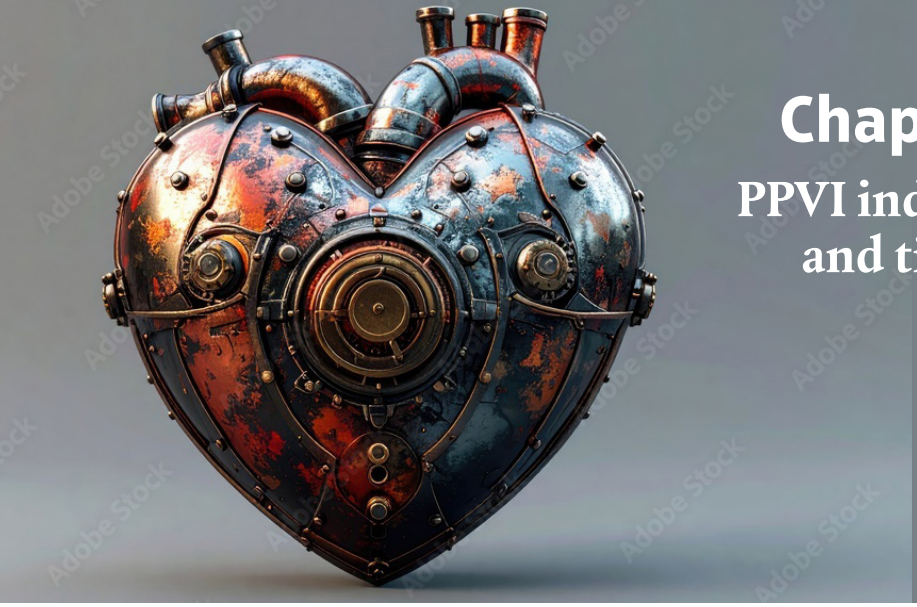


Chapter 8
PPVI indications and timing

Marc Gewillig, Bjorn Cools, Stephen C. Brown

Introduction

Of all four cardiac valves, the pulmonary valve is the least important. Some dysfunction of the pulmonary valve can be compensated for by the right ventricle for a long time, but excessive volume or pressure overload will eventually lead to right ventricular dysfunction. This RV dysfunction may lead to decreased pump performance and decreased quality of life, or to premature death.[1, 2]

Indications for pulmonary valve replacement

Indications for treatment emerge when the quality or quantity of life is compromised; a valve replacement is then indicated for symptomatic or prognostic reasons, respectively. For the pulmonary valve the nature of patient complaints is dependent on whether the valve is stenotic or regurgitant.

In pulmonary valve stenosis, the RV pressure will increase, inducing RV hypertrophy. The right heart can initially compensate for the pressure overload, but with increasing gradient, the RV stroke volume becomes compromised -initially during exercise, later at rest- with decreasing cardiac output or right-to-left shunting if an interatrial communication exists. At this stage, ventricular arrhythmias are uncommon. In clinical practice, this means a patient most likely will become symptomatic due to exercise intolerance before an unexpected arrhythmia may develop. The clinician can await symptoms before recommending an intervention; typically, a patient used to perform physical activities can become symptomatic with a RV outflow obstruction of ≥ 50 mmHg Doppler gradient, and patients with a sedentary lifestyle at ≥ 70 mmHg.

Pulmonary valve regurgitation has different symptomatology. It is usually well tolerated for years to decades, provided there is adequate pulmonary runoff (normal pulmonary vascular resistance and capacity) and the right ventricle is sufficiently compliant

to accept both the right atrial blood at low pressure and the pulmonary regurgitant fraction. Some surgical techniques may cause acute and important pulmonary regurgitation, such as a transannular patch at Fallot repair. Early after such acute pulmonary regurgitation, cardiac output may be compromised if the right ventricle is small and/or non-compliant, combined with a restrictive, high-resistance pulmonary vascular bed. Frequently the circulation adapts within days, allowing many patients to survive without a pulmonary valve for years to decades. The right ventricle reacts in different phases to the chronic volume overload. Initially, the RV cavity will dilate with increasing compliance and eccentric RV hypertrophy to maintain stable myocardial stress (similar to an athlete's heart). Continued excessive volume overload will lead to failed compensation, characterized by further dilation without adapted hypertrophy, resulting in increased myocardial stress and a decreased mass-to-volume ratio. These changes are supposed to be reversible. Continued excessive volume overload will further dilate the RV, change the regional architecture especially at the outflow tract with decreased contractility and systolic efficiency. Eventually, irreversible injury occurs due to excessive stress and possible coronary hypoperfusion, resulting in myocardial cell death with fibrosis. This becomes the substrate for additional electrical instability in an already carved and patched right ventricle, with the appearance of ventricular tachycardia and fibrillation; however, the timing of this transition is ill-defined and is the root cause of discussions about when to treat. The associated mechanical inefficiency may result in exercise intolerance, but many patients have by then adopted a sedentary lifestyle, keeping them "asymptomatic." During childhood, most patients with severe pulmonary valve regurgitation remain asymptomatic; with puberty, patients involved in athletic endurance sports start to deviate significantly from their peers or their own previous performances, but patients with a rather sedentary lifestyle may remain asymptomatic for decades. Symptoms of arrhythmia (palpitations, vertigo, syncope, and sudden death) or right heart failure may then be the presenting symptom.[3]

