

Design of a device for minimally invasive aortic valve resection

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Remerciements

“Ils ne savaient pas que c’était impossible, alors ils l’ont fait.”

Mark Twain.

Mener à bien une recherche doctorale mêlant les mondes de l’ingénierie et de la chirurgie cardiaque n’aurait jamais été possible sans l’intervention conjuguée, de près ou de loin, d’un grand nombre de personnes.

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Abstract

Context

The increase of life expectancy in Western countries over the past 30 years has resulted in an exponential increase of elderly patients presenting for cardiac surgery. In this population, aortic stenosis is the most important acquired heart disease, with a prevalence of 4.8 % in patients aged over 75 years [1], and represents more than 60 % of the indications for cardiac surgery in elderly patients [2, 3]. Despite the good results reported by many authors with conventional aortic valve replacement (AVR) in elderly patients [4, 5], many patients are denied surgery because of the high operative risk [6]. In this frail population, transcatheter aortic valve implantation (TAVI) can be a good compromise to achieve good results [7] and minimize morbidity and mortality [8]. TAVI was first introduced into clinical practice in 2002 [9] as a rescue approach for patients presenting with symptomatic severe aortic stenosis but not eligible for conventional AVR. This technique allows the implantation of a balloon expandable or a self-expandable bioprosthesis without the resection of the native aortic valve.

Several complications have been described as a consequence of the residual highly calcified valve being squeezed between the aortic wall and the stent of the implant. This can result in deformation of the metal stent and paravalvular leakage, risk of occlusion of the coronary ostia, or central and peripheral embolization of valvular debris. In a recent report, Astarci *et al.* [10] hypothesized that it is necessary to resect the native calcified aortic valve before TAVI in order to avoid those complications, and several authors have reported new experimental methods of endovascular aortic valve resection to reach the same goal.

Thesis

Starting from the initial need — *develop an assistance to the replacement of the aortic valve through a minimally invasive beating heart surgery* — this thesis firstly focuses on the detailed study of the heart, the pathology of the calcific aortic stenosis and of its different current medical treatments.

The clarification of the task starts with the analysis of the need and the functional analysis of the need leading to the establishment of the functional specifications.

Then, the choices for the different function from the functional specifications are performed. The conception of the different subsets of the solution follows a traditional design method, until the realisation of demonstrators.

A clinical trial on patients undergoing open heart surgery ends this work and validates the concept of the final solution. Finally, some prospects are given to improve the device before its marketing thanks to the results achieved throughout this work.

Technological and scientific contributions

The *technical and scientific contributions* of this thesis can be summed up in three points:

- a need analysis of the minimally invasive AVR, based on the problems of the surgical AVR and of TAVI and on a review of the existing resection systems;
- a rational and systematic study of an innovative mechanical device aiming to answer to the initial need of the surgeon with two international patent applications [11, 12] (see appendices A and B);
- a validation of the device during clinical trials on patients undergoing open heart surgery.

The *main results* achieved at the end of this thesis are on the one hand the design of mechanical device to resect the aortic valve and on the other hand, the experimental validation during open heart clinical trials performed with the designed device.

Scientific and industrial prospects

Several aspects of the final device have not been explored during this thesis but are mandatory for the final version of the minimally invasive device.

The deployment of the system has not been studied in details. The principle of the closing and the opening of the cones has been tested with a simple demonstrator to verify its functioning.

The attachment of a cone on a catheter is a tricky problem and has not been studied. There are many constraints on the attachment system (e.g. deployment, torque transmission, concentricity between the cone and the catheter, etc.). Find a solution is beyond the scope of this doctoral research.

The clinical trials were performed in only one hospital and by only one surgeon. The results of the clinical trials, and in particular the global satisfaction of the surgeon, are maybe too enthusiastic and should be used with caution. To have more objective results, a multicenter clinical trial needs to be organised prior to any marketing.

The next steps of the research project will be to have a fully expandable device to be used in a transapical way.

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List of abbreviations

ABS	Acrylonitrile Butadiene Styrene
AFNOR	Association Française de NORmalisation
AoV	Aortic Valve
APTE	APlication aux Techniques d'Entreprise
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVATAR²	Aortic VALve TransApically Resected and Replace
AVB	Atrioventricular Block
AVIC	Aortic Valve Isolation Chamber
AVR	Aortic Valve Replacement
CABG	Coronary Artery Bypass Grafting
CEREM	Center for Research in Mechatronics
CHF	Congestive Heart Failure
CO₂	Carbon Dioxide
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CT Scan	Computed Tomography Scanner
CVA	CerebroVasculair Accident
DOF	Degrees of Freedom
Er:YAG	Erbium YAG
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FAMHP	Federal Agency for Medicines and Health Products

FDA	Food and Drug Administration
HLM	Heart Lung Machine
Ho:YAG	Holmium YAG
LBB	Left Bundle Branch
LBBS	Left Bundle Branch Block
LCA	Left Coronary Artery
LV	Left Ventricle
IVOT	Left Ventricle Outflow Track
NYHA	New York Heart Association
PA2200	PolyAmide 2200
PABV	Percutaneous Aortic Balloon Valvuloplasty
PPM	Patient-Prosthesis Mismatch
PVL	Paravalvular Leak
RBB	Right Bundle Branch
RBSB	Right Bundle Branch Block
RCA	Right Coronary Artery
RVP	Rapid Ventricular Pacing
SD	Standard Deviation
SMA	Shape Memory Alloys
StapAVR	Sapler-based Aortic Valve Replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischemic Attack
TIPS	Theory of Inventive Problem Solving
Tm:YAG	Thulium YAG
TRIZ	Teoriya Resheniya Izobretatelskikh Zadach
TVIC	Transventricular Valve Isolation Chamber
VTI	Velocity Time Integral
ZnCl₂	Zinc Chloride

Introduction

The increase of life expectancy in Western countries over the past 30 years has resulted in an exponential increase of elderly patients presenting for cardiac surgery. In this population, aortic stenosis is the most important acquired heart disease, with a prevalence of 4.8 % in patients aged over 75 years [1], and represents more than 60 % of the indications for cardiac surgery in elderly patients [2, 3]. Despite the good results reported by many authors with conventional AVR in elderly patients [4, 5], many patients are denied surgery because of the high operative risk [6]. In this frail population, TAVI can be a good compromise to achieve good results [7] and minimize morbidity and mortality [8].

