Recent Progress in the Understanding and Management of Postoperative Right Ventricular Outflow Tract Dysfunction in Patients With Congenital Heart Disease

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Palliative surgery for conotruncal congenital cardiovascular defects such as tetralogy of Fallot and truncus arteriosus includes reconstruction of the right ventricular (RV) outflow tract (RVOT). Depending on patient age, anatomy, and other factors, a variety of techniques, prosthetic materials, and valves are used to reconstruct the RVOT, but essentially all become dysfunctional over time, with obstruction, pulmonary regurgitation (PR), or both. One of the challenges of managing patients with dysfunction of a surgically reconstructed RVOT has been balancing the risks of ongoing RVOT dysfunction against the risks and benefits of open heart surgery to replace the pulmonary valve. This calculus is complicated by the fact that the replacement valve will have a finite lifespan that is substantially shorter than the life expectancy of the patient, so the “wait-or-intervene” dilemma will recur again and again. In general, the information used to populate these risk-benefit calculations has been limited and confounded by a variety of factors, so clinicians caring for these patients have often been tasked with making recommendations that are based on inadequate or conflicting data. Moreover, there is such wide and often unexplained variability between patients in how the RV remodels in response to dysfunction of the RVOT that it is difficult to systematize practice and to serve all patients optimally. Given the expanding population of adults with tetralogy of Fallot and other disorders associated with RVOT dysfunction, who constitute a large proportion of adults with significant congenital heart disease, this clinical problem will only continue to grow.

In recent years, there have been numerous advances in our understanding of and methods for evaluating the physiological and clinical sequelae of RVOT dysfunction, as well as in the conceptual and technical aspects of managing such dysfunction and in therapeutic technologies. Although these advances have not resolved the difficulties that clinicians encounter in managing these patients, they have helped clarify and address some of the uncertainty. The purpose of this review is to summarize some of the fundamental dimensions of this evolution.

Clinical and Diagnostic Advances

Our understanding of the ramifications of prolonged RVOT dysfunction has been advanced dramatically in recent years, thanks in large part to the dissemination of imaging technologies that allow reliable quantification of RV and RVOT performance and pathophysiology, and to increasingly sophisticated investigations using these and other tools. Many of the important insights have resulted from a more incisive characterization of the extent to which RV dysfunction, electrophysiological abnormalities, and exercise dysfunction are associated with PR and abnormalities of RVOT contraction. With the emergence of such data, practices have begun to shift toward a more conservative approach to the management of RVOT dysfunction. Namely, pulmonary valve replacement (PVR) in patients with significant PR and consequent RV volume overload is being performed more often, and apparently at a younger age, than was the case even a decade ago, and data on the differential clinical benefits depending on age at PVR appear to support this trend.

It has long been known that surgical PVR reduces RV volume. With the introduction of volumetric cardiac MRI and MRI techniques for measuring flow, precise quantification of RV volume, RV function, and PR severity became possible and increasingly routine. One of the most confounding questions that arise in virtually every patient with RVOT dysfunction is when to implant or replace the pulmonary valve. The emergence of symptoms does not always correlate with the severity of obstruction, PR, or RV dilation or dysfunction. With the incorporation of MRI into the evaluation of these patients, it became clear that, although PVR reduces RV volume, all ventricles do not respond equally, and normalization of volume depends to some extent on the severity of enlargement before PVR. Even when the volume is reduced to normal, however, RV function does not necessarily improve, and PVR at advanced stages of RV dilation does not engender a survival benefit or improve electrophysiological parameters or outcomes. These disappointing realizations, along with evidence suggesting that younger age at PVR may lead to more consistent improvement in RV function, support the notion that chronic RV volume and/or pressure overload lead to changes that precede or are otherwise uncoupled from severe dilation or manifest dysfunction. Deeper insight into the tissue-level biology will be necessary to elucidate this problem, but other emerging imaging techniques, such as the assessment of global ventricular fibrosis, may aid in the understanding of the mechanisms and time frame in which RVOT dysfunction leads to adverse RV remodeling.
Technologies for integrating anatomic and physiological MRI evaluation with catheterization-based procedures have also shown promise both for planning and performing interventions in patients with congenital heart disease and RVOT dysfunction and for evaluating the implications and outcomes of such interventions. For example, Dori et al. recently reported a method of fusing 3-dimensional MRI data sets to fluoroscopic imaging using internal registration markers, which may facilitate increasingly complex interventions in patients with complicated anatomy while simultaneously helping to reduce radiation exposure. The idea of MRI-guided interventions for congenital heart disease has been around for a number of years and has been applied in animal models and pilot human studies, usually in relatively simple lesions such as aortic coarctation. Aside from true MRI-guided intervention, hybrid MRI/fluoroscopic imaging facilities that allow rapid transit between an MRI magnet and fluoroscopy-guided catheterization have been shown to facilitate immediate physiological assessment of catheter-based interventions on the RVOT, which may not only aid in our understanding of the physiological effects of interventions but help define and guide appropriate therapeutic endpoints in individual patients. Within the context of disease that can vary so markedly from patient to patient, such technological integration may ultimately facilitate point-of-care decision making that is based on more comprehensive patient-specific data.

