IMPACT OF NATIVE AORTIC VALVE RESECTION PRIOR TO PERCUTANE

AORTIC VALVE REPLACEMENT

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LIST OF ABBREVIATIONS

AVR	Aortic Valve Replacement
BV	Balloon Valvuloplasty
CABG	Coronary Artery Bypass Graft
CE	Community European
DW	Diffusion Weighted
DW-MRI	Diffusion Weighted-Magnetic Resonance Imaging
EOA	Effective Orifice Area (of a heart valve)
F	French (diameter size)
FU	Follow Up
L	Litre (volume)
LA	Left Atrium
LAD	Left Anterior Descending (coronary artery
LBB	Left Bundle Branch
LBBB	Left Bundle Branch Bloc
LM	Left Main coronary artery trunk
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
MRI	Magnetic Resonance Imaging
N	Newton (force)
NYHA	New York Heart Association
PPM	Permanent PaceMaker
PPMM	Prosthesis/Patient MisMatch
PVL	ParaValvular Leak
RBB	Right Bundle Branch
RBBB	Right Bundle Branch Bloc
STS	Society for Thoracic Surgery
TA	Trans Apical access

TAVI	Transcatheter Aortic Valve Replacement
TEE	Trans Oesophageal Echocardiogram
TF	Trans Femoral access
W	Watt (power)
YAG	Yttrium Aluminium Garnet (laser)

CHAPTER 1 : HISTORY OF THE HEART VALVE SURGERY

Secret dissections of cadavers in 15th centuries resulted in beautiful anatomical drawings of the heart and the arterial system. Leonardo da Vinci (1) in 1513 initiated the knowledge and the understanding of the aortic valve. He already drawn the tricuspid morphology of the aortic valve (Fig 1).

A few years later in 1543 the works of Andreas Vesalius (2) permit a wider understanding of the heart and the blood circulation (Fig 2).

However despite of the interesting work of many pioneers like William Harvey who marked the beginning of modern cardiology in 1628 (3) surgery of the heart was taboo. A warning and discouraging atmosphere was expressed by leading surgeons. During a speech in Vienna Medical Society meeting in 1880, Professor Theodor Billroth said: "*A surgeon who tries to suture a heart wound deserves to lose the esteem of his colleagues*". It is in September 1896 that Ludwig Rehn a surgeon from Frankfurt made the first successful suture of a heart wound and published it a year later in Archiv Fur Klinische Chirurgie (4).

The first clinical attempt to open a stenotic valve was carried out by Theodore Tuffier on July 13, 1912 (5). Tuffier used his finger to reach the stenotic aortic valve. He was able to dilate the valve by supposedly pushing the invaginated aortic wall through the stenotic valve. The 26-year-old patient recovered and

Figure 1

Leonardo da Vinci drawing and notes on the valve of the heart in 1513.

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returned to his home in Belgium. One must be sceptical as to what was accomplished. Russell Brock attempted to dilate calcified aortic valves in humans in the late 1940s by passing an instrument through the valve from the innominate or another artery (6). His results were poor, and he abandoned the approach. During the next several years, Brock and Bailey et al used different dilators and various approaches to dilate stenotic aortic valves in patients. Mortality for these procedures that were often done in conjunction with mitral commissurotomy was high (7,8).

Harvey Cushing attempted to create mitral stenosis in dogs but was not successful (9). He encouraged Elliott Cutler, a young surgeon working with him, to continue. In collaboration with a Boston cardiologist, Samuel Levine, Cutler worked 2 years on a mitral valvulotomy procedure in the laboratory (10). Their first patient was a desperately ill 12-year-old girl who was confined to bed for 6 months before operation. She underwent successful valvulotomy on May 20, 1923, using a teratomy knife. Unfortunately, most of Cutler's subsequent patients died because he created too much regurgitation with his valvulotome, and he soon gave up the operation. In 1925 Mr Souttar, an English surgeon, successfully performed a mitral valvulotomy using his finger to fracture the commissures in a young female who had been bedridden for 6 months (11).

In 1961 Dr Dwight Harken wrote Henry Suttar a letter and asked him why he did not continue with his mitral valvuloplasty. He replied: "*Thank you so much for your very kind letter. I did*

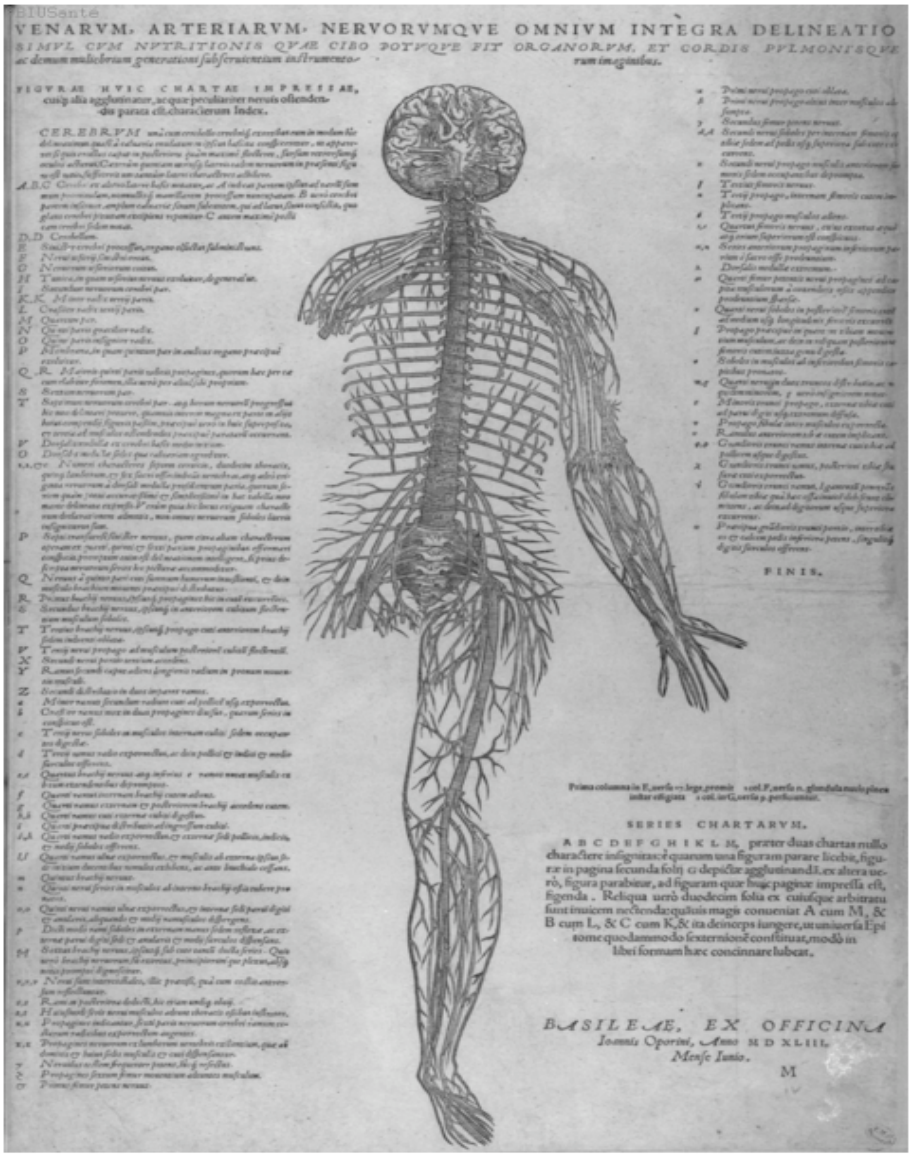

Figure 2

Andreas Vesalius images from "De humanis Corporis Fabrica" illustrating the human heart and blood circulation.

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not repeat the operation because I could not get another case. Although my patient made an uninterrupted recovery, the physicians declared that it was all nonsense and in fact the operation was unjustifiable. In fact, it is of no use to be ahead of one's time...." (12).

In Charles Bailey's 1949 paper titled "The Surgical Treatment of Mitral Stenosis," he states, "After 1929 no more surgical attempts on mitral stenosis were made until 1945. Dr Dwight Harken, Dr Horace Smithy, and the author recently made operative attempts to improve mitral stenosis. Our clinical experience with the surgery of the mitral valves has been 5 cases to date. During the past 8 years, the author and his associates have performed operations on the mitral valves of 60 mongrel dogs. (13). Bailey goes on to state several conclusions from their animal research. He then describes his five cases, four of whom died and only one of whom lived a long life.

Bailey's based in Hahnemann Hospital, refused to allow him to attempt any more mitral commissurotomy after two deaths. He became known as the "butcher of Hahnemann Hospital." However, his cardiologist Dr Durant, continued to support him. On June 10, 1948, Bailey scheduled cases 4 and 5. The patient operated on at Philadelphia General Hospital in the morning died (case 4). The surgical team regrouped and rushed to Episcopal Hospital, where the second operation was started promptly before the bad morning news was known and before the hospital administration forbade the procedure. The surgery was completed, and 1 week later Bailey brought the patient by

train 1000 miles to Chicago, where he presented the woman to the American College of Chest Physicians (14). A few days after Bailey's success, on June 16 in Boston, Dr Dwight Harken successfully performed his first valvulotomy for mitral stenosis. Three months later, Russell Brock in England did his first successful clinical case. He did not report this, however, until 1950, when he described success with six patients (15).

Thomas Holmes Sellers performed the first successful pulmonary valvulotomy on December 4, 1947. A systemic pulmonary artery shunt was planned on the left side, but the attempt was abandoned in this patient with severe tetralogy of Fallot and advanced bilateral pulmonary tuberculosis (16). The pericardium was opened. Dr Sellers could feel the stenotic valve each time it pushed through the pulmonary trunk during ventricular systole. Sellers used a tenotomy knife, which he passed through the right ventricle to perform the valvulotomy. The patient made a good recovery and was markedly improved.

In the early 1950s, Charles Hufnagel, in Washington, DC, and J. M. Campbell, in Oklahoma, independently developed and implanted artificial valves in the descending aorta of dogs. The valves consisted of a mobile ball inside a Lucite case (17,18). After presenting this first model of a mechanical prosthesis at the American College of Surgeons meeting in 1949, Hufnagel applied this concept clinically for the treatment of aortic valvular insufficiency. In his first clinical paper published in Surgery in 1954 Hufnagel reported a series of 23 patients starting September 1952 who had this operation for aortic insufficiency.

There were 4 deaths among the first 10 patients and 2 deaths among the next 13. Hufnagel's caged ball valve, which used multiple-point fixation rings to secure the apparatus to the aorta, was the only surgical treatment for aortic valvular incompetence until the advent of cardiopulmonary bypass and the development of heart valves that could be sewn into the aortic annulus position (19).

The first surgical treatment of multiple valvular diseases was by Trace et al (20). After closed mitral commissurotomy on May 2, 1952, in a 24-year-old woman, the surgeon noted that the right auricular appendage was gravely distended and pointed directly toward the left. Its pulsation was noticed and it was quite blue-purple in colour. The purse-string was being placed around the appendage in order to explore it when the patient's heart became arrhythmic. It was deemed advisable to terminate the surgical procedure at this point. The patient did poorly postoperatively. In the 2 weeks after the first operation, a tricuspid commissurotomy was performed. The patient made a good recovery and at 1-year follow-up remained improved.

Brofman performed combined mitral and tricuspid commissurotomy in 1953 (21). Likoff et al reported a series of 74 patients who had combined aortic and mitral valve commissurotomy in 1955 with up to a 2-year follow-up (22). Walton Lillehei was the first to report repair of multiple valvular lesions using cardiopulmonary bypass. On May 23, 1956, he successfully performed an open mitral commissurotomy and aortic valvuloplasty in a 52-year-old man with mitral stenosis

and combined aortic stenosis and incompetence (23). Borman performed a quadruple valve commissurotomy in October 1973 in a 12-year-old Israeli girl with stenosis of all four valves (24).

Cardiac valve repair or replacement under direct vision awaited the development of the heart-lung machine. The first successful aortic valve replacement in the subcoronary position was performed by Dr Dwight Harken and associates (25). A caged ball valve was used. Many of the techniques described in Harken's 1960 report are similar to those used today for aortic valve replacement.

That same year, Starr and Edwards successfully replaced the mitral valve using a caged ball valve of their own design (26). Starr later wrote : "In 1958, Lowell Edwards presented himself in my office with a proposal to develop an implantable artificial heart. I learned that he was a retired engineer with considerable financial resources. His visit was fortuitous, because just about that time, I had become interested in valvular prostheses.... Edwards agreed to begin the project by working on one valve at a time.... The obvious direction then was towards the ball valve prosthesis. I drew out for Edwards the general configuration of the Hufnagel valve. He then drew out for me how he thought that particular valve could be adapted for intracardiac use using an open cage. The first animal to have this implant survived for more than a year, but all other subsequent animals died of thrombosis.... The big breakthrough came at the end of 1958 when we developed the silastic shield for the ball valve, which allowed an 80 per cent long-term survival.... A silastic shield

over the area where thrombus formed on the valve would give us a chance to have long-term survivors." (27)

In 1964, Starr et al reported 13 patients who had undergone multiple valve replacement (28). One patient had the aortic, mitral, and tricuspid valves replaced on February 21, 1963.

By 1967, nearly 2000 Starr-Edwards valves had been implanted, and the caged ball valve prosthesis was established as the standard against which all other mechanical prostheses would be compared.

In 1967 Donald Ross reported on the first successful aortic valve placement with an aortic valve homograft (29). Some groups advocate the technique of aortic valve replacement with a pulmonary autograft initially described by Ross for younger patients who require aortic valve replacement. An aortic or pulmonary valve homograft is used to replace the pulmonary valve that has been transferred to the aortic position.

Other autogenous materials that have been used to manufacture valve prostheses include pericardium, fasciae latae, and dura mater. In the 1960, Binet et al began to develop and test tissue valves (30). Carpentier later wrote, "*In 1964 as a young resident in thoracic surgery, I was asked by J. P. Binet, chief of the service, to collect homograft valves from cadavers. Studies of the anatomy of the valves in various animal species showed that the valves from the pigs were the closest to those of humans*." Carpentier et al revitalized interest in xenograft valves by fixating porcine valves with gluteraldehyde. Carpentier

also mounted his valves on a stent, to produce a bioprosthesis. Carpentier-Edwards porcine valves and Hancock and Angell-Shiley bioprosthesis became popular and were implanted in large numbers of patients (31).

With the development of cardiopulmonary bypass, valves could be approached under direct vision, and for the first time mitral insufficiency could be attacked by reparative techniques. Techniques for mitral annuloplasty were described by Wooler (32), Reed (33) and Kaye (34).

The next step forward was development of annuloplasty rings by Carpentier and Duran. In the 1970s, few groups were involved in valve repairs. Slowly, techniques evolved, were tested clinically, and were followed over the years. Carpentier led the field by establishing the importance of careful analysis of valve pathology, described in detail several techniques of valve repair, and reported good results after early and late follow-up, especially with concomitant use of annuloplasty rings (35).

It is a matter of fact that all this surgical advancements have been possible by the use of cardiopulmonary bypass. It is in 1930 that John Gibbon, doctor in Boston became fascinated by the idea of supporting the body with an artificial perfusion system to temporary replace the heart and the lung function. His fascination turned into a lifetime achievement. Over the following next 20 years his road to success was ought with setbacks, delays, technical difficulties but his perseverance eads him to pursue his dream to its end. On May 6 1953,

Gibbon (36) performed his first successful open heart operation of atrial-septal defect closure in an 18 years old girl using the heart-lung machine (Fig3).

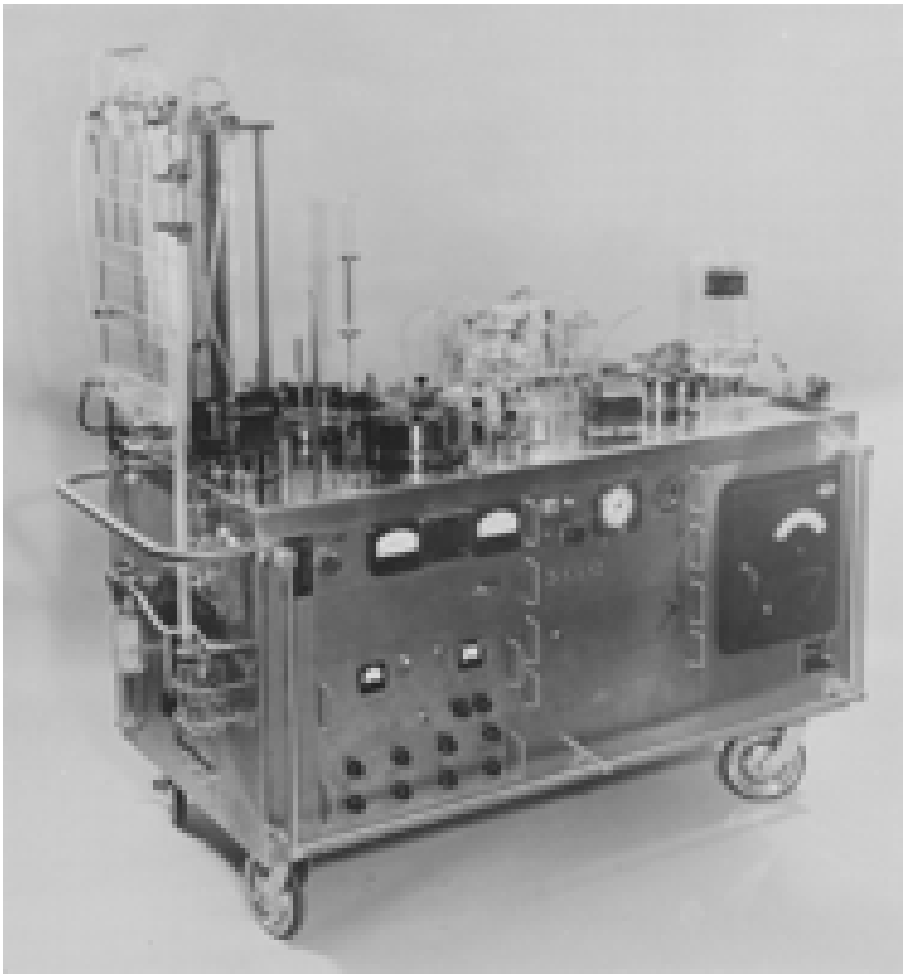

Figure 3

The John Gibbon heart-lung machine.

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CHAPTER 2 : INTRODUCTION TO TRANSCATHETER VALVE

Hufnagel started the early clinical work on mechanical heart valve in 1858 inspired by a bottle stopper patent (Fig 1). Hufnagel ‘s valve was a silicon coated nylon poppet into a surrounding cage of lucent methacrylate Plexiglas. The first human implantation has been done in 1952 but never reported (1). The development of the first successful artificial heart valve started in 1958, the year in which Lowell Edwards, a retired electrical engineer, at the age of 65, stepped into Albert Starr’s office. Their collaborative efforts prompted in the first human mitral valve replacement in August 25, 1960 (2). A silicone rubber ball was placed within a methyl methacrylate cage composed of four thick struts. The Starr-Edwards valve functioned well and became the most successfully and widely implanted prosthetic valve. The power of the Edwards laboratories was the development of the 9-Key-Items charta in 1968 :

1- Embolism prevention (free floating ball, no hinge points)
2- Durability (introduction of stainless steel struts)
3- Ease and Security of attachment (sewing ring)
4- Improved preservation of the surrounding tissues (less traumatic cage)
5- Minimizing turbulence (increasing the orifice/ball ratio)

6- Noise reduction (silicone ball)
7- Hemolysis reduction (neo-endothelialisation)
8- Increase biocompatibility (stainless steel, Teflon, Silicone)
9- Improve method of sterilization and storage.

J. B. Williams,
Bottle Stopper.
No 19,323. Patented Feb. 9, 1858.

Fig. 1.

Fig. 2.

UNITED STATES PATENT OFFICE.

J. B. WILLIAMS, OF NEW YORK, N. Y.

IMPROVED BOTTLE-STOPPER.

Specification forming part of Letters Patent No. 19,323, dated February 9, 1858.

To all whom it may concern:

Be it known that I, JEREMIAH B. WILLIAMS, of the city and county of New York, in the State of New York, have invented a new and useful Improvement in the Manufacture of Bottle-Stoppers; and I do hereby declare the following to be a full, clear, and exact description of the construction of the same, reference being had to the accompanying drawings, making a part of this specification, in which—

Figure 1 represents a perspective view of the article in question; and Fig. 2 represents a central vertical section through the same.

Similar letters of reference where they occur in the separate figures denote like parts of the stoppers in both of them.

I am aware that several kinds of valves have been used in bottle-stoppers which open when the bottle is tipped up. It is unnecessary to allude to those that are hinged, as they are materially different from mine. That which most resembles my article is where a ball is fastened to a rod and the rod passing through guides in the interior of the orifice. Such an arrangement not only checks the flow of liquid through the stopper, but it is more expensive to manufacture, difficult to repair, and when clogged, which will happen, as the interior cannot be readily get at for cleansing, the valve opens suddenly by the weight of the liquid and allows it to gush out. My invention consists in making a new article of manufacture for a bottle-stopper, in which and use my invention, I will proceed to describe the same with reference to the drawings.

a represents a tube of metal, either cast, struck up, or made in any of the usual well-known ways, and furnished with the accustomed flanges, *b b*—one to rest on the top of the neck of the bottle and the other to form a lip over which the liquid flows. The lower end of the tube is incased by a conical cork cylinder or belt, *c*, which, when slipped on, is retained in its place by turning a flange, *d*, against it on the lower end of the tube *a*. To the top flange *b* are fastened two or more wires, *e*, so as to form a guide or frame in which a loose ball, *f*, may freely roll when the bottle is corked, so as to leave a free passage through the tube *a*. When the bottle is righted up, the ball *f* runs back to its seat, being guided thereto by the wires. The ball *f* I prefer to make of glass, either plain or colored, as being more easily cleansed, and not liable to stain by contact with the liquids poured from the bottle. The article as a whole is cheaper, cleaner, and more easily repaired than any heretofore used, and it leaves the bore of the tube entirely free from any impediment to the steady flow of the liquid therefrom.

Having thus fully described the nature and object of my invention, I would state that I am aware a ball-valve is not new, and I lay no claim to it in its general application; but

What I do claim as a new article of manufacture is—

Figure 1

Jeremiah Williams : Improved bottle-stopper US patent 19323 February 9, 1858. This patent is the precursor of the first Ball-Cage mechanical valve design.

The Achilles's heel of the mechanical valves leading to frequent thromboembolic complications seemed insolvable (Fig 2).

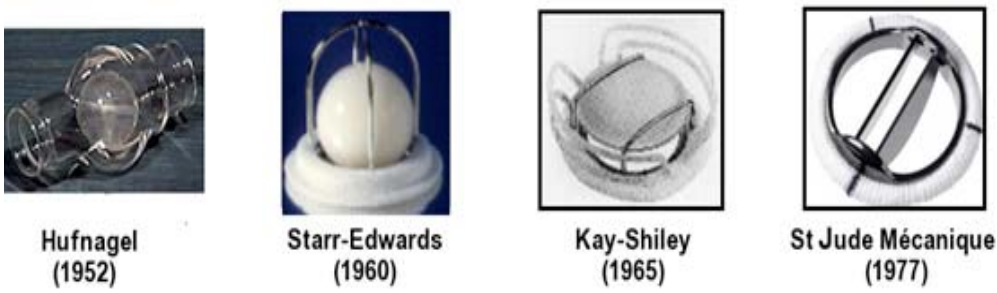

Figure 2

Evolution of the mechanical valves

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New investigations into biological tissue valve were initiated. Successful aortic valve replacement using aortic homograft was reported by Donald Ross in 1962 (3). Various autogenous materials underwent experimental usability testing with a strong emphasis on the pericardium, dura mater and facia latae. Ake Senning in Switzerland revealed a significant reduction of thromboembolic complication using fascia latae compare to mechanical valve (4). Alain Carpentier in Paris started to explore xenograft like porcine aortic valve (5). The results revived the interest to xenograft valves. In 1966 Carpentier

started to mount his valves on the stent to facilitate the handling and the suturing. From then, bioprosthetic tissue valves became a permanent feature of valvular surgery (Fig 3).

