Congenital heart disease (CHD) is the most common birth defect, affecting one in every 125–150 births, with approximately 40,000 children diagnosed with CHD every year in the United States. As a result of dramatic improvements in survival seen over the past several decades, there are now an estimated 1.5–2.0 million adults with CHD in the United States. When grouped together, lesions that require surgical correction of the right ventricular outflow tract (RVOT) are among the most common types of CHD. Typically, RVOT operations are performed early in childhood (as early as the neonatal period) and involve either a patch correction to relieve a stenotic outflow tract (e.g., Tetralogy of Fallot) or placement of a valved conduit or bioprosthetic valve in the pulmonary position. Unfortunately, no current operation offers a lifetime cure, as all artificial valves that have been placed in the RVOT will ultimately fail, either secondary to stenosis, regurgitation or a combination of both. This problem is exaggerated in children where an aggressive host response to bioprosthetic tissue, size constraints of a small thoracic cage, and somatic growth combine to limit the functional lifespan of bioprosthetic valves and conduits to only a few years in some cases. Thus, while surgical mortality for defects involving the RVOT have fallen dramatically over the past 20 years, the cumulative morbidity these patients must endure in the course of their lifetime remains high, often consisting of two to five open heart operations to re-replace the pulmonic valve by the time a patient reaches adulthood.

Fortunately, this less than optimal treatment algorithm has undergone a dramatic shift recently with the introduction of transcatheter pulmonary valve replacement (TPVR). First described by Philipp Bonhoeffer, MD, in 2000, the Melody® transcatheter pulmonic valve (Fig. 1) was the first percutaneous valve to receive humanitarian device exemption (HDE) approval* in the U.S. following a rigorous, prospective, multicenter trial centered upon treatment of dysfunctional RVOT conduits. This valve is constructed of a segment of bovine jugular venous valve whose walls have been thinned and sewn to the struts of a platinum-iridium stent. The device is crimped onto a simple but elegant self-sheathing, balloon-in-balloon delivery system that passes

*Continued on page 2 (see “Valve”)

Figure 1: The Melody valve is composed of a bovine jugular venous valve mounted within a platinum iridium stent (top). The valve after final balloon expansion as would be seen with implantation (bottom).
Valve: continued from page 1
easily from a femoral or jugular venous approach to the target area within the RVOT. Results from the initial clinical trial indicated a clinical success rate of 93 percent and a complication rate of 9 percent, with the majority of patients discharged within 24 hours.¹ The most frequent complication seen in our initial patient series was restenosis, nearly always secondary to fracture of the stent upon which the valve was supported.

We subsequently discovered that pre-treating the RVOT with aggressive balloon angioplasty and “pre-stenting” (placement of one or more stainless steel bare-metal stents into the target area prior to Melody valve implant) greatly reduced the incidence of stent fracture and restenosis.² As our experience with the Melody valve grew, we realized that it could be used to treat many other types of bioprosthetic valve dysfunction within the right heart as well as selected cases of native outflow tract dysfunction (i.e., patients who have had surgery on the RVOT but have no conduit or bioprosthetic valve in place).

In 2008, we implanted the first percutaneous valve to treat tricuspid valve dysfunction in a 10-year-old boy who had undergone numerous open heart operations since he was a newborn for treatment of severe Ebstein’s anomaly. We subsequently published the first worldwide multicenter experience of transcatheter tricuspid valve replacement, demonstrating an implant success rate of 100 percent with a reduction in tricuspid valve gradient from 12.9 to 3.9 mmHg (p<0.01) and regurgitation reduced to mild or none in all patients.²

While the Melody valve has provided thousands of patients with a viable alternative to repeated open heart surgery, it has some limitations, including small patient size (owing to the large size of the delivery system) and conduits which are simply too big to anchor the device in place. To combat the first of these, we have developed a unique hybrid technique where the cardiac surgeon provides direct access to the RVOT via a small incision in the apex or anterior wall of the RV, allowing the interventional cardiologist to pass the device directly into position under fluoroscopic guidance. Using this approach, we have successfully treated patients as small as 4 kg with this emerging technology. On the opposite end of the spectrum, some older children and adults have received surgical conduits that are simply too large in diameter to securely anchor the Melody valve, which has an upper delivery size of 22 mm. To combat this limitation, we have joined with only a few other sites nationwide in the COMPASSION II trial. This trial is designed to...

Figure 2: Melody deployment sequence. The Melody valve, mounted upon the delivery systems, is passed across the deteriorated valve within the RVOT and the protective sheath is slowly withdrawn (A–B). Once the sheath is withdrawn, the inner balloon is inflated to partially deploy the valve (C). After final positioning, the outer balloon is inflated, resulting in complete deployment of the valve (D).

