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Editorial

Timing and Results of Pulmonary Valve Replacement for Pulmonary Regurgitation in Repaired Tetralogy of Fallot: A Challenge for Evidence-Based Medicine

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See article by Mongeon et al., pages 1772–1783 of this issue.

The Pulmonary Valve in Tetralogy of Fallot

There are now more adults than children with repaired tetralogy of Fallot (rTOF).[1] Operative repair includes relief of pulmonary stenosis, which comes at the expense of pulmonary regurgitation. Despite development of valve-preserving surgical techniques at the time of primary repair, postoperative pulmonary regurgitation remains the most important clinical problem for adults with rTOF. Although pulmonary regurgitation can be well tolerated with a long asymptomatic period, it is associated with right ventricular dilation and dysfunction, exercise intolerance, and increased risk of ventricular arrhythmias and sudden cardiac death.[2] Evidence from observational studies confirms that pulmonary valve replacement (PVR) improves symptoms and reduces right ventricular volume.[3] Consensus guidelines agree that PVR is indicated for rTOF patients with symptoms from pulmonary regurgitation.[4,5] However, for the asymptomatic patient with severe pulmonary regurgitation, uncertainty exists about which parameters and what thresholds merit referral for PVR. The recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines propose a constellation of parameters (ventricular dysfunction, right ventricular dilatation, right ventricular pressure overload, and exercise intolerance), of which any 2 in combination may be an indication for PVR in asymptomatic patients.[5]

What Are the Benefits of Pulmonary Valve Replacement for Adults With rTOF?

Although it is plausible that PVR will reduce morbidity and mortality in rTOF, data demonstrating the beneficial effect of PVR on nonsurrogate, clinically relevant outcomes are surprisingly scant. Mongeon et al.[6] conducted a systematic evidence review to explore this issue. Their meta-analysis focuses exclusively on adults (≥ 18 years of age) with ToF (excluding other forms of congenital heart disease that undergo PVR) and brings the literature up to date by including several recently published cohorts (including 6 studies published in 2017-2018), making it particularly relevant to contemporary adult congenital heart disease practice. The primary objective was to determine if PVR reduced mortality in adults with ToF compared with conservative management. Mongeon et al. found no randomized controlled trials (RCTs) or cohort studies that addressed mortality in relation to PVR and met the criteria for their meta-analysis, so the primary objective could not be answered. A secondary goal was to determine the postoperative incidence of death and sustained ventricular tachycardia (VT), as well as the impact of PVR on functional capacity and right ventricular volume and function. Incidence of both death and ventricular arrhythmia were 1 per 100 patient-years, based on a sample size of 560 rTOF patients. The reported rate of ventricular arrhythmia after PVR is not lower than historical cohorts[2] of adults with rTOF and suggests, as have other studies,[7] that PVR is not protective against late ventricular tachycardia. As was previously known, this meta-analysis confirmed that PVR improves New York Heart Association (NYHA) functional class and reduces right ventricular volumes, but does not improve right ventricular ejection fraction.

Mongeon et al.'s systematic review did not include the International Multicenter TOF Registry (INDICATOR) cohort, a multicenter observational study of 977 rToF patients.[8] In the subset of INDICATOR patients who underwent PVR (n = 444), the absolute rate of death, resuscitated sudden cardiac death and sustained VT was ~ 0.6% per patient per year. The INDICATOR investigators assessed the impact of PVR on death, resuscitated sudden cardiac death, and sustained VT and found no significant difference compared with patients managed conservatively who had not undergone PVR. Furthermore, the investigators assessed the impact of PVR on heart failure, sustained VT, and atrial tachycardia and found no significant reduction in these events in the PVR group compared with conservative management when propensity matching was performed.

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Taken together, both the systematic review by Mongeon et al. and the INDICATOR cohort highlight the lack of evidence that PVR improves mortality in rTOF. Although this can be viewed as disappointing, it is on par with the evidence gap for surgery for other regurgitant valvular lesions. Unlike the coronary disease population, which is homogeneous and prevalent, with outcomes that are frequent and measurable (death, myocardial infarction, and reintervention), valvular heart lesions are far more heterogeneous in their etiologies, less prevalent, and have lower rates of death and heart failure that accrue over long periods of time, making it challenging to design and conduct clinical trials. Moreover, given entrenched patterns of practice for valvular heart disease, clinical trials to prove benefit of established guidelines seem to be of low priority. To examine this further, consider the case for aortic valve surgery for aortic regurgitation.