What is TAVI?

TAVI, as shown in figure 1, was first introduced into clinical practice in 2002 [9] as a rescue approach for patients presenting with symptomatic severe aortic stenosis but not eligible for conventional AVR. This technique allows the implantation of a balloon expandable or a self-expandable bioprosthesis without the resection of the native aortic valve.

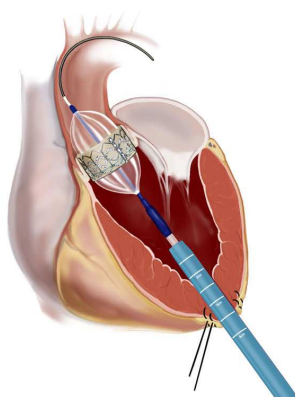


Figure 1: Schematic illustration of the transapical valve implantation technique [13].

Why resect the native aortic valve?

Several complications have been described as a consequence of the residual highly calcified valve being squeezed between the aortic wall and the stent of the implant. This can result in deformation of the metal stent and paravalvular leakage, risk of occlusion of the coronary ostia, or central and peripheral embolization of valvular debris. In a recent report, Astarci *et al.* [10] hypothesized that it is necessary to resect the native calcified aortic valve before TAVI in order to avoid those complications, and several authors have reported new experimental methods of endovascular aortic valve resection to reach the same goal. The new experimental methods consist either in a high pressure water jet scalpel, either in a Thulium YAG (Tm:YAG) laser or either in blade-based techniques to resect the aortic valve. But, to date, none of these experimental methods do efficiently and rapidly resect and replace the aortic valve through a minimally invasive beating heart surgery.

Objectives of the thesis

From this statement, the research project AVATAR² lies in this context by aiming to design an integrated device to resect the native aortic valve and implant an endo valve prosthesis during a minimally invasive beating heart surgery. This research project is the beginning of the collaboration between the Center for Research in Mechatronics (CEREM) and the Cardiosurgery department of the Cliniques Universitaires Saint Luc both from the Université catholique de Louvain.

To carry out this project, four scientific objectives have been laid at the beginning of the research:

1. study the heart, the calcific aortic stenosis and its medical treatment by reviewing the literature, meeting surgeons and attending open heart and minimally-invasive surgeries to **identify the problems and the needs**;
2. based on this study and on the analysis of the state of the art, **design and develop an innovative solution** for the identified problem, respecting the constraints relative the medical environment;
3. **verify, on hearts of cadavers, that the proposed solution** meets the expectations of the surgeons, define improvements to implement on the device, and eventually reword the needs in the light of the acquired experience;
4. **validate the resection concept on patients undergoing open heart surgery.**

Followed approach

Designing a product is an iterative process. This thesis presents the iterative and effectual design process from the initial need of the surgeon *develop an integrated device to resect the aortic valve and to implant an endoprosthesis through a minimally invasive beating heart surgery* to the final solution, *two cones to firmly hold the aortic valve and one resection cone to cut the valve*, developed to replace the aortic valve.

Furthermore, a solution to a design problem is never unique and the final result will depend on the initial conditions (the analysis of the need, the functional specification, etc.) and on the followed approach. A lot of design methods exist to help the designer to develop the best and the most objective solution as possible by ignoring the preferences of the concepthor.

The approach followed during this thesis is the method proposed by Cross in [14] which helps the designer from the initial need to the final product through the analysis of the need, the functional analysis of the need, the functional specifications, the comparison criteria, the technical functional analysis and the device development.

The part I presents the medical context in order to identify the initial need and to clarify the task. To start, the chapter 1 presents the anatomy and the physiology of the heart to understand the environment in which the device will be used. Then, in the chapter 2, the physiopathology, the epidemiology, the signs and symptoms and the diagnosis of the calcific aortic stenosis are described. In the chapter 3, the medical treatments of the aortic stenosis are presented with their advantages and disadvantages which will allow to set the basis for the design process.

Following the medical context, the part II describes the design method that will be used to develop the solution for the replacement of the aortic valve. The chapter 4 presents the analysis of the need and the functional analysis of the need resulting in the formulation of the functional specifications required to develop a device meeting the expectations of the surgeon. The state of the art of the new experimental methods of endovascular aortic valve resection is given in the chapter 5 and is compared with the functional specifications. Finally, the chapter 6 presents the different solutions for each function of the functional requirements : the percutaneous approach, the resection system (with the resection movement, the deployment of the blade, the abutment support and the centering system) and the collection system.

The part III gives the development of the device from the preliminary project (chapter 7) to the AVATAR² device (chapter 9). Three iterations have been necessary before finding the best and the safest working solution for the resection system. A demonstrator of each concept has been designed and manufactured before being tested with calcified aortic valve (coming from open heart surgery or from embalmed cadavers).

