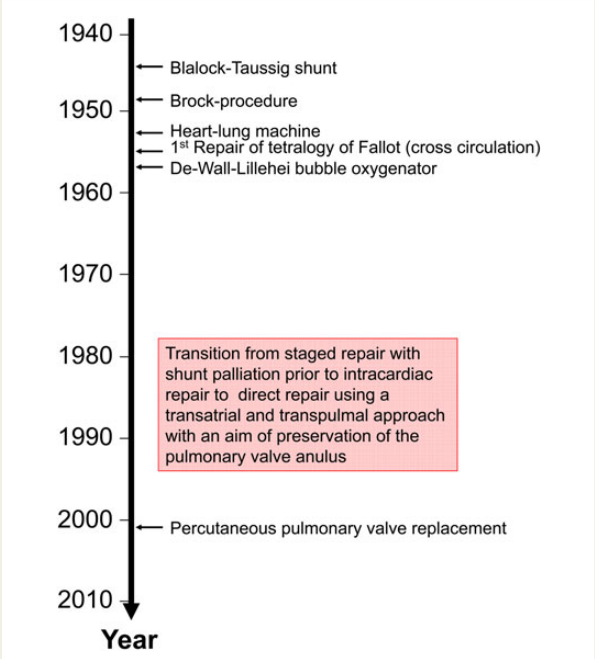

Figure 1 Milestones in the treatment of tetralogy of Fallot.

long-term outcomes is rather weak, and it may be worth reviewing some of the aspects pertinent to these issues.

Hypothesis 1: pulmonary regurgitation leads to progressive right ventricular dilatation and dysfunction in adults

The time course of RV remodelling after repair of TOF is not well defined. Interestingly, in individual patients with the same degree of residual PR, the extent of RV dilatation and dysfunction differ widely. Known determinants of RV remodelling after repair of TOF are illustrated in *Figure 2*.

The time-course of the remodelling process of the right venticle after childhood repair is not well studied but major remodelling probably occurs relatively early after repair. In contrast, most adults with severe PR seem to have reached a 'steady state', and, in clinical practice, progressive RV dilatation and progressive RV dysfunction during follow-up in adulthood are rare. Changes of RV volumes and function over time have been formally assessed only in a few small studies with limited follow-up duration. Some studies reported no significant changes in RV volumes and function, while in others a small increase in average RV volumes was observed.[10–12] Importantly, even in the studies that found an increase in RV volumes over time, the observed changes are markedly smaller compared with the expected intra- and interobserver variability of CMR measurements for RV volumes and ejection fraction in an individual patient.[13] Interestingly, looking at the data presented in these studies, a significant number of patients even had a decrease of RV volumes and an increase in RV ejection fraction over time, certainly caused by the variability of CMR measurement. Therefore, in the individual patient, changes in RV volumes between two CMR studies should be interpreted with caution, and, when these measurements are used as the main determinants of clinical decision-making, a confirmatory study with blinded CMR measurements may be prudent.

Hypothesis 2: pulmonary regurgitation and right ventricular dilatation determine the risk for clinical endpoints

The major concerns in adults with repaired TOF are the occurrence of sustained ventricular tachycardias and sudden (cardiac) death, while the occurrence of heart failure is relatively rare. Although initial studies have shown an association between PR and the occurrence of sustained ventricular tachycardias, later studies with more detailed analysis have identified a multitude of other risk factors, not directly related to PR and RV dilatation (see *Figure 2*). Interestingly the most recent multicentre study that included 873 patients with TOF found neither PR nor RV end-diastolic or end-systolic volumes to be predictive of death or sustained ventricular arrhythmias but, along with many other variables, previous implantation of RV to pulmonary artery conduits was associated with adverse outcomes in univariable analysis.[14]

Hypothesis 3: pulmonary valve replacement improves long-term outcomes

There is no reported prospective or randomized study that has provided evidence that PVR reduces adverse clinical outcomes compared with medical treatment.

The only (retrospective) study that has compared the outcome of TOF patients after PVR with a cohort of patients matched for age and QRS duration (one of the more robust surrogate risk markers for ventricular arrhythmias and sudden death) has found no evidence for a reduction of the risk of sustained ventricular tachycardia or death after PVR.[15] While no study has shown a clear reduction in hard endpoints, there are definitive risks associated with PVR. Potential benefits and risks of PVR are illustrated in *Figure 3*.

