Guest Lecture

The Odyssey of TAVR

from Concept to Clinical Reality

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On 16 April 2002, my colleagues and I performed, in an inoperable and desperately ill man with critical calcific aortic stenosis (AS), the first clinical percutaneous implantation of an aortic valve bioprosthesis. As of 2013, more than 80,000 patients have been treated; and transcatheter aortic valve replacement (TAVR), so strongly criticized by all the experts throughout the early years, continues to grow in parallel with its constant technological improvements. Transcatheter aortic valve replacement can now be recognized as a medical breakthrough. It is a revolutionary technology that meets an unfulfilled clinical need for a common disease, is validated by rigorous evidence-based studies, and is applicable worldwide. We report here the main phases of this 20-year odyssey and briefly consider the prospects of TAVR, which remains in continuous development.

Balloon Aortic Valvuloplasty: Meeting an Unfulfilled Clinical Need

The high prevalence of degenerative AS is well documented: approximately 5% to 7% of people above the age of 65 have moderate-to-severe AS, and the prevalence increases with age.[1,2] Because of our aging population, the optimal treatment of AS has turned into an important healthcare concern. In the absence of any effective medical option, open-heart surgical aortic valve replacement (SAVR) has been the standard of care for decades. In view of the natural course of the disease (survival usually does not exceed 3 years after the onset of symptoms), the recommendation since 1968 has been to perform SAVR promptly after the onset of even minor symptoms.[3] However, several surveys, including the well-known EuroHeart Survey of 2004,[4,5] have shown that more than one third of patients eligible for SAVR are for many reasons (chief among them advanced age and comorbid diseases) denied surgery and left untreated. In the 1980s, age above 70 years was by itself considered sufficient to deny SAVR; this practice pushed us to consider a less invasive option for the management of the large population of patients with inoperable AS.

The catheter-based procedure of balloon aortic valvuloplasty (BAV) was developed by us in 1985 to offer a solution for such patients. The first patient treated with BAV, in September 1985, was a highly symptomatic 72-year-old woman who had been denied SAVR because of her age and concomitant coronary artery disease. After BAV, she remained asymptomatic for 2 years. The reported results[6] of our first series of patients (who had been denied SAVR but subsequently were treated with BAV) were received enthusiastically by the medical community. However, after thousands of such treatments worldwide and despite marked mid-term improvement in quality of life, it became clear that BAV by itself was insufficient to alter the natural evolution of AS.[7] The main limitation of BAV was a high rate of restenosis, which affected 80% of patients at one postoperative year.[8,9] For these reasons, BAV was progressively discarded. In the early 1990s, finding a solution to this problem became for us a passion.

Birth of the Idea of TAVR

The concept of TAVR emerged from the routine observation that high-pressure balloon inflation (4–5 atm) could open all calcified aortic valves in a circular fashion. Not only might a balloon-expandable stent with a high radial force be expanded within the native valve to prevent restenosis, but a valvular structure might be inserted within the stent to mimic native valve function. This combination of stent frame and valvular structure might make possible the replacement of the aortic valve by using mini-invasive catheterization techniques, even though the idea was particularly challenging. Over the past half century, several animal studies[10-14] did indeed explore the implan-

tation of nonsurgical heart valves. In 1992, Andersen and colleagues,[15] using a hand-made porcine valve contained within a metallic mesh, first reported successful implantations of a stented valve at various cardiac sites in a pig model. However, none of these animal studies proceeded to human application. The first human implantation of a percutaneous stented valve (a bovine jugular valve sewn within a large balloon-expandable stent) was performed in 2000 by Bonhoeffer and colleagues[16] in a pediatric patient who had a degenerated right ventricle-to-pulmonary artery conduit.

In 1993 and 1994, we implanted 12 Palmaz stents, each 23 mm in diameter, in 12 fresh specimens of calcific aortic valve and thereby circularly opened each native valve, regardless of the amount of calcification. The ideal height of the stent appeared to be 14 to 16 mm, to avoid impinging on the coronary ostia, the intraventricular septum, or the anterior mitral valve leaflet, thereby duplicating the subcoronary position of any surgical bioprosthesis. The stents were well anchored within the aortic annulus and would have required a high traction force (>2 kg) to be dislodged and embolized. Although this study validated the concept of aortic valvular stenting in a model of human calcific AS and was therefore a milestone, the stented-valve prosthesis and its physical properties did not extend beyond drawings and hand-made models that corresponded to our expectations.

