Percutaneous pulmonary valve implantation in India: Quo Vadis?

Surgical treatment of tetralogy of Fallot (TOF) represents the triumph of modern medicine. Long-term follow-up data, in general, have shown excellent survival and quality of life, but the survival is less than that of the general population as heart failure and sudden death may occur in some of these patients. An annual mortality of 0.24%–0.5% in the initial 20 years, and nearly 1% beyond 25 years have been observed in the long-term follow-up studies.[1-4] Mortality in a favorable subset of TOF may even be equal to that of the general population. In others, progressive right ventricular outflow tract (RVOT) stenosis and/or pulmonary regurgitation, worsening ventricular function, and arrhythmias may pose problems. In a multicenter study of postoperative adult patients followed up for 10 years, 2% incidence of sudden cardiac death, 1% heart failure, and 5% incidence of ventricular tachycardia (VT) or atrial flutter/fibrillation were found.[5] These and other data have convincingly shown that late age at initial operation, dysfunctional RVOT (severe regurgitation or stenosis), ventricular dysfunction (right [RV] as well as left ventricle[LV]), wide QRS complex (>180 ms), and presence of arrhythmias increase the risks of adverse events on follow-up in these patients.[1-6] The RVOT obstruction and/or pulmonary regurgitation tend to progress with time and need to be tackled before the ventricle is irreversibly damaged. Based on this paradigm, several guidelines have suggested the appropriate time to intervene relying on ventricular volumes, ejection fraction, QRS duration, and presence of arrhythmias even in asymptomatic patients.[7-10] In patients with RVOT gradient >64 mm Hg (or >80 mm Hg), RV systolic pressure >2/3 systemic pressure, or moderate-to-severe pulmonary regurgitation (regurgitation fraction >25% or more), pulmonary valve replacement (PVR) is indicated if the patient has symptoms due to these, or is asymptomatic but has one or more indicators of RV dysfunction namely RV end diastolic volume (RVEDV) >140–160 ml/m^2, RV end systolic volume (RVESV) >80 ml/m^2, (RVESV more important than RVEDV), progressive decline in RV ejection fraction, or RV ejection fraction <47%, QRS duration >180 ms, sustained atrial or ventricular arrhythmia, or exercise intolerance (<60% maximal oxygen consumption). Others have recommended PVR in patients with RV/LV EDV >2 or LV ejection fraction <55% or in patients requiring open heart surgery for other reasons with less stringent criteria.[11,12] Following PVR, symptomatic improvement, improved exercise performance, reduction in RV volumes, and in QRS duration is reported in some, but not in all studies.[13,14] However, there may be no change in QRS duration if it was >160 ms preoperatively.[15] Reversion of RV volumes to preoperative status during follow-up has been reported in some studies.[16] It may be that we are performing PVR too late, or alternatively we are chasing the wrong targets in trying to improve the long-term outcomes.[17] It may be too simplistic to think that complex question of sudden death may be predicted by one QRS duration, or the ventricular remodeling that has numerous variables in an individual patient can be predicted by any particular ventricular volumes. In fact, hard endpoints of death have not been shown to be altered by PVR.[18-20] In a more recent multicentric cohort follow-up, the RV volumes did not even correlate with adverse events, but RV mass/volume ratio, and LV ejection fraction were important correlates of VT and sudden cardiac death.[6] Thus, a refinement of our tools to identify the predictors of sudden cardiac death and heart failure in postoperative TOF patients are needed. Whether myocardial fibrosis on cardiac magnetic resonance imaging, mass/volume ratio, or other indicators such as global ventricular function index on echocardiography, or any biomarker may yield better results remains to be investigated.[21,22]

On the other hand, earlier TOF corrective surgery, better myocardial preservation during operation, technical improvements such as transatrial and transpulmonary correction, infundibular sparing, and valve sparing techniques are likely to improve the long-term outcomes and also possibly decrease or delay the need for PVR but such has not been shown yet.

Percutaneous pulmonary valve implantation (PPVI) in the year 2000 represents a remarkable watershed event in the management of patients with congenital heart disease.[23] Initially limited to postoperative patients with conduits, now the PPVI can be offered to many patients with native RVOT as well. With increasing experience and availability of different devices, the proportion of patients that may be suitable for PPVI has significantly increased. Over 15,000 procedures have been performed world over, and the

effectiveness of PPVI has been well established in general, but the issues of patient selection, learning curve (device specific), complications, and long-term data remain. Possibility of complications such as coronary or aortic compression by the device, conduit rupture, device or stent embolization, and vascular complications, although not common, demand a thorough understanding of the procedure and a certain level of technical skills from the interventional cardiologists.

Surgical PVR (SPVR) is an established and effective procedure[24,25] and PPVI has to match or improve upon those results. Since both procedures commonly use a bioprosthesis, they require reinterventions. A mechanical valve in SPVR may be considered in specific circumstances,[26] but is uncommon and may be more problematic in Indian patients. Freedom from reintervention at 5 years of 95% and at 10 years of 54% is reported with SPVR using bioprosthesis.[24,25] A reintervention rate of 15%–30% by 5 years is reported on follow-up of PPVI, mostly using melody valve, although requirement for surgery may be lower.[27,28] Long-term data with other devices are limited.

