Progress in Transcatheter Valve Therapy

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Myxomatous mitral valve disease is a significant cause of morbidity and mortality in dogs. It is the most common cause of cardiovascular death in canines. Approximately 7 million dogs in the United States are estimated to have cardiac disease; the majority of those cases are due to valvular disease. A significant portion of those animals have severe enough regurgitation to develop clinical signs and suffer chronic progression of the disease. As in humans with chronic valvular disease, despite years of clinical experience and clinical drug trials, there is no definitive medical treatment for the disease that will prevent the progression to CHF. As a result, surgery is the gold standard of treatment in people. The AHA/ACC and ESC guidelines for treatment of valvular heart disease state that mitral valve repair is the treatment of choice for patients with symptomatic severe MR. (1,2) However, many patients (estimated to be 50%) in USA and Europe do not undergo surgical repair for a variety of reasons. Interventional transcatheter valve devices and procedures have been developed to help address the unmet surgical need of those patients. The transcatheter devices tend to be constructed of some combination of a metal alloy, various polymers and biologic materials. They are designed to modify or repair the defective valve or insert a new valve within the defective native valve.

Surgical repair has also shown to be effective in reducing or eliminating regurgitations in dogs. (3,4) However, surgical replacement or repair of cardiac valves in dogs is rarely done due to the high cost, small number of existing surgical programs and technical barriers that inhibit new surgical valve programs from becoming established. The development of successful interventional transcatheter or transapical therapies for the treatment of valvular diseases in dogs could dramatically improve our success at treating these patients.

The human experience began with animal models. The potential for interventional transcatheter valves was first demonstrated by Andersen et al. in 1992, who implanted a porcine bioprosthesis attached to a balloon expanding stent at various aortic positions into closed chest pigs.(5) In 2000 Bonhoeffer et al successfully placed bovine jugular vein valves mounted on balloon expanding stents within the pulmonic outflow tract in lambs.(6) That same year the first human percutaneous valve replacement was performed by Bonhoeffer, where a transcatheter valve made from bovine jugular vein mounted on a platinum-iridium stent was successfully placed in a failed RVOT to PA surgical conduit.(7) This prototype was eventually developed into the Melody Transcatheter Pulmonic Valve (Medtronic) which was the first transcatheter valve device that was approved for use by the FDA. The valve has also been placed successfully within failed surgically implanted bioprosthetic valves in the mitral, aortic and tricuspid positions. (8)

Subsequently, most of the R&D efforts and investments have been made developing devices for the aortic and mitral valves in people. Billions of dollars have been invested in the effort to develop transcatheter aortic and mitral valve devices. There are now numerous companies with devices in clinical trials, first-in-man studies or animal studies, all vying to establish market share. Currently the market for transcatheter aortic valves is valued over $1B annually. The estimated market value for mitral valve devices once they are commercially available is $3-5B annually

Aortic Valve – After years of experimental animal work, in 2002 Alain Criber successfully placed the first transcatheter aortic valve in man. His company, Percutaneous Valve Technologies was bought by Edwards Lifescience in 2004. Today the Edwards-Sapien valve (Edwards Lifescience) and Core valve (Medtronic) are the two most commercially used devices for transcatheter aortic valve replacement (TAVR) for cases of severe aortic stenosis or severe aortic insufficiency. Both valves have good procedural results but serious complications can still occur including; death, bleeding, complete AV block and stroke. At 30 days, there was no difference in the rate of all-cause mortality, cardiovascular mortality, MI, stroke, or device success, as well as no major difference in the rate of major vascular complications or life-threatening bleeding events. The incidence of these adverse outcomes has decreased as more operator experience has been gained and additionally, there have been iterative modifications made to the devices over the last 10 years. (9, 10, 11) Worldwide, TAVR procedures are expected to exceed 300,000 per year by 2025. In the American Heart Association (AHA)/ACC Focused Update on Valvular Heart Disease published online March 10, 2017, TAVR was given a class I recommendation (Level of Evidence A) in patients with symptomatic severe AS who are at prohibitive or high surgical risk. Transcatheter aortic valve replacement (TAVR) has advanced rapidly and has become an accepted treatment for patients who are inoperable or at high risk for surgical aortic valve replacement . The procedure is now being evaluated in patients with intermediate risk for surgery (“risk creep”).

Mitral Valve - Device development for transcatheter mitral interventions have focused on mitral valve repair (TMVRe) or mitral valve replacement (TMVR). Repair devices that are in development include ones that fall into certain categories, including: leaflet plication, leaflet ablation, leaflet coaptation, in-direct annuloplasty, direct annuloplasty, chordal implants, and LV remodeling devices.

Ultimately the most successful transcatheter repair method may utilize a combination of repair techniques (i.e. annuloplasty, leaflet placation and chordal implants) to more closely mimic current open heart surgical repair techniques.