Over the following 4-year period (1995–1999), the search for a biomedical company that might be interested in the project failed completely. Experts consistently cited a long list of engineering issues and potential complications, including coronary obstruction, aortic and mitral valve complications, early dislodgment of the device, stroke, and mechanical complications. Some even declared the project "the most stupid I've ever heard."

First Prototypes of Transcatheter Aortic Valve and Experimental Results

To accomplish this venture, we formed our own start-up company, Percutaneous Valve Technologies (PVT, New Jersey) in 1999. Engineers from Israel designed the first models of a balloon-expandable transcatheter heart valve (THV). In doing so, they had to integrate several challenging technologies: a balloon-expandable stent, a balloon for predilation and stent expansion, a valvular structure, and a delivery system. They had to accomplish the following highly challenging goals: 1) make a prosthesis consisting of a highly resistant frame containing a valve structure that could be homogeneously compressed (for transfemoral insertion) to 7–9 mm over a high-pressure balloon and then expanded to a diameter of 23 mm by balloon inflation, without damage to the frame or leaflets; and 2) choose the valve material, its method of attachment to the frame, and the valve design itself (uni-, bi-, or trileaflet) to best provide strength, low profile, and durability. The first "finalized" device consisted of a stainless-steel stent, 23 mm in diameter and 17 mm in height, which contained a trileaflet valve (at first made of polyurethane, but soon changed to bovine pericardium). The device was compatible with a 24F (8-mm) introducer sheath.

The method of delivering the valve accurately, within the calcified valve of a beating heart, was yet another issue.

With the help of my collaborator Helene Eltchaninoff, experiments on a sheep model began in September 2000. Through the brachiocephalic trunk, we achieved the first successful implantation of a THV within a native aortic valve, with excellent results. The presentation of this first case at various meetings was the tipping point at which the medical community began to take notice and to show enthusiasm. More than 100 sheep implantations at different cardiac sites were subsequently performed by us. In the course of this experiment, substantial improvements in the THV, delivery systems, and implantation techniques were achieved. We also conceived an original model for the chronic evaluation of the THV in the systemic circulation,[17] which showed the persistence of excellent valve function and the integrity of the THV on pathologic examination at 5 months.

First Human Implantation

The memorable day of the first implantation in a human being was 16 April 2002.[18] Three days before, a 57-year-old patient with severe AS had presented in cardiogenic shock with major left ventricular dysfunction (ejection fraction, 0.12), severe AS, and multiple comorbidities that contraindicated SAVR. After failed emergent BAV, TAVR was proposed as the last-resort option for this relatively young patient. The indication was particularly challenging in this critically ill man, who also had subacute leg ischemia arising from an aortofemoral bypass occlusion—together with severe contralateral atherosclerosis that prevented transfemoral retrograde access. The procedure was performed with my collaborators Helene Eltchaninoff and Christophe Tron, using an unplanned antegrade transseptal approach. In spite of this unplanned approach, each step of the procedure was amazingly straightforward. After the implantation, hemodynamic and echocardiographic results were considerably improved, with no transvalvular gradient and a return of blood pressure to normal, enabling the discontinuation of vasopressors. There was no impairment of the coronary ostia or the mitral valve, no atrioventricular block, and only mild paravalvular aortic regurgitation (AR), which corresponded well with our 1994 autopsy findings.

The international reaction to this spectacular case after the first report[18] defied imagination. Clearly, this

first clinical case can be considered a breakthrough in the history of interventional cardiology.

First Rouen Series of TAVR: Compassionate Use

After 3 other human cases, our center initiated 2 successive feasibility trials[18,19] restricted to compassionate use, which applied a modified valve structure (equine pericardium). These studies confirmed the feasibility of TAVR via the transseptal approach with elevated success rates (85%) and durable postprocedural hemodynamic and functional improvements. Although some patients died of their severe comorbidities shortly after implantation, others survived for up to 6.5 years, with no complication or prosthesis dysfunction. A striking example is that of an 84-year-old woman in whom TAVR was performed as a last-resort option. One year later, she was able to travel from Paris to Washington, DC, to appear on stage at the 2004 Transcatheter Cardiovascular Therapeutics meeting, as the first 1-year post-TAVR patient. Protocol extension to other centers in Europe, the United States, and Canada was started, but the antegrade delivery was associated with substantial technical complexity and adverse outcomes. Obviously, further expansion of TAVR required technical improvements, procedure simplification, and friendlier approaches.