It is noteworthy that while SPVR might be the most common surgery for adult congenital heart disease in the Western countries, the SPVR volumes are quite small in the current Indian scenario. Why PVR volumes are so low? Although surgery for TOF was done in India since early 1960s, only a few cardiac centers were there. Open heart surgery has picked up more since 1990 onward with tripling in the capacity in the last 20 years or so. However, even in the high-volume centers that performed TOF surgery earlier, SPVR volumes are low. For example, some of the largest single center series of TOF were reported from Christian Medical College, Vellore and All India Institute of Medical Sciences of 813 (in the year 1993) and 2715 patients (in the year 2002), respectively.[29,30] PVR volumes in these centers are also low with <20 cases each in the last 5 years. These data clearly indicate a lack of systematic follow-up of patients and other resource constraints in the patient population. Thus, patients requiring PVR are expected to increase steadily with time and with overall socioeconomic improvement. Similar state of affairs regarding PVR status is likely in other low-and middle-income countries as well.

Conversely, Is the PPVI over done? There is a tremendous increase in the number of PVR procedures done recently, both surgically and percutaneously.[11,12,31,32] The enthusiasm of newly found effective technology for an unmet need of patients might explain some of the increase. However, it could also reflect self-referral and enthusiasm of interventional cardiology community in the face of an uncertain and evolving field of postoperative TOF patients, akin to adult interventional cardiology practices. Therefore, it is imperative that data are scientifically collected and analyzed so that best practices can be fostered for an individual patient care.

INDIAN EXPERIENCE

In this issue of annals, there are reports of initial Indian experience of PPVI using three different devices, namely the Melody valve, Venus *P* valve, and MyVal that is approved for transcatheter aortic valve implantation.[33-35] These authors should be congratulated for their intervention skills and leading the way for this therapy that potentially will benefit patients with congenital heart diseases. Taken together, the total experience till date amounts to 54 PPVI, and reflects the nature of market forces and regulatory environment rather than many other scientific factors. The regulatory environment for medical devices need not be extremely restrictive, nor empirical and amenable to individual manipulations; but pragmatic and transparent. Nevertheless, the initial reported experience augurs well for further cautious expansion of PPVI.

The self-expanding Venus *P* valve was used in 29 patients. There were 2/29 (9%) procedural failures due to problems in design that was later modified. Stent embolization in 2 (6%), endocarditis in 1 (3%), and vascular complication were seen in 1 (3%) of the patients. These devices were done over 6 years and the results would improve with experience and improvements in device design. On the follow-up over 46 months, 3/27 (9%), insignificant wire fractures were seen. The fracture in the scaffold usually do not interfere with device function, but it should not be forgotten that it might worsen with time and insignificant fractures reported on intermediate follow-up may become significant on longer follow-up.[36] The study reported as multicenter retrospective observational study of the data from compassionate use of a new device could perhaps been better standardized.

The other study of MyVal in right-sided conduits also represents the first report of an off-label use, but a retrospective analysis of cases based on compassionate use of a new device. There was a valve failure in 1/7 (14%, confidence interval 0.3%–58%) that was managed by implantation of another valve but is a matter of concern for a new device. The encouraging early results call for a cautious systematic data collection and long-term follow-up. The multicentric Melody valve implantation in 15 patients with RVOT conduit over 3 years represents a systematic proctor-based planned exercise. The authors rightly emphasized the need for skilled interventionalists, an adequately furnished cath lab inventory, and the costs involved in the procedure.

Further, infective endocarditis on the pulmonary valve remains an important concern, and an incidence 1%–3%/year has been reported in many studies.[37,38] The risks

seem to persist over time and data about the risks of endocarditis with many devices that have larger scaffolds in the ventricle are not available. Whether the oro-dental hygiene was routinely evaluated pre-PPVI in the reported Indian patients is not known, but that may be important in Indian settings where routine dental check-ups are not commonly done.

PPVI procedures require high-quality imaging back up and patient-specific tailored device with industry support will facilitate the procedures. Eventually, wider adoption of any procedure is possible when it becomes user-friendly. Due to the vagaries of postoperative right ventricular outflow tract obstruction shape and other complexities, the number of patients in whom PPVI can be done is not known but is growing.[39,40] There are growing options with number of devices available now including Melody, Sapien-S3, Venus *P* valve, Medtronic Harmony transcatheter pulmonary valve, Pulsta, Alterra present, and Med-Zenith PT amongst others.[11,12,41] Hybrid surgical procedures and other innovative technologies will certainly continue to expand the field of PPVI. The long-term effects of a foreign material in RVOT, durability of stents and valve prosthesis, and finally outcome analysis are important: All of these need continued careful follow-up. A tissue engineered valve with growth potentials at the time of initial surgery may be the ultimate solution for TOF patients.

IS PPVI COST EFFECTIVE?

Cost-effectiveness is a complex issue and is highly contextual, but relevant. Resources are never infinite, but the cost-effectiveness becomes even more relevant in low- and middle-income countries. The new technology is always costlier initially. However, the right use of technology is becoming increasing difficult in a flat, but heterogeneous world. The out-of-pocket expenditure by the patients has an impact on their lives and has to be accounted for. Even with state operated medical schemes, the opportunity costs to the society remains important. As such, currently the PPVI may be 2–16 times costlier to the patient than SPVR depending on many other factors. The need for reinterventions, other patient specific factors should be integrated with a long view of the patient's life for decision-making. Eventually cost may reduce as patient population increase or other market forces take over. Indigenization is an important way to reduce the costs, but unless the benefit goes to the patient, indigenization by itself might not be of much value. It is erroneous to think that the medical decisions should be based only on "science," there are no value free medical decisions. Nevertheless, avoiding or postponing surgery by PPVI is no small achievement that is available to Indian patients now. Each patient's decision needs to be individualized. We surely are living in exciting times!

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