**Therapeutic Advances**

Although valved allografts have been the mainstay prosthesis for surgical PVR for decades, their limitations and drawbacks have been recognized, and the search for a better option has been underway for many years. More recently, in part as a result of improved anatomicopathological evaluation with MRI, there has also been an effort to understand how surgical factors other than the valve or conduit per se may affect outcomes related to the dysfunctional RVOT.

**Bioengineered Replacement Valves**

One of the most common choices for RVOT reconstruction has been allograft valved conduits, which have been used in this capacity for >35 years, usually after cryopreservation or other forms of treatment. Aside from the fact that the availability of allografts is inherently limited by virtue of their source (ie, human cadavers), they are subject to nearly inevitable degeneration and dysfunction, particularly when implanted in growing children. The mechanisms by which this occurs are incompletely understood, but 2 apparently important factors are lack of growth potential and an immunological response by the recipient against the allograft. One of the major goals and challenges in the science of valve replacement in recent years has been the development of more highly biocompatible valves and conduits that have the potential to grow. Although many such efforts have revolved around in vitro tissue engineering, other approaches also are being taken. In general, the most common approach to engineering a biocompatible pulmonary valve with growth potential is to seed cells onto a bioabsorbable scaffold in culture and to subject the graft to conditioning in a bioreactor. Many avenues have been followed in this quest, with endothelial cells, stem cells, amniotic fluid–derived cells, autologous progenitor cells, or other cells used to populate various scaffolds composed of bioabsorbable polymers, autologous tissue, or allograft or xenograft matrices. As this line of investigation has evolved, it has become apparent that dynamic culturing conditions that simulate the in vivo state provide superior endothelial cell coverage and more natural anisotropic tissue organization. Although encouraging preliminary results have been achieved with tissue-engineered valves and conduits in animal models, tissue-engineered valves have been implanted successfully in humans. In vitro tissue engineering has yet to reshape the clinical landscape for managing RVOT dysfunction.

Alternative approaches to modifying more traditional biological prostheses or developing biocompatible valves are also being pursued. In early studies, for example, fresh decellularized pulmonary allograft conduits showed promise as an alternative to standard cryopreserved allografts, although this approach addresses primarily biocompatibility rather than growth potential and does not circumvent the inherently limited availability, unless the same techniques can be translated to xenograft valves. Another approach to fabricating an autogenous prosthesis, which has been reported in animal models but not humans, is subcutaneous implantation of a silicon mold in the form of semilunar valve root with sinuses, leaflets, and vessel, which is encased in connective tissue that effectively grows into the desired 3-dimensional shape. This connective tissue prosthesis is then harvested and implanted in the RVOT where it is populated with autologous endothelial cells.

The promise of bioengineered heart valves continues to move closer to clinical reality, but for the time being, surgeons are left with various suboptimal options for prosthetic valve implantation within the dysfunctional RVOT. In this context, there are various ongoing efforts to use other therapeutic tools and strategies to improve outcomes related to the dysfunctional RVOT.

**Surgical RVOT Remodeling**

As more studies have been published on the physiological and clinical outcomes of surgical PVR, one of the vexing realizations has been that relieving PR and reducing RV volume alone do not seem to improve RV pump function or to reduce the risk of RV-related adverse outcomes in this patient population. In patients with a surgically reconstructed RVOT, particularly those with tetralogy of Fallot in whom the initial surgery included a transannular or subvalvar RVOT augmentation, there is inevitably some degree of scar and noncontractile patch/prosthetic material, which eventuate in both electrical and mechanical abnormalities.

A recently reported alternative approach to addressing the RVOT at the time of PVR in patients with a dilated RVOT and/or transannular patch is surgical excision of not only the noncontractile RVOT patch but also the adjacent infundibular scar and devitalized myocardium. To assess the potential benefits of this approach, Geva et al. performed a study in which patients with tetralogy of Fallot referred for surgical
PVR were randomized to undergo either standard resection of RVOT patch material or more extensive surgical remodeling along with valve implantation. The authors did not find any benefit of the more aggressive approach when it came to RV volume, function, or electrical characteristics. There are a number of possible reasons for this, and further work in this area is ongoing.

