**Surgical Management of Chronic Pulmonary Regurgitation After Relief of Right Ventricular Outflow Tract Obstruction**

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Relief of right ventricular (RV) outflow tract obstruction in tetralogy of Fallot or similar physiology often results in pulmonary regurgitation (PR). The resultant chronic volume overload can lead to RV dilatation, biventricular dysfunction, heart failure symptoms, arrhythmias and sudden death. Although pulmonary valve replacement (PVR) can lead to improvement in the functional class and a substantial decrease or normalization of RV volumes, the optimal timing of PVR is not well defined. Benefits of PVR have to be weighed against the risks of this procedure including subsequent reoperation. This article reviews the pathophysiology of chronic PR, evidence-based benefits and risks of PVR, options for valve substitute, and optimal timing of PVR in patients with chronic PR after relief of RV outflow tract obstruction.  

**KEY WORDS:** Magnetic resonance imaging; Pulmonary regurgitation; Surgery; Tetralogy of Fallot.

**Introduction**

Relief of right ventricular (RV) outflow tract obstruction in tetralogy of Fallot (TOF) or similar physiology often results in pulmonary regurgitation (PR). The resultant chronic volume overload can lead to RV dilatation, biventricular dysfunction, heart failure symptoms, arrhythmias and sudden death. Pulmonary valve replacement (PVR) can lead to improvement in the functional class and a substantial decrease or normalization of RV volumes. However, there are some unsolved problems related to PVR in patients with chronic PR. These include optimal valve substitute for PVR and optimal timing of PVR in asymptomatic patients. This article reviews the pathophysiology of chronic PR, evidence-based benefits and risks of PVR, options for valve substitute, and optimal timing of PVR in patients with chronic PR after relief of RV outflow tract obstruction.

**Pathophysiology of Chronic Pulmonary Regurgitation**

Although PR resulting from relief of RV outflow tract obstruction (most typically after transannular repair of TOF) was originally considered to be a benign lesion, it is now evident that chronic PR can cause progressive RV dilatation and dysfunction as a consequence of chronic volume overload. PR is often well tolerated during childhood and adolescence. However, if left untreated, chronic PR can ultimately lead to heart failure symptoms, arrhythmias, and most importantly, sudden death. These clinical deteriorations typically manifest after the second postoperative decade. Fig. 1 shows the pathophysiologic consequences of chronic PR.

Currently, magnetic resonance imaging (MRI) is regarded as a gold standard for evaluating RV volumes and function and studies using MRI have led to a deeper understanding of the pathophysiologic consequences of chronic PR. Several studies have demonstrated a close correlation between the degree of PR and RV diastolic volumes (Fig. 2). As long as the compensatory mechanisms of the RV work, RV end-systolic volume and ejection fraction (EF) are maintained within a normal range. However, similar to chronic aortic regurgitation, once the compensatory mechanisms of RV fail, RV end-systolic volume increases and RV EF decreases (Fig. 3). Although decreased RV systolic function plays a central role in clinical deterioration of patients with chronic PR, concurrent left ventricular (LV) systolic dysfunction is also known to contribute to clinical de-
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Geva et al. demonstrated that LV systolic dysfunction was independently associated with impaired clinical status in long-term survivors of TOF repair. A study by Knauth et al. also showed similar results. The so-called “RV-LV interaction” plays an important role in the development of LV systolic dysfunction seen in some patients with chronic PR and RV systolic dysfunction. Because the RV shares myocardial fibers with the LV, disfunction of RV can adversely impact the function of LV. Studies using MRI have demonstrated this “RV-LV interaction” by showing correlations between RV EF and LV EF.

Sudden cardiac death is the most dreadful consequence of chronic PR and the most common mode of death in patients with repaired TOF. The annual incidence of sudden cardiac death is known to be approximately 0.15% per year in long-term survivors of TOF repair. Several studies have identified risk factors for sudden cardiac death late after TOF repair. Gatzoulis et al. in a study of 178 adult survivors of TOF repair, reported that chronic RV volume overload correlated with QRS prolongation and the risk of symptomatic arrhythmias was high when marked RV enlargement and QRS prolongation developed. Gatzoulis et al., in a multicenter study that consisted of 793 patients with repaired TOF, reported that QRS duration of 180 ms or more was predictive of ventricular tachycardia (VT) and sudden death. They found that the electrophysiological and hemodynamic substrate of sudden death resembled that of sustained VT, with PR being the predominant hemodynamic lesion.