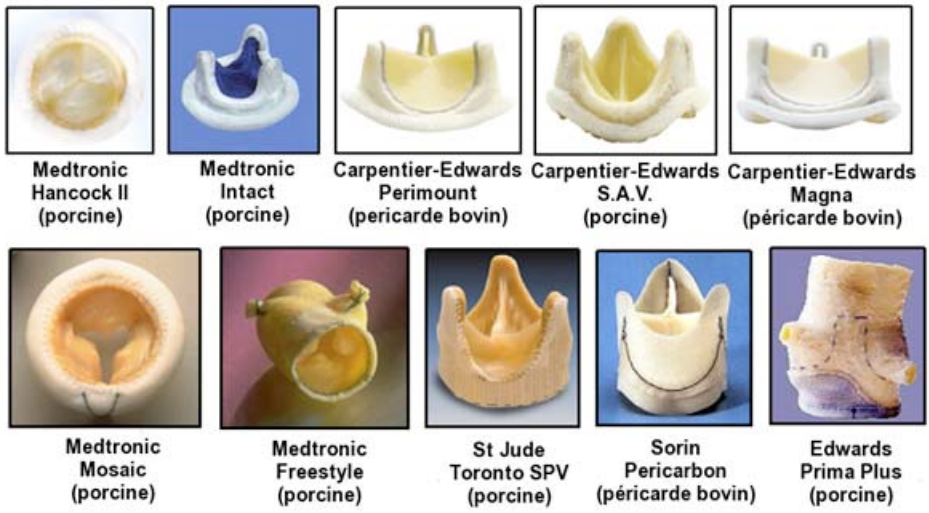

Figure 3

Evolution of the biological valves

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All this developments in the treatment of heart valve disease thrive towards increasing performance and decreasing invasiveness of the cardiac procedure. Less invasive treatments are new opportunities to improve patient care and decrease procedural morbidity and mortality. Novel approaches

widen treatment indications and increase the patient pool eligible for curative therapy (6). Even if sometimes the new ideas are criticized and called stupid or crazy when they have done their proof they lead the future therapies. Wilson already said this in 1926 (7): ”*There are 3 stages in the history of every medical discovery. When it is first announced, people say that is not true. Then a little later, when truth has been born in on them, so that it can no longer be denied, they say it is not important. After that if its importance becomes sufficiently obvious, they say that anyhow it is not new.”*

The era of the sutureless heart valve started in 1965 when Davies reported a catheter-mounted unicuspid valve that was deployed above the aortic valve position for temporary relief of aortic regurgitation (8). In the 1970’s Moulopoulos (9) and Philips (10) designed a catheter-mounted aortic valves for experimental use. However all those devices did miss the one essential feature: the capability of endovascular anchoring. They have been used in a very limited temporary purpose. The next leading development of valved stents was reached in 1987 when Henning-Rud Andersen, a 39 years old Danish cardiology resident working in Arizona Heart Institute, was watching the metal mesh being crimped around a balloon catheter and in a later step being inserted and re-expanded in the target coronary stenosis. Andersen became inspired bay what he first called a ridiculous idea: a similar scaffold allowing anchoring of a valve in the heart. On his flight back to Denmark, he focused his researches on this topic. He went down the butcher shop and

bought some pig hearts. He removed the aortic valves and placed them into a metal tube and squeezed them around a balloon. The valved stent was born. Despite of lack of equipment, simply self-made valves, Andersen reported the first successful implantation in May 1, 1989 (11). Surprisingly the paper was first rejected: too crazy idea that might be worth being patented but not published in a high impact scientific journal. The second report was published two years later (12) and the patent of Andersen was sold for 10.000$ to an American company. His initial device was 12mm diameter expanding to 32 mm using a bulky 41F delivery sheath through the ascending or descending aorta.

The same year a Czech radiologist, Dusan Pavcnik, demonstrated the feasibility of transcatheter implantation of a caged ball valve in the aortic position of a dogs (13). His devise was quite complicate and consisted to first implant a self-expandable stainless steel scaffold creating a doming cage. The second step is to implant a balloon-ball within the cage and inflate the ball with either air or contrast-medium o polymerized silicone.

In parallel to aortic valved stents, the pulmonary valve was also addressed in an experimental setting by Philipp Bonhoeffer and Younes Boudjemline in 2000, reporting a valved stent transcatheterly implanted in pulmonary position in lambs (14). The device consisting of a biological bovine jugular vein conduit of about 25 mm length sutured into a platinium-iridium alloy stent material. He reported the first human valved stent

implantation in a failing right ventricle to pulmonary artery prosthetic conduit in October 21, 2000 (15). The same team investigates on the aortic devices by modifying their pulmonic valved stents in the descending aorta (16).

In 2002, a German cardiac surgeon, Georg Lutter deployed successfully a valved stent in the porcine aorta. Six of these valved stents were implanted in the descending aorta and eight in the ascending aorta of anaesthetized pigs (17). The device made from porcine aortic valve sutured into a 21 mm length nitinol stent with anchoring barbs was delivered within a 22F sheath.

The best milestone was definitely achieved by Alain Cribier, a cardiologist from Rouen in France. He successfully implanted the first human aortic valved stent on April 16, 2002, as a life-saving last-resort option in an inoperable patient. The patient survived 17 weeks and he died from non-cardiac cause (18). The device used was the precursor of the Edwards Sapiens valve widely used today during percutaneous aortic valve implantation.

Since this first step, a large number of patients have been implanted worldwide. Transcatheter Aortic Valve Implantation (TAVI) is targeting the so-called inoperable or not-eligible aortic valve stenosis patients. The inoperability criteria were defined as described in methods of PARTNER trial (19): patients with severe aortic stenosis and cardiac symptoms for whom conventional surgery to replace the aortic valve was associated

with high risk. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mm Hg or more, or a peak aortic-jet velocity of 4.0 m per second or more. All the patients had New York Heart Association (NYHA) class II, III, or IV symptoms. Patients were divided into two cohorts: those who were considered to be candidates for surgery despite the fact that they were at high surgical risk, as defined by a Society of Thoracic Surgeons (STS) risk score of 10% or higher (on a scale of 0% to 100%, with higher scores indicating greater surgical risk) or by the presence of coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of 15% or higher, and those who were not considered to be suitable candidates for surgery because they had coexisting conditions that would be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators had to agree that the patient was not a suitable candidate for surgery.

In all those patients the valved stent is deployed into the native stenotic aortic valve. This technique did not remove the calcified diseased native valve. This means that the results obtained since many years by the surgeons who treat the aortic stenosis by resecting the native valve and replacing it using bioprosthesis is not achieved by TAVI because this new technology did not resect the native valve.

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CHAPTER 3 : WHY DO WE NEED TO RESECT THE NATIVE AORTIC VALVE ?

The remaining native valve is the cause of post-TAVI complications that I will describe below. For this reason I decided to focus my research on the native aortic valve resection prior to transcatheter valve implantation.

The complications due to the compression and the squeezing of the diseased native aortic leaflets between the endovalve and the aortic wall are listed and clearly demonstrated.

1- Paravalvular leak
2- Atrio-ventricular bloc
3- Coronary ostia occlusion
4- Continuous calcium embolization
5- Mismatch prosthesis/patient.

The rapid and substantial improvements in TAVI technology and the increasing centre experience in the past few years, the results obtained in multi-centre registries and, more importantly, the results from the high-risk cohort of the PARTNER trial have provided the basis for evaluating whether TAVI should be used for the treatment of a lower-risk population with aortic stenosis. Indeed, some preliminary results of TAVI in intermediate- risk patients with severe aortic stenosis have been promising (1).

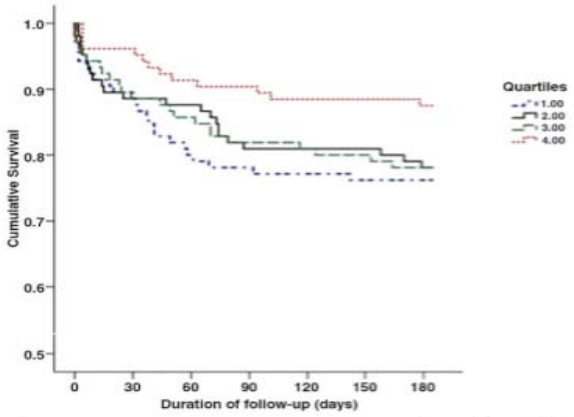
There are already reports about TAVI in low risk patients. Lange (2) reported a series of 420 patients who underwent TAVI using Corevalve or Edwards Sapiens valve. Patients undergoing TAVI in the first quartile had significantly higher logistic EuroSCORES than those in the second, third, or fourth quartiles (Q1: 25.4±16% vs. Q2: 18.8±10% vs. Q3: 18.3±11% vs. Q4:17.8±12%, analysis of variance $p < 0.001$). The Society of Thoracic Surgeons (STS) score was significantly lower in Q4 than in Q1, Q2, or Q3 (Q1: 7.1±5.4% vs. Q2: 6.2±3.5% vs. Q3: 5.8±3.9% vs. Q4: 4.8±2.6%, analysis of variance $p < 0.001$).

From Q1 to Q4, the crude 30-day mortality rate significantly decreased from 11.4% to 3.8% (chi-square test, p=0.03) (unadjusted HR: 0.33; 95% confidence interval [CI]: 0.11 to 1.01; p=0.051) and the 6-month mortality rate significantly decreased from 23.5% to 12.4% (chi-square test, p=0.031) (unadjusted HR: 0.49; 95% CI: 0.25 to 0.95; p=0.072) (Fig 1A).

There were no significant differences in mortality rate observed between Q1 and Q4 after adjustment for baseline characteristics at 30-day and 6-month follow-up (30-day mortality rate adjusted HR: 0.29; 95% CI: 0.08 to 1.08; p=0.07) (6-month adjusted mortality rate HR: 0.67; 95% CI: 0.25 to 1.77; p=0.42) (Fig. 1B).

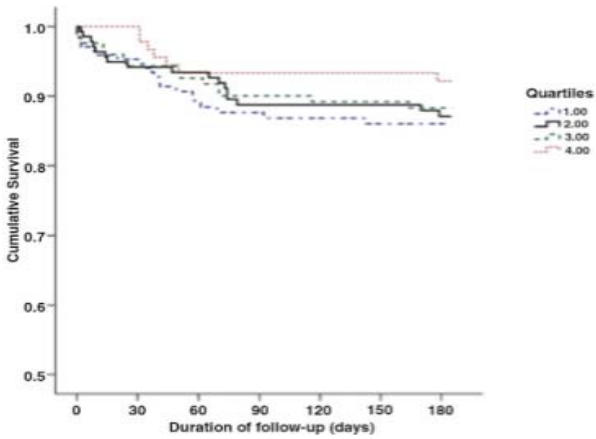
This suggests that baseline characteristics play a role in the clinical outcomes of transcatheter aortic valve implantation patients at 30-days and 6-month follow-up. They conclude that the results of the study demonstrate an important paradigm shift

A



	30-day mortality			6-month mortality	
	HR (95% CI)	p-value		HR (95% CI)	p-value
Q4 vs. Q1	0.33 (0.11-1.00)	0.053	Q4 vs. Q1	0.49 (0.25-0.95)	0.035
Q4 vs. Q2	0.32 (0.11-1.01)	0.053	Q4 vs. Q2	0.54 (0.28-1.07)	0.07
Q4 vs. Q3	0.32 (0.11-1.01)	0.053	Q4 vs. Q3	0.54 (0.28-1.07)	0.07
Q3 vs. Q1	0.99 (0.44-2.21)	0.99	Q3 vs. Q1	0.89 (0.51-1.57)	0.69
Q3 vs. Q2	0.99 (0.44-2.22)	0.99	Q3 vs. Q2	1.00 (0.56-1.79)	0.99
Q2 vs. Q1	0.99 (0.44-2.21)	0.99	Q2 vs. Q1	0.89 (0.51-1.57)	0.69

B



	30-day mortality			6-month mortality	
	HR (95% CI)	p-value		HR (95% CI)	p-value
Q4 vs. Q1	0.29 (0.08-1.08)	0.07	Q4 vs. Q1	0.67 (0.25-1.77)	0.42
Q4 vs. Q2	0.48 (0.13-1.87)	0.053	Q4 vs. Q2	0.49 (0.18-1.32)	0.16
Q4 vs. Q3	0.28 (0.08-1.06)	0.061	Q4 vs. Q3	0.68 (0.26-1.82)	0.44
Q3 vs. Q1	0.93 (0.40-2.16)	0.86	Q3 vs. Q1	0.74 (0.35-1.57)	0.44
Q3 vs. Q2	0.91 (0.39-2.13)	0.83	Q3 vs. Q2	0.84 (0.40-1.79)	0.65
Q2 vs. Q1	0.95 (0.42-2.19)	0.91	Q2 vs. Q1	0.85 (0.42-1.72)	0.65

Figure 1.

Unadjusted and Adjusted Cox Proportional Hazards Model for All-Cause Mortality Rate Through 6-Month Follow-Up

(A) Significant differences in the 30-day and 6-month crude hazard ratios for all-cause mortality rate between the fourth quartile.
(B) After adjusting for baseline characteristics, there were no statistically significant differences in 30-day and 6-month.

toward the selection of lower surgical risk patients for TAVI. Significantly better clinical outcomes can be expected in lower than in higher surgical risk patients undergoing TAVI. As TAVI becomes more routine and widely available, operators may be tempted to implant the device in younger patients with less comorbidity. Uncertainties about the long-term durability, in addition to the unresolved issues of paravalvular leak and conduction abnormalities, should be cautiously weighted against the immediate benefits being widely reported.

So clearly performing TAVI in young patients without native leaflets resection is unacceptable regarding the excellent results that surgical aortic valve replacement in those young patients.

Two new TAVI studies on intermediate- risk patients are planned in the near future. The first one is the cohort A of the PARTNER II trial (3), investigators will randomly assign patients with aortic stenosis and STS score of 4–8% (that is, intermediate risk), or specific qualifying intermediate risk criteria requiring formal petition to the executive committee heart-valve team (which will include cardiac surgeons and interventional cardiologists), to TAVI or AVR. Patients with concomitant coronary artery disease will be substratified to percutaneous coronary intervention plus TAVI versus CABG surgery plus AVR. The estimated sample size is 1,500–2,000 patients, and ~50 US centres are expected to participate. The second one is

the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial 120 will include elderly (≥70 years) patients with aortic stenosis and an STS score of 3–8%. Approximately 1,200 patients will be randomly assigned to TAVI or SAVR, and ~40 European centres are expected to participate. The results of these randomized trials should determine the exact role of TAVI for the treatment of low-risk patients with severe aortic stenosis valves, which opens up a new avenue for the treatment of this challenging group of patients (4,5).

In this chapter we will demonstrate the necessity of resecting the native aortic valve prior to the deployment of the endovalve. The cited five major complications related to the remaining native valve are going to be reviewed in detail.

3.1 Paravalvular leak post TAVI

Percutaneous TAVI has extended our ability to treat patients with severe symptomatic aortic stenosis being no or poor candidates for open heart surgery (6). At the present time two different devices are available, one self-expandable, porcine pericardial leaflet, and nitinol frame, and the other one balloon-expandable, bovine pericardial leaflet, and Cobalt-Chromium frame. Both devices have shown good performance once implanted, with transvalvular gradient and effective orifice area that are respectively lower and higher than that observed in

surgical valves (7-13). However, TAVI may result in severe complications, starting with vascular injuries, cerebral or peripheral embolization, pericardial effusion, ventricular rupture, conduction abnormalities, aortic dissections aortic regurgitation and paravalvular leak.

Regurgitation originating between the prosthetic sewing ring and the native valve annulus is a well-known phenomenon reported as paravalvular, perivalvular and peri/ or paraprosthetic leaks. In surgical series, the occurrence of PVL has been reported in very few cases, being 2% and 8% after a bioprosthesis or mechanical prosthesis implantation, respectively (14). Thus, it does not represent a main issue in the context of surgical aortic valve replacement and is not addresses in the current guidelines for valvular heart disease (15).

In contrast to surgical aortic valve replacement, during TAVI procedure the native valve is not removed but crushed. Thus, a slight aortic insufficiency is not uncommon and has been reported in about 70% of patients for both available types of percutaneous valves (16-19). On the other hand, a moderate regurgitation has been observed in up to 40% of the cases (17-19). In most cases, aortic insufficiency is clinical acceptable, however, severe insufficiency can occur and although current reports mention treatment of such severe insufficiencies only very briefly (8-12), the problem is not trivial because the underlying pathophysiology can be very different. It should be also acknowledged that discrepancies in the prevalence of

valve regurgitation after TAVI [7-8,20-21] are mainly due to the absence of standardized definition and protocols to detect (i.e angiography versus echocardiography) and score (qualitative or semiquantitative methods) the leak. Moreover the definition of clinically “significant” PVL is not fully established because of the lack of evidence exploring the pathophysiology of the valvular leak and its impact on outcome. More recently the Valve Academic Research Consortium provided a consensus aimed to standardize definitions on technical and clinical end-points in TAVI procedure (22). Nevertheless, trying to estimate and quantify the valve regurgitation they adopted arbitrarily a standard classification that is commonly used to describe regurgitation in native valve.

Mechanism of the paravalvular leak.

The aortic insufficiency after TAVI might be classified taking into account the type of regurgitation, its mechanism, and the aetiology. Paravalvular insufficiency may derive from a prosthesis/patient mismatch due to an undersizing of the implanted device, incomplete expansion of the prosthesis stent frame and to incorrect site of prosthesis implantation. On the other hand, intravalvular insufficiency might be due to the opening failure of the prosthesis’ leaflets, to leaflets damage occurring during the crimping manoeuvre or during the implantation phase (post dilatation) or again to a prosthesis/patient mismatch because of an incorrect sizing of the valve.

Differently from surgical series, the direct sizing of native aortic annulus is not possible during TAVI, thus an accurate assessment of the latter is mandatory during the screening phase of the patient. The selection of the prosthesis that matches properly with the native aortic annulus is paramount to final procedural success, as the goal is to displace the native valve leaflets and deploy the device within the valve annulus. The native annulus should be identified with the virtual basal ring below the nadir of the aortic cusps, which provides the right plane of the annulus, that is not the anatomic ventriculo-aortic junction Different methods are used to assess aortic annulus measurement: echocardiogram (transthoracic or transesophageal), angiography, and computed tomography. There is not a gold standard for annulus measurement, and a multimodal assessment is strongly recommended (23), since the aortic annulus is not circular but might be ovoid in shape.

Tops et al. (24) reported that the annulus had an oval configuration in approximately 50% of patients evaluated for TAVI, with a mean difference between coronal and sagittal measurements of 3.0 ± 1.9 mm. An oval configuration of the annulus was also noted by Delgado et al. (25), who reported a significant difference between mean coronal (25.1 ± 2.4 mm) and sagittal (22.9 ± 2.0 mm) measurements in 53 patients with severe aortic stenosis. This oval geometry of the annulus has been previously underappreciated on imaging but has been well described in the surgical literature. Therefore multiple measurements in different planes are recommended. To this

regard, the clinical use of 3D echocardiogram may improve pre-TAVI evaluation, when compared to 2D echo, by the assessment of the aortic annulus in 3 planes. Moreover, a balloon-based annular measurement is an adjunctive tool to select the proper valve size. In fact, intraoperative evaluation of aortic regurgitation during balloon inflation for valvuloplasty increases the accuracy of the optimal device size selection (26).

Clinical impact of the paravalvular leak.

Clinical implications of valvular leak are not fully established. Although, in most cases, aortic insufficiency is stable during follow-up (12-16) and clinical acceptable, severe insufficiency can occur. More recently, some authors have shown that even less than severe valvular leak might be related to higher 1-year mortality after TAVI (12). When severe regurgitation is present, a multimodality imaging for an accurate assessment of the underlying pathophysiology of the valve regurgitation is of utmost importance to select the adequate therapy.

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in which we can implant an endovalve that fits much better the surrounding aortic annulus. The ovoid shape of the annulus is than transformed into a perfectly circular hole. The blade that we plan to use will be a circular sharp blade in order to remove the majority of the calcified leaflets. The diameter of the blade

should be slightly lower than the native annulus in order to avoid any damage of the aortic wall and all the myocardial tissues.

3.2 Atrioventricular bloc post TAVI.

The incidence of conduction abnormalities after TAVI has been reported widely. Conduction disorders necessitating a permanent pacemaker (PPM) implantation are frequent complications associated to the procedure. In particular, the need for PPM implantation following TAVI ranges from 5.7% to 39% depending on the type of percutaneous prosthesis used (27,28). Studies assessing predictors of PPM implantation in the TAVI setting identified a number of candidate variables but were limited by the small sample size.

This complication may affect significantly the outcome of the patient, increase hospital stay, and overall cost and may be associated with an increased risk of sudden death.

The left bundle branch exits 2 to 3 mm below the base of the triangle formed by the non-coronary and right coronary cusps of the aortic valve, close to the annulus and left ventricular outflow tract. Therefore, aortic valve surgery and any cardiac catheterization procedure requiring crossing the aortic valve with guidewires and catheters carries the risk of trauma to the septal conduction pathways and particularly to the LBB. Risk of

AV block should be subsequently higher in case of pre-existing right RBBB.

The reported incidence of AVB requiring PPM after CoreValve implant ranges from 18% to 39% while the incidence of LBBB is about 50%. New onset conduction disorders and requirement of a PPM after implantation of an Edwards Sapien aortic bioprosthesis are infrequent (incidence of PPM 4.3%). The Edwards Sapien prosthesis was specifically designed to respect nearby anatomic structures. Indeed, the lower limit of the Edwards valve should not reach the upper part of the interventricular septum and in contrast to the nitinol CoreValve's self-expandable frame, the stainless-steel stent used with the Edwards model does not keep expanding after valve deployment, thus decreasing the risk of delayed conduction disturbance (29).

Piazza et al. (28) in their series of CoreValve implantations reported the occurrence of new- onset widening of the QRS complex in 30% of cases immediately after preimplantation balloon valvuloplasty. Of note, in 1 of our patients who required permanent pacing, complete AV block occurred immediately after balloon valvuloplasty. The large valves used in TAVI can also result in compression of the upper transventricular septum and impair AV conduction. In their series of Edwards Sapien valve implantation, Sinhal et al reported that 10% of patients presenting with pre- existing RBBB might need implantation of a pacemaker. Interestingly, 7 patients in our series had complete

RBBB before implantation and none of them developed significant conduction disturbances after TAVI.

For technical reasons, a deeper intraventricular insertion of the self-expanding CoreValve is generally observed. In the report by Piazza, the length of stent below the noncoronary cusp was calculated to be on average 10.3 mm (range 6.7 to 14.6) in a series of 40 patients., the cutting distance being 6.7 mm. In contrast to the CoreValve's nitinol frame, the stainless-steel stent used with the Edwards Sapien model does not keep expanding after valve deployment, thus decreasing the risk of delayed conduction disturbances and allowing a safe retrieval of the temporary pacing lead at the end of the procedure (29).

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in order to remove the majority of the calcified leaflets. This should lead to avoid the compression of the conduction tissues and preserve the native cardiac rhythm. The resection should decrease the incidence of new onset of AV bloc and decrease the pacemaker implantation after TAVI.

3.3 Coronary ostia occlusion post TAVI.

A life-threatening complication is coronary artery stenosis or occlusion with a reported incidence of 0.6–7%. Those data are

coming from SOURCE registry (33) and large series like the Canadian experience (34). Rapid diagnosis and a staged management are mandatory immediately to save the life of your patient. Any hemodynamic instability of a patient after or during TAVI might be suspicious for coronary artery obstruction or occlusion. The only treatment option after diagnosis is immediate reestablishment of blood flow by percutaneous techniques or CABG. In some cases, a cardiopulmonary support is necessary. The need for a heart team involved not only in decision-making, but also in the procedure itself is obvious.

Several conditions might predispose to coronary occlusion. A low-lying coronary ostium, bulky native leaflets, a narrow root, an excessively enlarged valve leaflet or the new valve prosthesis might result in coronary occlusion (35).

Crimi at al (36) report a case of a transapical aortic valve implantation complicated by acute LM occlusion, cardiac arrest, and hemodynamic collapse, successfully treated by balloon angioplasty and stent implantation. He state that Coronary occlusion is a rare, life-threatening complication of TAVI. Complete occlusion of coronary ostia occurs at the time of valve deployment and is usually associated with hemodynamic collapse. Immediate percutaneous recanalization can successfully restore normal hemodynamic conditions. Several patient- and procedure-related factors potentially associated to this event have been proposed and should be considered during the selection of the patients and work-up. Although their

predictive value has to be confirmed by additional data, the prevision of coronary occlusion can allow the operator to establish measures such as positioning of a protective wire in the coronary artery at risk.