At this point in time the only approved mitral device is the MitraClip (Abbott) which is an MVRe device. The MitraClip works as a leaflet plication device by creating a double inlet mitral valve similar to the Alfieri suture technique that is performed surgically. The device is advanced into the left atrium via a femoral vein approach and atrial septal puncture. The device is maneuvered under 3D TEE guidance to stabilize and grab the anterior and posterior leaflets of the valve and then clip them together thereby reducing the regurgitant flow. In some cases a second or third clip may be placed if there is still significant MR seen on TEE. This device is used in both degenerative MR cases and functional cases. In the Everest II Trial, the MitraClip was shown to be non-inferior to surgical repair of 3+ or 4+ MR in high risk patients. The functional MR patients had less residual MR than the degenerative MR patients did when compared to the surgically treated patients. (12, 13, 14)

The other mitral valve approach is TMVR. There are many different designs in development. These devices utilize different stent designs and bioprosthetic valves and are delivered either transapically or transseptally. Some are at the first-in-man level of development. The other valves are still in the animal model stage of development. Transcatheter mitral valve replacement (TMVR) has not progressed as rapidly as TAVR. There are several reasons for this difference. First, as stated above, surgical mitral valve repair as opposed to replacement is the treatment of choice whenever possible in degenerative MR in order to maintain function of the mitral valve complex, including left ventricular function. Additionally, the aorta has a semi ridged wall structure to support placement of a device. The mitral valve complex is significantly more complex, both anatomically and physiologically, than is the aortic valve. Despite that level of complexity, there are numerous competing designs focusing on either repair or replacement that are in various stages of development. The early success of TMVR has faced many more challenges compared to TAVR. Mortality in the early first-in-man trials is much higher than what was seen with early TAVR studies, range from 25 to 48 %. (15, 16) Problems include LVOT obstruction, thrombosis and device dislocation. Many of the devices are undergoing iterative design changes to address these challenges.

VETERINARY PROGRESS

Tricuspid Valve - The Tucker Valve™ (Ultravet Medical Devices) is being developed by the author for placement in the tricuspid position in cases of severe tricuspid regurgitation (e.g. tricuspid dysplasia). The device is a leaflet coaptation device that can be placed through an 8 Fr delivery sheath. The device is anchored in the RV apex through active fixation. A small coaptation balloon is inflated within the RV cavity and extends across the tricuspid annulus. The valve is still in the prototype stage and has been placed in three clinical cases for a proof of concept study. Significant reduction of the tricuspid regurgitant jet was achieved in all three cases. Results of that study were presented as an abstract at a previous ACVIM Forum. The small profile of the valve also makes it feasible for use in the mitral position via a trans-septal approach.

Mitral Valve – Current veterinary devices in development and testing for degenerative mitral valve disease fall into three categories: valve replacement (MitralSeal™), chordal replacement (Harpoon™) and leaflet coaptation (CoApt Valve™). The MitralSeal and Harpoon are both transapical devices, whereas the CoApt Valve is delivered by a transseptal approach. (17) The MitralSeal is a self-expanding bioprosthesis with an atrial cuff and a ventricular tether anchoring system. The Harpoon device is an ePTFE chordal replacement system. Both devices are hybrid surgical-transcatheter systems requiring a small thoracotomy and collaboration between a veterinary surgeon and cardiologist to place the device. The CoApt Valve can be place by an interventional cardiologist with a combination of fluoroscopic and TEE guidance.

The CoApt Valve (Ultravet Medical Devices), designed by the author, is a self-expanding nitinol anchoring system that has a skirt consisting of SIS (porcine small intestinal submucosa) that increases leaflet coaptation to reduce or eliminate the regurgitation. Bench-top testing of the CoApt Valve in a pulse duplicator reduced regurgitation in a mitral model from a regurgitant fraction of 80% to 20% (which meets FDA requirements for valve design). Positive results have also been demonstrated in laboratory animal testing. The next step in development for the CoApt Valve is a multicenter clinical trial which will be enrolling patients into two arms. The trial design will compare matched populations with severe mitral regurgitation. One arm will receive optimal medical therapy and the other will have the CoApt Valve implanted. Primary end-points of the trial include hospitalization for CHF or death.

Future Development

Multiple iterations may be needed before any of these veterinary devices are ready for commercial use. Additionally, other devices should be developed in the future for veterinary use to treat some of the conditions we commonly see in veterinary cardiology. We have plenty of unmet clinical need in the veterinary space that could be addressed and treated by veterinary specific device development programs. If the human experience can act as a guidepost, we must realize that interventional device development takes time and one must expect failures along the way and learn from them; but in the long run progress and success can be achieved.

References: [1] Nishimura RA, et al. **J Am Coll Cardiol**. 2008;52(8):676-685. [2] **Eur Heart J** 2012 & **Eur J Cardio-Thoracic Surg** 2012. [3]Griffiths LG, et al. **J Am Vet Med Assoc** 2004;224:1941–1945. [4] Masami U. et al. (2012) **J Am Vet Med Assoc 240**:10, 1194-1201. [5] Andersen HR, et.al. **Eur Heart J** 1992;13:704–8. [6] Bonhoeffer P, et al. **Circ** 2000;102:813– 6. [7] Bonhoeffer P, et al. **Lancet** 2000;356:1403–5. [8]Hasan BS, **Circ Cardiovasc Interv**. 2011 Dec 1;4(6):615-20. [9] Grube E, et al. **J Am Coll Cardiol** 50 2007 69-76. [10] Moynagh AM, et al. **J Am Coll Cardiol**. 2011;57(5):634-635. [11]Smith CR, et al **N Engl J Med** 2011; 364:2187-2198. [12]Ussia GP, **Inter J Cardio** 2012: 155(2) 194-200. [13] Feldman, T., et al. **ACC late breaking clinical trial** (2010). [14]Thomas M, et al.**Circulation**. 2011**;** 124: 425-433. [15] Maisano F, et al. **Eur Heart J** 2015;36: 1651–9. [16] Van Mieghem NM, et al. **J Am Coll Cardiol** 2010;56:617–26. [17]Orton C, **ACVS Veterinary Symposium** 2011:311-312