The Input of Edwards Lifesciences

The acquisition of PVT by Edwards Lifesciences (Irvine, Calif) in 2004 enabled rapid improvements to the TAVR bioprosthesis and the delivery systems, and the development of new approaches. The Edwards SAPIEN valve (initially the Cribier-Edwards valve) consisted of a trileaflet bovine pericardium valve, pretreated to decrease calcification and mounted in a balloon-expandable stainless-steel stent. The prosthesis became available in 2 sizes: 23 and 26 mm, the larger size having been designed as a solution to the high degree of paravalvular AR frequently observed in the Rouen series. The delivery system incorporated a deflectable retroflex catheter, conceived for the transfemoral retrograde approach and initially evaluated by Webb and colleagues[20] in Vancouver. Simultaneously, the minimally invasive transapical approach was developed with use of another delivery system (Ascendra Balloon Catheter), evaluated by Walther and associates[21] in Leipzig. Several European feasibility studies (REVIVE, PARTNER, and TRAVERSE trials) were set to evaluate these new technologies and approaches. The satisfactory results of these trials, despite specific complications with the 2 approaches, led to a growing acknowledgment and considerable expansion of TAVR worldwide. Since 2004, a concurrent device, the CoreValve® (Medtronic, Inc.; Minneapolis, Minn), a self-expandable nitinol frame containing a porcine pericardial valve, has also been developed.[22] This device could be inserted via a transfemoral approach through smaller-diameter sheaths (21F, then 18F) than those required for Edwards devices (22F and 24F). As an alternative to femoral delivery, subclavian access is proposed for the CoreValve. Feasibility studies on the Edwards SAPIEN and the CoreValve resulted in both models' obtaining the CE (Conformité Européenne) mark in 2007.

From Feasibility Trials to Real Life

Thereafter, acceptance and expansion of TAVR has been striking, with an annual 40% increase in the number of procedures. Numerous post-marketing national and international registries of the 2 models of bioprosthesis have enrolled several thousand elderly patients, all inoperable or at high risk, in accordance with the recommendations of European and U.S. Societies of Cardiology and Cardiothoracic Surgery.[23] These registries have included single-valve evaluation: for example, the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry,[24] which since 2007 has enrolled 1,123 patients receiving transfemoral or transapical TAVR; the Evaluation of the Medtronic CoreValve System in a "Real-World" (ADVANCE) Registry (presented at the EuroPCR meeting, Paris, 21-24 May 2013), which included 1,015 patients enrolled at 44 centers; 2-valve evaluations, such as the French Aortic National CoreValve and Edwards (FRANCE) registry[25]; and the FRANCE 2 registry,[26] which reported the French experience in a series of 3,500 patients—the largest and most exhaustive clinical overview of TAVR.

These registries have contributed to a better appraisal of patient screening, technical methods, and complications. The procedural success rate has increased to over 95%, while advanced technologies, together with immediate and long-term results, have kept improving. The hemodynamic results have compared favorably with those of surgical valve replacement in similarly ill patients. The results of TAVR have become more predictable, and the mortality rate in the SOURCE registry[24] (after transfemoral implantation) decreased to 6%–10% at 1 month and 20% at 1 year. A dramatic and long-lasting improvement in quality of life[27] was observed in all registries and was further confirmed in the remarkable and only evidence-based evaluation of TAVR (the Edwards SAPIEN device): the pivotal PARTNER (Placement of Aortic Transcatheter Valves) trial in the U.S.

From 2007, 1,056 high-surgical-risk patients enrolled in 26 centers in the U.S. have been assigned to either of 2 arms: a surgical arm (cohort A) in which transfemoral or transapical TAVR was compared with traditional SAVR; or a nonsurgical arm (cohort B) in which TAVR was compared with medical therapy (including BAV). Briefly, the results confirmed the high superiority of TAVR over medical treatment for inoperable patients,

with an absolute increase in survival rate of 20% at 1 year, and the noninferiority of TAVR versus SAVR in high-risk operable patients in terms of all-cause death and repeat hospitalization at 1 year.[28-31] Similar results were reported at 2 and 3 years.[31] In view of these results, TAVR was approved by the U.S. Food and Drug Administration (FDA) for these indications. Subsequent to FDA approval, many centers have been certified to practice TAVR in the U.S., the current number reaching about 250 centers. To obtain the approval of the FDA is for any new medical technology an almost inaccessible objective. In our case, it was achieved after a long and bumpy road, 20 years after the concept of TAVR was introduced, and 10 years after the first human implantation. We are proud of it.