In all those reports, the coronary occlusion is not due to the endovalve itself but due to the native leaflets calcium or native leaflets height. Webb described it clearly in his report about 1 patient (37). Coronary obstruction by a displaced native valve was observed in a single patient. Until this is better understood, the presence of an unusually bulky left coronary leaflet appears to be a relative contraindication to percutaneous valve implantation.

Of course the distance between coronary ostia and the aortic annulus is crucial. The team from Vancouver published those data in the paper of Tops in 2008 (24). Mean distance between the aortic annulus and the ostium of the right coronary artery was 17.2±3.3 mm, and mean distance between the annulus and the ostium of the left coronary artery was 14.4 ± 2.9 mm. In 82 patients (49%), the length of the left coronary leaflet exceeded the distance between the annulus and the ostium of the left coronary artery. There were no significant differences in the diameter of annulus, diameter of sinus of Valsalva, or the distance between the annulus, left coronary leaflet, and the ostium of the left coronary artery, between the patient with and without severe aortic stenosis.

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in order to remove the bulgy calcification of the native leaflets. Even without any bulgy calcification the resection will decrease the height of the native leaflet, which are responsible of the coronary ostia occlusion.

By resecting the native valve we expect to decrease this life-threatening complication in patients who underwent TAVI.

3.4 Continuous embolization of calcium post TAVI.

Neurological complication is a dramatic postoperative event, especially in this population with poor life expectancy (37). Indeed, cerebral damage after conventional aortic tool for diagnosing acute ischemic brain lesions, and has become a surrogate marker for clinical and sub-clinical brain embolism [6]. DW MRI has already been used to evaluate the stroke after AVR ranges from 0.21% to 2.0% for neurological death rate and from 1.1% to 6.6% for clinical stroke rate (38).

The rate of stroke reported in the TAVI literature is an important matter. In the PARTNER trial Smith reported a rate of stroke that increases over the time (39). Rates of all neurologic events (i.e., all strokes and transient ischemic attacks) were higher in the transcatheter group than in the surgical group at 30 days (5.5% vs. 2.4%, P = 0.04) and at 1 year (8.3% vs. 4.3%, P = 0.04). Rates of major stroke were 3.8% in the transcatheter

group and 2.1% in the surgical group at 30 days (P = 0.20) and 5.1% and 2.4%, respectively, at 1 year (P = 0.07). Most strokes appeared to be procedure-related and embolic. Rates of stroke were similar whether the access was transfemoral or transapical. Despite a higher frequency of stroke with transcatheter replacement, the composite end point of death from any cause or major stroke was similar in the two study groups at both 30 days and 1 year. Future studies will determine whether delivery systems with smaller diameters, procedural changes, or embolic-protection devices can reduce the incidence of stroke after transcatheter replacement (Fig 2).

Benefit of the native valve resection.

If we look to those data, this is for me, a clear argument to first use a protection device during TAVI procedure in order to decrease the rate of procedural stroke but also to resect the native rubbish calcified leaflets squeezed between the endovalve and the aortic wall. That remaining calcium is at the origin of the increased stroke rate at 1 year. I believe that if we clean this aortic annulus by resecting the native valve we will decrease the continuous embolisms and late strokes.

Outcome	30 Days			1 Year		
	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
	no. of patients (%)			*no. of patients (%)*		
Death						
From any cause	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
From cardiac causes	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
Stroke or transient ischemic attack						
Either	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
Transient ischemic attack	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
Stroke						
Minor	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Major	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Death from any cause or major stroke	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68
Myocardial infarction	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Vascular complication						
Any	59 (17.0)	13 (3.8)	<0.001	62 (18.0)	16 (4.8)	<0.001
Major	38 (11.0)	11 (3.2)	<0.001	39 (11.3)	12 (3.5)	<0.001
Acute kidney injury						
Creatinine >3 mg/dl (265 μmol/liter)	4 (1.2)	4 (1.2)	0.95	12 (3.9)	8 (2.7)	0.41
Renal-replacement therapy	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56
Major bleeding	32 (9.3)	67 (19.5)	<0.001	49 (14.7)	85 (25.7)	<0.001
Endocarditis	0	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New-onset atrial fibrillation†	30 (8.6)	56 (16.0)	0.006	42 (12.1)	60 (17.1)	0.07
New pacemaker	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68

* All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.
† The presence of new-onset atrial fibrillation was determined in an electrocardiography core laboratory.

Figure 2

Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population of the PARTNER Trial published in 2011 (39).

3.5 Mismatch prosthesis/patient post TAVI.

Aortic valve replacement in patients with severe aortic stenosis and a small aortic annulus has been associated with a high incidence of prosthesis–patient mismatch (41-43). Prosthesis-patient mismatch has in turn been associated with diminished extent of regression of left ventricular hypertrophy, reduced coronary flow reserve, increased incidence of congestive heart failure, diminished functional capacity, and increased risk of early and late mortality (44-47). In order to allow implantation of an appropriately sized prosthetic valve and prevent mismatch in a patient with a small aortic annulus, an aortic annular enlargement procedure or a complete replacement of the aortic root may be necessary at the time of aortic valve replacement. These procedures significantly enhance the complexity of the operation, and may increase morbidity and mortality, especially in elderly patients (48,49).

Transcatheter aortic valve implantation has emerged as an alternative to AVR in high-risk patients with AS. However, no specific data exist on the results of TAVI in patients with a small aortic annulus. So far, only a few small series (50-52) have described the incidence of PPMM after transcatheter aortic valve implantation (TAVI), and little is known about its impact on LV performance and clinical outcomes in these patients.

3.5.1 Incidence of PPMM in patients undergoing TAVI.

The present evaluation demonstrated that PPMM is rather common and occurred in 18% to 20% of patients undergoing TAVI with balloon-expandable valves and between 30 to 40 % using self expandable valves. This difference can be partially explained by the fact that only 1 size of the device (26 mm, the smallest) was available at the time of TAVI in one-fourth of the patients (27%) in the reported series (52). In addition, the differences in prosthesis design may play a role. The Edwards SAPIEN valve is a trileaflets valve mounted on a balloon-expandable stainless stent frame that is 14.5 mm or 16 mm in height (for the 23- or 26-mm valve, respectively) and is implanted intra-annularly. Conversely, the CoreValve (designed for supra-annular implantation) has a longer frame of 53 or 55 mm (for the 26- or 29-mm device, respectively), with the lower third sitting within the LVOT

Patients with PPMM were accompanied by less favourable changes post-TAVI compared with patients without PPMM, with higher transvalvular gradient, limited LV mass regression, and LA volume reduction, and with persistent elevated LV filling pressures. Finally, more patients reported a lack of clinical improvement in the group with PPMM.

To minimize paravalvular regurgitation and to ensure adequate annular sealing, it is generally recommended that the implanted prosthesis be slightly larger than the native aortic annulus for the currently applied percutaneous systems. For example, in

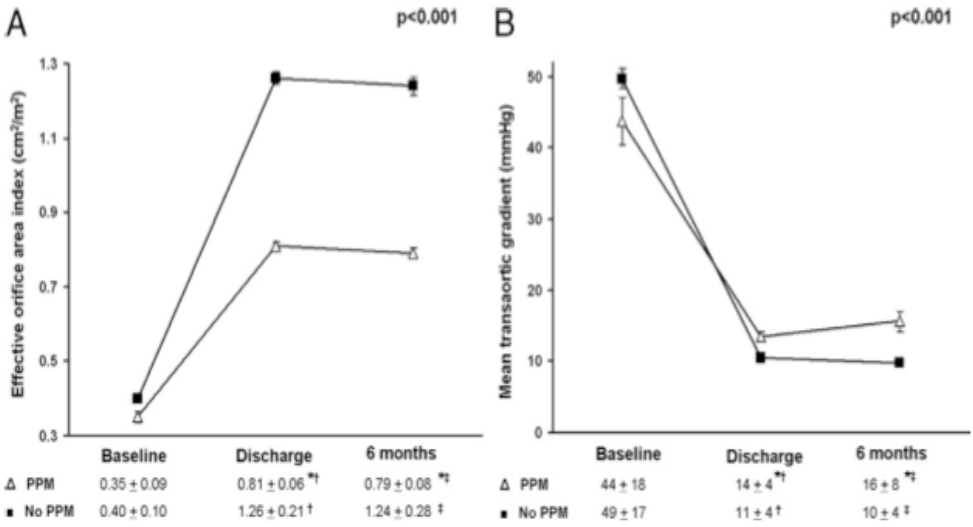
the balloon-expandable delivery system of the Edwards SAPIEN valves, the 23-mm valve is used for aortic annulus between 18 and 22 mm, whereas the 26-mm valve is used for aortic annulus between 21 and 25 mm. Despite these indications, the current study showed that PPMM developed before hospital discharge in 18 to 30% of patients who underwent TAVI.

3.5.2 Hemodynamic impact of PPMM

In all the reports, patients with a PPMM have less reduction of the mean transvalvular gradient compare to patients without PPMM. The effective orifice area of the valve is higher in patients without PPMM than in patients with PPMM. The left ventricular mass index decrease much more in patients without PPMM than in patients with PPMM (Fig 3ABC). This has been clearly demonstrated by Ewe in 2011 (53).

3.5.3 Clinical impact of PPMM

The presence of PPMM negatively affected the improvement in NYHA functional class at 6 months post-TAVI. The suboptimal improvements in valvular hemodynamic and the higher residual afterload post-TAVI in patients with PPMM could have contributed to the lack of clinical improvement. According to the literature, female gender is an independent risk factor for PPMM. Using the indexed EOA as a parameter to define



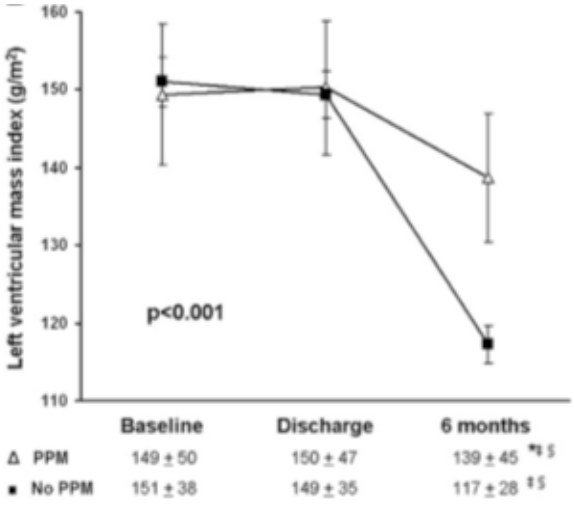


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Figure 3

A- Effective Orifice Area at baseline, discharge, 6 months.

B- Mean Transaortic Gradient at baseline, discharge, 6 months.

C- Left Ventricle Mass Index at baseline, discharge, 6 months.

PPMM, recent series (50-54) demonstrated that patients without significant PPMM had better early and late mortality benefits. In addition, patients without PPMM exhibit more freedom from congestive heart failure after aortic valve replacement.

Benefit of the native valve resection.

In conclusion surgeons who operate patients with a small annulus tends to perform additional steps to enlarge the annulus in order to avoid PPMM because this is a complication who have a clear impact on patient post operative hemodynamic, post operative clinical status and long term myocardial effect. So, during TAVI we have to think about PPMM and the resection of the native valve before implantation of the endovalve must increase the EOA. By doing the resection we can offer a better post operative result to our TAVI patients.

This review of the TAVI induced complications has been published as an Editorial by our team (54) (Annexe Publication 1).

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CHAPTER 4 : ACCESS IS AN ISSUE.

The access to the aortic valve during TAVI is dependent of many factors dictated mainly by the patient anatomy but also by the operator's experience.

4.1 Transfemoral approach

The transfemoral route (Fig 1a) is the first choice of approach in the vast majority of centres performing TAVI procedures. First described by Andersen in 1992 (1), this approach has been described by many authors (2-4). As stated above, an accurate evaluation of the iliofemoral anatomy is of major importance in determining the appropriateness of this approach for each individual patient. The procedure is performed in a catheterization laboratory or a hybrid operating room. Although surgical cut down was the technique used for the transfemoral approach at the beginning of the TAVI experience, most centres are now using a fully percutaneous technique for this approach. In our centre we use a Perclose® system to close the femoral access under local anaesthesia. This strategy makes it possible to avoid the use of general anaesthesia, especially if the procedure is performed without transesophageal echocardiographic guidance (5).

4.2 Transapical approach

The transapical approach (Figure 1b) was first reported as an alternative to the transfemoral approach in 2006 by Litchenstein and colleagues (6), who used the Cribier-Edwards valve system. The approach requires a small left lateral thoracotomy and a direct puncture of the left ventricular apex. A 24 French (for the 23 mm and 26 mm valves) or 26 French (for the 29 mm valve) sheath is used to advance the Edwards SAPIEN XT® valve, and implantation is performed in a similar way to that used with the transfemoral approach (Fig 1b). In the era when larger catheters (≥22 French) were used for the transfemoral approach, about half of the TAVI procedures with the Cribier-Edwards and Edwards SAPIEN® valves were performed using the transapical approach. This percentage is expected to decrease with the use of smaller (18 French) catheters. Potential advantages of the transapical approach include the avoidance of using large catheters though the iliofemoral system, aortic arch, ascending aorta, and aortic valve; improved coaxility of the valve prosthesis within the aortic annulus, which can be especially helpful in cases of horizontal aorta (7); and the possibility of obtaining very accurate transesophageal echocardiographic images for valve positioning, which might lead to a reduction in the amount of contrast used during the procedures (8) The main disadvantages are the need for a thoracotomy; a greater degree of myocardial injury, owing to the apical perforation of the left ventricle; and the potentially life-

threatening bleeding complications associated with the surgical repair of the apex (9).

4.3 Transaortic approach

In 2009 and 2010, the use of the transaortic approach through a small right or mid sternotomy (Figure 1c) was proposed as an alternative approach with the Corevalve® and Edwards systems. Although requiring sternotomy, this approach avoids the use of large catheters through the iliofemoral system and aortic arch, and avoids puncture of the ventricular apex (10-13).

4.4 Subclavian approach

The left subclavian approach (Figure1d) has emerged as an alternative to the transfemoral approach with the CoreValve system (14-15). A surgical cut-down is needed to isolate the subclavian artery (usually the left vessel). The very short distance between the vascular access and the native aortic valve might be associated with better control of the CoreValve® prosthesis during positioning and deployment. However, any injury of the subclavian artery would translate into a major intrathoracic bleeding that might be difficult to control.

4.5 Transaxillary approach

First-in-human CoreValve® implantation by the trans- axillary approach (Figure 1e) has been reported (16). Like the subclavian approach, a surgical cut-down is per- formed to isolate the left axillary artery, and the sheath and delivery catheters are advanced through the axillary artery. The potential advantage of this approach versus the subclavian approach is that any injury to the axillary artery could be easily repaired with no major clinical consequences, as compared with the potentially life-threatening consequences of a subclavian-artery injury. Indeed, and unlike in iliofemoral vessels, occlusion of the axillary artery would be compensated by the collateral circulation between the thyrocervical trunk of the subclavian artery and the subscapular artery.

4.6 Our access choice: Transapical.

In our centre we used the transfemoral approach for 65% of our cases and transapical approach for the 35% of patients who did not have sufficient femoral access. Our research was focused on the native valve resection prior to TAVI. The first prototype of instrument to resect the native valve was a 20 mm diameter strait metallic instrument. We thought that the best and easy access to the native aortic valve will be the transapical access. In our department TAVI is performed in a hybrid operative

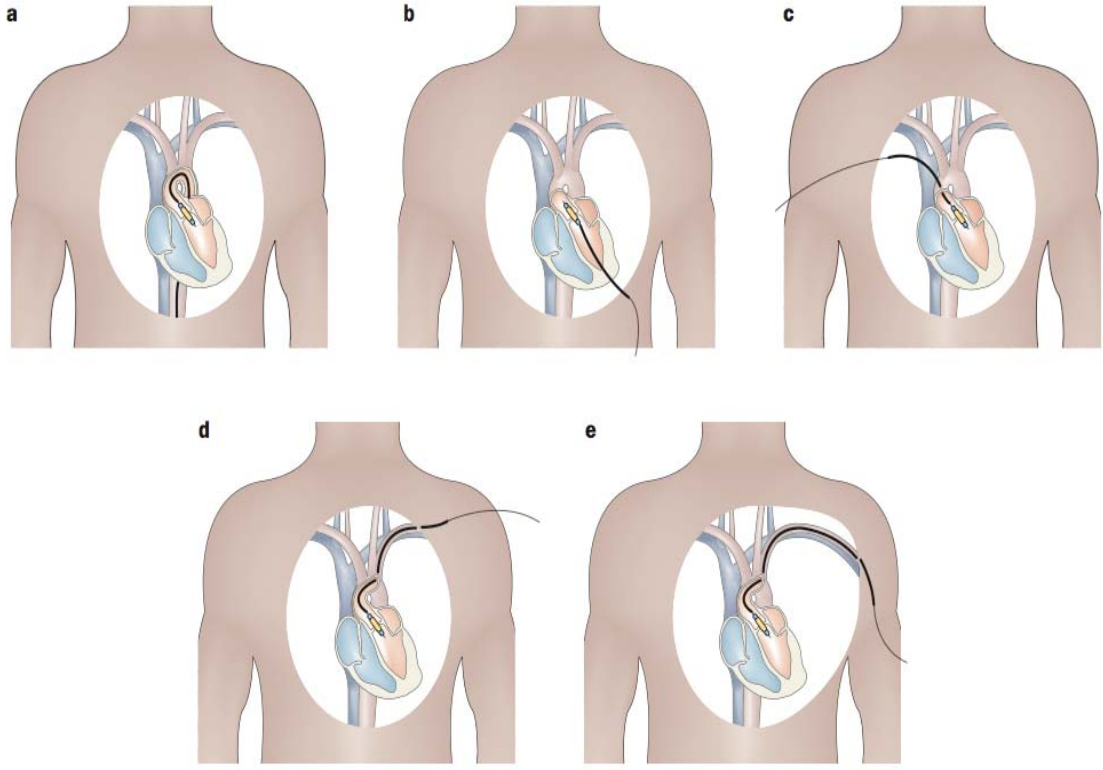

Figure 1

The five different accesses for transcatheter valve implantation (17).

suite designed and equipped to accommodate tools and personnel required for performing both open surgical and interventional procedures. TAVI procedures are performed by a multi-disciplinary team including a cardiac surgeon, an

interventional cardiologist and a cardiac anaesthesiologist experienced in TEE. Other team members include a perfusionist, a surgical scrub nurse trained in transcatheter procedures, a circulating nurse, a radiology or catheterization laboratory technician and a surgical assistant. At least one member of the team must be trained in preparation and loading of the valve device, which is performed on the back table at the time of the procedure using a proprietary crimping device.

The apex is preferable to the free wall due to greater convexity and reduced wall stress. Select an area free of epicardial fat, take full-thickness bites in the myocardium and gain access with a needle precisely at the central point within the sutures to reduce the likelihood of extending the enlarging myocardial defect beyond the control sutures. Avoid severe hypertension especially when tying the sutures. Occasionally the sutures are tied during a period of rapid ventricular pacing.

However complications of apical access have been described (9). The critical part of the procedure consists on the perfect closure of the apex with two purse-string sutures and multiple Teflon pledgets.

We deplore two apex rupture among the 98 transapical aortic valve implantation. To avoid apical rupture during the closure we designed a single circular Teflon pledget, which provides a more secure global shrinkage of the entire apex to close the hole of the delivery sheath. A step-by-step technique for transapical aortic valve implantation has recently been

described by Walther et al (8). In his detailed description, a left antero-lateral mini-thoracotomy is performed in the sixth intercostal space. After pericardial opening, the apex of the left ventricle is exposed. Careful attention is given to the location of the LAD and an ideal site for apical puncture is chosen lateral to the LAD. Two purse-string sutures with interrupted Teflon pledgets are placed with a large needle in order to get sufficient depth in the myocardium. The apex is punctured in the middle of the purse-string sutures and the apical wire is inserted for the successive insertion of 14 and 36 French sheaths for valvuloplasty and valve delivery, respectively. At the end of the procedure the sheath is removed and the apical defect is closed with the purse-string sutures.

However, even if particular care is taken with regards to the depth of the purse-string sutures, a ventricular muscle tear can appear while tightening the purse-string in these patients that have extremely fragile tissue. Additional sutures and pledgets may then be required to achieve complete haemostasis. In 2 patients, we encountered muscular disruption of the apex after removal of the 36 French sheath.

The first patient was a 78-year old female with severe chronic obstructive pulmonary disease on high dose steroids. Her logistic Euroscore were 30 % (STS score 15) and her LVEF was 32%. When we tied the purse-string, the pledgets tore the apical muscle and created a defect the size of two Teflon pledgets. Complete haemostasis was finally achieved with multiple extra sutures with concomitant ligation of the distal LAD

which was mandatory to get enough muscular tissue to close the ventricular rupture. This led to a further decrease in LVEF (28% at 3 months FU).

The second patient was a 87- year old female with a logistic Euroscore 31 % (STS score 12). A similar complication occurred in this second patient and complete haemostasis was achieved with two extra sutures and a larger band of pledget far from the LAD.

These two cases of ventricular rupture prompted us to develop two technical modifications to the initial procedure described by Walther (8) in order to reduce the risk of this complication.

Firstly, we have developed the concept of a “ring pledget” for safe LV apex closure. The aim is to get secure global shrinkage of the entire apex to close the hole of the delivery sheath. Rather than using small pieces of Teflon pledget we use a “ring pledget” of one-cm width, which is cut from a sheet of Teflon felt. (Fig 2) The two purse-string sutures are passed through the ring pledget. This “ring pledget” provides uniform tension around the apical defect and minimizes the risk of muscular tears.

The second modification is that the purse-string sutures are tied under rapid pacing, in order to decrease the tension on the myocardial wall and to achieve a secure tension-free suture of the apex. To date, we have performed 98 transapical procedures with these technical modifications providing a

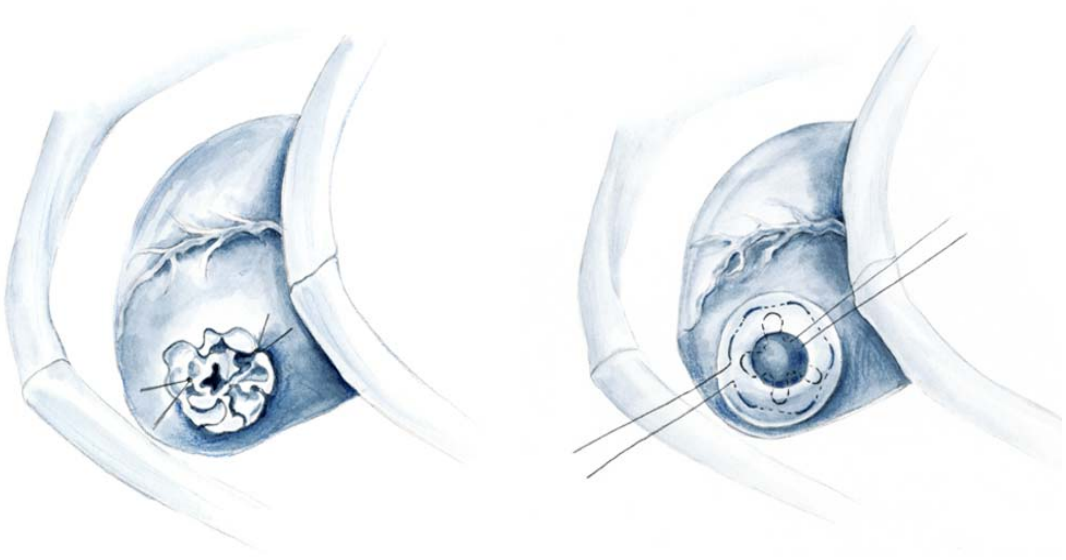

Figure 2

The Ring Pledget concept published by our team (18) (Annexe Publication 2)

secure closure of the apex without the need for extra sutures. This new concept of « ring pledget » has been published (18) (Annexe Publication 2).

We found another interest of the transapical access during a transapical procedure. We faced a ventricular embolization of an Edwards Sapiens valve. The patient was a 85-year old female (Euroscore – 30%; STS score – 15) with severe chronic obstructive pulmonary disease with a LV ejection fraction of

32%. The annulus was measured at 21 mm diameter we decided to use a 23 mm valve according to the completion aortogram performed during the balloon valvuloplasty. Just after the implantation the valve migrate into the ventricle. Therefore, we started percutaneous femoral extracorporeal circulation. The extra-support Amplatz® wire was still in place.