Finally, the part IV starts with the development of the AVATAR² device that will be used on patients undergoing a surgical AVR during an open heart surgery. The device development is presented in the chapter 10 while the results of the clinical trials are given in the chapter 11.

This work will be concluded by a discussion about the final results and on the design method implemented to achieve them. Finally, some prospects will be proposed to give possible evolutions of the device.

Contribution of the collaboration with the final user

The device has been designed, developed and tested in close collaboration with Prof. Astarci, who is the instigator of the project and the final user of the device. Working

together during the research was very productive and very instructive for all the collaborators and allowed to develop a product that best meets the initial need of the surgeon.

In a usual way, when a client has an initial need, he asks to a research team to develop and design a product which answers his need. At the beginning of a project, the researchers analyse the need in order to elaborate the functional specifications. Then, the functional specifications are presented and discussed with the client to be sure that everyone is on the same wavelength. The following steps of the design method are often done with limited interactions and contacts between the client and the researchers. This usual way often results in good solution for the wrong problem instead of a wrong solution for the right problem. Indeed, to earn time, the designers work with an incomplete or a wrong information believing that it is a good one. It is only when the product is almost entirely developed that the client and the researchers discover a misunderstanding of the problem. This involves additional delays and costs and an unhappy client.

In the present work, every step of the design method was done with a very close collaboration resulting in a good solution for the good problem, even if several iterations were needed before finding the final solution. Indeed, when a information was uncertain or misunderstood, a meeting was organised to discuss about the problem and to avoid additional delays, costs and iterations. Moreover, each time a demonstrator was designed, it was presented to the surgeon to be criticised and improved before its manufacturing. Then, all the tests on cadavers with the different demonstrators of the device were performed with the surgeon for direct discussions on how the device is working and to know what improvements to make and how to implement them on the next version.

This close collaboration allows to be ready to perform clinical trials on patients undergoing open heart surgery less than three years after the beginning of the research. It took almost a year to have the approbation of the Federal Agency for Medicines and Health Products (FAMHP) required to start the clinical trials.

Part I

Medical context

Chapter 1

The heart

Secret dissection of cadavers made in the 15th century by Leonardo da Vinci (see figure 1.1) [15] and Andreas Vesalius (see figure 1.2) [16] resulted in beautiful detailed anatomical drawings of the heart valves but also in their functional understanding, and even in name giving. It is said that da Vinci compared the left-sided atrioventricular valve as resembling a “bishop’s miter” and gave the “mitral valve” its name [17].

One hundred years later, in 1628, William Harvey established the concept of the blood circulation (figure 1.3) which has marked the beginning of the modern cardiology [18].

Despite these works, the surgery of the heart remained 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*”. The first successful suture on a heart wound was made in 1896 by Ludwig Rehn, a surgeon from Frankfurt [19, 20].

1.1 Anatomy of the heart

The heart, shown in figure 1.4, is a complex muscle in humans which pumps blood through the blood vessels of the circulatory system. It sucks, into its cavities, the blood flowing through the veins and then expels it in the arterial system through the aorta and the pulmonary trunk.

The heart is divided into two halves similarly constituted: the right heart in which circulates the deoxygenated blood and the left heart in which oxygenated blood circulates. Each half is also divided into two chambers: one upper, with thin walls, called atrium and one lower, with thicker and more resistant walls, called ventricle. Each atrium communicates with the relative ventricle through a large hole, the atrioventricular valve. The two hearts are separated from each other by a wall called interatrial septum at the level of the atria and by the interventricular septum at the level of the two ventricles.



Figure 1.1: Leonardo da Vinci's notes on the valve of the heart and flow of blood within it.