Transcatheter PVR
Transcatheter pulmonary valve (TPV) replacement was first reported in an animal model and then in humans in 2000 by Bonhoeffer et al. In early and midterm evaluations of their experience, Bonhoeffer’s group demonstrated encouraging outcomes, with few serious procedural adverse events, effective acute relief of RVOT obstruction and PR, and maintenance of pulmonary valve competence over several years. The initial US experience with this therapy was through an investigational device exemption protocol for the treatment of RVOT dysfunction with the Melody TPV (Medtronic Inc, Minneapolis, MN), in which the valve was implanted percutaneously in 150 patients at 5 US centers. Preliminary results from that trial were very similar to those reported in Europe, with excellent valve competence over 1 to 2 years in all patients and stable relief of RVOT obstruction in most. In a subsequent report, those results were sustained, and the freedom from RVOT dysfunction, defined as recurrent obstruction, moderate or greater PR, or reintervention, was 87±3% and 73±7% at the end of the 2- and 3-year evaluation windows, respectively.

One of the few concerns with the Melody TPV in early reports from Europe and the preliminary US experience was fracture of the balloon-expandable stent in which the valve is mounted. Stent fracture was also a relatively common finding in bare metal stents implanted in RVOT conduits, a therapeutic option used to treat RVOT conduit obstruction before the availability of TPV therapy and in conduits that are too small for currently available TPV devices. In a recent analysis of the US trial cohort, it was found that a fracture of the Melody valve stent occurred in 23% of patients within 1 year of implantation and in 40% of patients within 3 years, and that fracture with apparent loss of stent integrity occurred in 26% within 3 years. The risk of fractures was higher in patients with more severe conduit obstruction before TPV implantation and in valves that were implanted in high-risk mechanical environments, either apposed to the anterior chest wall or in settings that caused stent compression for other reasons. TPV implantation within a bare metal stent, which effectively increases the radial strength of the stents, was protective, even in the highest-risk implantation environments, namely, when the valve was directly apposed to the anterior chest wall and subject to compression from adjacent structures.

Although protruding before TPV implantation did not completely eliminate stent fractures, they were significantly less common, which may enhance the durability of transcatheter valves in some of the more challenging implantation environments.

The US trial included only patients with RVOT conduits within a certain size range and patients with predefined thresholds of RVOT dysfunction and PR. Although experience thus far is encouraging for TPV therapy in those limited circumstances, there is a much larger population of patients with repaired congenital heart disease and RVOT dysfunction in whom the RVOT is too large or otherwise outside the indications for use of the Melody valve. A number of devices designed for implantation into larger and anatomically diverse RVOTs are under development, but there is also interest in alternative off-label applications of approved valves that may extend their utility to a wider range of patients. For example, experimental studies and case reports have demonstrated the feasibility and physiological efficacy of implanting a TPV in each proximal branch pulmonary artery when complex anatomy precludes seating a device within the RVOT per se. Extending this concept, TPV implantation into only a single branch pulmonary artery might be beneficial in certain circumstances, given the finding that PR often arises with considerable asymmetry from the left and right pulmonary arteries. The clinical incentive to extend TPV therapy beyond the approved indications is further evidenced by other creative, off-label approaches to TPV replacement in patients with a large RVOT such as seating the Melody valve in a scaffold of bare metal stents that are anchored in the branch pulmonary arteries and extend proximally into the outflow tract.

The limits and long-term benefits and risks of TPV therapy have yet to be fully defined. In a study that included patients who underwent Melody valve implantation within various high-pressure environments in the pulmonary and systemic circulations, for example, it appeared that this valve may have utility in high-risk patients who do not otherwise fit standard implantation criteria such as those with pulmonary hypertension and patients with congenital heart disease and important dysfunction of other valves. Ultimately, this technology remains young, and additional data will be necessary to understand its place within the broader landscape of congenital heart disease associated with RVOT dysfunction. However, as our understanding of the indications for and outcomes of this therapy continues to advance and newer and better transcatheter valves enter the clinical arena, this disruptive technology will almost certainly force a paradigm shift in how we conceive of and manage postoperative RVOT dysfunction in congenital heart disease.

Disclosures
Dr McElhinney serves as an investigator, proctor, and consultant for Medtronic Inc., the manufacturer of the Melody valve.

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