Figure 3: Ten-year-old boy with severe RVOT conduit stenosis as demonstrated by three-dimensional rotational angiography (A) underwent RVOT pre-stenting and Melody valve implantation, resulting in marked improvement of the stenotic area (B). Standard two-dimensional lateral plane pulmonary angiography shows no evidence of Melody valve regurgitation (C), which is confirmed by intracardiac echocardiographic assessment of the Melody valve leaflets (D).
Renal Sympathetic Denervation for Hypertension

Florian Rader, MD, MSc

Hypertension (HTN) affects 70 million Americans, one billion people worldwide, and accounts for 50 percent of coronary heart disease and 70 percent of cerebrovascular disease. Despite a plethora of available antihypertensive medications, blood pressure (BP) remains above the recommended level of 140/90 mmHg in 50 percent of hypertensive Americans, whose risk of a cardiovascular event is threefold higher than if their BP were treated to goal. Therefore, a great interest exists in new treatment options that could eliminate the two main barriers against HTN control on a population level: (1) medication non-adherence and (2) physician inertia (i.e., the resistance of treating physicians to start or increase antihypertensive medications despite unmet BP goals). A novel catheter-based technique using low-energy radiofrequency to disrupt sympathetic nerve fibers that surround the renal arteries has emerged as a potential non-pharmacologic treatment option for resistant HTN, and is now being studied at Cedars-Sinai in a pivotal U.S. multicenter trial.

The link between sympathetic activation and essential hypertension has been demonstrated by regional norepinephrine spillover and direct measurement of sympathetic nerve activity with microelectrodes. A large body of literature has demonstrated the importance of the interplay between the kidneys and the sympathetic nervous system in the development of HTN: Efferent renal sympathetic nerves, which carry nerve impulses from the kidneys to the central nervous system, regulate central sympathetic output and therefore affect BP indirectly via cardiac output, adrenal epinephrine secretion and peripheral vasoconstriction. The modulation of central sympathetic output may have therapeutic implications in hypertensive comorbid disease processes known to be associated with high sympathetic tone.

For decades, medical and surgical therapies attempted to modulate sympathetic output in the treatment of HTN. Unfortunately, central sympatholytic medications did not perform well in clinical trials, and have a poor side effect profile, making them fifth-line therapy for most hypertensive patients. Surgical sympathectomy in the 1940s and 1950s successfully reduced BP, but was associated with high perioperative morbidity and mortality. In contrast, catheter-based renal sympathetic denervation can now be done in the cardiac catheterization lab with a low complication rate. From standard endovascular femoral artery access, the Symplicity® catheter is advanced under fluoroscopic guidance to the renal arteries (Fig. 1). Low-energy radiofrequency treatments are delivered from the catheter tip to disrupt sympathetic nerve fibers located just outside the renal arteries (Fig. 2). The procedure takes about 45 minutes and recovery is similar to standard cardiac catheterization.

Renal sympathetic denervation has been tested in one nonrandomized proof-of-concept study and one randomized clinical trial in Europe and Australia. These studies have shown a substantial office BP reduction of 32/12 mmHg at six months (Fig. 3). Recent data from 24-month follow-up studies of the Symplicity-HTN-2 trial confirmed a sustained effect on BP.

However, there were some inconsistencies in these trials. First, the BP-lowering effect on ambulatory blood pressure was only assessed in a subgroup of patients, and renal denervation had a much smaller effect on what is considered the gold standard medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation. 2010 Aug 5;122(5):507–16.

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of BP measurement. Second, a sham procedure was not performed in patients randomized to the control arm. This open label design could have introduced a significant bias. These shortcomings have been corrected in the ongoing double-blinded Symplicity-HTN-3 trial, in which a sham procedure is being performed in control patients and ambulatory blood pressure is being measured in all participants.

The safety profile of the procedure has been encouraging. Vascular access complications are rare but can occur. After hundreds of procedures performed worldwide, no procedure-related worsening of kidney function has been reported in patients with no more than mild kidney disease. However, a glomerular filtration rate of less than 45 currently disqualifies patients from undergoing the procedure. Recently, a small study demonstrated positive results for renal denervation in patients with more severe kidney disease,19 potentially expanding the currently limited target patient population in the future.

Other small hypothesis-creating studies identified potential secondary treatment benefits from reduced sympathetic tone after renal denervation: In patients with metabolic syndrome and obstructive sleep apnea, renal denervation improved glucose tolerance and the apnea/hypopnea index.14,15 There is also early evidence suggesting stabilization of atrial and ventricular arrhythmias after renal denervation.16,17 An exploratory trial studying the effects of renal denervation on left ventricular function in chronic heart failure is currently underway.18

While the Symplicity catheter is approved and supported by expert consensus19 in Europe and Australia, FDA approval for its use in the United States is pending the results of Symplicity-HTN-3. The Cedars-Sinai Heart Institute is currently enrolling patients with treatment-resistant HTN (defined as office systolic BP ≥160 mmHg while on maximum tolerated dose of three antihypertensive medications, including a diuretic). Due to stringent enrollment criteria, recruitment will continue for at least two more years, and results are not expected to become available before 2015.

In summary, renal sympathetic denervation is an exciting new approach to the treatment of hypertension. One of the critical questions left to be answered from ongoing clinical trials is whether renal sympathetic denervation will be a treatment option reserved for patients who failed medical therapy, or whether it might also be used for those with less severe hypertension, in whom the procedure potentially could be curative. Considering the rampant prevalence of hypertension as a major cause for cardiovascular disease worldwide, global health implications could be enormous.

References

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