Does Aortic Valve Replacement for Aortic Regurgitation Reduce Morbidity and Mortality?

Similarly to pulmonary regurgitation, chronic aortic regurgitation is well tolerated by the left ventricle (LV), leading to a long asymptomatic period. Chronic severe aortic regurgitation results in LV dilation and dysfunction, and eventually symptoms. It is known that worse symptom status and greater degrees of LV enlargement and impairment are associated with worse postoperative outcomes.[9] ACC/AHA[9] and European Society of Cardiology[10] guidelines have recommendations for severe aortic regurgitation and surgical intervention that closely parallel each other. Severe aortic regurgitation with symptoms or LV ejection fraction $< 50\%$ are class I, and LV dilation (LV systolic dimension > 50 mm or diastolic dimension $>$ 65-70 mm) without symptoms is a class II indication for aortic valve replacement (AVR) in both sets of guidelines. Scrutiny of the evidence for these recommendations (as tabulated in the online 2014 Valvular Heart Disease Guideline Data Supplement[11]) reveals that they are based on natural history studies and outcome studies of small numbers of patients in single centers ($n < 200$ for most cohorts) undergoing AVR without comparison groups. There are no RCTs or observational studies comparing AVR for severe aortic regurgitation with conservative management, so it is unknown whether AVR improves morbidity or mortality or whether the benefit is greater in symptomatic compared with asymptomatic patients. An observational study in 170 patients with severe aortic regurgitation comparing guideline-directed referral for AVR with "late" referral of patients with advanced symptoms (NYHA functional class 3-4) and severe LV dilation and dysfunction[12] found late referral to be associated with increased mortality, worse symptom status, and less reverse remodelling of the LV after surgery. On the opposite end of the spectrum, an observational study comparing proactive referral for patients with severe aortic regurgitation without symptoms, LV dysfunction, or severe LV dilatation versus standard guideline-directed referral for AVR[13] found that proactive AVR did not improve mortality but was associated with increased cardiovascular events (such as reoperations). Taken together, these studies suggest a "Goldilocks" moment, not too early and not too late, during which AVR is most beneficial for patients with severe aortic regurgitation, and thus they appear to justify the current guidelines as written.

The Goldilocks moment no doubt exists for patients with rTOF and pulmonary regurgitation. Although RCTs may never be done, or even justifiable, in symptomatic patients, large cohorts are emerging that may inform care of the asymptomatic rTOF patient.[8] The INDICATOR investigators analyzed their cohort according to a proactive versus conservative threshold of referral for PVR. Similarly to proactive AVR,[13] proactive PVR does not appear to improve mortality and is associated with increased cardiovascular events (heart failure, nonsustained VT, and atrial arrhythmias). One may hypothesize that proactive surgery for the asymptomatic patient without severe RV dilation or dysfunction may expose the patient to all of the risks (perioperative arrhythmias, operative related myocardial insult, endocarditis, prosthetic valve deterioration) without the benefits (symptom reduction and reduction in RV volume) of PVR. Future studies should be directed toward assessing whether new guidelines[5] have altered clinical practice and whether guideline-directed referral for PVR is associated with improved outcomes compared with those referred earlier or later than guideline recommendations.

How Should We Counsel Patients With Severe Pulmonary Regurgitation and Repaired Tetralogy of Fallot?

In light of this evidence review, adult rToF patients with symptoms due to pulmonary regurgitation can expect an improvement in symptom status and beneficial reverse remodelling of the right ventricle. PVR will not improve right ventricular function, does not appear to ameliorate the risk of ventricular tachycardia, and has not been shown to improve mortality. Patients and clinicians need to be vigilant for arrhythmias after PVR, as well as prosthetic valve complications including endocarditis and structural valve deterioration. As Mongeon et al. point out, to propose PVR to an asymptomatic adult with rTOF, ideally the intervention should be known to decrease morbidity (arrhythmias and heart failure) and mortality. The current evidence review[6] as well as the recent large cohort study[8] highlight the fact that data are lacking to support the benefits of PVR for asymptomatic patients on clinical outcomes beyond an improvement in right ventricle size. This fact should temper enthusiasm for proactive PVR in the asymptomatic patient with rTOF and encourage further research that focuses on clinically relevant (not surrogate) outcomes in this population.

Disclosures

The author has no conflicts of interest to disclose.

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