To avoid a conversion through median sternotomy we decided to remove the embolized valve through the apical access. We inflated the balloon into the embolized valve and pulled all the system through out the apex. We used a mosquito clamp to crush the valve and to re-crimp it on the balloon in order to decrease the size of the all system to remove it through the apex (Fig 3). Once the sheath and the valve were removed out of the patient we used the purse string sutured to close the apex while we reinsert the 32 F sheath into the apex.

We decided to prepare a second Edwards Sapien valve of 26 mm. We implanted successfully the second valve. Apical closure was obtained by ligation of the 2 purse string sutures and 2 more extra pledgeted sutures using prolene sutures. After 48 minutes, extracorporeal circulation has been stopped. A pleural drain has been inserted in the left pleural cavity. The patient went to the intensive care unit with a stable hemodynamic condition. After review of the aortic annulus size, we concluded that the reason of embolization was an undersizing of the aortic annulus. Unfortunately this patient had a non cardiac relate death at day 3 from multiple organ failure due to her comorbidities.

Ventricular embolization of the Edwards valve is a major complication of TAVI however transapical access offer the advantage of explanting the embolized valve through the apex and also to implanted properly and safely the second valve to treat the aortic stenosis of the patient without conversion to sternotomy. This transapical access advantage has been published (19) (Annexe Publication 3).

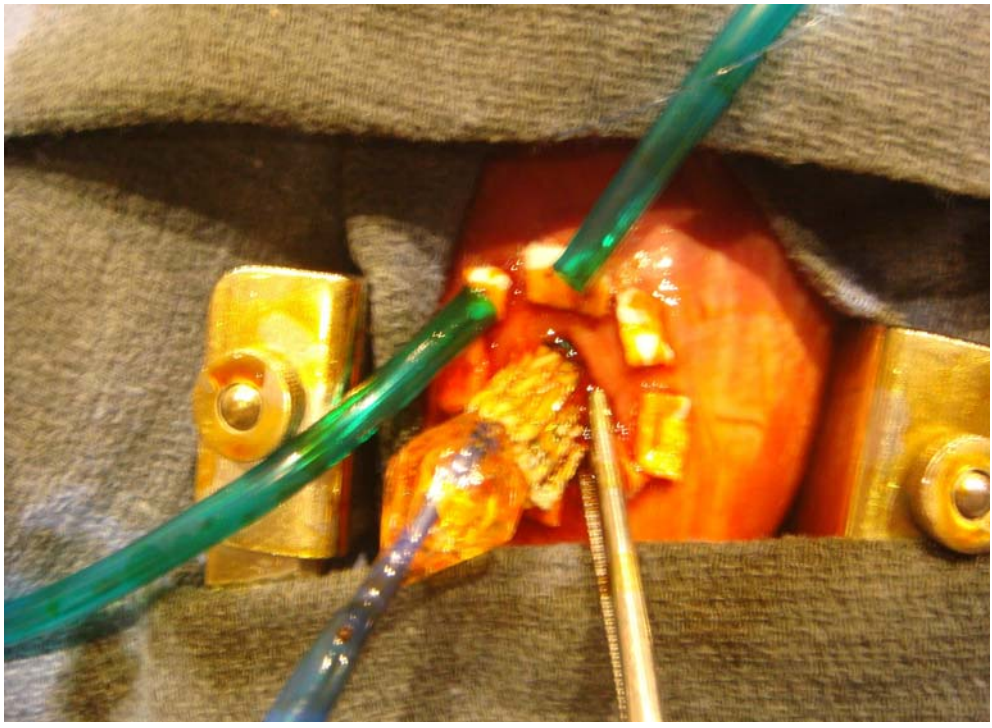

Figure 3

Transapical embolised valve extraction published by our team (19) (Annexe Publication 3)

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CHAPTER 5: CEREBRAL EMBOLIZATION DURING RESECTION.

The main issue of resecting the valve in patients will be the risk of leaflets debris embolization. We can easily imagine that the resection device cut a calcified leaflet and some calcic particles could be sent into the blood circulation and went to the brain.

In order to quantify this risk we decided to perform first study that will give us an answer on what is the cerebral impact to day, using such a new technology like TAVI. We enrolled all our TAVI patients in a study protocol of DW-MRI of the brain before and after standard TAVI procedure without resection of the native valve.

5.1 Stroke rate after TAVI

The early experience with TAVI indicates that the incidence of clinically apparent neurological events varies widely. A broad review of all reported series reveals a range of such events of from 0% to 10% (Fig 1). It is important to note that these reports describe initial experiences with a variety of approaches to TAVI, including transfemoral and transapical procedures, as well as utilization of both the Edwards valve and the CoreValve.

The most recent trial to be completed and published is PARTNER US (1). Cohort B randomized 1058 patients deemed not suitable for surgical AVR to transfemoral TAVI

Incidence of stroke with TAVI

Study	Year	Valve type	Patient Population	Incidence of stroke	
Thomas et al	2008	Edwards	TA 575	TA :	2.6%
		Edwards	TF 463	TF :	2.4%
Walther et al	2006	Edwards	TA 50	TA :	3%
Grube et al	2006	Corevalve	TF 86	Major Stroke	4%
				Minor Stroke	7%
Bleiziefer et al	2009	Edwards	TA 50	TA :	0%
		Edwards	TF 151	TF :	7%
Rodes-C. (4)	2011	Edwards	TA 177	TA :	0.6%
		Edwards	TF 168	TF :	0.6%
Leon (1)	2010	Edwards	TA 71	TA :	2.8%
		Edwrards and Corlvalve	TF 161	TF Edwards	4.2%
				TF Corvalve	4.5%
King (3)	2011	Edwards	TAVI	TAVI	5.5%

Figure 1

Incidence of Stroke rate in the literature.

The mean Stroke rate is ranged from 0.6 % to 7 % in TF access

The mean Stroke rate is ranged from 0 % to 3 % in TA access

or medical treatment. At 30 days, the overall incidence of stroke was 6.7%; 5% were defined as “major” and 1.7% as “minor.” At

1 year, the overall rate was 10.0% (7.8% major, 2.2% minor). As compared to medically managed patients, the overall stroke rate was greater in the TAVI group (6.7% vs. 1.7%, P=0.03). Moreover, the occurrence of a major stroke was associated with significantly greater mortality (p<0001). Due to the lack of a consistent definition of neurological events in the PARTNER trial, it is hard to understand the exact timing of these events and their relation to procedures performed (e.g., TAVI procedure or balloon aortic valvuloplasty in the medical therapy group). This issue was address by constructing the Valve Academic Research Consortium definitions for adverse neurological events (2). Atrial fibrillation was present in a significant proportion of patients with neurologic events in both groups. Of note, there was no standardized protocol for anticoagulation in the TAVI group, so it is impossible to assess the effect of various anticoagulant regimens on the incidence of neurological events.

In cohort A of PARTNER US (3), 699 high-risk patients were randomized to TAVI (n=348) or surgical AVR (n=351). The results showed that the incidence of all strokes or transient ischemic events at 30 days was significantly higher in the TAVI group (n=19, 5.5%) compared to the surgical group (n=8, 2.4%, p=0.04). However, no significant differences were found in the major and minor subgroups. The results at 1 year also demonstrated a significantly higher risk of stroke in the TAVI group (p=0.04). Since the transapical approach to TAVI avoids the risk of catheter manipulation in an atherosclerotic aorta, it

was anticipated that this approach might avoid some of the stroke risk associated with the femoral approach.

5.2 Silent cerebral lesions after TAVI

As is true of surgical AVR, silent cerebral events are more frequent than clinical stroke with TAVI procedures. There are several reports (Fig 2) of DWMRI before and 48 h to 5 days after TAVI. The intent of each study was to detect new cerebral lesions and to compare those results to clinical events. In some studies, an additional MRI was performed several months after the TAVI to look for long-term changes. Moreover, most of the study protocols included neurological examination and comprehensive neuropsychological assessment. These reports describe a high incidence (68%–84%) of new lesions at the MRI (4-7). Most were multiple and had characteristics of ischemic lesions, probably due to emboli. Comparable studies with surgical AVR suggest that such lesions are more frequent with TAVI. Kahlert et al. directly compared the incidence of silent lesions in surgical AVR and TAVI (6). There were no overt neurological events with either approach, but new “silent” lesions were found in 84% in the TAVI group and 48% in the AVR group. Patients undergoing TAVI were significantly older than those undergoing open cardiac surgery (80.0 versus 67.4 years; $P<0.001$). In addition, patients in the TAVI group had significantly higher logistic EuroSCORE and significantly more comorbidities than did patients in the AVR group. Importantly,

80% of the new lesions had disappeared by the 3-month MRI exam. Thus, it appears that “silent” DW-MRI lesions are significantly more frequent after TAVI. The majority resolve within a few months.

Incidence of silent cerebral lesions with TAVI

Study	Year	Valve type	Patient Population	Incidence of stroke
Ghanem (5)	2008	Corevalve	TF : 30	TF : 72.7%
Kahlert (6)	2006	Edwards	TF : 22	TF : 84%
		AVR	AVR : 21	AVR : 48%
Rodes-C. (4)	2011	Edwards	TA : 31	TA : 71%
		Edwards	TF : 29	TF : 66%
Arnold (7)	2011	Edwards	TA : 25	TA : 66%

Figure 2

Incidence of Silen Cerebral Lesions rate in the literature.

The mean Stroke rate is ranged from 66% to 84 % in TF access

The mean Stroke rate is ranged from 66% to 72% in TA access

Reports from the initial TAVI series suggest that new procedurally related brain injury is more frequent after TAVI than after surgical AVR. As noted earlier in this review, 84% of

TAVI patients have DW-MRI identified cerebral lesions as compared to 48% of patients after surgical AVR. These observations must be regarded as tentative. The available data are limited, and TAVI patients are very different with regard to age and the prevalence of comorbid illness from those accepted for surgical AVR. A potential tool for assessment of the timing of embolism during TAVI is the transcranial Doppler; however, no systematic study has used this tool to determine timing of intraprocedural brain embolism.

5.3 Differences between the access sites

Intuitively, one would expect that as compared to the transfemoral approach, transapical TAVI might be associated with fewer cerebral embolic events. In transfemoral TAVI, repeated manipulation of large catheters in the aortic arch, crossing of the calcified valve, balloon dilatation, and valve deployment all promote embolism. On the other hand, transapical TAVI, an anterograde procedure, limits manipulation within the aorta. Although it is intuitively unlikely, embolism attributable to catheter manipulation in the aorta or retrograde crossing of the aortic valve may not be the only, or even the primary, mechanism. Thus, embolism-provoking mechanisms common to both approaches must be considered. One such possibility is that air embolism attendant on the use of very large catheters and the necessity for multiple catheter exchanges may increase the risk of embolization (4). This

possibility reemphasizes the necessity for careful flushing of the catheter before insertion and assiduous checking for air bubbles within the catheter throughout the procedure. It is also plausible that emboli originate from the aortic valve itself. Importantly, both transapical and transfemoral TAVI involve two manoeuvres during which the aortic valve leaflets are maximally stretched. This happens with preparatory dilatation of the aortic valve and during the valve implantation itself. These manoeuvres could be associated with dislodgment of calcium fragments and cerebral embolism. Embolism is not the only potential reason for the development of new periprocedural lesions.

5.4 First Brain MRI Study during TAVI without resection

Neurological complication is a dramatic postoperative event especially in this population with poor life expectancy. Therefore, TAVI was first proposed to this very frail population with the expectancy to decrease the mortality and morbidity related to the procedure.

Magnetic Resonance Imaging, and especially the diffusion-weighted imaging, is nowadays the most powerful tool for diagnosing acute ischemic brain lesions, and is become a surrogate marker for clinical and subclinical brain embolism (8). DWI has already been used to evaluate the incidence of silent

infarcts after angiographic procedures and carotid endarterectomy or stenting (9).

Therefore, we analysed clinical and subclinical brain embolism by DW-MRI in a single-centre, prospective, non-randomized study to evaluate per procedural embolic events in patients undergoing TAVI. We compared the cerebral embolic events between the TF and TA approach using Edwards Sapiens valve. We also compared the TAVI group to a conventional AVR group.

Incidence of new cerebral lesion was 90% in Transfemoral access, 92 % in Transapical access and only 7% in the control surgical group.

The mean number of cerebral embolus per patient was 6.0 in Transfemoral, 6.6 in Transapical and only 0.1 in the surgical group.

The mean volume of cerebral ischemic lesion was 475 mm3 in Transfemoral, 2170 in Transapical and only 36 in the surgical group.

The majority of the lesions were located in the left brain. The new embolic lesions were located in supr-(superficial) and infra-(deep) tentoral regions.

This study confirms that silent neurological lesions occur more often after transcatheter aortic valve implantation than after conventional aortic valve replacement. None of the patients with embolism were symptomatic.

We failed to demonstrate that antegrade approach by Transapical access have less embolization than retrograde approach by Transfemoral access with a higher rate od aortic arch manipulation. Those results have been published (10) (Annexe Publication 4)

Therefore we analysed the fact that embolization have nothing to do with the antegrade or retrograde approach. Embolization rate being similar in both approaches we thought that it could occur during balloon valvuloplasty manoeuvres or during stent deployment.

We designed a second study with another group of patient who underwent only balloon valvuloplasty without endovalve implantation.

5.5 Second Brain MRI Study during TAVI without

In previous work, we established a higher incidence of post-procedure embolic events with TAVI compared to AVR. In the current work, we employed DW-MRI in a prospective study of clinical and subclinical brain embolism following TAVI in an expanded patient group, comparing the transfemoral and the transapical approaches. We also compared TAVI-related embolic outcomes with those of percutaneous balloon valvuloplasty in addition to results with AVR. For comparison and to determine the influence of balloon inflation relative to valve implantation, we included 11 patients undergoing balloon

valvuloplasty alone and 22 patients undergoing conventional AVR, all of whom also had pre- and post-procedural DW-MRI. Thus, the study population consisted of four groups: TF, TA, BV, and AVR.

The incidence of new lesions was 92% in the TF group, 94% in the TA group, 27% in the BV group, and 27% in the AVR group. No statistical difference was found between TF and TA and between BV and AVR. A clear statistical difference was found between TA-TF and BV-AVR with a $p<0.0001$.

The mean number and volume of embolic lesions per patient were respectively 5.4/438 mm3 for TF, 11.6/3414 mm3 for TA, 0.7/46 mm3 for BV, and 0.4/48 mm3 for AVR (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$).

This study confirms again that silent neurological lesions occur more often after TAVI than after conventional aortic valve replacement (11) (Annexe Publication 5).

As documented in our previous work (10), embolization may arise during retrograde or antegrade arch catheterization, during BV, or during endovalve implantation. In this study, we included as a fourth group patients undergoing BV alone, allowing analysis of the effect on embolism occurrence of balloon inflation alone without valve deployment. As the results indicate, only 27% of the BV patients had embolism, compared to over 90% for each of the TAVI groups. This outcome suggests that embolism is much more associated with valve

deployment than with balloon inflation. No patients had clinical stroke after BV in our study.

The incidence of cerebral silent embolic lesions is high during TAVI, whether the TF or TA approach is used. The embolization seems to be associated with valve deployment rather than with balloon inflation. The conventional on-pump aortic valve replacement is still the “gold standard” treatment and is associated with a lower risk of cerebral embolization, but the potential benefits of using protection devices must be assessed in further studies.

5.6 MRI Study of the brain: TAVI with resection

Next step will be a brain MRI study in TAVI patient with native valve resection.

The engineering work on developing the resection tool is on going. As soon as the pre-clinical evaluation of the resection will be finished we plan to design a new brain MRI study in patients who will benefit of native valve resection prior to endovalve deployment.

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CHAPTER 6 : ENDOVASCULAR RESECTION DEVICE.

To day, percutaneous aortic valve replacement either via transfemoral or transapical access is a fast developing new approach to minimize concomitant trauma and is currently even suggested as an alternative to heart valve surgery in selected high-risk risk patients.

However, the calcified native valve remains in situ and has to be squeezed into the aortic wall by balloon valvuloplasty prior to the endovalve implantation procedure. As demonstrated in chapter 3, the prosthesis may be implanted in an inhomogeneous and non-circular calcific layer, leading to distortion and geometry change of the prosthesis and of the aortic annulus, respectively. Paravalvular leakage and a high percentage of total heart block are of concern with a potential negative influence on long term durability of the implanted prosthesis. Therefore, the endovascular resection of the degenerated native heart valve would be advantageous prior to TAVI.

6.1 State of art in the literature

The first published paper on resection prior to TAVI is from Quaden et al in 2005 (1) about his initial experience with aortic valve resection in 10 porcine models using a high-pressure water stream scalpel.

He used a high-pressure water stream with a maximal pressure of 150 bars from. An inflated polyethylene balloon was positioned directly beneath the aortic valve to protect the subvalvular area.

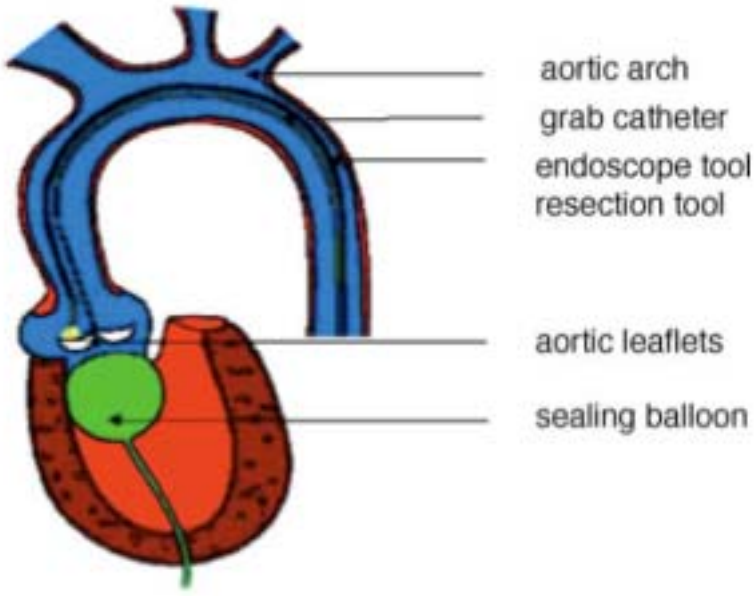


Figure 1

Transapical aortic valve resection tool using a water stream jet hold into an endoscope as drawn in this set-up (1).

The aortic wall, the coronary ostia, the mitral valve and the left ventricular out flow tract were macroscopically and microscopically analysed for possible lesions. The resection stream was manually controlled by a flexible endoscope. The resection of healthy porcine leaflets was easily performed and ablated completely using a mean pressure of 60 bars. The endoluminal resection took 12.2±0.8 min.

Macroscopic examination revealed four superficial lesions in the aortic wall and one on the aortic annulus and the coronary ostium. The aortic annulus was injured in 6 cases by the process but no perforation occurred.

Microscopic analysis demonstrated superficial lesions of the aorta of 1600 um.

The interesting finding of this paper is the concept of an aortic valve resection chamber between two balloons. However the stream jet is too powerful that in 4 cases the balloons have ruptured. The other inconvenient is the resection time of more than 12 minutes. Finally the resection has been done on non-calcified leaflets. We could easily speculate that the resection of calcified leaflets will need more powerful water jet and more time to achieve the resection.

The same team published another paper three years later using a YAG laser (2). An aortic valve isolation chamber has been additionally developed to avoid the escape of any debris during valve excision, consequently preventing central or peripheral

embolization. The aim of this study was to analyse the laser-assisted endovascular resection of sclerotic human aortic valves in situ in 10 human cadavers using a YAG laser with a 20-W power rating.

The mild-to-severely sclerotic aortic valves were resected by a diode-pumped continuous-wave YAG laser emitting at a wave-length of 2.01 mm with 20W power rating catheter. The endoscope was inserted through the right carotid artery (Fig 2).

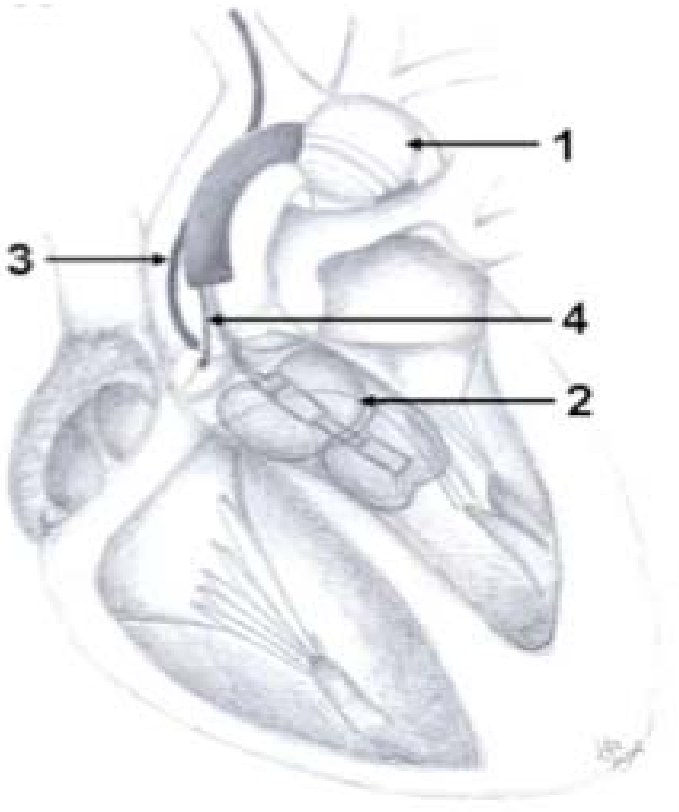


Figure 2

Transapical aortic valve resection tool using a YAG laser (2).

1-Distal balloon, 2-Proximal balloon, 3- YAG fiber, 4-Optic fiber.

A permanent lavage of 1.58 L/min was established by a rotary pump to ensure a clear view during the resection process. Additionally, the debris was washed out.

The resection process took a mean of 6.0±3.6 minutes per cusp so the total time of resection was over 18 minutes per valve.
Macropathology and micropathology demonstrated superficial lesions and one complete perforation of the aortic wall. The mitral valve, left ventricular outflow tract, and endomyocardium remained unaffected.
Visualization was adequate to display the structures of interest during the entire experiment using the permanent lavage of 1.5L/min saline. The endoscope allowed acceptable guidance of the laser fiber during resection.
The results demonstrate that endoluminal resection with percutaneously inserted instruments is feasible. Except for the perforation of the aortic wall seen in one case, the macroscopic and microscopic analysis showed only mild damage.
However, efforts must be undertaken to improve the tractability and the preciseness of the resection tools and to shorten the required resection time. In the case of highly calcified aortic valves, the implemented continuous laser was not effective.
In the same way, Bombier published a paper in 2009 (3) about histological analysis of the YAG laser aortic valve resection. In opposition with Quaden who use the retrograde transcarotidien approach, Bombier used a transapical approach. They resected

20 human cadaver aortic valves. Three lesions in the aortic annulus were observed (Fig 3). Gross anatomy of the ascending aorta shows no abrasions of the intima. Aortic annulus was affected in 4 cases. The mitral valve was not affected.