The further improvement of TAVR arose on the remarkable translational pathway between engineers and physicians, aimed at improving the technological aspects of TAVR while reducing the complications. Severe vascular sequelae (3%–16%), stroke (2%–7%), paravalvular AR (5% were >grade 2), and complete heart block requiring a pacemaker (Edwards, 3%–12%; CoreValve, 16%–35%) were the leading factors.[32] Improvements were achieved by creating new models of both the bioprosthesis and delivery systems, decreasing sheath sizes, offering better coverage of the annulus (additional valve sizes), and facilitating sealing and positioning of the bioprosthesis. In parallel, additional technologies were developed for patient screening and procedures (new multimethod imaging technologies), vascular complications (improved vascular closure devices), and stroke (embolic protection devices). Even the procedural "milieu" was modified with the development of a "hybrid environment" that enabled the integration (in the same setting) of interventional and surgical therapies. This shows the considerable impact of TAVR on the medical industry.

The Future of TAVR

In 2014, innovations in valves and delivery system are ongoing. The Edwards SAPIEN bioprosthesis has been replaced in Europe by the SAPIEN XT device, comprising a highly resistant cobalt-chromium stent frame, improved valve and leaflet design, an additional size (29 mm), and implantation with a new delivery system that is compatible with much smaller sheath sizes (16F–20F). This leads to a potential increase of transfemoral access to about 85% of cases. Subsequently, transfemoral TAVR is now increasingly performed via a pure percutaneous minimal approach, with local anesthesia leading to improved patient comfort and early discharge from the hospital (after 1 to 3 days). This device has been evaluated in the large (2,166 patients) multicenter SOURCE-XT registry (presented at the EuroPCR meeting, Paris, 21-24 May 2013), which reported a decrease in all-cause and cardiac mortality rates at one year to 19.5% and 10.8% respectively, among the highest reported survival rates for TAVR. Reduction of sheath size has significantly reduced the rate of vascular complications. New models of the Edwards bioprosthesis, the SAPIEN 3 and the CENTERA, are being investigated in Europe and will be launched early in 2014. The SAPIEN 3, which shows highly promising results, has been specifically designed to reduce paravalvular AR (new sealing cuff) and vascular complications (sheath size reduced to 14F). Simultaneously, the CENTERA will be available as a self-expanding device that also uses a small 14F introducer sheath. The new CoreValve® Evolut™ device (Medtronic) has been modified in height and in shape of the frame to improve anatomic fit and sealing. There is no doubt that these improvements will contribute to further expansion of TAVR in the near future.

A number of next-generation transcatheter valves, markedly different from existing devices, are in early clinical evaluation. They incorporate features to reduce delivery catheter profile, to facilitate repositioning and retrieval, and to reduce paravalvular AR. It is too early to say whether these new bioprostheses will represent the future of TAVR, but these advances create active and stimulating competition, which is in essence positive.

Transcatheter aortic valve replacement, now in the guidelines of the European Society of Cardiology and the European Association for Thoracic Surgery,[33] is indicated for patients with severe symptomatic AS who are not suitable for surgery, as determined by a multidisciplinary heart-valve team comprising cardiologists, cardiac surgeons, imaging specialists, anesthetists, and other specialists, including geriatricians. In addition, TAVR should be considered in high-risk patients who might be candidates for surgery, but in whom a less invasive approach is favored in accordance with individual risk profile. In the U.S., TAVR is similarly recommended in patients with prohibitive surgical risk (estimated risk of death or irreversible morbidity, or other factors, including frailty).[34]

In the near future, TAVR might be extended to younger, lower-risk patients, as recent observational reports would indicate.[35] More evidence-based clinical data should soon be provided by the ongoing Surgical Valve Replacement versus Transcatheter Aortic Valve Implantation (SURTAVI) trial with the CoreValve in Europe, and by the PARTNER II valve trial with the SAPIEN XT device in the U.S. Other forthcoming indications for TAVR might include its use for failing surgical bioprosthetic valves (valve-in-valve). In this indication, TAVR is particularly appealing because it can achieve adequate valvular function for symptomatic relief, without prolonged recovery.[36] For the time being, the long-term durability of the THV has not been confirmed. What we do know, however, is very encouraging. Normal valve function has been reported more than 5 years

after TAVR[37] and, as an anecdote, we might observe that one of our patients has reached the longest clinical follow-up so far (8 years) with no change in hemodynamic status and no device deterioration.

Conclusions

The successful development of TAVR has been a 20-year journey from concept to the real world. The procedure appears today to be a breakthrough technology that has enabled thousands of patients with severe AS to receive a life-saving alternative treatment to SAVR. Further technological improvements will soon make TAVR simpler and safer. Within 10 years, TAVR might become the treatment of choice for most patients with symptomatic AS.

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