In the contemporary era, survival to age 40 years is expected in at least 88% of patients born with TOF, and conditional survival of those reaching adulthood may even be better.[1,16] Late increase in hazard for death seems to be slow.[3] In a recent study assessing the outcome of adult CHD patients >60 years of age, patients with repaired TOF represented 12% of all patients, providing further evidence that many patients with repaired TOF will survive to advanced age.[17]

This is important, as all studies that have reported on outcomes of TOF patients after PVR, including the study by Bokma and colleagues in this issue of the journal, reported an average follow-up in years in the single digit range. This is certainly not long enough to draw firm conclusions in a cohort of patients in whom the majority are expected to survive for decades without intervention. 'Long-

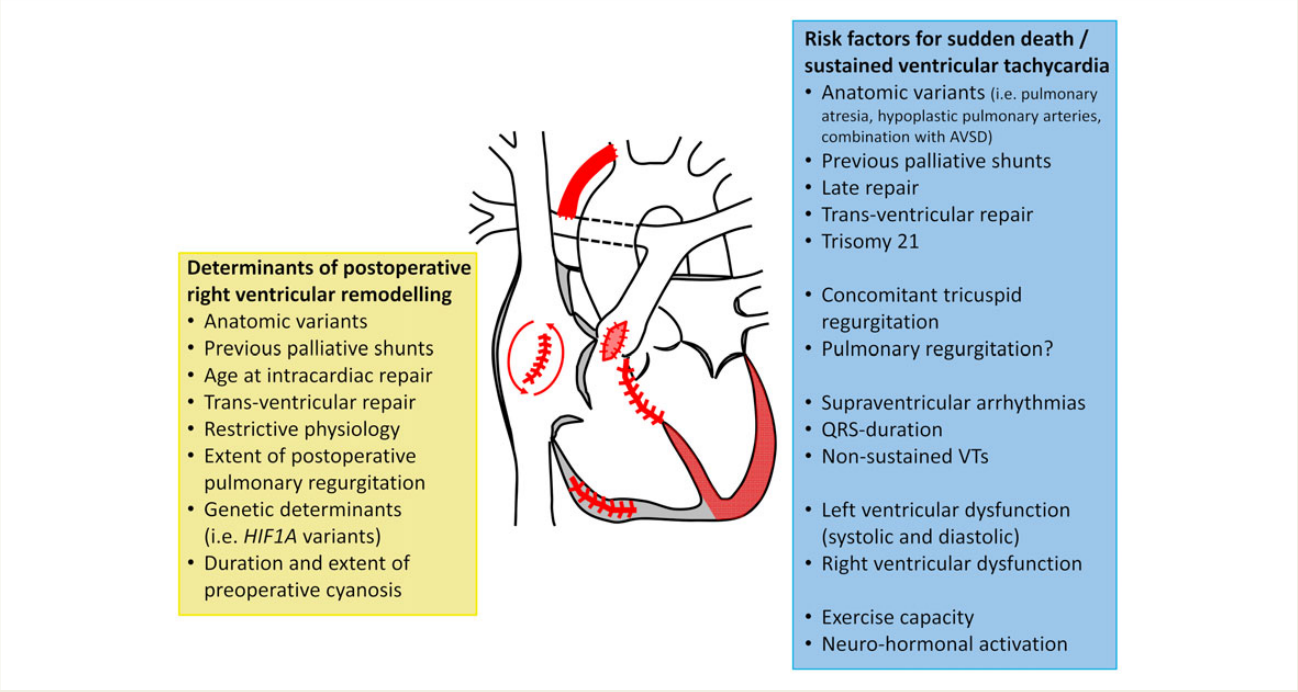

Figure 2 Determinants of right ventricular remodelling after intracardiac repair and risk factors for sudden death and sustained ventricular arrhythmia. AVSD, atrioventricular septal defect; VT, ventricular tachycardia.