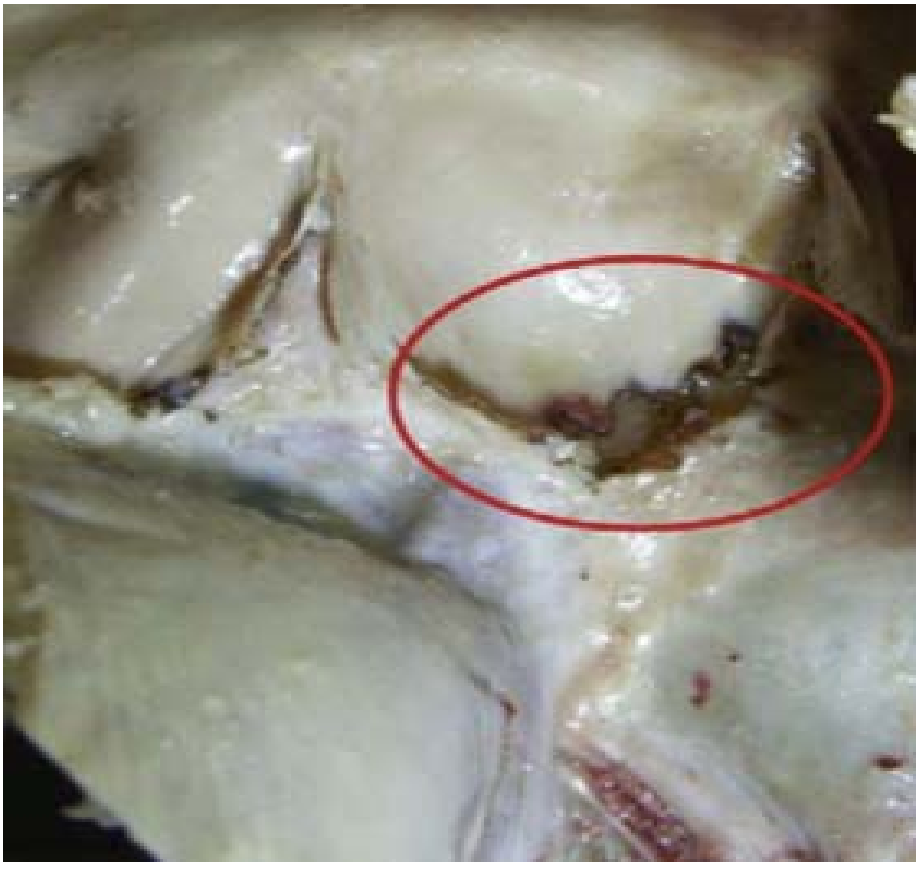


Figure 3

Macroscopic analyse of the injured aortic annulus resected by YAG laser

This study shows that the transapical access to the aortic valve is less traumatic than retrograde approach. This reinforces our access choice that we described in chapter 4.

In 2009, Wendt et al published a new minimal invasive aortic valve resection tool (4). The basic idea of this innovative tool is the easy handling and short time procedure concept (Fig 4).

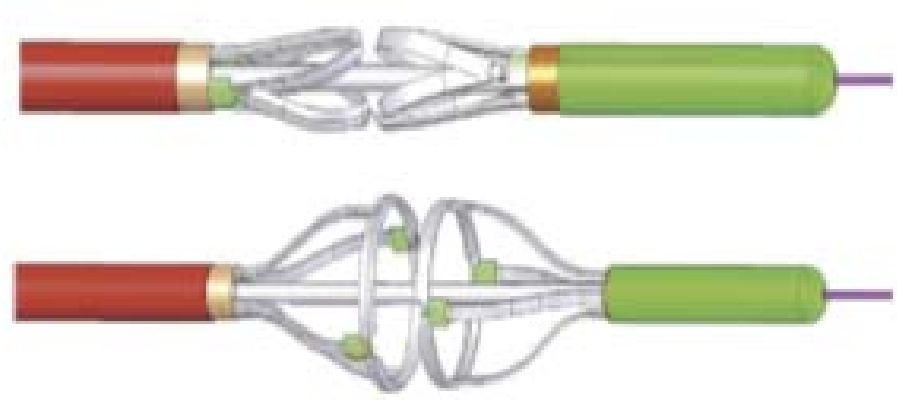


Figure 4

Nitinol expandable blade concept form Wendt team (4).

Aortic valve resection should be performed by a blade-expanding mechanism, enabling different cutting diameters depending on the previous mounted cutting edge. In this approach, the major aim of the author was to reduce the resection time to less than 30 seconds. An interim solution cutting device prototype for the open situation as a primary step

towards the transapical approach was designed. In the open situation only one blade (distal one) is used and a fixed ring acts as the counterpart.

The experiments were performed with 21 mm diameter cutting edges. The whole structure could be folded and retracted into the sleeve of the instrument. The real cutting procedure was obtained by counter rotating the blade against the stable counterpart.

They tested the resection on commercially available aortic bioprosthetic valves calcified using ingredients like calcium, collagen, bone glue and hydroxy-apatite.

They showed a significant lower resection time compare to the other authors. In 8 moderately calcified specimens the resection time was 15.5±3 seconds and in 8 severely calcified specimens the resection time was 34.9±15 seconds.

In my opinion, this nitinol blade seems to be a step towards the endovascular resection device solution.

6.2 Development of our own resection device.

For this purpose, in 2008, I developed an innovative prototype of a novel heart valve resection tool based on a circular blade of 18 mm diameter. This first prototype has been tested on animal aortic valve. We bought 10 sheep hearts from a Boucher shop in order to test the handling of the device. The device prototype

has been introduced through the apex of the heart and the non-calcified aortic valve has been reached easily. The resection of this very thin tissue was perfect. Those are our unpublished. Further developments on the novel circular blade device have been performed in collaboration of the engineering department of our University.

We developed a second a 20 mm diameter resection tool because the first one was eroded during a sterilization process. With this second tool we tested the resection on fresh cadavers.

The device trials were performed in human cadavers undergoing necropsy analysis. Inclusion criteria were the presence of aortic valve stenosis and leaflet calcification observed after aortic trans-section at the level of ascending aorta. From June 2009 to January 2011, 15 suitable cases were selected. The outcomes for the study were resectability and the measurements of forces needed to the cut.

The heart was explanted with a segment of ascending aorta. The instrument was inserted through the apex and the resection was performed under visual inspection (Fig 5). Once completed. The resected area was measured directly by the insertion of a surgical probe.

The resected leaflets were sent to the engineering bench to cut them again and the force needed was quantified. Force results were reported in Newton. The resected leaflets were mounted on a circular platform. The platform was clamped on 6 degrees of freedom force sensor. The 3 reaction forces and 3 reaction

torques needed to perforate the leaflet and to cut the leaflet were measured by the sensors. Four experiments were performed using a perforation blade and ten experiments were performed using a cutting blade. A post treatment then computed the longitudinal force (leaflet perforation force) and the transversal force (leaflet cutting force).

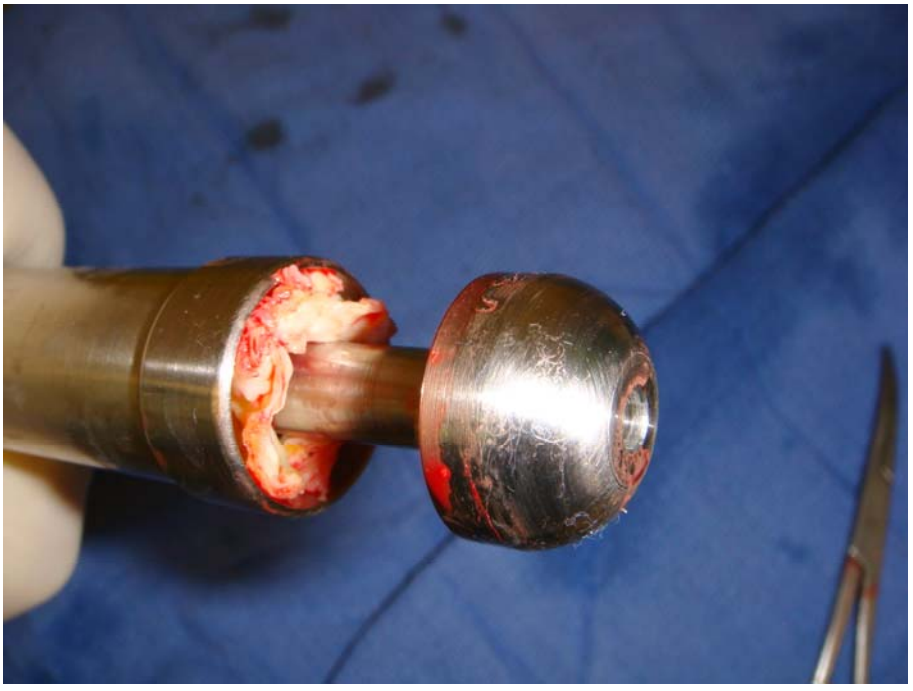


Figure 5

Our second prototype of transapical aortic valve resection device used on fresh cadavers (5).

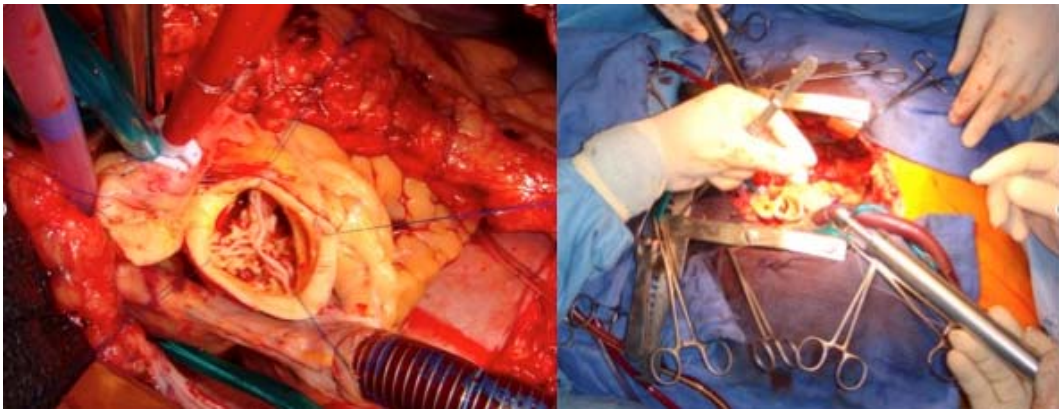
The resection was successfully completed in 14/15 (93%) cases. All the resected leaflets and debris have been captured successfully in 15/15 (100%) procedures. One case with a bicuspid valve had a prominent calcification of his median raphe. The resection tool could only perform a partial resection.

The mean annulus diameter of aortic specimens measured by probe insertion was 24.2± 1.9 mm. The mean resected area diameter measured by probe insertion was 20.0mm. This is perfectly correlated to our instrument blade size of 20mm. The surrounding myocardial tissue examination did not reveal any injury of the anatomical structures. Analysis of the resected leaflets provided a mean leaflet thickness of 0.5±0.1 mm and a mean calcifications thickness of 4.1±0.5mm. The mean leaflet resection force was 7.1±3.7 N (Min=2.0 N and Max=11.5 N). The mean leaflet perforation force was 7.3±7.2 N (Min=1.0 N and Max=16.3 N). The mean duration of the resection was 45 ± 30 seconds. Our results have been published recently (5) (Annexe Publication 6)

The third prototype has been made using surgical instrument material. The aim was to use it in operating theatre during conventional aortic valve surgery. Once the patient is on-pump and the ascending aorta is opened, rather than removing the native leaflets classically we used our resection device by transaortic approach. The aortic valve is exposed and the device is inserted carefully through the aortotomy (Fig 6a). After the resection we obtained an orifice of 20mm diameter, which is fixed by the diameter of our device. In patients with an annulus

diameter superior to 20mm, he remaining leaflet cuff was resected by a classical surgical blade (Fig 6b).

a



b

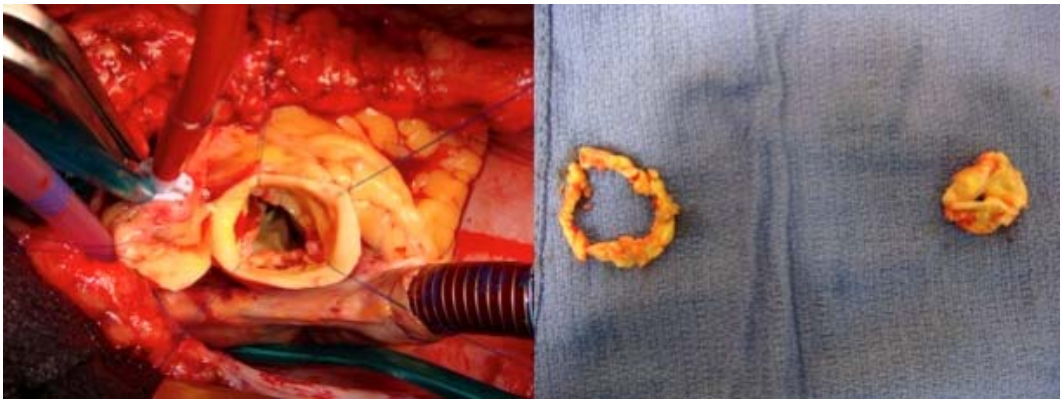


Figure 6

Our third prototype of transaortic aortic valve resection device used in the operation room during conventional AVR

a- Stenotic aortic valve and device insertion.

b- Device resected orifice and obtained leaflet fragments.

References of chapter 6.

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CHAPTER 7 : FUTURE PROSPECTIVES.

The future goal of catheter-based aortic valve replacement will be use of the percutaneous approach. The transapical method has a good chance to become relevant in clinical routine, but preparations of the annulus even to complete removal of the native diseased valve will be key issue, especially in younger patients. If a safe surgical percutaneous technology with an equal outcome to current open aortic valve replacement is available in 5 to 10 years, every patient would choose this technique. Therefore, the tractability and the preciseness of the resection tools have to improve to perform a safe, fast and complete pre-treatment of the valve.

Our transcatheter resection device is now patented and for further development a BIOWIN project has been accepted. The close collaboration between our surgical team of Clinique Universitaires Saint-Luc, Engineering department of Université Catholique de Louvain and the Mediline industry to manufacture the device will give us all the chances to finalise the motorised and miniaturised expandable transcatheter aortic valve resection blade. A research work line of 4 years is established and we should have a new fourth generation device very soon to test it. Our plan is to follow all the steps to validate our tool as a CE marked medical device.

CHAPTER 8 : CONCLUSIONS

Based not only on our 6 original articles but also in all the surgical trends that we feel reading the most recent scientific papers on TAVI, I conclude to the fact that in the nearest future all the aortic valves will be replaced after careful resection of the native diseased leaflets using transcatheter based technology. I would like to make a philosophical digression on TAVI. The adoption of TAVI or any other technology will be driven by: user-friendliness, teachability, validation of clinical benefit, patient preference, regulation and reimbursement. Regarding patient preference, he will almost always choose the less invasive approach even if it's less effective. If a less-invasive therapy is not inferior compared to a more invasive conventional procedure, then it is superior.

All this new technology arrives at a time when our equanimity is shaken by new less invasive and endovascular technology. To day we no longer control the non-surgical approaches of coronary disease, of some congenital disease and now of the adult valvular disease. The pendulum swing away and changes occur.

This is a disruptive time in the history of cardiothoracic surgery. In the beginning, our specialty was a fount of innovation. It is tempting to say that percutaneous technologies are not within the domain of cardiac surgeons and that we as a specialty are not going to be able to move into this technological arena. If this

is the case, our specialty is going to become smaller and the impact of our specialty on the anatomic treatment of heart disease is going to become much less important. The same evolution has been seen in vascular surgery when the interventional radiologist started to treat iliac and femoral occlusion by balloon angioplasty and stenting. Hopefully the vascular surgeons have dived into the percutaneous procedures very quickly. To day the vascular surgeon have in his therapeutic artillery both open surgery and endovascular technology. Cardiac surgeons need to follow the same clever steps than vascular surgeons have done to embrace new techniques.

I don't have crystal balls about the future but what I know is the fact that our future is predicated by on our past experiences. In my humble opinion, cardiac surgery as it is now, is neither dead, nor dying. This statement is may be exaggerated but like any other successful profession or florid business that grow and at some point die. It is how we make the adaptation to change, which will determine our future. There is a long list of things we could or must do as a cardiac surgeon to secure our future. There are some themes that we must partner with industry and embrace new technology, we must have better control of imaging, we must participate in solid scientific prospective clinical trials, we must work harder to recruit the best and the brightest to our specialty, we must understand and practice the art of mentorship, we must retrain, we must be proactive and

bottom line, we must be patient obtaining real data, we must constructively adapt to disruptive challenges.

We are involved as surgeons in the development of that new valve technology. We must have dynamic leadership in all aspects of the clinical, academic, educational, administrative, and political arenas. We are also seeing the unrealistic expectations and favourable early published results of percutaneous technologies coming back down to statistical reality. Fro example, the unbelievable clinical results with drug eluting stents might not be as wonderful as initially reported, and in fact, may be even more dangerous long term than coronary bypass surgery. Hopefully such emerging data will allow better comparison with outstanding long-term historical surgical controls. The pendulum is swinging again and now backs towards us.

Cardiothoracic surgery is a fantastic speciality and cardiothoracic surgeons are uniquely qualified to be able to use multiple technologies to solve complex cardiac problems including percutaneous valve replacement technologies. Certainly our cardiology colleagues have become skilled and imaginative in the use of percutaneous catheter-based technologies, but they are limited to that one technological strategy. As cardiovascular surgeon, we do procedures and have responsibility that few of other physicians are given the opportunity to have. We take care of some of the sickest patients but we effect some of the most dramatic favourable outcomes. We truly make differences in peoples lives.

I am very proud to be a fully trained cardiovascular surgeon for open surgery and for endovascular techniques. I am proud to work in Cliniques Universitaires St-Luc, which is for me one of the most prestigious place in the world.

Annexe Publication 1

TAVI induced complications will push us to perform transcatheter resection of the native aortic valve prior to endovalve implantation.

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Editorial

Key words : TAVI, valve resection, novel tools

The remaining native valve is the cause of transcatheter aortic valve implantation (TAVI) complications that I will describe below. For this reason I decided to focus my research on the native aortic valve resection prior to transcatheter valve implantation.

The complications due to the compression and the squeezing of the diseased native aortic leaflets between the endovalve and the aortic wall are listed and clearly demonstrated.

1- Paravalvular leak
2- Atrio-ventricular bloc
3- Coronary ostia occlusion
4- Continuous rubbish calcium embolisation
5- Mismatch of the size of the implanted endovalve.

The rapid and substantial improvements in TAVI technology and the increasing center experience in the past few years, the results obtained in multi-center registries and, more importantly, the results from the high-risk cohort of the PARTNER trial have provided the basis for evaluating whether TAVI should be used for the treatment of a lower-risk population with aortic stenosis. Indeed, some preliminary results of TAVI in intermediate- risk patients with severe aortic stenosis have been promising (1).

There is already reports about TAVI in low risk patients. Lange (2) reported a series of 420 patients who underwent TAVI using Corevalve or Edwards Sapiens valve. Patients undergoing TAVI in the first quartile had significantly higher logistic EuroSCORES than those in the second, third, or fourth quartiles (Q1: 25.4±16% vs. Q2: 18.8±10% vs. Q3: 18.3±11% vs. Q4:17.8±12%, analysis of variance $p < 0.001$). The Society of Thoracic Surgeons (STS) score was significantly lower in Q4 than in Q1, Q2, or Q3 (Q1: 7.1±5.4% vs. Q2: 6.2±3.5% vs. Q3: 5.8±3.9% vs. Q4: 4.8±2.6%, analysis of variance $p < 0.001$).
From Q1 to Q4, the crude 30-day mortality rate significantly decreased from 11.4% to 3.8% (chi-square test, p=0.03) (unadjusted HR: 0.33; 95% confidence interval [CI]: 0.11 to 1.01; p=0.051) and the 6-month mortality rate significantly decreased from 23.5% to 12.4% (chi-square test, p=0.031) (unadjusted HR: 0.49; 95% CI: 0.25 to 0.95; p=0.072).
There were no significant differences in mortality rate observed between Q1 and Q4 after adjustment for baseline characteristics at 30-day and 6-month follow-up (30-day mortality rate adjusted HR: 0.29; 95% CI: 0.08 to 1.08; p=0.07) (6-month adjusted mortality rate HR: 0.67; 95% CI: 0.25 to 1.77; p=0.42).
This suggests that baseline characteristics play a role in the clinical outcomes of transcatheter aortic valve implantation patients at 30-days and 6-month follow-up. They conclude that the results of the study demonstrate an important paradigm shift toward the selection of lower surgical risk patients for TAVI. Significantly better clinical outcomes can be expected in lower than in higher surgical risk patients undergoing TAVI. As TAVI becomes more routine and widely available, operators may be tempted to implant the device in younger patients with less comorbidities. Uncertainties about the long-term durability, in addition to the unresolved issues of paravalvular leak and conduction abnormalities, should be cautiously weighted gainst the immediate benefits being widely reported.
So clearly performin TAVI in young patients without native leaflets resection is unacceptable regarding the excellent results that surgical aortic valve replacement in those young patients.

Two new TAVI studies on intermediate- risk patients are planned in the near future. The first one is the cohort A of the PARTNER II trial (3), investigators will randomly assign patients with aortic stenosis and STS score of 4–8% (that is, intermediate risk), or specific qualifying intermediate risk criteria requiring formal petition to the executive committee heart-valve

team (which will include cardiac surgeons and interventional cardiologists), to TAVI or aortic valve replacement (AVR). Patients with concomitant coronary artery disease will be substratified to percutaneous coronary intervention plus TAVI versus CABG surgery plus AVR. The estimated sample size is 1,500–2,000 patients, and ~50 US centers are expected to participate. The second one is the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial 120 will include elderly (≥70 years) patients with aortic stenosis and an STS score of 3–8%. Approximately 1,200 patients will be randomly assigned to TAVI or AVR, and ~40 European centers are expected to participate. The results of these randomized trials should determine the exact role of TAVI for the treatment of low-risk patients with severe aortic stenosis. valves, which opens up a new avenue for the treatment of this challenging group of patients (4,5).

In this editorial we will demonstrate the necessity of resecting the native aortic valve prior to the deployment of the endovalve. The cited five major complications related to the remaining native valve are going to be reviewed in detail.

1-Paravalvular leak post TAVI

Percutaneous TAVI has extended our ability to treat patients with severe symptomatic aortic stenoses being no or poor candidates for open heart surgery (6). At the present time two different devices are available, one self-expandable, porcine pericardial leaflets, and nitinol frame, and the other one balloon-expandable, bovine pericardial leaflets, and Cobalt-Chromium frame. Both devices have shown good performance once implanted, with transvalvular gradient and effective orifice area that are respectively lower and higher than that observed in surgical valves (7-13). However, TAVI may result in severe complications, starting with vascular injuries, cerebral or peripheral embolisation, pericardial effusion, ventricular rupture, conduction abnormalities, aortic dissections aortic regurgitation and paravalvular leak.

Regurgitation originating between the prosthetic sewing ring and the native valve annulus is a well-known phenomenon reported as paravalvular, perivalvular and peri/ or paraprosthetic leaks. In surgical series, the occurrence of paravalvular leak (PVL) has been reported in very few cases, being 2% and 8% after a bioprosthesis or mechanical prosthesis implantation, respectively (14). Thus, it does not represent a main issue in the context of surgical aortic valve replacement and is not addresses in the current guidelines for valvular heart disease (15).

In contrast to surgical aortic valve replacement, during TAVI procedure the native valve is not removed but crushed. Thus, a slight aortic insufficiency is not uncommon and has been reported in about 70% of patients for both available types of percutaneous valves (16-19). On the other hand, a moderate regurgitation has been observed in up to 40% of the cases (17-19). In most cases, aortic insufficiency is clinical acceptable, however, severe insufficiency can occur and although current reports mention treatment of such severe insufficiencies only very briefly (8-12), the problem is not trivial because the underlying pathophysiology can be very different. It should be also acknowledged that discrepancies in the prevalence of valve regurgitation after TAVI [7-8,20-21] are mainly due to the absence of standardized definition and protocols to detect (i.e angiography versus echocardiography) and score (qualitative or semiquantitative methods) the leak. Moreover the definition of clinically “significant” PVL is not fully established because of the lack of evidence exploring the pathophysiology of the valvular leak and its impact on outcome. More recently the Valve Academic Research

Consortium provided a consensus aimed to standardize definitions on technical and clinical end-points in TAVI procedure (22). Nevertheless, trying to estimate and quantify the valve regurgitation they adopted arbitrarily a standard classification that is commonly used to describe regurgitation in native valve.

Mechanism of the PVL.

The aortic insufficiency after TAVI might be classified taking into account the type of regurgitation, its mechanism, and the etiology. Paravalvular insufficiency may derive from a prosthesis/patient mismatch due to an undersizing of the implanted device, incomplete expansion of the prosthesis stent frame and to incorrect site of prosthesis implantation. On the other hand, intravalvular insufficiency might be due to the opening failure of the prosthesis' leaflets, to leaflets damage occurring during the crimping manoeuvre or during the implantation phase (postdilatation) or again to a prosthesis/patient mismatch because of an incorrect sizing of the valve.