Guidelines and endpoints

The Merriam-Webster dictionary defines a guideline as a general rule, a principle or piece of advice. A guideline should always clearly define its endpoint, as different endpoints are possible. Possibilities for endpoints for medical procedural guidelines are: avoid procedural death or complications, avoid complications during early, medium, or– long-term follow-up, avoid lack of /or insufficient success (vs natural history or alternative treatment), avoid litigation or claim of overtreatment, make life easy for clinician with the perception that when performing "a procedure within limits of guidelines" makes the clinician almost unassailable. In contrast, when no guidelines are defined, some clinicians feel that "no (safe)" treatment is available. If asked what endpoint a guideline should aim for, the patient would most likely say "an event-free good quality of life for nine decades or more."

However, the ultimate endpoint of "event-free good quality of life for nine decades" is not practical: in order to assess the long-term results of an intervention, the clinician

would need several decades to determine superiority of either intervention or strategy. The time span of a PhD student is typically 3 to 4 years, and that of a career clinician is 30 years; these scientists therefore require surrogate endpoints that can be studied with shorter follow-up. However, the relation between the surrogate endpoint and the ultimate endpoint obviously also needs to be defined. Many surrogate endpoints lack such proven relationship with the ultimate endpoint, but are accepted by the clinical community because they "feel reasonable" or because of lack of a better alternative.

Furthermore, a single intervention may not result in an "event-free good quality of life up to nine decades." Different additional interventions may be required, each with its own risks and long-term problems. Guidelines must therefore make compromises: a guideline may aim for the least number of interventions, or the least risk of complications, or the least severe unpredictable sudden complications, or the best functional performance early while accepting accelerated functional decline, or the lowest-risk strategy early with the longest acceptable functional performance. And as always, a patient may change his priorities over time.

Timing of treatment

The timing of any treatment is influenced by the natural history of the disease (symptoms, imminent or unexpected irreversible damage) versus the characteristics of the intended procedure. The timing must balance between intervening not too late (to avoid exercise intolerance, atrial and ventricular arrhythmia, irreversible ventricular damage, and premature death) but also not too early, as any procedure is associated with risk or events caused by the valve itself (arrhythmia, dysfunction, endocarditis) and the need for repeated replacements over a lifetime. Important characteristics of the procedure to consider include expected beneficial effect, possible risks and complications, scarring, rehabilitation, cost for the patient and thessociety and the insurers, the unnatural history post-procedure with its complications, dysfunction, outgrowth, need for reoperation(s) and their risks, and feasibility. Depending on these variables, some treatment options may be considered sooner than others even for the same disease status. As outcomes of treatment options evolve, the timing of an intervention may also change over time. If a pulmonary valve were available at low cost, no pain, no convalescence, no complications during placement or long-term follow-up, and a longevity of several decades, the timing for pulmonary valve replacement would be easy: as soon as an adult-sized valve can be inserted. That way the asymptomatic valveless time during childhood can be tolerated, and a valve inserted before the ill-predicted but irreversible myocardial damage occurs. However, such a valve is not yet available, and therefore compromises must be made regarding how best to avoid or defer problems of the natural or unnatural history, and at what cost or risk.

In the last century, only surgical valves were available. Surgical placement of such a valve was associated with significant cost, pain, risk and convalescence, and the valve would last typically less than a decade; surgical techniques then allowed for at most 3 to 4

replacements in a lifetime.[4] Understandably, guidelines then concentrated on initial insertion as late as possible, and replacement of the valve only when severe dysfunction set in. Current surgical and percutaneous valves have a significantly better performance and risk profile, allowing a shift in timing from predominantly symptomatic indications to more prognostic ones.

Over the last decades, the guidelines have therefore changed tremendously. In the 1980s, surgeons performing repair of tetralogy of Fallot had learned that a residual RV outflow gradient was associated with high postoperative mortality, while a transannular patch was much better tolerated. The guideline for survival of the operation was "accept any degree of pulmonary valve regurgitation but not stenosis." These patients not only survived the operation but also fared well for many years and decades. Clinicians were impressed by the progressive RV dilation; however, most patients were asymptomatic, and the guidelines evolved to "accept any degree of pulmonary valve regurgitation" for an unspecified time.