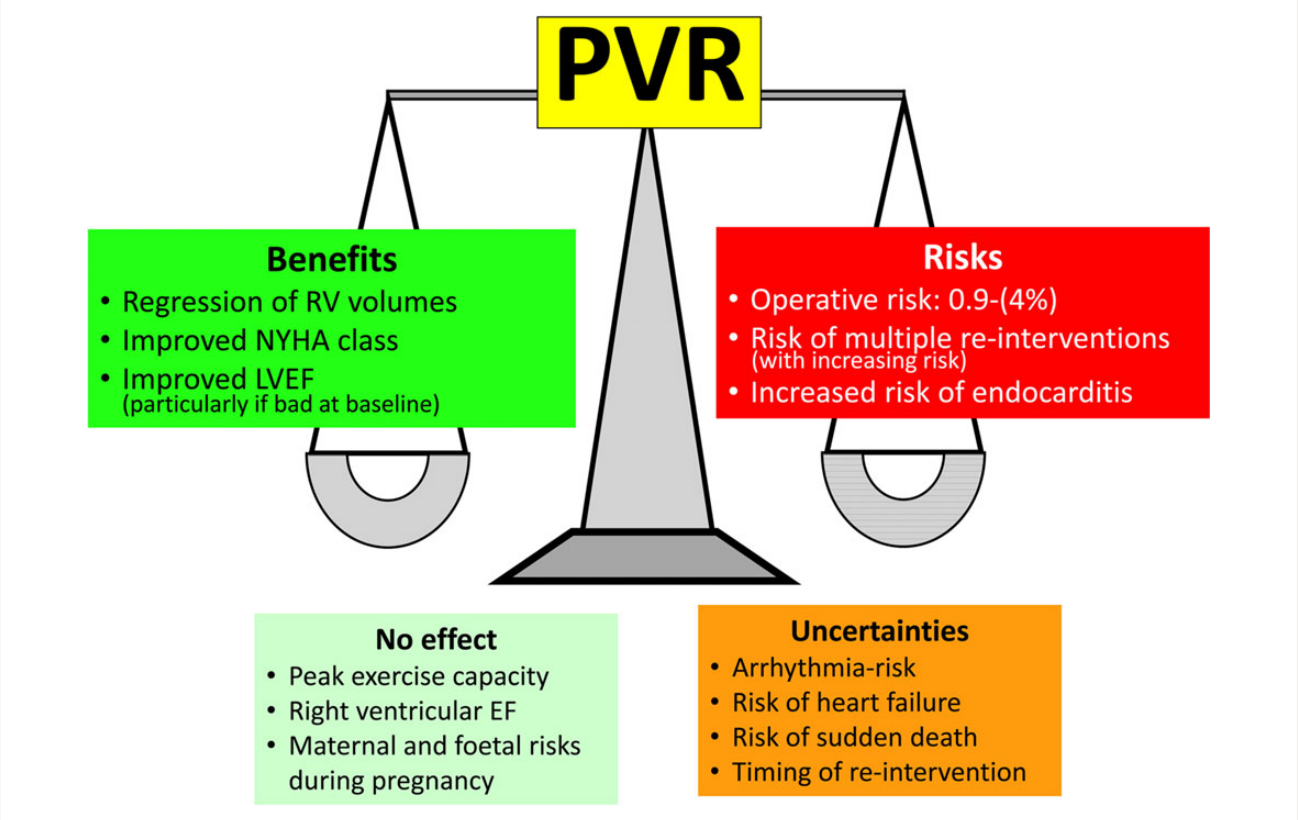

Figure 3 Risks, benefits, and uncertainties about pulmonary valve replacement (PVR). LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular.

term outcomes' in patients with TOF must aim to improve life-long outcomes. All patients after prosthetic PVR will eventually have graft failure and will need to undergo redo surgery or intervention. Each redo procedure will probably have an increased risk, and this has to be taken into account at the time of initial decision-making regarding PVR, particularly in asymptomatic patients. Another important concern is the high risk of infective prosthetic valve endocarditis that has gained increasing attention over the last years.

As outlined above, the impact of PVR on long-term outcomes in patients with preserved right ventricular function remains uncertain. In the study reported by Bokma and colleagues,[5] patients with end-systolic RV volumes >95 mL/m^2 had a very high risk of adverse events during follow-up. This raises the question of whether PVR in patients with end-systolic RV volumes >95 mL/m^2 should be generally avoided.

Once PVR has been performed, degeneration of the prosthetic pulmonary valve will inevitably occur, and redo surgery or intervention will be required in the majority of patients. The timing for redo PVR is difficult. Large proportions of these patients have impaired RV systolic function and thus present a classical 'low-flow–low-gradient' situation. With progressive stenosis of the prosthetic pulmonary valve, ventricular function may further deteriorate—sometimes without an increase of systolic gradients across the stenotic conduit, particularly in the case of concomitant progressive tricuspid regurgitation. Currently we do not have appropriate evidence to guide timing of re-intervention (i.e. reliable and reproducible measurement of contractile reserve) in such patients. This may be of particular interest, as RV hypertrophy, which often accompanies conduit stenosis, seems to be one of the key risk factors for adverse outcomes.[14]

Summary

The timing of PVR in adults with haemodynamically significant PR after childhood repair of TOF remains one of the major challenges in the care of these patients. Timing solely based on RV volumes may be an oversimplification of a complex issue, particularly in asymptomatic patients. In the absence of valid prospective studies with long follow-up duration over decades, careful individual decision-making is mandatory. Given the relatively small absolute risk of adverse events without PVR, we have to adopt a true long-term perspective in adult patients after childhood TOF repair with the aim of improving life-long outcomes. To allow the individual patient to make an informed decision, uncertainties must be discussed openly and carefully, including discussions about potential long-term risks, such as the largely unknown risks of repeat redo procedures (with difficult timing) and an increased risk of infective endocarditis. Multicentre and ideally international clinical registries with meticulous long-term follow-up protocols are extremely important for patients with and without PVR as only the careful analysis of such long-term follow-up data will finally allow improvement of our knowledge regarding the best future strategies for adults with TOF under our care.

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