Differently from surgical series, the direct sizing of native aortic annulus is not possible during TAVI, thus an accurate assessment of the latter is mandatory during the screening phase of the patient. The selection of the prosthesis that matches properly with the native aortic annulus is paramount to final procedural success, as the goal is to displace the native valve leaflets and deploy the device within the valve annulus. The native annulus should be identified with the virtual basal ring below the nadir of the aortic cusps, which provides the right plane of the annulus, that is not the anatomic ventriculo-aortic junction Different methods are used to assess aortic annulus measurement: echocardiogram (transthoracic or transesophageal), angiography, and computed tomography. There is not a gold standard for annulus measurement, and a multimodal assessment is strongly recommended (23), since the aortic annulus is not circular but might be ovoid in shape.

Tops et al. (24) reported that the annulus had an oval configuration in approximately 50% of patients evaluated for TAVI, with a mean difference between coronal and sagittal measurements of 3.0 ± 1.9 mm. An oval configuration of the annulus was also noted by Delgado et al. (25), who reported a significant difference be- tween mean coronal (25.1 ± 2.4 mm) and sagittal (22.9 ± 2.0 mm) measurements in 53 patients with severe aortic stenosis. This oval geometry of the annulus has been previously underappreciated on imaging but has been well described in the surgical literature. Therefore multiple measurements in different planes are recommended. To this regard, the clinical use of 3D echocardiogram may improve pre-TAVI evaluation, when compared to 2D echo, by the assessment of the aortic annulus in 3 planes. Moreover, a balloon-based annular measurement is an adjunctive tool to select the proper valve size. In fact, intraoperative evaluation of aortic regurgitation during balloon inflation for valvuloplasty increases the accuracy of the optimal device size selection (26).

Clinical impact of the PVL.

Clinical implications of valvular leak are not fully established. Although, in most cases, aortic insufficiency is stable during follow-up (12-16) and clinical acceptable, severe insufficiency can occur. More recently, some authors have shown that even less than severe valvular leak might be related to higher 1-year mortality after TAVI (12). When severe regurgitation is present, a mul- timodality imaging for an accurate assessment of the underlying pathophysiology of the valve regurgitation is of utmost importance to select the adequate therapy.

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in which we can implant an endovalve that fits much better the surrounding aortic annulus. The ovoid shape of the annulus is than transformed into a perfectly circular hole. The blade that we plan to use will be a circular sharp blade in order to remove the majority of the calcified leaflets. The diameter of the blade should be slightly lower than the native annulus in order to avoid any damage of the aortic wall and all the myocardial tissues.

2-Atrioventricular bloc.

The incidence of conduction abnormalities after TAVI has been reported widely. Conduction disorders necessitating a permanent pacemaker implantation are frequent complications associated to the procedure. In particular, the need for pacemaker implantation following TAVI ranges from 5.7% to 39% depending on the type of percutaneous prosthesis used (27,28). Studies assessing predictors of pacemaker implantation in the TAVI setting identified a number of candidate variables but were limited by the small sample size.

This complications may affect significantly the outcome of the patient, increase hospital stay, and overall cost and may be associated with an increased risk of sudden death.

The left bundle branch exits 2 to 3 mm below the base of the triangle formed by the non-coronary and right coronary cusps of the aortic valve, close to the annulus and left ventricular outflow tract. Therefore, aortic valve surgery and any cardiac catheterization procedure requiring crossing the aortic valve with guidewires and catheters carries the risk of trauma to the septal conduction pathways and particularly to the left bundle branch (LBB). Risk of AV block should be subsequently higher in case of pre-existing right bundle branch block (RBBB).

The reported incidence of AVB requiring a pacemaker after CoreValve implant ranges from 18% to 39% while the incidence of LBBB is about 50%. New onset conduction disorders and requirement of a pacemaker after implantation of an Edwards Sapien aortic bioprosthesis are infrequent (incidence of 4.3%). The Edwards Sapien prosthesis was specifically designed to respect nearby anatomic structures. Indeed, the lower limit of the Edwards valve should not reach the upper part of the interventricular septum and in contrast to the nithinol CoreValve's self-expandable frame, the stainless-steel stent used with the Edwards model does not keep expanding after valve deployment, thus decreasing the risk of delayed conduction disturbance (29).

Piazza et al. (28) in their series of CoreValve implantations reported the occurrence of new-onset widening of the QRS complex in 30% of cases immediately after preimplantation balloon valvotomy. Of note, in 1 of our patients who required permanent pacing, complete AV block occurred immediately after balloon valvotomy. The large valves used in TAVI can also result in compression of the upper transventricular septum and impair AV conduction. In their series of Edwards Sapien valve implantation, Sinhal et al reported that 10% of patients presenting with pre- existing RBBB may need implantation of a pacemaker. Interestingly, 7 patients in our series had complete RBBB before implantation and none of them developed significant conduction disturbances after TAVI.

For technical reasons, a deeper intraventricular insertion of the self-expanding CoreValve is generally observed. In the report by Piazza, the length of stent below the noncoronary cusp was calculated to be on average 10.3 mm (range 6.7 to 14.6) in a series of 40 patients., the cutting distance being 6.7 mm. In contrast to the Cor- eValve's nitinol frame, the stainless-steel stent used with the Edwards Sapien model does not keep expanding after valve deployment, thus decreasing the risk of delayed conduction disturbances and allowing a safe retrieval of the temporary pacing lead at the end of the procedure (29).

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in order to remove the majority of the calcified leaflets. This should lead to avoid the compression of the conduction tissues and preserve the native cardiac rhythm. The resection should decrease the incidence of new onset of AV bloc and decrease the pacemaker implantation after TAVI.

3-Coronary ostia occlusion.

A life-threatening complication is coronary artery stenosis or occlusion with a reported incidence of 0.6–7%. Those data are coming from SOURCE registry (33) and large series like the Canadian experience (34). Rapid diagnosis and a staged management are mandatory immediately to save the life of your patient. Any haemodynamic instability of a patient after or during TAVI might be suspicious for coronary artery obstruction or occlusion. The only treatment option after diagnosis is immediate reestablishment of blood flow by percutaneous techniques or CABG. In some cases, a cardiopulmonary support is necessary. The need for a heart team involved not only in decision-making, but also in the procedure itself is obvious.

Several conditions might predispose to coronary occlusion. A low-lying coronary ostium, bulky native leaflets, a narrow root, an excessively enlarged valve leaflet or the new valve prosthesis might result in coronary occlusion (35).

Crimi at al (36) report a case of a transapical aortic valve implantation complicated by acute left main (LM) occlusion, cardiac arrest, and hemodynamic collapse, successfully treated by balloon angioplasty and stent implantation. He state that Coronary occlusion is a rare, life-threatening complication of TAVI. Complete occlusion of coronary ostia occurs at the time of valve deployment and is usually associated with hemodynamic collapse. Immediate percutaneous recanalization can successfully restore normal hemodynamic conditions. Several patient- and procedure-related factors potentially associated to this event have been proposed and should be considered during the selection of the patients and work-up. Although their predictive value has to be confirmed by additional data, the prevision of coronary occlusion can allow the operator to establish measures such as positioning of a protective wire in the coronary artery at risk.

In all those reports, the coronary occlusion is not due to the endovalve itself but due to the native leaflets calcium or native leaflets height. Webb described it clearly in his report about 1 patient (37). Coronary obstruction by a displaced native valve was observed in a single patient. Until this is better understood, the presence of an unusually bulky left coronary leaflet appears to be a relative contraindication to percutaneous valve implantation.

Of course the distance between coronary ostia and the aortic annulus is crutial. The team from Vancouver published those data in the paper of Tops in 2008 (24). Mean distance between the aortic annulus and the ostium of the right
coronary artery was 17.2±3.3 mm, and mean distance between the annulus and the ostium of the left coronary artery was 14.4 ± 2.9 mm. In 82 patients (49%), the length of the left coronary leaflet exceeded the distance between the annulus and the ostium of the left coronary artery. There were no significant differences in the diameter of annulus, diameter of sinus of Valsalva, or the distance between the annulus, left coronary leaflet, and the ostium of the left coronary artery, between the patient with and without severe aortic stenosis.

Benefit of the native valve resection.

The aim of the resection is to perform a circular clean orifice in order to remove the bulgy calcification of the native leaflets. Even without any bulgy calcification the resection will decrease the height of the native leaflet which are responsible of the coronary ostia occlusion.

By resecting the native valve we expect to decrease this life-threatening complication in patients who underwent TAVI.

4-Continious embolisation of the rubbish calcium.

Neurological complication is a dramatic postoperative event, especially in this population with poor life expectancy (37). Indeed, cerebral damage after conventional aortic tool for diagnosing acute ischemic brain lesions, and has become a surrogate marker for clinical and sub-clinical brain embolism [6]. DWI has already been used to evaluate the aortic valve replacement (AVR) ranges from 0.21% to 2.0% for neurological death rate and from 1.1% to 6.6% for clinical stroke rate (38).

The rate of stroke reported in the TAVI literrature is an important matter. In the PARTNER trial Smith reported a rate of stroke that increases over the time (39). Rates of all neurologic events (i.e., all strokes and transient ischemic attacks) were higher in the transcatheter group than in the surgical group at 30 days (5.5% vs. 2.4%, P = 0.04) and at 1 year (8.3% vs. 4.3%, P = 0.04). Rates of major stroke were 3.8% in the transcatheter group and 2.1% in the surgical group at 30 days (P = 0.20) and 5.1% and 2.4%, respectively, at 1 year (P = 0.07). Most strokes appeared to be procedure-related and embolic. Rates of stroke were similar whether the access was transfemoral or transapical. Despite a higher frequency of stroke with transcatheter replacement, the composite end point of death from any cause or major stroke was similar in the two study groups at both 30 days and 1 year. Future studies will determine whether delivery systems with smaller diameters, procedural changes, or embolic-protection devices can reduce the inci- dence of stroke after transcatheter replacement.

Benefit of the native valve resection.

If we look to those data, this is for me, a clear argument to first use a protection device during TAVI procedure in order to decrease the rate of procedural stroke but also to resect the native rubish calcified leaflets squizzed between the endovalve and the aortic wall. That remaining calcium is at the oriin od the increased stroke rate at 1 year. I believe that if we clean this

aortic annulus by resecting the native valve we will decrease the continious embolisms and late strokes.

5-Mismatch prosthesis/patient.

Aortic valve replacement in patients with severe aortic stenosis and a small aortic annulus has been associated with a high incidence of prosthesis–patient mismatch (41-43). Prosthesis-patient mismatch (PPM) has in turn been associated with diminished extent of regression of left ventricular hypertrophy, reduced coronary flow reserve, increased incidence of congestive heart failure, diminished functional capacity, and increased risk of early and late mortality (44-47). In order to allow implantation of an appropriately sized prosthetic valve and prevent mismatch in a patient with a small aortic annulus, an aortic annular enlargement procedure or a complete replacement of the aortic root may be necessary at the time of aortic valve replacement. These procedures significantly enhance the complexity of the operation, and may increase morbidity and mortality, especially in elderly patients (48,49).

Transcatheter aortic valve implantation has emerged as an alternative to AVR in high-risk patients with AS. However, no specific data exist on the results of TAVI in patients with a small aortic annulus. So far, only a few small series (50-52) have described the incidence of PPM after TAVI, and little is known about its impact on LV performance and clinical outcomes in these patients.

Incidence of PPM in patients undergoing TAVI.

The present evaluation demonstrated that PPM is rather common and occurred in 18% to 20% of patients undergoing TAVI with balloon-expandable valves and between 30 to 40 % using self expandable valves. This difference can be partially explained by the fact that only 1 size of the device (26 mm, the smallest) was available at the time of TAVI in one-fourth of the patients (27%) in the reported series (52). In addition, the differences in prosthesis design may play a role. The Edwards SAPIEN valve is a trileaflet valve mounted on a balloon-expandable stainless stent frame that is 14.5 mm or 16 mm in height (for the 23- or 26-mm valve, respectively) and is implanted intra-annularly. Conversely, the CoreValve (designed for supra-annular implantation) has a longer frame of 53 or 55 mm (for the 26- or 29-mm device, respectively), with the lower third sitting within the LVOT
Patients with PPM were accompanied by less favorable changes post-TAVI compared with patients without PPM, with higher transvalvular gradient, limited LV mass regression, and LA volume reduction, and with persistent elevated LV filling pressures. Finally, more patients reported a lack of clinical improvement in the group with PPM.

To minimize paravalvular regurgitation and to ensure adequate annular sealing, it is generally recommended that the implanted prosthesis be slightly larger than the native aortic annulus for the currently applied percutaneous systems. For example, in the balloon-expandable delivery system of the Edwards SAPIEN valves, the 23-mm valve is used for aortic annulus between 18 and 22 mm, whereas the 26-mm valve is used for aortic annulus between 21 and 25 mm. Despite these indications, the current study showed that PPM developed before hospital discharge in 18 to 30% of patients who underwent TAVI.

Hemodynamic impact of PPM

In all the reports, patients with a PPM have less reduction of the mean transvalvular gradient compare to patients without PPM. The effective orifice area of the valve is higher in patients without PPM than in patients with PPM. The left ventricular mass index decrease much more in patients without PPM than in patients with PPM (Fig 3ABC). This has been clearly demonstrated by Ewe in 2011 (53).

Clinical impact of PPM

The presence of PPM negatively affected the improvement in NYHA functional class at 6 months post-TAVI. The suboptimal improvements in valvular hemodynamics and the higher residual afterload post-TAVI in patients with PPM could have contributed to the lack of clinical improvement. According to the literature, female gender is an independent risk factor for PPM. Using the indexed EOA as a parameter to define PPM, recent series (50-54) demonstrated that patients without significant PPM had better early and late mortality benefits. In addition, patients without PPMexhibit more freedom from congestive heart failure after aortic valve replacement.

Benefit of the native valve resection.

In conclusion surgeons who operate patients with a small annulus tends to perform additional steps to enlarge the annulus in order to avoid PPM because this is a complication who have a clear impact on patient post operative hemodynamic, post operative clinical status and long term myocardial effect. So, during TAVI we have to think about PPM and the resection of the native valve before implantation of the endovalve must increase the ejection orifice area. By doing the resection we can offer a better post operative result to our TAVI patients.

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Annexe Publication 2

"Ring Pledget"

A New Concept for Secure Apex Closure During Transapical Aortic Valve Implantation

Parla Astarci, MD, David Glineur, MD, Joelle Kefer, MD, Jean Renkin, MD, Jean-Louis Vanoverschelde, MD, PhD, and Gebrine El Khoury, MD

Abstract: Transapical aortic valve implantation requires puncture of the left ventricle apex and insertion of a 32-French delivery sheath. A critical step in the procedure consists of secure closure of the ventricular apex. We describe 2 cases of apical rupture of 42 transapical aortic valve implantations. Furthermore, we describe the use of a newly designed single circular Teflon pledget that can help to avoid this complication. This pledget provides a more secure and uniform shrinkage of the entire apex to close the defect left by the delivery sheath.

Key Words: Transapical, Apex closure, Aortic valve.

(*Innovations* 2010;5:136–137)

Transcatheter aortic valve replacement was first described by Cribier et al[1] in 2002 as a minimally invasive approach in high-risk patients. Two different approaches are currently under intense clinical investigation: the transfemoral and the transapical techniques.[2] In this report, we describe new technical modifications to prevent left ventricular (LV) apical tears during transapical aortic valve implantation.

A step-by-step technique for transapical aortic valve implantation has recently been described by Walther et al.[3] In this description, a left anterolateral mini-thoracotomy is performed in the 6th intercostal space, the pericardium is opened, and the LV apex is exposed. By giving careful attention to the location of the left anterior descending artery (LAD), an ideal site for apical puncture is chosen lateral to the LAD. Two purse-string sutures with interrupted Teflon pledgets are placed using a large needle to get sufficient depth in the myocardium. The apex is punctured in the middle of the purse-string sutures, and the apical wire is introduced with successive insertion of 14- and 32-French sheaths for valvuloplasty and valve delivery, respectively. At the end of the procedure, the sheath is removed, and the apical defect is closed by tying the purse-string sutures. However, because of the extreme fragility of the muscular tissue in these frail and elderly patients, a ventricular muscle tear can occur when the purse-string suture is tightened. Additional sutures and pledgets often need to be placed through already fragile and torn muscular tissue to achieve hemostasis, and nearby vital structures may be compromised.

Since January 2008, we have performed 42 transcatheter valve implantations with the SAPIENS Edwards valve at our institution. In 2 patients, the procedure was complicated by disruption of the LV apex after sheath removal. The first patient was a 78-year-old woman (Euroscore = 30%; Society of Thoracic Surgeons score = 15) with severe chronic obstructive pulmonary disease, on high-dose steroids, with a LV ejection fraction of 32%. When we tied the purse-string suture, the pledgets tore the apical muscle, creating a defect of the size of 2 Teflon pledgets. Hemostasis was finally achieved with multiple extra sutures and required ligation of the distal LAD to have enough muscle to securely close the LV defect. This led to a further decrease in LV ejection fraction (28% at 3 months). The second patient was an 87-year-old woman (Euroscore = 31%; Society of Thoracic Surgeons score = 12). A similar complication occurred in this second patient, and complete hemostasis was achieved with 2 extra sutures and a larger band of pledget far from the LAD. These 2 cases of ventricular rupture prompted us to develop 2 technical modifications to the initial procedure described by Walther et al[3] to reduce the risk of this complication.

First, we have developed a "ring pledget" for safe LV apex closure. The ring pledget is a contiguous circular pledget cut from a sheet of Teflon. It measures ~1 cm in width with a hole in its center to accommodate valve delivery apparatus (Figs. 1A and 2A). This pledget is placed on the LV apical surface, and 2 purse-string sutures (Prolene 2.0; Ethicon, INC Somerville, NJ) are passed in and out through the ring pledget. This technical modification provides 2 important advantages compared with the use of individual small Teflon pledgets. First, because both

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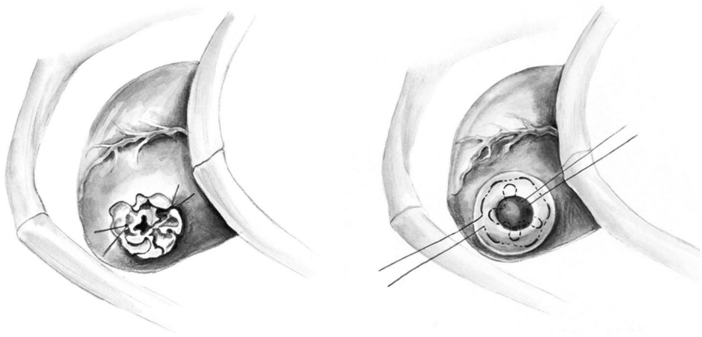

FIGURE 1. Illustration of the ring pledget and the purse-string suture, before and after the transapical delivery sheath insertion.

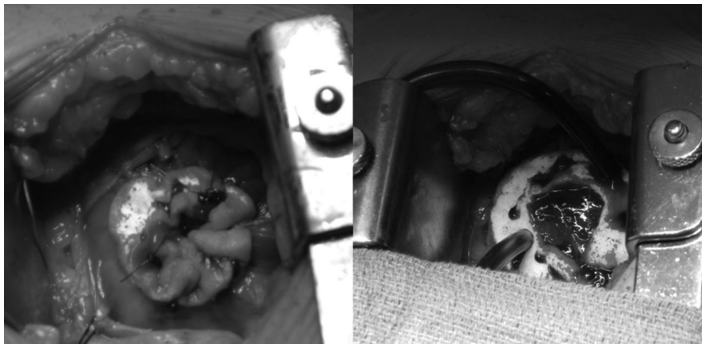

FIGURE 2. Operative view of the ring pledget, before and after the transapical delivery sheath insertion.

purse-string sutures are placed within the same piece of Teflon, they allow the tension on the LV apex to be more uniformly distributed as the sutures are tightened, thus, reducing the risk of muscular tears. Second, if a muscular tear does occur, additional sutures can be applied to the same Teflon pledget to obtain hemostasis, thus, keeping the defect size limited and minimizing the risk of injury to adjacent vital structures such as the LAD (Figs. 1B and 2B).

The second modification is that the purse-string sutures are tied under rapid pacing to reduce the tension on the ventricular wall and minimize the risk of apical tears. To date, we have performed 15 transapical procedures with these technical modifications, providing a secure closure of the apex without the need for extra sutures (Fig. 2).

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CLINICAL PERSPECTIVE

Transcatheter aortic valve replacement can be performed either via a femoral artery or left ventricular apical approach. Bleeding from the apex of the left ventricle after insertion of the delivery sheath can be problematic and lead to significant morbidity. This "How-To-Do-It" article describes a very simple use of a single circular Teflon pledge to help avoid this complication and ensure secure closure of the left ventricular apex.

Annexe Publication 3

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New ideas - Valves

Transapical explantation of an embolized transcatheter valve

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Abstract

Prosthesis embolization represents a severe complication following transcatheter aortic valve implantation (TAVI). We describe a case of ventricular embolization of the Edwards Sapien valve following transapical TAVI. The prosthesis was extracted successfully using the same transapical access. This approach obviated the need for conversion to a median sternotomy to explant the embolized valve.

Keywords: Transapical; Transcatheter aortic valve implantation; Valve embolization

Transcatheter aortic valve implantation (TAVI) was first described by Cribier et al. in 2002, as a minimally-invasive approach in high-risk patients [1]. Two different approaches are currently under intense clinical investigation — the transfemoral and transapical techniques [2]. In this report, we describe the use of the transapical access route to explant an Edwards Sapien valve after embolization into the left ventricle (LV) during implantation.

A step-by-step technique for transapical aortic valve implantation has recently been described by Walther et al. [3]. In this technique, a left antero-lateral mini-thoracotomy is performed in the sixth intercostal space, the pericardium is opened and the LV apex is exposed. An ideal site for apical puncture is chosen lateral to the left anterior descending coronary artery (LAD). Taking care not to damage the LAD, two purse-string sutures with interrupted Teflon pledgets are placed using a large needle in order to get sufficient depth in the myocardium. The apex is punctured in the middle of the purse-string sutures and the apical wire is introduced with successive insertion of 14-F and 32-F sheaths for valvuloplasty and valve delivery, respectively. At the end of the procedure the sheath is removed and the apical defect is closed by tying the purse-string sutures.

Ventricular embolization of the prosthesis is a rare but severe complication of the TAVI procedure. It usually necessitates conversion to median sternotomy, aortic cross-clamping and aortotomy to remove the embolized valve and perform a conventional aortic valve replacement [4].

Since January 2008, 102 TAVIs have been performed in our center using the Edwards Sapien valve. We performed 64 using transfemoral access and 38 using transapical approach.

Over the course of all procedures only one case of ventricular embolization of the prosthesis has occurred. The patient was an 85-year-old female with severe chronic obstructive pulmonary disease (COPD) and a LV ejection fraction of 32%. Her preoperative EuroSCORE was 30%, the Society of Thoracic Surgeons' (STS) score was 15. The aortic annulus was measured to be 21 mm in diameter according to the aortogram performed during balloon valvuloplasty. As such a 23-mm prosthesis was selected. Immediately following valve deployment, the valve was observed to have embolized into the LV. Percutaneous femoral extracorporeal circulation was immediately instituted. The extra-support Amplatz wire was still in place. We inflated the balloon into the embolized valve and extracted the entire system through the apex (Fig. 1). A mosquito clamp was used to crush the valve and to re-crimp it on the balloon in order to decrease the size of the entire system and to facilitate removal through the apex (Fig. 2). Once

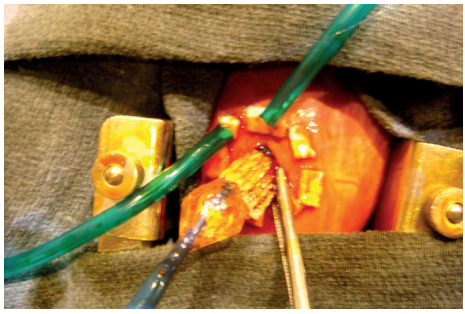

Fig. 1. Crushed valve with a mosquito clamp through the apex.