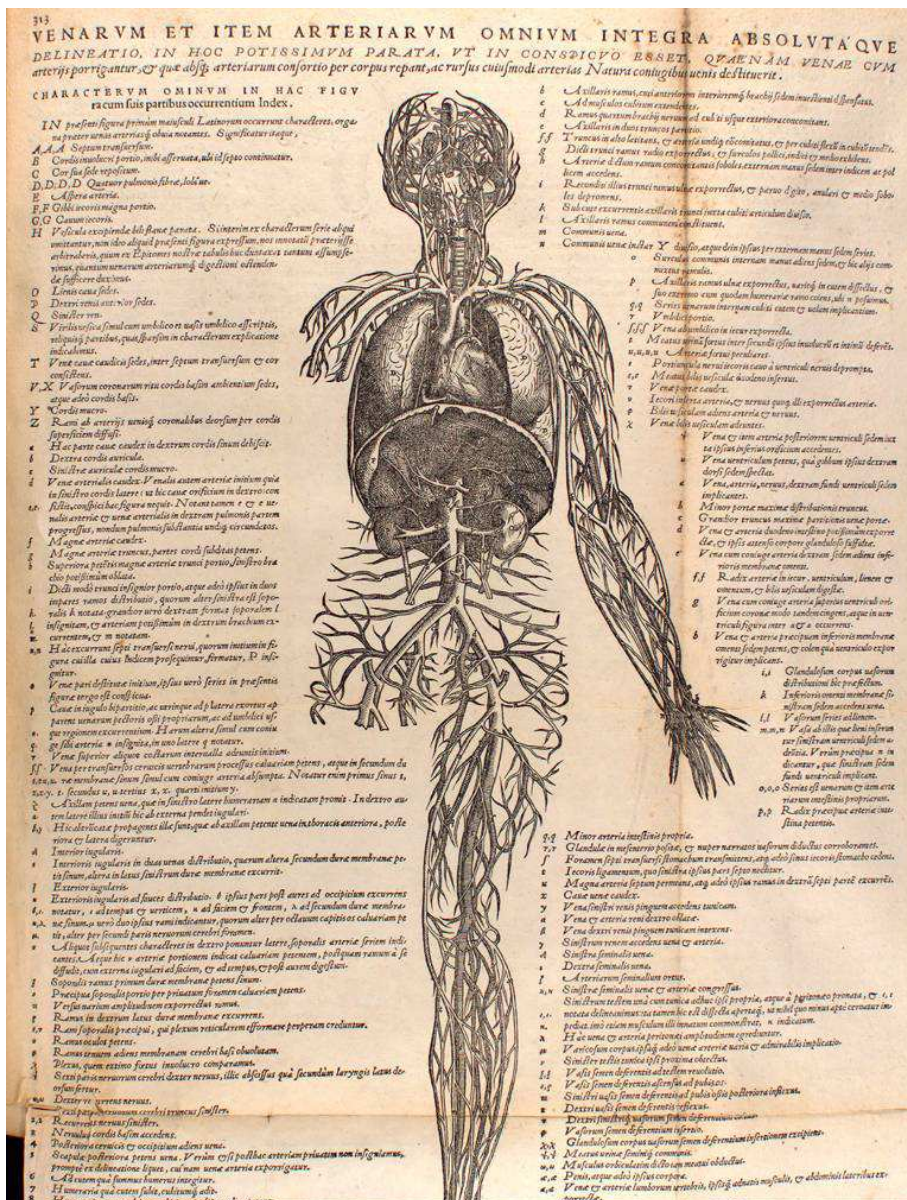


Figure 1.2: Andreas Vesalius' illustration and notes on the arteries and the heart.

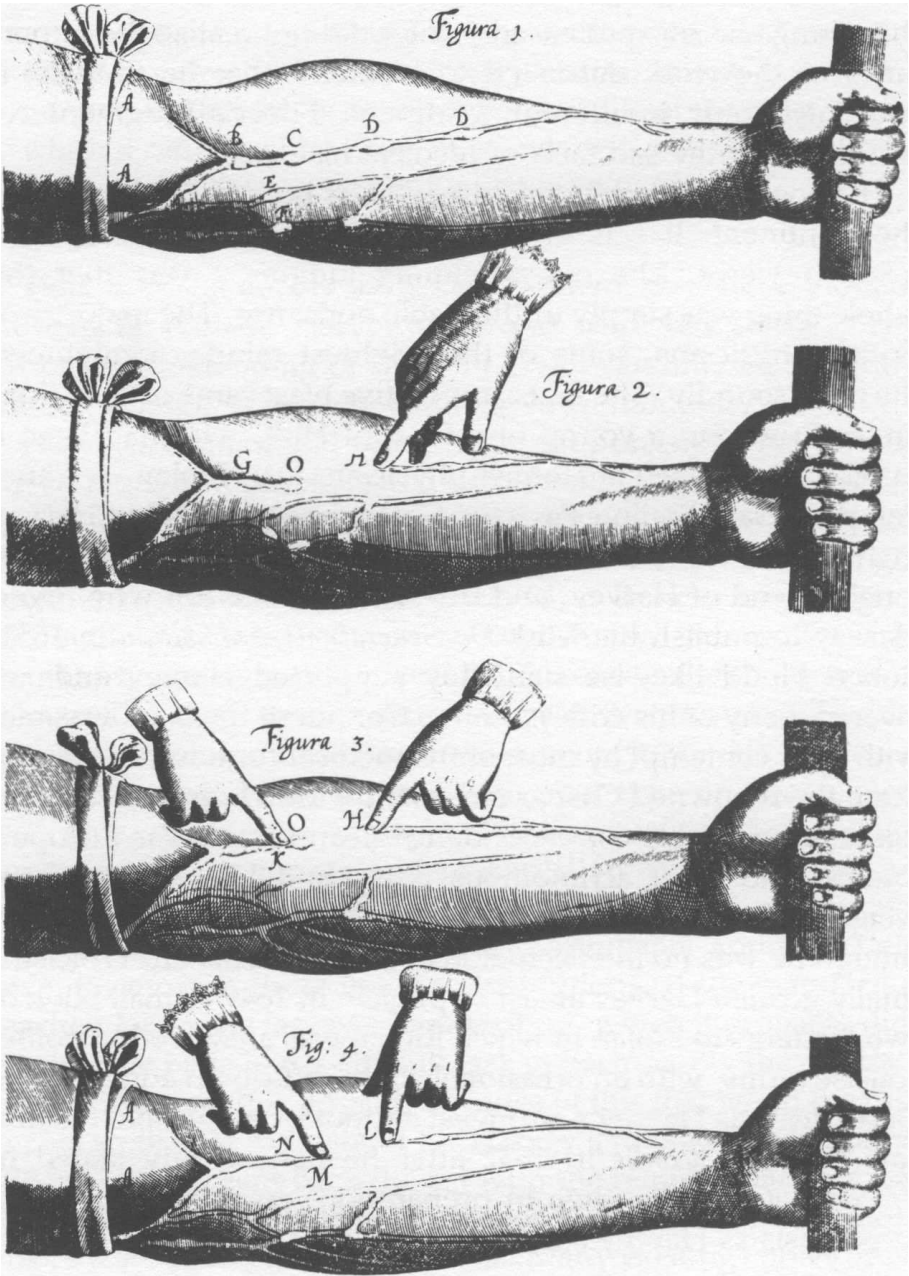


Figure 1.3: Illustrations of the experiment made by William Harvey which demonstrate the blood flow. He ligatured an arm to make obvious the veins and their valves, then pressed blood away from the heart and showed that the vein would remain empty because blocked by the valve.