In the late 1980s, patients presented with exercise intolerance, arrhythmias and heart failure, and pulmonary valves were implanted in symptomatic patients. It was observed that if the RV had dilated beyond 170 mL/m^2 there was no regression of RV dilation and no improvement of RV contractility after valve replacement. This value was therefore suggested as a threshold for replacing the pulmonary valve. The endpoint at this stage was not long-term survival, but the possibility of regression of RV dilation and recovery of RV function. In the following years, it became clear that the criterion of RVEDV ≥170 mL/m^2 was well beyond the upper limit for long-term survival. In order to allow avoidance of poor late outcome, other surrogate endpoints or algorithms were defined such as RVEDi, RVESi, RVEF, LVEF, RVOT aneurysm, tricuspid valve regurgitation, QRS duration, objective exercise capacity with still incomplete clinical success.[5-7]

The international cardiac societies as the European Cardiac Society,[8] the Canadian Cardiovascular Society[9] and the American Heart Association/American College of Cardiology[10] regularly publish updated guidelines. Unfortunately, the endpoints of these guidelines are rarely formulated. They all agree that pulmonary valve replacement is recommended in symptomatic patients with severe pulmonary regurgitation and/or at least

The informed reader will understand that these guidelines are not absolute, but human constructions reflecting the current view on how to avoid irreversible damage and how to offer the patient the best outlook for a long-lasting, good quality of life. Despite these guidelines, some patients still develop complications and arrhythmias with devastating consequences; therefore, current guidelines must still be challenged and explored at their limits and need to be updated as insights change.[11, 12] As no single surrogate endpoint can perfectly discriminate, the final decision remains multifactorial. Additional strategies combining medication, invasive arrhythmia detection and ablation, and anti-tachycardia devices will expand the therapeutic options for these patients.[13]

Treatment is always a balance between the natural history of the disease and the unnatural history of treatment. As results continue to improve, so do the indications and timing for treatments. The clinician must recognize that medicine still does not know the optimal timing for pulmonary valve replacement, but progress is being made.

moderate RVOTO. In asymptomatic patients the following criteria are suggested: RVESi ≥ 80 mL/m^2, RVEDi ≥150-160 mL/m^2, progression of TR to at least moderate, QRS duration >160-180 ms, progressive RV systolic dysfunction, RVOTO with RVSP ≥80 mmHg, and decline in objective exercise capacity (peak VO2).

References

1. Gatzoulis MA, Balaji S, Webber SA, *et al.* Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975–81.
2. Cheung MM, Konstantinov IE, Redington AN. Late complications of repair of tetralogy of Fallot and indications for pulmonary valve replacement. Semin Thorac Cardiovasc Surg 2005;17:155–9.
3. Therrien J, Siu SC, McLaughlin PR, *et al.* Pulmonary valve replacement in adults late after repair of tetralogy of fallot: are we operating too late? J Am Coll Cardiol 2000;36:1670–5.
4. Jang W, Kim YJ, Choi K, *et al.* Mid-term results of bioprosthetic pulmonary valve replacement in pulmonary regurgitation after tetralogy of Fallot repair. Eur J Cardiothorac Surg 2012;42:e1–8.
5. Bokma JP, Winter MM, Oosterhof T, *et al.* Severe tricuspid regurgitation is predictive for adverse events in tetralogy of Fallot. Heart 2015;101:794–9.
6. Gatzoulis MA, Till JA, Somerville J, *et al.* Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231–7.
7. Babu-Narayan SV, Diller GP, Gheta RR, *et al.* Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. Circulation 2014;129:18–27.
8. Baumgartner H, De Backer J, Babu-Narayan S, *et al.* ESC Scientific Document Group , 2020 ESC Guidelines for the management of adult congenital heart disease: The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). Eur Heart J 2021;42:563–45.
9. Marelli A, Beauchesne L, Colman J, *et al.* Canadian Cardiovascular Society 2022 guidelines for cardiovascular interventions in adults with congenital heart disease. Can J Cardiol 2022;38:862–96.
10. Stout KK, Daniels CJ, Aboulhosn JA, *et al.* 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:1494–563.
11. Valente AM, Gauvreau K, Assenza GE, *et al.* Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. Heart 2014;100:247–53.
12. Geva T, Mulder B, Gauvreau K, *et al.* Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort Circulation 2018;138:2106–15.
13. Bessiere F, Gardey K, Bouzeman A, *et al.* Impact of pulmonary valve replacement on ventricular arrhythmias in patients with tetralogy of Fallot and implantable cardioverter-defibrillator. J Am Coll Cardiol EP 2021;7:1285–93.