Benefits and Risks of Pulmonary Valve Replacement

Most studies dealing with PVR in patients with chronic PR have consistently reported subjective improvements in functional class. However, there are conflicting results regarding objective improvements in exercise capacity as assessed by cardiopulmonary exercise tests. Ghez et al. reported that although most patients showed clinical improvement after PVR, maximal exercise capacity as assessed by maximal oxygen consumption did not improve after PVR. Frigiola et al. also found that there was no improvement in
maximal oxygen consumption after PVR. However, they reported that the ventilatory response to carbon dioxide production at anaerobic threshold improved after PVR and normalization of the ventilatory response to carbon dioxide production was most likely to occur when PVR was performed at an age younger than 17.5 years. Numerous studies using MRI have confirmed a substantial decrease or normalization of RV volumes after PVR. In a study of 71 patients with repaired TOF, showed a decrease in RV volumes of approximately 30% after PVR and reported that they could not find a threshold above which RV volumes did not decrease after surgery. There is a question of whether the reported decrease in RV volumes after PVR is merely the result of surgical RV reduction (resection or plication of RV outflow tract aneurysm). Although surgical RV reduction at the time of PVR can result in a greater relative decrease in RV volumes, substantial decrease in RV volumes was also noted in patients who did not undergo surgical RV reduction. Interestingly, two large studies using MRI have found that LV end-diastolic volumes significantly increased after PVR, suggesting a reversal of the adverse RV-LV interaction.

Although PVR can consistently lead to a substantial decrease of RV volumes, improvement in RV systolic function has not been uniformly demonstrated. Studies reporting no improvement of RV function had patients with already depressed RV function (RV EF <49%), whereas studies reporting improvement in RV function had patients with preserved RV function. This implies that PVR should be performed before irreversible RV dysfunction occurs. Some authors have advocated the use of corrected RV EF (calculated after excluding the PR volume) to demonstrate improvement in RV function after PVR.

There are conflicting results regarding the impact of PVR on QRS duration and arrhythmia propensity, and this may be due to the different characteristics of the study population. Studies reporting no change of QRS duration had patients with relatively longer baseline QRS duration or larger RV volumes compared with those reporting improvement in QRS duration. This implies that timely PVR before the occurrence of severe RV dilatation may have a beneficial effect on QRS duration.

Currently, there is no data showing a clear long-term survival benefit of PVR. Gengsakul et al. in a matched comparison study, reported that there was no difference regarding the composite outcome of death and VT between PVR and non-PVR subjects. Recently, Harrild et al. also reported similar results. Long-term follow-up results of carefully designed studies are mandatory to draw a definitive conclusion on this important issue.

Benefits of PVR have to be weighed against the risks of this procedure. Nowadays, PVR can be performed with low operative mortality. Cheung et al., in a meta-analysis of PVR after TOF repair, reported that the pooled early mortality rate was 2.1% (95% confidence interval 1.1% to 4.0%). The majority of patients experience an uncomplicated postoperative course, although postoperative morbidities are not negligible. Most importantly, patients are exposed to the risk of repeat PVR and this is a weak aspect of determining the optimal timing of PVR.

Valve Options for Pulmonary Valve Replacement

There are several valve options for PVR, including bioprostheses, homografts, mechanical valves, and hand-sewn polytetrafluoroethylene valves. Among these, bioprosthetic valves are probably the most widely used because they are readily available and do not need permanent anticoagulation therapy. However, most of these bioprostheses will eventually fail and require replacement mainly due to structural valve deterioration and more specifically, leaflet calcification. Although modern design techniques and anti-calcification treatments applied to currently available bioprosthetic valves have greatly improved the durability of bioprostheses implanted into adult patients, dystrophic calcification leading to early bioprosthetic valve failure is still a great problem in children and young adults. A dominant risk factor predictive of early bioprosthetic pulmonary valve failure is a younger age at the time of initial PVR, as reported in previous studies. Currently, the exact cause and mechanism of accelerated bioprosthetic valve failure in children is not completely understood. Traditionally, active calcium metabolism of rapidly growing children has been regarded as a culprit. More recently, however, some evidence suggests that greater immune system competence of children and young adults may contribute to accelerated bioprosthetic valve failure.