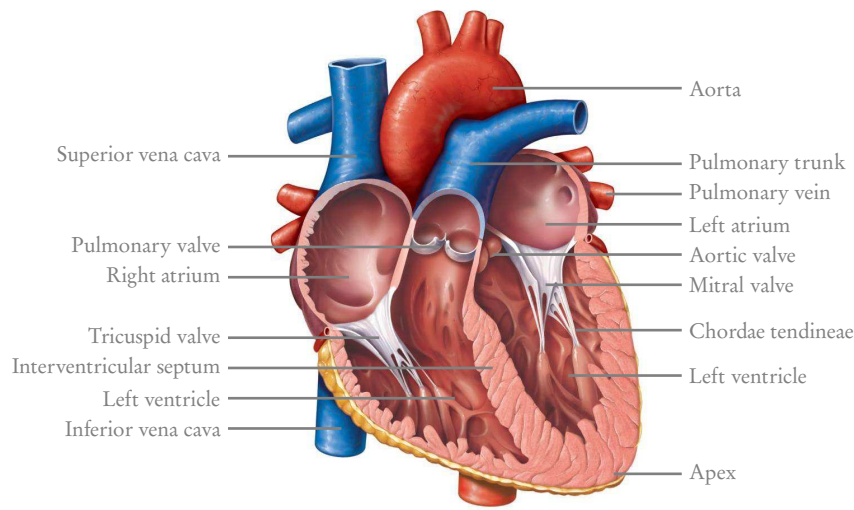


Figure 1.4: Anatomy of the heart (viewed from the patient side - adapted from www.human-anatomy101.net).

The heart is cone-shaped with its base positioned upwards and tapering down to the apex, its size is approximatively of 10 cm height, 10 cm wide and 11 cm long for a weight of about 275 gr. Its size and weight depend on the sex and on the physical condition of the person.

As shown in the figure 1.5, the heart is located into the chest, below the sternum. The apex is positioned at the level of the fifth left intercostal space (space between the fifth and the sixth ribs), at 8 cm of the sagittal plane. The two thirds of the heart volume are located to the left of the sagittal plane. Only the right atrium and a half of the left atrium are located to the right of the sagittal plane.

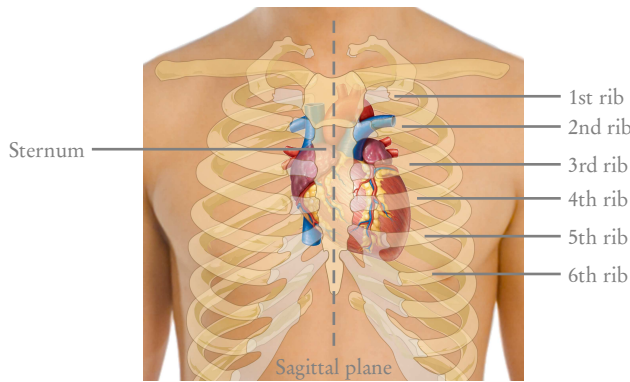


Figure 1.5: Location of the heart in the chest (adapted from commons.wikimedia.org).

1.1.1 Chambers

The heart consists of four chambers: the right and left atria, located in the upper part of the heart and the right and left ventricles, located in the lower part of the heart. The chambers permit the blood to circulate into the entire body.

Atria

The atria collect the blood from the veins and then expel it into the ventricles. The left atrium collects the oxygenated blood from the four pulmonary veins whereas the right atrium collects the deoxygenated blood from the two venae cavae (inferior and superior) and from the coronary sinus.

Ventricles

The two ventricles, the left and the right, have a conoid shape with the major axis directed to the apex. The base of each ventricle has two orifices: one very wide, called the atrioventricular valve and the other narrower, called the arterial valve. The ventricles have thicker walls than the walls of the atria because they expel the blood out of the heart. The walls of the left ventricle are thicker than the walls of the right ventricle because it is more difficult to expel the blood into the entire body than into the lungs.

1.1.2 Valves

The heart comprises two atrioventricular valves and two arterial valves, as shown in figure 1.6.

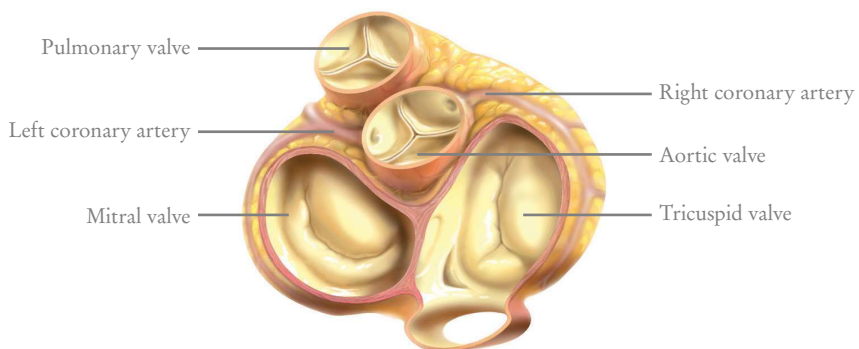


Figure 1.6: The four valves and the two coronary arteries of the human heart. The atria have been removed to expose the valves (adapted from [21]).

Atrioventricular valves

There are two atrioventricular valves into the heart: the mitral valve, in the left heart and the tricuspid valve, in the right heart. They are located between the atria and the ventricles and prevent blood leakage from the ventricles to the atria. These valves are anchored to the walls of the ventricles by the chordae tendineae, which prevent the valves from prolapsing into the atria when they close. The mitral valve has only two cusps, also called leaflets, whereas the tricuspid has, as indicated by its name, three cusps.