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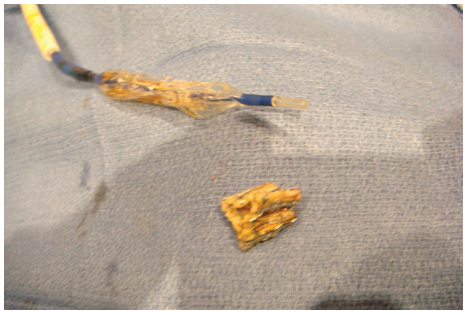

Fig. 2. Destroyed embolized valve removed through the apex between the purse-string sutures.

the sheath and the valve were removed, the purse-string sutures were snared around a reinserted 32-F sheath. A second Edwards Sapien valve of 26 mm diameter was selected. Aortic valve implantation was performed successfully with the second prosthesis. Apical closure was obtained by tying the two purse-string sutures and the addition of two additional 2-0 pledgeted prolene sutures (Prolene 2.0, Ethicon Inc, Somerville, New Jersey, USA). Total extracorporeal circulation support time was 48 min. A thoracic drain was inserted into the left pleural cavity. The patient was transferred to the intensive care unit (ICU) in a stable hemodynamic condition.

Upon postoperative review of the intraoperative images, it was concluded that the embolization was a result of the selection of an undersized prosthesis. This patient experienced a non-cardiac death on postoperative day 3 as a result of multiple organ failure due to her comorbidities.

The outcome of a distal aortic embolization of the Edwards Sapien valve remains positive [5]. The embolized prosthesis was repositioned into the aortic arch without the need for removal. However, ventricular embolization of the Edwards Sapien valve is a rare and severe complication of TAVI, usually necessitating conversion to median sternotomy. The use of transapical access offers a potential option of explanting the embolized valve through the apex. A second prosthesis can be implanted properly and safely to treat the aortic stenosis of the patient without conversion to sternotomy.

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Annexe Publication 4

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Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve☆

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Abstract

Objective: Cerebral embolization during trans-catheter aortic valve implantation (TAVI) has not been assessed clearly in the literature. Therefore, we compared the rate of cerebral embolisms with diffusion-weighted magnetic resonance imaging (DWI) in transfemoral (TF) and trans-apical (TA) approaches. **Method:** Eighty patients benefited from TAVI between January 2008 and June 2010. Out of these, 35 were included in the study. Twenty-one were TF (group 1) and 14 TA (group 2). During the same period, 285 patients benefited from a conventional aortic valve surgery (aortic valve replacement (AVR)). Thirteen of these were also analyzed and considered as the control group (group 3). We systematically performed a DWI the day before the procedure and 48 h after. DWI studies were blindly analyzed by a neuroradiologist, and all patients had a clinical neurological assessment before and after the procedure, according the National Institutes of Health Stroke Scale (NIHSS). **Results:** Thirty-two patients in the TAVI group had new cerebral lesions: 19 in the TF group and 13 in the trans-apical group (p = NS). Mean number of embolic lesions per patient was 6.6 in group I and 6.0 in group II (p = NS). Mean volume of embolic lesions was 475.0 mm^3 in group I and 2170.5 mm^3 in group II (p = NS). In group III, one patient had one new cerebral lesion ($p < 0.05$ vs TAVI) of 36.5 mm^3 (p = NS vs TAVI). All patients were neurologically asymptomatic. **Conclusions:** The incidence of silent cerebral embolic lesions after TAVI is significantly higher compared with the standard surgical AVR. The number of emboli is similar in the TF and TA groups but the volume tended to be higher in the TA group. However, there is no clinical impact of those lesions.

Keywords: Diffusion-weighted magnetic resonance; Trans-catheter aortic valve; Cerebral embolization

1. Introduction

Cardiac surgery is increasingly performed on elderly patients. This population has more co-morbidities such as impaired ventricular function, coronary disease, peripheral vascular disease and renal insufficiency. These co-morbid factors have been described as independent factors of mortality in this older population [1].

Neurological complication is a dramatic postoperative event, especially in this population with poor life expectancy [2,3]. Indeed, cerebral damage after conventional aortic valve replacement (AVR) ranges from 0.21% to 2.0% for neurological death rate and from 1.1% to 6.6% for clinical stroke rate [4,5]. Therefore, from 1.1% to 6.6% (trans-catheter aortic valve implantation, TAVI) was first proposed to this very frail population with the expectancy to decrease the mortality and morbidity related with the procedure.

Magnetic resonance imaging (MRI), and especially diffusion-weighted imaging (DWI), is nowadays the most powerful tool for diagnosing acute ischemic brain lesions, and has become a surrogate marker for clinical and sub-clinical brain embolism [6]. DWI has already been used to evaluate the incidence of silent infarcts after angiographic procedures and carotid endarterectomy or stenting [7].

Therefore, we analyzed clinical and sub-clinical brain embolism by DWI in a single-center, prospective, non-randomized study to evaluate per procedural embolic events in patients undergoing TAVI. We compared the cerebral

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embolic events between the transfemoral (TF) and the transapical (TA) approach. We also compared the TAVI group to a conventional AVR group.

2. Materials and methods

From January 2008 to June 2010, we performed 355 isolated aortic valve surgery. Eighty were TAVI procedure using Edwards Sapiens (Edwards Lifesciences Inc, Irvine, CA, USA) and 275 were conventional AVR.

The TAVI were divided as 50 TF and 30 TA. All patients were screened for inclusion into this prospective study. Exclusion criteria were: carotid artery stenosis >70% on duplex, presence of permanent pacemaker or defibrillator, patients who refused to participate in the study. Indication for TAVI was in concordance with the recent consensus statement [8].

Concomitantly, we included in the study 13 patients undergoing conventional AVR defined as the control group (CG). Patients' characteristics are listed in Table 1.

The study population was divided in three groups: group 1 TF, group 2 TA, and group 3 CG.

Cerebral DWI was performed in patients 24 h before implantation. For group 1 and 2 post-procedural DWI was performed after 48 h, and for group 3 after 72–96 h because of the external pacemaker leads.

The systematic clinical neurological examination was assessed following a standardized protocol according to the National Institutes of Health Stroke Scale (NIHSS) before and after implantation.

2.1. MRI protocol

A standardized protocol using fast spin echo-fluid attenuated inversion recovery sequence (FSE-FLAIR) and diffusion-weighted-spin echo-echo planar imaging (DWI SE-EPI) was applied in all patients before and after the procedure. The MR examination was performed at 1.5T (NT-Philips Healthcare or Intera-Philips Healthcare) in five patients in group 1, five in group 2, and one in group 3. The other patients were examined at 3T (Intera-Philips Healthcare or Verio-Siemens). The DWI sequence consisted of an initial T2-weighted acquisition followed by a second acquisition with the application of diffusion-sensitizing gradients in the three orthogonal directions with a *b* factor = 1000 s mm^{-2}. The exact repetition time and echo time differed slightly, according to the scanner.

A 1.5T, 24 axial slices with a thickness of 5 mm and a gap of 0.5 or 1 mm were acquired. The in-plane resolution at the acquisition was $1.9 \times 2.4\ mm^2$, interpolated to $0.95\ mm^2$ at the reconstruction. A 3T, 32 axial slices with a slice thickness of 4 mm, a gap of 0.4 mm, and an in-plane resolution of $1.8 \times 2.3\ mm^2$ interpolated to $0.9\ mm^2$ (Philips) or $1.3 \times 1.6\ mm^2$ (Siemens) were obtained.

One neuroradiologist blinded to the surgical protocol reviewed all MR examinations and rated the DWI trace images for the presence of acute ischemic parenchymal damage. Lesions were quantified using the following scoring system: number of lesions, location according to the vascular territory (anterior, middle, posterior cerebral arteries, or vertebrobasilar arteries), side and cortical versus subcortical or deep gray matter. Moreover, a planimetry of each lesion was performed by manual contouring, and the lesion volume was calculated by multiplying the surface by the slice thickness and slice gap.

2.2. TAVI procedure

The Edwards Sapiens (Edwards Lifesciences Inc, Irvine, CA, USA) valve consists of a tri-leaflet bioprosthetic bovine pericardial tissue valve mounted and sutured in a balloon-expandable stainless-steel frame. The TF technique was performed as described by Cribier [9]. The TA technique was performed as described previously by Walther [10], and modified by our team [11].

2.3. Conventional AVR procedure

All conventional patients were operated by median sternotomy under classical cardiopulmonary bypass. Arterial cannulation was performed in the ascending aorta and venous cannulation in the right atrium. Myocardial protection was achieved with an intermittent antegrade warm blood cardioplegia every 15 min. Valve implantation was realized with a pledget below the annulus suture.

2.4. Statistical analysis

Descriptive statistics were performed using Statistical Package for Social Sciences (SPSS) statistical software. A *p*-value less than 0.05 was considered significant. Continuous variables are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to compare continuous variables between the three groups.

To analyze the relationships between the embolic cerebral lesions and type of procedure, we used two strategies. In a first strategy, we used negative binomial regression to model the relationships between the number of embolic cerebral

Table 1. Patients characteristics.

	Group 1	*p*-value (1 vs 2)	Group 2	Group 3	*p*-value (1, 2 vs 3)
Age, years	86.3 ± 3.8	*p* = NS	83.43 ± 4.87	76.00 ± 6.05	***p* < 0.01**
Male	18 (85%)	***p* < 0.01**	8 (57%)	7 (53%)	*p* = NS
Log EuroSCORE %	31.3 ± 15.3	***p* < 0.01**	35.93 ± 17.05	9.85 ± 3.55	***p* < 0.01**
NYHA class	2.7 ± 0.48	*p* = NS	2,86 ± 0.36	2.31 ± 0.48	***p* < 0.01**
Ejection fraction %	43.76 ± 14.06	***p* < 0.01**	31.43 ± 11.91	44.00 ± 10.06	*p* = NS
Ao valve area (cm^2)	0.59 ± 0.12	*p* = NS	0.61 ± 0.15	0.66 ± 0.13	*p* = NS
Peak gradient (mmHg)	71.33 ± 22.83	*p* = NS	74.36 ± 26.31	84.54 ± 25.03	*p* = NS

Values are mean ± SD, *n* (%). NYHA: New York Heart Association functional class.

lesions and type of procedure, taking confounders into account. Negative binomial regression was preferred over Poisson regression because of observed overdispersion (variance > mean). The SAS procedure GENMOD was used. In a second strategy, we used logistic regression to model a binary variable (presence of absence of embolic cerebral lesion). Type of procedure was introduced in the form of dummy variables; other covariates were not transformed. The SAS procedure LOGISTIC was used. SAS procedures were run under SunOS (SAS 9.1 release).

3. Results

Forty-eight patients completed cerebral DWI pre- and postoperatively. Procedural success for valve implantation was 100% for all three groups.

3.1. Clinical results

Neurological examination after the procedure was similar to the neurological examination prior to the procedure in all patients. None of them had a clinical neurological deficit.

3.2. DWI results

Of the 48 patients, 33 had new embolic cerebral lesions. The median (mean, SD) number of lesions were four (mean = 5.9, SD = 6.8) in group 1, 4.5 (mean = 6.6, SD = 7.1) in group 2, and 0 (mean = 0.08, SD = 0.28) in group 3.

Attack rate (presence of new lesions/number of patients) was 90% in group 1 (19/21), 93% in group 2 (13/14), and 8% in group 3 (1/13).

The mean number of emboli per patient was 6.0 in group 1, 6.6 in group 2 and 0.1 in group 3 (group 1 vs 3: $p = 0.02$; group 2 vs 3: $p = 0.01$ and group 1 vs 2: p = NS).

The mean volume of ischemic lesion was 475.0 mm^3 in group 1, 2170.5 mm^3 in group 2, and 36.5 mm^3 in group 3 (group 1 vs 2 vs 3: p = NS).

The majority of the lesions were located in the left brain (Fig. 1). The new embolic lesions were located in supra- (superficial) and infra-tentorial (deep) regions.

Negative binomial regression adjusted for age and European System for Cardiac Operative Risk Evaluation (EuroSCORE) showed that type of lesion was significantly associated with the number of lesions. In comparison with group 3, parameter estimate of group 1 was 3.2 (standard error = 1.09, chi-square = 8.55, $p = 0.0035$) and parameter estimate of group 2 was 3.4 (standard error = 1.09, chi-square = 9.67, $p = 0.0019$). EuroSCORE was not significantly associated with the number of events, while age was positively associated.

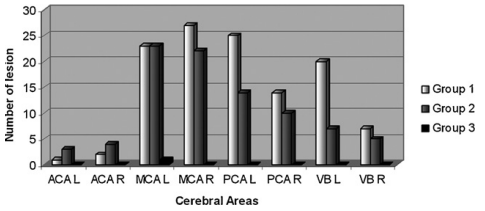

Fig. 1. Distribution of DW-MRI lesions in the cerebral areas. Number of lesions counted in the different cerebral areas. ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VB: vertebrobasilar arteries; L: left; and R: right.

Logistic regression resulted in similar associations. In comparison with groups 1 and 2, group 3 was strongly associated with the presence of lesions: parameter estimate = −4.85, standard error = 1.2, Wald chi-square = 16.3, $p < 0.0001$, and odds ratio (OR) = 0.008 (95% confidence limits = 0.001 and 0.083). No other variable was significantly associated with the presence of lesions once group 3 was in the regression model. Model fit was quite acceptable according to likelihood ratio and Hosmer–Lemeshow statistics.

As it can be seen, both strategies led to similar parameter estimates indicating a strong association of TA and TF procedures with new embolic lesions, as compared with the surgical approach.

4. Discussion

This study confirms that silent neurological lesions occur more often after TAVI than after conventional AVR. None of the patients with embolism were symptomatic.

However, in this study, we performed a standard neurological motricity examination before and after the procedure; we did not performed fine neurocognitive testing. Barber described in 2008 [12] that, after cardiac surgery, 63% had embolic events on cerebral DWI. Of those 5% had a clinical stroke, but neurocognitive decline was observed on cerebral DWI in 100% of patients who had silent embolic events. We strongly believe that neurosensitive testing is mandatory in further studies.

Recent articles reported a clinical stroke rate after TAVI less than 72% [13,14]. In this study, there was no incidence of clinical stroke, but we were surprised by the high incidence of the silent ischemic events during TAVI.

Embolization could occur during retrograde or antegrade arch catheterization, during balloon valvuloplasty or during endovalve implantation. We report a rate of new ischemic lesion of 90% in the TF approach compare with 92% in the TA approach. We were expecting a higher rate of emboli in the retrograde TF group because of the manipulation of the stiff devices into the aortic arch but antegrade TA approach did not reveal a lower rate of embolic events. Our results could help to elucidate the potential sources of embolism because there is no statistical difference between antegrade and retrograde approach in terms of mean number of embolic lesions. However, there is a statistical difference ($p = 0.02$) between TAVI (groups 1 and 2) and conventional surgery (group 3) with a rate of embolism of only 7%. We observed that the volume of the lesions is higher in the TA approach (2170.5 mm^3) compared to the TF (475.0 mm^3) approach and to conventional surgery (36.5 mm^3), but this was not statistically significant.

The localization of the embolic lesions was also preponderant on the left cerebral hemisphere to a greater extent in the TF than in the TA group. We were expecting a

higher rate of right hemisphere embolism in the TA group because, during the antegrade approach, the guiding would to go often into the right brachiocephalic trunk. Again, there is no difference in terms of the localization of the embolic lesions. Even in CG, the embolic side was the left hemisphere. Ghanem reported exactly the same results [15] with respect to CoreValve (Medtronic Inc, Minneapolis, Minnesota, USA) prosthesis implantation by the TF approach. We developed three hypotheses to understand why embolisms occur in the left hemisphere.

First, position of the left subclavian artery in the arch is in the direct way of the emboli released by the sheath when it runs from the descending thoracic aorta to the aortic arch. The external curve of the device scratches the aortic wall when you push it forwards to reach the aortic valve. The second hypothesis is regarding the total amount of emboli coming from the ascending aorta. We could say that one-third is going in each supraaortic arch vessel. However, the amount of embolus going into the brachiocephalic trunc is divided into three vessels: right carotid, right vertebral, and right axillary arteries. On the other hand, one-third of emboli goes directly into the left carotid and one-third into the left vertebral artery; hence, there are more emboli in the left brain than in the right. This is just our own analysis of the problem. The third hypothesis is based on an experimental fluid mixing model published by Lutz [17] to understand why anticancer drugs do not reach the left brain and the right brain. They propose that there is a stratification of the flow even into the Willis polygone. The drug injected by the left vertebral artery is not mixed into the Willis polygone and only the left brain receives the drug, and not the right brain. So, this means that the phenomenon is complex and we need further analysis of the emboli process using, for instance, an intracranial Doppler during the procedures.

To reduce the risk of cerebral embolism during TAVI, we have to develop and use efficient protection devices. There are already some of them available on the market; but no strong data in the literature support the efficiency of those devices.

One option to reduce the risk of embolism could be the 'no touch' technique described by Bagur [16] using a TA approach to deploy the valve with no wire and no catheter manipulation in the arch. In this article, the authors assume that the embolism occurs during the aortic arch manipulation. This is an isolated case report in which silent embolic lesions were not assessed by DWI. Further studies are mandatory to prove that absence of wire in the aortic arch signifies the absence of cerebral embolization.

4.1. Study limitation

This is not a randomized trial and the number of patient included in the three groups is limited.

Regarding the control group 3, we agree that the population is younger than in groups 1 and 2. We had some difficulties to convince old people, who were eligible for AVR, to have preoperative and postoperative DW-MRI. Many of them refused because they had been already into a long preoperative work-up and they were unhappy to have surgical AVR rather than TAVI. On the other hand, old patients selected for TAVI knew that they are going to receive an expensive, less invasive, and new technique; hence, they accepted easily any additional investigations such brain DW-MRI before and after the procedure. Anyway, we still continue to further enroll older patients for further publication.

The neurological examination did not take into account neurocognitive testing. This is a clear weakness of our study, which needs to emphasized.

5. Conclusions

The incidence of cerebral silent embolic lesions is very high during TAVI and is similar in the TF and TA approaches.

The conventional on-pump AVR is still the 'gold standard' treatment with a lesser risk of cerebral embolization.

The impact of neurocognitive dysfunction need to be assessed in further studies.

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Appendix A. Conference discussion

Dr T. Walther (*Bad Nauheim, Germany*): There is increasing evidence that there are some lesions on MRI, and we do not know what clinical relevance that has. So probably in the future you are very right that we need a multicenter study. We need a broader picture that has neurocognitive function testing pre-, postop, and even at follow-up, to really have a better understanding of the relevance of those lesions.

I would like to congratulate you for a very low rate of such lesions in your conventional group, so this is excellent, whereas it is higher than expected in the trans-catheter group. And the question is, it is kind of disappointing the results are not better than transfemoral. Is it due to case mix that you of course didn't randomize? You kind of selected sicker patients to the trans-apical cohort? Do you have the vascular status of those patients? How much calcification do they have around the aorta, including the aortic valve? You probably didn't really examine that in more detail. We probably need such an evaluation. So first question, do you have any assessment on the vascular status of the patients?

The second question would be, you could include only half of your overall patients into this study. Of course, there are dropouts. Is there any change over time by learning, by better de-airing, for example, when bringing a sheath from the apex into the heart? Maybe that has an effect when you have improved de-airing, that in the future these rates are going down.

Dr Astarci: First of all, for the first question, I don't have objective evaluation of the vascular disease, but the selection method in our institution is easy: when the access is possible we go for transfemoral, and if there is no access, then the patient is consented for trans-apical. So clearly trans-apical patients are really sicker than the transfemoral from a vascular point of view.

And for the second question, we enrolled only half of the patients, because we selected the patients without a contraindication and we could not include more with those data.

Dr V. Falk (*Zurich, Switzerland*): I think we need to seriously discuss your findings. You presented a 90% incidence of new brain lesions in MRI after TAVI procedures, indicating a significant embolic load that affects large areas of the brain. So we are talking cerebral volume here. I wonder what your thoughts are on when these emboli actually occur, during balloon valvuloplasty or during device placement? I disagree with Professor Walther who suggested that these emboli are mostly air emboli. If the lesions are visible 12 to 24 hours after the procedure, it is more likely that we see the correlate of solid emboli, and to me this is a serious concern.

Dr Astarci: On the diffusion-weighted MRI, it is impossible to distinguish between air embolism and solid embolism. It detects a necrosis of the brain. That is the first point. The other point, we started the study because I was very convinced that I would have less embolism in the trans-apical than my cardiologist colleagues in the transfemoral, but it is absolutely not the case. So when this embolism occurs, I think it is during the frame deployment, because we don't touch the aortic arch, really.

Dr Falk: Your findings are in line with the previous presentations in this session. In the British registry we saw a 3.5% stroke rate overall. In the Belgian registry a 5% stroke rate was reported, going up to 10% in the trans-apical group. You are presenting a 90% incidence of new brain lesions. I think this is really of concern.

Dr F. Mohr (*Leipzig, Germany*): I think this is, again, an example where we need a combined approach with our neurologists and radiologists. There is a parallel study for AF ablation. I don't know whether you recall these numbers. If the EP guys perform trans-catheter atrial fibrillation ablation, they report an incidence up to 25% of lesions on MRI, and, of course, everything resolves, so we don't really know the definite neurological outcome.

Peter Kappetein and I are always fighting in terms of coronary artery disease to better define incidences of stroke and to reduce the stroke rate somehow. I think it is a real concern for us, and we should somehow connect with the neurologists to have a kind of objective reading and diagnosis of these incidences, otherwise it may be under-reported.

Dr R. Dion (*Genk, Belgium*): Maybe just a short question. Wouldn't it be possible to register all the hits going to the carotid or to the vertebral arteries during the procedure, because then you would at least know when it happens. Maybe during the balloon valvuloplasty?

Dr Astarci: I am sure it is a good suggestion, but it is a new technique and the setup is quite difficult at the beginning, and we did not perform any transcranial Doppler or other investigation. But you are completely right, we have to do something to find out when this embolism occurs.

Annexe Publication 5

European Heart Journal

Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty

--Manuscript Draft--

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Full Title:	Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty
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Abstract:	Objective We sought to define the timing of cerebral embolization events during transcatheter aortic valve implantation (TAVI) and to determine if events were more closely associated with valve implantation or with balloon inflation. Method From January 2008 to November 2011, 114 patients underwent TAVI; of these, 44 had imaging performed before and after the procedure and were included in the study (26 transfemoral, TF; 18 transapical, TA). Eleven patients who had only balloon valvuloplasty (BV) during the same period were included, as were 22 patients who had open aortic valve surgery (AVR), as a control. All 77 patients underwent neurological examination, and all patients had cerebral MRIs before and after their procedures. Results A total of 50 of the 77 patients undergoing post-procedure MRI had new cerebral lesions, as follows: 24/26 (92%) in TF, 17/18 (94%) in TA, 3/11 (27%) in BV, and 6/22 (27%) in AVR (TF and TA vs BV and AVR, $p<0.0001$). Mean number and volume of embolic lesions per patient were respectively 5.4/438 mm3 for TF, 11.6/3414 mm3 for TA, 0.7/46 mm3 for BV, and 0.4/48 mm3 for AVR (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$). We found no association of either Euroscore or age with the number of events.

	Conclusions This study identified an incidence of silent cerebral embolic lesions after TAVI that was significantly higher than that for BV or AVR, indicating an association of embolism with valve implantation rather than with balloon inflation.
Suggested Reviewers:	Vahanian Alec, PhD Cardiologist, Hopital Bichat Paris France alec.vahanian@bch.aphp.fr Leader opinion in TAVI guidelines

Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty.

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Original article

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Abstract

Objective

We sought to define the timing of cerebral embolization events during transcatheter aortic valve implantation (TAVI) and to determine if events were more closely associated with valve implantation or with balloon inflation.

Method

From January 2008 to November 2011, 114 patients underwent TAVI; of these, 44 had imaging performed before and after the procedure and were included in the study (26 transfemoral, TF; 18 transapical, TA). Eleven patients who had only balloon valvuloplasty (BV) during the same period were included, as were 22 patients who had open aortic valve surgery (AVR), as a control. All 77 patients underwent neurological examination, and all patients had cerebral MRIs before and after their procedures.

Results

A total of 50 of the 77 patients undergoing post-procedure MRI had new cerebral lesions, as follows: 24/26 (92%) in TF, 17/18 (94%) in TA, 3/11 (27%) in BV, and 6/22 (27%) in AVR (TF and TA vs BV and AVR, $p<0.0001$). Mean number and volume of embolic lesions per patient were respectively 5.4/438 mm^3 for TF, 11.6/3414 mm^3 for TA, 0.7/46 mm^3 for BV, and 0.4/48 mm^3 for AVR (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$). We found no association of either Euroscore or age with the number of events.

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This study identified an incidence of silent cerebral embolic lesions after TAVI that was significantly higher than that for BV or AVR, indicating an association of embolism with valve implantation rather than with balloon inflation.