Currently, there is limited experience in implanting mechanical valves in the pulmonary position. Although mechanical pulmonary valves are expected to be more durable than bioprosthetic valves and homografts, permanent anticoagulation carries inherent risk of serious bleeding events and can impair the quality of life in children and young adults. Currently, it seems reasonable that mechanical PVR
can be considered in highly selected patients with multiple prior operations or another need for anticoagulation such as the presence of mechanical valve in other positions.

In an effort to overcome the limited durability of bioprosthetic valves in the pulmonary position, Quintessenza et al. 52)53) introduced a new method of implanting a bicuspid pulmonary valve using polytetrafluoroethylene (PTFE) material (Fig. 5). Their rationale for the development of this technique was based on favorable experimental and clinical results of PTFE monocusp valve.54) Earlier, they used 0.6 mm thickness PTFE material and experienced a few cases of redo PVR due to immobile and calcified leaflets.55) Freedom from redo PVR of this valve was approximately 70% at 8 years. Currently, they are using 0.1 mm thickness PTFE membrane anticipating improved valve durability due to the nonporous nature of this material which does not allow cellular in-growth and thickening. Certain-ly, long-term follow-up of this valve is mandatory to determine the true value of this new technique.

**Timing of Pulmonary Valve Replacement**

PVR is absolutely indicated when symptoms or decreased exercise tolerance attributable to PR are present. However, there is insufficient evidence and no detailed consensus to guide optimal timing of PVR in asymptomatic patients with repaired TOF and significant PR. The recently published guidelines from the American College of Cardiology/American Heart Association state that PVR is reasonable in patients with severe PR in association with "moder-
ate to severe RV dysfunction or enlargement.”

However, the specific thresholds for “moderate to severe RV dysfunction or enlargement” have not been defined. If PVR can be performed with negligible mortality and morbidity, and durable prosthetic valves are available, PVR should be recommended as early as possible for all patients with dilated RV. However, because this is not the case, we should decide the “upper threshold” to the point at which we can delay PVR and above which optimal outcome cannot be expected after PVR. Therrien and colleagues reported this “upper threshold” for the first time. They found that in no patients with a RV end-diastolic volume index (EDVI) >170 mL/m² or a RV end-systolic volume index (ESVI) >85 mL/m² before PVR were RV volumes “normalized” after surgery. Oosterhof et al. reported that normalization of RV volumes could be achieved when preoperative RV EDVI was <160 mL/m² or RV ESVI was <82 mL/m². Geva et al. reported that RV ESVI <90 mL/m² was associated with optimal outcome (normal RV size and function). Frigiola et al. suggested the most aggressive policy of performing PVR when RV EDVI <150 mL/m². What about the “lower threshold” above which we should consider PVR? Definitely, it primarily depends upon the clinical status of an individual patient. In asymptomatic patients, Geva et al. and Dave et al. recommended PVR when RV EDVI >150 mL/m². Although many studies identified cutoff values of RV EDVI as an indication for PVR, Geva et al. and Henkens et al. stressed the importance of RV ESVI in determining the timing of PVR. Other factors influencing the timing of PVR include moderate or severe tricuspid regurgitation, sustained tachyarrhythmia, severe branch pulmonary artery stenosis, and large RV outflow tract aneurysm.

Summary

PVR for patients with chronic PR after relief of RV outflow tract obstruction can be performed safely with low operative mortality and morbidity. PVR in these patients consistently leads to improvement in the functional class and a substantial decrease or normalization of RV volumes. Although currently there is no evidence showing the long-term survival benefit of PVR, timely PVR before severe RV dilatation and/or dysfunction occurs may have a beneficial effect on QRS duration and RV function, consequently improving long-term survival. Suboptimal durability of currently used bioprosthetic valves is a weak aspect of determining the optimal timing of PVR. Optimal timing of PVR in asymptomatic patients needs to be further refined.

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