Arterial valves

The heart has two arterial valves, also called “semilunar valves” (see figure 1.7): the aortic and pulmonary valves. They are located at the base of the aorta and the pulmonary trunk respectively. These two arteries receive blood from the ventricles and their semilunar valves permit blood to be forced into the arteries, and prevent backflow from the arteries into the ventricles. Unlike artioventricular valves, these valves do not have chordae tendineae. Both of the arterial valves have three cusps.

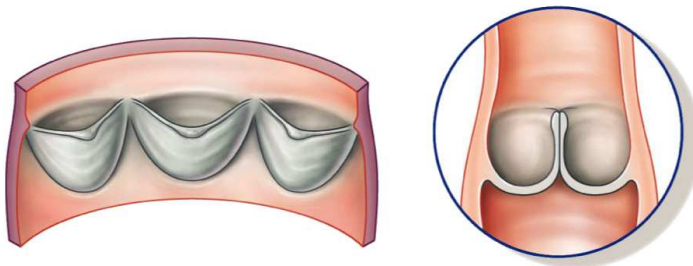


Figure 1.7: Shape of the arterial valves [22].

1.1.3 Coronary arteries

The coronary arteries, shown in figure 1.6, supply blood to the myocardium, the muscle tissue of the heart, and other components of the heart. The two coronary arteries originate from the left side of the heart at the beginning (root) of the aorta, just after the aorta exits the left ventricle. The origin of the coronary arteries are called the coronary ostia (see figure 1.8).

The left coronary artery (LCA) distributes blood to the left side of the heart (*i.e.* the left ventricle, the left atrium and the interventricular septum). The right coronary artery (RCA) distributes blood to the right atrium and to the right ventricle.

1.2 Conduction of the heart

The muscular wall of the atria and ventricles is able to contract spontaneously. The cardiac conduction system initiates and coordinates the contractions. This system,

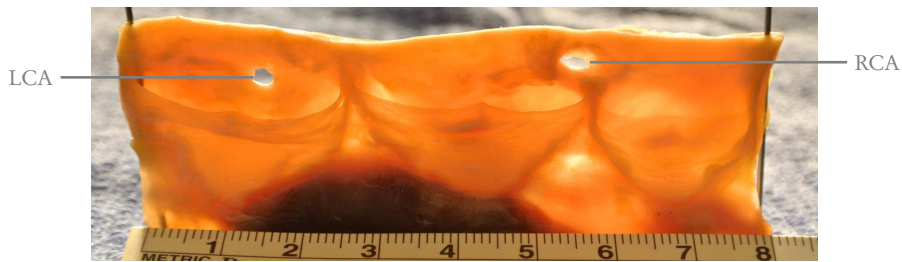


Figure 1.8: Dissected aortic root with the aortic valve and the ostia of the two coronary arteries (adapted from [23]).

shown in figure 1.9, is composed of nodes and bundles of specialized myocardial cells, organized in four elements:

- the sinoatrial node;
- the atrioventricular node;
- the atrioventricular bundle with its left and right bundle branches;
- the Purkinje fibers.

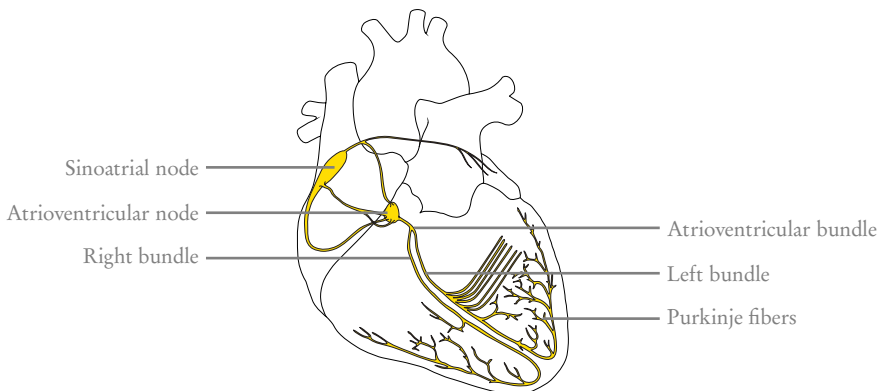


Figure 1.9: The cardiac conduction system (adapted from commons.wikimedia.org).

Impulses begin at the sinoatrial node, the cardiac pacemaker. The excitation signals generated by the sinoatrial node spread across the atria, causing the muscle to contract. Simultaneously, the wave of excitation in the atria stimulates the atrioventricular node, which is located near the opening of the coronary sinus, close to the attachment of the septal cusp of the tricuspid valve, and within the atrioventricular septum. The atrioventricular bundle is a direct continuation of the atrioventricular node. It follows along the lower border of the membranous part of the interventricular septum before splitting into right and left bundles. The right bundle branch (RBB) transmits the impulse to the ventricular muscle of the right ventricle. As with the right side, the left bundle branch (LBB) and its network (the Purkinje fibers), spreads the excitation impulses throughout the left ventricle [22].

1.3 Physiology of the heart

The heart functions as a pump in the circulatory system to provide a continuous circulation of the blood throughout the body. This circulation consists of the systemic circulation to and from the body and the pulmonary circulation to and from the lungs. Blood in the pulmonary circulation exchanges carbon dioxide (CO_2) for oxygen in the lungs through the process of respiration. The systemic circulation then transports oxygen to the body and returns CO_2 and relatively deoxygenated blood to the heart for transfer to the lungs [24].