Key words: Diffusion-weighted magnetic resonance, transcatheter aortic valve, cerebral embolization

Introduction

High-risk patients undergoing aortic valve replacement, especially elderly patients, may have one of several factors associated with mortality, including impaired ventricular function, coronary disease, peripheral vascular disease, and renal insufficiency. Post-operative neurological complications can be especially devastating in the older population (2,3), with related death rates of 0.21% to 2.0% and stroke rates of 1.1% to 6.6% (4,5). One approach to aortic valve replacement in this population is transcatheter aortic valve implantation (TAVI), which holds the potential to decrease procedure-related mortality and morbidity.

What remains unknown is the incidence of silent cerebral embolic lesions following TAVI compared to other approaches, and specifically whether or not these events are more closely linked to valve implantation or balloon inflation. One tool for assessing clinical and subclinical brain embolisms is magnetic resonance imaging (MRI), especially diffusion-weighted imaging (DWI). This technique serves for diagnosing acute ischemic brain lesions and as a surrogate marker for embolism (6). Indeed, other studies have involved DWI for evaluation of silent infarct incidence after angiography and carotid endarterectomy or stenting (7).

In previous work, we established a higher incidence of post-procedure embolic events with TAVI compared to aortic valve replacement (AVR). In the current work, we employed DWI in a prospective study of clinical and subclinical brain embolism following TAVI in an expanded patient group, comparing the transfemoral (TF) and the transapical (TA) approaches. We also compared TAVI-related embolic outcomes with those of percutaneous balloon valvuloplasty (BV) in addition to results with AVR.

Materials and Methods

From January 2008 to June 2011, we performed 459 isolated aortic valve surgeries. Of those, 114 were TAVI procedures using Edwards Sapiens valves (Edwards Lifesciences Inc., Irvine, CA). During the same period, 144 patients underwent BV alone either as a bridge to TAVI or palliative treatment. A total of 73 of the TAVI cases were TF, and 41 were TA. Of these, 44 underwent pre- and post-procedure MRI evaluation (26 TF, 18 TA).

Study exclusion criteria were carotid artery stenosis >70% on duplex ultrasound, the presence of a permanent pacemaker or defibrillator, and/or failure to provide informed consent. The indications for TAVI were in concordance with the recent consensus statement (8).

For comparison and to determine the influence of balloon inflation relative to valve implantation, we included 11 patients undergoing BV alone and 22 patients undergoing conventional AVR, all of whom also had pre- and post-procedural MRIs. Thus, the study population consisted of four groups: TF, TA, BV, and AVR.

Cerebral DWI was performed in patients 24 hours prior to the procedure. For TF, TA, and BV, DWI was performed at 48–72 hours after the procedure; for AVR, the imaging was done at 72–96 hours because of the presence of external pacemaker leads. Furthermore, a systematic clinical neurological examination following a standardized protocol according to the National Institutes of Health Stroke Scale was performed before and after implantation.

MRI protocol

A standardized protocol using a fast-spin echo fluid-attenuated inversion recovery sequence (FSE-FLAIR) and DWI spin echo planar imaging (DWI SE-EPI) was applied in all imaged patients before and after the procedure. The MRI examination was performed with a 1.5 T scanner (NT-Philips Healthcare or Intera-Philips Healthcare) in six patients in TF, seven in TA, and two in AVR. The other patients were examined using a 3 T scanner (Intera-Philips Healthcare or Verio-Siemens). The DWI sequence consisted of an initial T2-weighted

acquisition followed by a second acquisition with the application of diffusion-sensitizing gradients in the three orthogonal directions with a b factor=1000 s/mm^2. The exact repetition time and echo time differed slightly according to the scanner.

With the 1.5 T scanner, 24 axial slices with a thickness of 5 mm and a gap of 0.5 or 1 mm were acquired. The in-plane resolution at the acquisition was 1.9 × 2.4 mm^2, interpolated to 0.95 mm^2 at the reconstruction. With the 3 T scanner, 32 axial slices with a slice thickness of 4 mm, a gap of 0.4 mm, and an in-plane resolution of 1.8 × 2.3 mm^2 interpolated to 0.9 mm^2 (Philips) or 1.3 × 1.6 mm^2 (Siemens) were obtained.

One neuroradiologist blinded to the surgical protocol reviewed all MRI examinations and rated the DWI trace images for the presence of acute ischemic parenchymal damage. Lesions were quantified using the following scoring system: number of lesions, location according to the vascular territory (anterior, middle, posterior cerebral arteries, or vertebro-basilar arteries), and side and cortical versus subcortical or deep grey matter. Moreover, the planimetry of each lesion was performed by manual contouring, and the lesion volume was calculated by multiplying the surface by the slice thickness and slice gap.

TAVI procedure

An Edwards Sapiens (Edwards Lifesciences Inc., Irvine, CA) valve consists of a tri-leaflet bioprosthetic bovine pericardial tissue valve mounted and sutured in a balloon-expandable stainless-steel frame. The TF technique was performed as described by Cribier (9), and the TA technique was performed as described previously by Walther (10) and modified by our team (11).

Balloon valvuloplasty

BV was performed using a previously established retrograde technique (12,13). Sequential single balloon inflation was carried out with a Cristal Balloon (BALT, Montmorency, France). The size of the balloon was selected according the annulus size measured on the echocardiogram.

Conventional AVR procedure

All conventional patients were operated by median sternotomy using cardiopulmonary bypass. Arterial cannulation was performed in the ascending aorta and venous cannulation in the right atrium. Myocardial protection was achieved with an intermittent antegrade warm blood cardioplegia.

Statistical analysis

Descriptive statistics were performed using SPSS statistical software. A p value less than 0.05 was considered significant. Continuous variables are presented as mean ± standard deviation. One-way ANOVA was used to compare continuous variables among the four groups.

To analyze the relationship between embolic cerebral lesions and type of procedure, we used two strategies. In a first strategy, we applied negative binomial regression to model the relationships between the number of embolic cerebral lesions and type of procedure, taking confounders into account. Negative binomial regression was preferred over Poisson regression because of observed overdispersion (variance > mean). The SAS procedure GENMOD was used. In a second strategy, we used logistic regression to model a binary variable (presence or absence of an embolic cerebral lesion). The type of procedure was introduced in the form of dummy variables, and other covariates were not transformed. The SAS procedure LOGISTIC was used. SAS procedures were run under SunOS (SAS 9.1 release).

Results

Table 1 lists patient characteristics. Seventy-seven patients underwent both a pre- and post-operative cerebral DWI. Procedural success for valve implantation was 100% for TF, TA, and AVR. Procedural success for valve dilatation was 100% for BV.

Clinical results

In terms of the neurological exam, results were similar for before and after the procedure. One patient in the TA group, an 88-year-old man with a Euroscore of 35, had a stroke. His medical history included insulin-dependent diabetes associated with peripheral vascular disease, polyneuropathy, retinopathy, sleep-apnea syndrome, previous stroke, previous bilateral pulmonary embolisms, and atrial fibrillation. This patient died at day 16 after the procedure as a result of multiple organ failure.

DWI results

Of the 77 patients who had both pre- and post-procedural MRI, 50 (71.4%) had a new embolic cerebral lesion. The incidence of new lesions was 24/26 (92%) in the TF group, 17/18 (94%) in the TA group, 3/11 (27%) in the BV group, and 6/22 (27%) in the AVR group (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$).

The mean number and volume of embolic lesions per patient were respectively 5.4/438 mm^3 for TF, 11.6/3414 mm^3 for TA, 0.7/46 mm^3 for BV, and 0.4/48 mm^3 for AVR (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$).

Multivariable analysis revealed a significant correlation between patient characteristics and number of DWI lesions for age ($r=0.41$, $p<0.01$) and log Euroscore ($r=0.21$, $p<0.01$). There were no significant correlations identified for New York Heart Association functional class

(r=0.81, p=0.03), sex (r=0.09, p=0.15), ejection fraction (r=0.19, p=0.75), aortic valve area (r=0.26, p=0.14), or trans-valvular peak gradient (r=0.046, p=0.142).

Negative binomial regression adjusted for age and Euroscore showed that type of procedure was significantly associated with the number of MRI lesions. In comparison with AVR (surgery=reference), the parameter estimate for TF was 2.34 (standard error=0.61, chi-square=14.9, p=0.0001), the parameter estimate for TA was 2.89 (standard error=0.62, chi-square=21.7, p<0.0001), and the parameter estimate for BV was 0.21 (standard error=0.74, chi-square=0.08, p=0.77). Euroscore and age were not significantly associated with the number of events.

Logistic regression identified similar associations. In comparison with balloon and surgical procedures, the TA and TF groups were strongly associated with the presence of lesions (for BV: parameter estimate=-3.60, standard error=0.77, chi-square=22.0, p<0.0001, odds ratio=0.027 [95% confidence limits=0.006 and 0.123]; for AVR: parameter estimate=-3.60, standard error=0.90, Wald chi-square=15.8, p<0.0001, odds ratio=0.027 [95% confidence limits=0.005 and 0.161]). No other variable was significantly associated with the presence of lesions.

Discussion

This study confirms again that silent neurological lesions occur more often after TAVI than after conventional aortic valve replacement. As documented in our previous work (14), embolization may arise during retrograde or antegrade arch catheterization, during BV, or during endovalve implantation. In this study, we included as a fourth group patients undergoing BV alone, allowing analysis of the effect on embolism occurrence of balloon inflation alone without valve deployment. As the results indicate, only 27% (3/11) of the BV patients had

embolism, compared to over 90% for each of the TAVI groups. This outcome suggests that embolism is much more associated with valve deployment than with balloon inflation. No patients had clinical stroke after BV in our study; the reported rate of stroke after BV is 3% in the literature (12,13).

Recent work from Kahlert in 2010 identified comparable results to the current findings, with a rate of embolization of 84% during TAVI using 22 balloon-expandable and 10 self-expandable valves (16). One of the patients in that study had a clinical stroke (5%). In the current series, one patient (2%) among the 45 TAVI patients had a clinical stroke. This rate is comparable to the 2.5% reported in the SOURCE European registry (17).

The US Partner trial (18) reported that the overall neurological event rate of cohort A at 30 days was 5.6% in the TAVI arm and 2.6% in the surgical arm. As noted, the stroke rate in our study was 2% in the TAVI group, and it was 0% in both the BV and AVR groups. The risk of stroke was also two times greater in the TAVI arm at one year: 8.3% versus 4.3%.

To the best of our knowledge, reports are lacking on transcatheter valve implantation with the use of a cerebral protection device. We have previously reported the benefit of using such a device during carotid stenting (7), and there may be a role for its use during TAVI. The challenge, however, remains to protect all cerebral arteries without adding risk through the addition of several guidewires and filters.

As we already mentioned in our previous paper, we have to develop and use efficient protection devices in order to reduce the risk of cerebral embolism during TAVI. Some of them available on the market but no strong data in the literature support the efficiency of those devices. One option could be the use of bilateral carotid stenting filters but this means a bilateral selective carotid artery catheterization within the same procedure. The TAVI procedure will become so complex that we are not sure if this will be benefic.

Study limitations

The study has some limitations. First, it was not a randomized trial. Furthermore, the number of patients included in each of the four groups was limited. Finally, the neurological examination did not include neurocognitive testing. In 2008, Barber described (15) that after cardiac surgery, 63% of patients had embolic events, based on cerebral DWI. Of those, 5% had a clinical stroke, but neurocognitive decline was observed in 100% of patients who had silent embolic events on cerebral DWI. Thus, neurocognitive testing would be a useful tool.

CONCLUSIONS

The incidence of cerebral silent embolic lesions is high during TAVI, whether the TF or TA approach is used. The embolization seems to be associated with valve deployment rather than with balloon inflation. The conventional on-pump aortic valve replacement is still the "gold standard" treatment and is associated with a lower risk of cerebral embolization, but the potential benefits of using protection devices must be assessed in further studies.

Table 1. Patient characteristics.

Values are mean ± SD, n (%).

NYHA=New York Heart Association functional class.

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Table 1

	TF	TA	p (TF vs TA)	BV	p (TF-TA vs BV)	AVR	p (BV vs AVR)	p (TF-TA vs AVR
Age, y	86.2±4.8	82.7±5.3	p=NS	83±9.4	p=NS	78.1±6.7	**p<0.01**	**p<0.01**
Male	21 (81%)	10 (55%)	**p<0.01**	6 (55%)	p=NS	9 (41%)	p=NS	p=NS
Log EuroScore %	29±15.1	35.7±15.4	**p<0.001**	34.6±10.7	p=NS	9.8±4.7	**p<0.001**	**p<0.001**
NYHA class	2.6±0.5	2.9±0.4	p=NS	3.5±0.5	**p<0.01**	2.2±0.4	**p<0.01**	p=NS
Ejection Fraction %	45.3±14	34.7±12.8	**p<0.01**	29.1±11.8	**p<0.01**	49.2±10.8	**p<0.01**	**p<0.01**
Ao valve area, cm^2	0.6±0.1	0.6±0.1	p=NS	0.5±0.2	p=NS	0.7±0.1	p=NS	p=NS
Peak gradient, mmHg	72.8±21.4	74.1±24.1	p=NS	65.4±22.5	p=NS	84.3±25.3	p=NS	p=NS

*Word count

Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty.

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Original article

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*Permissions information

Dear Sir:

We are submitting our manuscript, “Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty.” for consideration for publication in your European Heart Journal.

There has been no duplicate publication or submission of any part of the work. In addition, all authors have read and approved the manuscript, and there is no financial arrangement or other relationship that could be construed as a conflict of interest.

Thank you for your time.

Sincerely yours,

Parla Astarci, MD

Abstract

Objective

We sought to define the timing of cerebral embolization events during transcatheter aortic valve implantation (TAVI) and to determine if events were more closely associated with valve implantation or with balloon inflation.

Method

From January 2008 to November 2011, 114 patients underwent TAVI; of these, 44 had imaging performed before and after the procedure and were included in the study (26 transfemoral, TF; 18 transapical, TA). Eleven patients who had only balloon valvuloplasty (BV) during the same period were included, as were 22 patients who had open aortic valve surgery (AVR), as a control. All 77 patients underwent neurological examination, and all patients had cerebral MRIs before and after their procedures.

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A total of 50 of the 77 patients undergoing post-procedure MRI had new cerebral lesions, as follows: 24/26 (92%) in TF, 17/18 (94%) in TA, 3/11 (27%) in BV, and 6/22 (27%) in AVR (TF and TA vs BV and AVR, $p<0.0001$). Mean number and volume of embolic lesions per patient were respectively 5.4/438 mm^3 for TF, 11.6/3414 mm^3 for TA, 0.7/46 mm^3 for BV, and 0.4/48 mm^3 for AVR (TF vs TA and BV vs AVR, not significant; TF and TA vs BV and AVR, $p<0.0001$). We found no association of either Euroscore or age with the number of events.

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Annexe Publication 6

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A novel device for endovascular native aortic valve resection for transapical transcatheter aortic valve implantation

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Abstract

We developed a novel resection device to use during transapical transcatheter aortic valve implantation (TAVI) using a circular blade. We assessed the device in 15 human cadavers by transapical approach. After the resection, the aortic annulus was measured using standard probes. A careful examination of the aortic wall, left ventricular outflow tract, coronary ostia and mitral valve was performed using an endpoint checklist, developed specifically for the new device. The resection was successfully completed in 14 out of 15 (93%) cases. All the resected leaflets and debris have been successfully evaluated in 15 out of 15 (100%) cases. One case of a bicuspid valve had a prominent calcification of the median raphe. The resection tool could only perform a partial resection. The mean duration of the resection was 45 ± 30 s. The surrounding tissue examination did not reveal any injury to the anatomical structures. Endovascular resection of the native valve using transapical approach is feasible and effective. Further developments are necessary before the definitive clinical use during percutaneous aortic valve implantation.

Keywords: Transcatheter aortic valve • Aortic valve resection device • Percutaneous resection device

INTRODUCTION

Cardiac surgery is increasingly performed on elderly patients with increasing comorbidities including impaired ventricular function, coronary disease, peripheral vascular disease and renal insufficiency. The factors of these comorbidities have been described as independent factors for mortality in the elderly population [1]. Open heart surgery using cardiopulmonary bypass to replace the aortic valve is associated with a higher morbidity and mortality in the elderly population [2, 3].

Transapical transcatheter aortic valve implantation (TAVI) is an approach to minimize morbidity and mortality in selected high-risk patients [4, 5]. With this technique, the calcified native valve remains *in situ* and has to be squeezed between the transcatheter valve and the aortic wall. This may lead to several complications. Implantation of the valve into a non-circular calcified annulus with a risk of severe paravalvular leak [6], risk of coronary ostia occlusion [7] and embolization of debris [8, 9] increase the mitral insufficiency [10] and prosthesis patient mismatch [11]. For these reasons, resection of the native valve before TAVI may be advantageous. Several resection methods have been published, using waterjet [12], laser cut [13, 14] or foldable cutting edges [15]. In this study, we describe a novel resection device designed for use in the setting of transapical access.

MATERIALS AND METHODS

Study design

The device trials were performed in human cadavers undergoing necropsy analysis. Inclusion criteria were the presence of aortic valve stenosis and leaflet calcification observed after aortic transection at the level of the ascending aorta. From June 2009 to January 2011, 15 suitable cases were selected. The outcomes for the study were resectability and the measurement of forces needed for the cut.

The heart was explanted with a segment of the ascending aorta. The instrument was inserted through the apex, and the resection was performed under visual inspection (Fig. 1). Once completed, the resected area was measured directly by inserting a surgical probe.

Finally, the force needed to cut the valve was quantified. Force results were reported in Newton (N). The resected leaflets were mounted on a circular platform. The platform was clamped on a 6 degrees-of-freedom force sensor [Assurance Technologies Inc. Model: FT3025, 15/50 (force,±15 lb; torque, ±50 lb)]. The three reaction forces and the three reaction torques needed to perforate the leaflet and to cut the leaflet were measured by the sensors. Four experiments were performed using a perforation blade and 10 experiments were performed using a cutting blade (Fig. 2). A post-treatment then computed the longitudinal force

(leaflet perforation force) and the transversal force (leaflet cutting force).

RESULTS

The resection was successfully completed in 14 out of 115 (93%) cases. All the resected leaflets and debris have been captured successfully in 15 out of 15 (100%) cases. One case with a bicuspid valve had a prominent calcification of his median raphe. The resection tool could only perform a partial resection.

The mean annulus diameter of aortic specimens measured by probe insertion was 24.2 ± 1.9 mm. The mean resected area diameter measured by probe insertion was 20.0 mm. This is perfectly correlated to our instrument blade size of 20 mm (Fig 3).The surrounding myocardial tissue examination did not reveal any injury to the anatomical structures. Analysis of the resected leaflets provided a mean leaflet thickness of 0.5 ± 0.1 mm and a mean calcifications thickness of 4.1 ± 0.5 mm. The mean leaflet resection force was 7.1 ± 3.7 N (min = 2.0 N and max = 11.5 N). The mean leaflet perforation force was 7.3 ± 7.2 N (min = 1.0 N and max = 16.3 N). The mean duration of the resection was 45 ± 30 s.

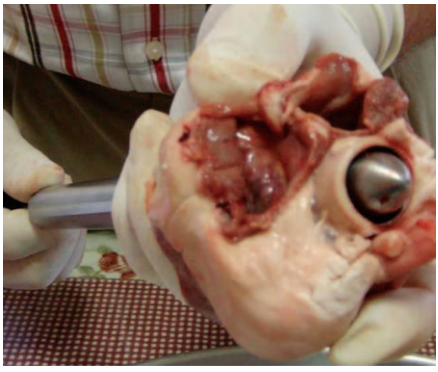

Figure 1: Resection tool inserted into the apex of the cadaver heart

DISCUSSION

This study confirms that transapical aortic valve resection is feasible in human heart. The analysis of the strength of calcified leaflets provides novel information about the force required to cut a native human calcified valve. To the best of our knowledge, such data have never been published in the medical literature. Wendt *et al.* [15] report the maximum force needed to resect artificially calcified bioprosthesis but not human native valve. In this study, 3.0 ± 0.6 N was required for moderate calcification and 3.5 ± 0.6 N for severe calcification. This is somewhat lower than the current finding of 11.5 ± 3.7 N. Possible explanations include the fact that human native valves may be stronger than the commercially available bioprosthesis. A second explanation could be that natural calcification over the course of many years could lead to stronger calcification than artificial calcification process performed within a few weeks. The force measured on the bench model gives an initial idea of the perforating and cutting forces required, but more sophisticated measurements should be conducted for different types of motion. In fact, it appears that the motion made by the surgeons (e.g. up and down motion) may have an influence on the resection force. It is also important to estimate in advance the limit of calcification that the tool can handle.

This study represents an important initial step to develop an adequate instrument to perform the resection of a native human calcified valve by an endovascular approach. The idea of native valve resection before TAVI was initially introduced by Quaden in 2005 [15]. This device involved a waterjet scalpel and a

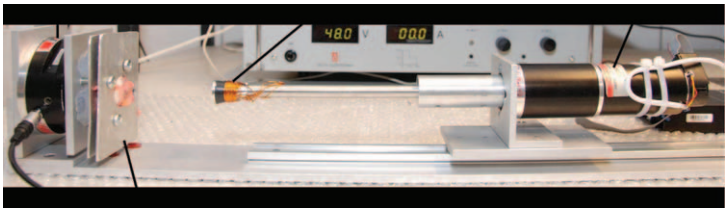

Figure 2: Resection force measurement bench

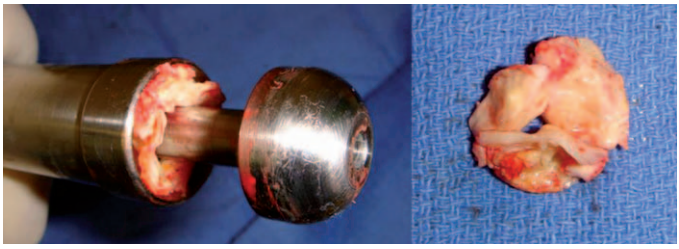

Figure 3: Resected fragments and the resected area

resection chamber using YAG laser. Unfortunately, this report did not involve an *in vivo* trial of the device. In 2008, we started to develop a mechanical resection tool using a simple 20 mm stainless-steel circular blade.

A number of developments must still occur prior to using the device on live patients. First of all, the transapical tool should be smaller than 20 mm in diameter. For this reason, our team is developing a new prototype of expandable blade in order to reduce the access size through the apex. The tool also needs to be more flexible in order to penetrate with an adequate angle in the aortic valve. Eventually, we envision a multi-functional wire-mounted system to resect the native valve and deploy the new valve simultaneously.

One of the arguments of people who are against the resection of the native valve prior to TAVI is that the endovalve remains in place because of its fixation into the native leaflets. Their hypothesis is that if one resects the native leaflet, there is no way to stabilize the endovalve into the aortic annulus. The advantage of this resection device is the fact that the size of the resection blade is 20 mm and there is still a calcified ring of a few millimeters left in place to fix the stented valve properly. Most of the endovalves rely on radial forces for anchoring. We believe that a partial resection, as we propose with our 20 mm blade, would provide a good anchoring calcified ring left in place. The anchoring force of the endovalve into the native valve and then into a calcified ring left after resections need to be measured on a bench. This experiment is ongoing in our department and our data will be published in the near future.

We believe that this novel device will be very useful in decreasing the amount of calcium before the implantation of the endovalve by the transapical approach. This will lead to a decrease in the rate of paravalvular leak, AV block, coronary occlusion and even in the rate of late cerebral embolization.

There are two main questions left before clinical use. The first one is the risk of embolization of leaflet debris during the resection and the second is the acute aortic regurgitation induced by the resection. These two questions need to be addressed on a dynamic model. We work on an animal model but the problem is to calcify an aortic valve and to perform resection by the transapical way on the same animal. This is an ongoing work in our animal laboratory but many practical problems still remain unsolved.

Directions for future study will include the trial of this instrument during conventional aortic surgery. Under aortic cross-clamping for the replacement of aortic valve, the instrument will be inserted in a retrograde fashion through the aortotomy to resect the native valve prior to the replacement of the aortic valve.

CONCLUSIONS

This cadaver experiment demonstrates that transapical aortic valve resection requires a maximal cutting force of 11.5 N and can be performed in <60 s. The creation of a clean circular annulus prior to TAVI may provide many advantages such as the decrease in paravalvular leak, decrease in the rate of AV block and decreased risk of coronary ostia occlusion.

Conflict of interest: none declared.

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