1.3.1 Right heart

In the right heart, the deoxygenated blood is collected from two large veins, the superior and inferior venae cavae, into the right atrium and is then pumped through the tricuspid valve into the right ventricle where it is pumped into the pulmonary trunk through the pulmonary valve. The blood here enters the pulmonary circulation where carbon dioxide can be exchanged for oxygen in the lungs [24].

1.3.2 Left heart

The left heart collects the oxygenated blood which is returned from the lungs to the left atrium via the four pulmonary veins. The blood is then pumped into the left ventricle through the mitral valve and into the aorta through the aortic valve for systemic circulation. The aorta is a large artery that branches into many smaller arteries, arterioles, and ultimately capillaries. In the capillaries, oxygen and nutrients from blood are supplied to body cells for metabolism, and exchanged for CO_2 and waste products [24].

1.3.3 Cardiac cycle

The cardiac cycle, as shown in figure 1.10, is a complete heartbeat which includes systole and diastole and the intervening pause. A cycle begins with the contraction of both atria and ends with the relaxation of both ventricles. The systole (steps b and c) is the moment when the ventricles of the heart contract to expel blood out of the heart into the body. The diastole (steps a, d and e) is when the ventricles relax and are filled with blood. The atria and ventricles work in concert: in systole, when the ventricles are contracting, the atria are relaxed and collecting blood; when the ventricles are relaxed, in diastole, the atria contract to pump blood to the ventricles. This coordination ensures that the blood is efficiently expelled into the body [24].

Five events (see figure 1.11) occur during each cardiac cycle [25]:

1. During the *atrial systole*, both atrioventricular valves are open whereas both arterial valves are closed. The atria contract and expel the blood to the ventricles. The ventricles, already partially filled from phase 5, receive the last 30 % of blood, for a final resting volume of approximately 130 ml.

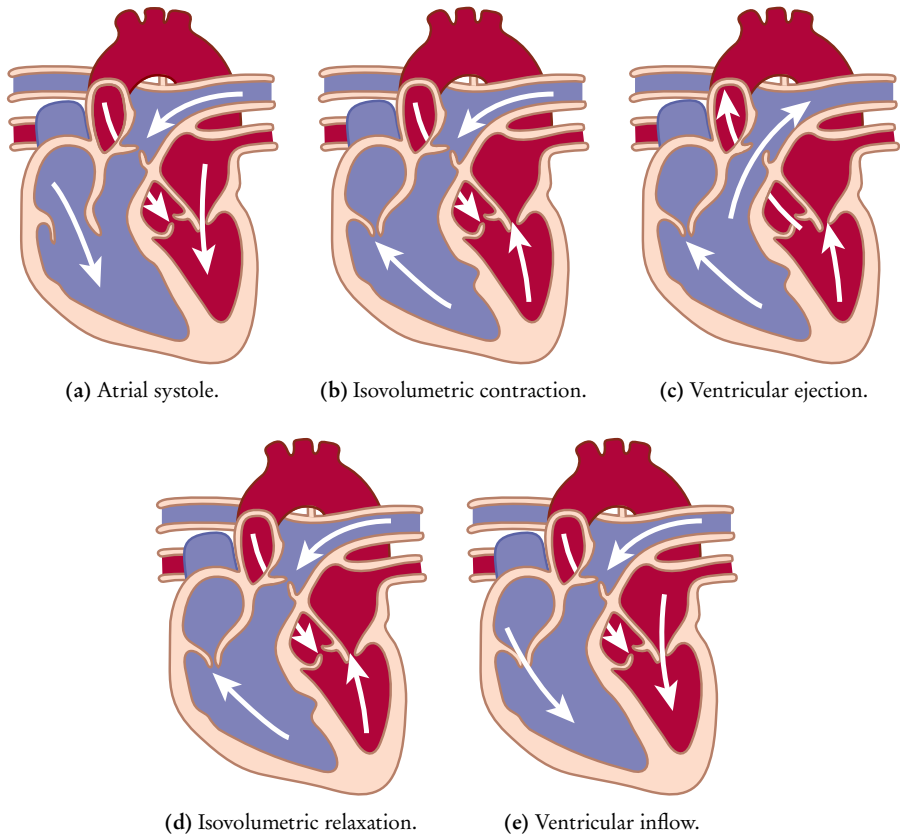


Figure 1.10: Cardiac events occurring during a complete cardiac cycle (adapted from [25]).

2. The four valves are closed during the *isovolumetric contraction*. The ventricles begin to contract. The ventricular muscle initially shortens only a little, but intraventricular pressure rises sharply. The volume of the ventricles don't change.
3. For the *ventricular ejection* stage, the atrioventricular valves are closed and the arterial valves are open. The pressures in both ventricles exceed pressures in aorta (80 mmHg) and pulmonary artery (10 mmHg). The ejection is rapid at first and slowing down as systole progresses. The amount of blood ejected by each ventricle per stroke at rest is comprised between 70 ml and 90 ml. At the end of the systole, approximately 50 ml of blood remains in each ventricle.
4. All the valves are closed for the *isovolumetric relaxation*. The ventricles relax and the ventricular pressure drops below 120 mmHg. This stage ends while the ventricular pressure falls below the atrial pressure and while the atrioventricular valves open. The blood is pumped to the rest of the body.
5. During the last stage, the *ventricular filling*, the ventricles are relaxed and are passively filled with approximately 70 % of their final volume. As the

ventricles fill, the rate of filling decreases and the atrioventricular valves drift towards closing. The atria expand and are filling with the blood coming from the veins.

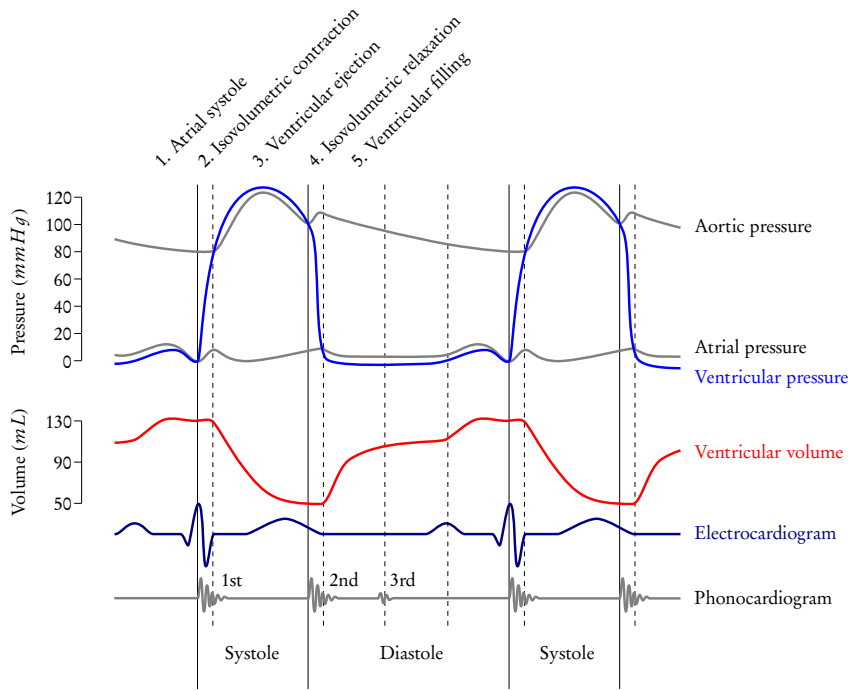


Figure 1.11: Wiggers diagram of the cardiac events occurring in the cardiac cycle. Two complete cycles are illustrated (adapted from www.wikipedia.org).

A complete cardiac cycle lasts about 0.8 s: 0.27 s for the systole and 0.53 s for the diastole. It means that a heart, in normal conditions, beats 75 times per minute.

Chapter 2

Calcific aortic stenosis

Calcific aortic stenosis is a progressive heart valve disease that narrows the exit of the left ventricle and increases the leaflet stiffness resulting in increased pressure gradients across the valve [26]. The earliest description of calcific aortic stenosis is attributed to the French physician Lazare Rivière [27] who, in 1663, reported the necropsy findings from a patient with palpitations, progressive dyspnea and loss of peripheral pulses. He noted left ventricular enlargement and identified large caruncle-like masses obstructing the left ventricle outflow track (LVOT) to the aorta [28].

2.1 Pathophysiology

A healthy aortic valve, as shown in figure 2.1, consists of three cusps and has an opening area of about 3.5 cm^2 [28, 29]. When the left ventricle (LV) contracts, it forces blood to pass through the aortic valve into the aorta and subsequently to the rest of the body. When the left ventricle expands again, the aortic valve closes hermetically and prevents the blood in the aorta from flowing backward into the ventricle.

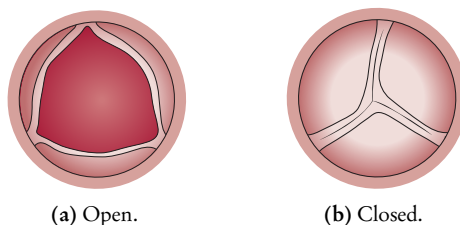


Figure 2.1: Healthy aortic valve (adapted from [30]).

In aortic stenosis, the opening of the aortic valve becomes narrowed and the closing non-hermetic due to calcifications (figure 2.2). Degenerative aortic stenosis begins

with damage to endothelial cells from increased mechanical stress [29, 31]. Inflammation is thought to be involved in the earlier stages of the pathogenesis of aortic stenosis (AS) and its associated risk factors are known to promote the deposition of cholesterol and a highly damaging substance known as Lipoprotein(a) into the aortic valve resulting in significant damage and stenosis over time [28, 29].

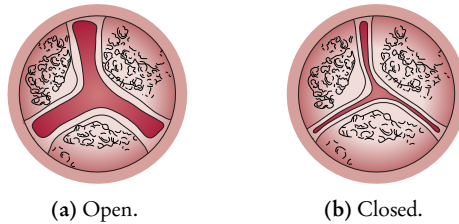


Figure 2.2: Stenosed aortic valve (adapted from [30]).

One of the consequence of this stenosis is that the LV must generate a higher pressure with each contraction to effectively move blood forward into the aorta [32, 33]. Initially, the left ventricle generates this increased pressure by thickening its muscular walls. The type of hypertrophy most commonly seen in AS is known as concentric hypertrophy [32], in which the walls of the LV are approximately equally thickened. In the later stages, the left ventricle dilates, the wall thins, and the systolic function deteriorates, resulting in impaired ability to pump blood forward.

2.2 Epidemiology

Approximately 2% of the population over the age of 65, 3% of the population over age 75 and 4% of the population over age 85 have aortic valve stenosis [32, 34]. The prevalence is increasing with the ageing population in North America and Europe [1]. Aortic stenosis is the most common acquired valvular disorder found in developed countries. More than 200,000 aortic valve replacements are performed each year worldwide [35], including 65,000 in Europe and 60,000 in United States [36, 37]. This valvulopathy is the most common valvular abnormality in Europe [1, 38]. The observed rise in the number of patients with severe AS in recent decades is related to the significant increase in the average lifespan [5, 39].

The main factors responsible for the development of aortic stenosis are hypertension, smoking, diabetes, renal failure, etc. [40].

2.3 Signs and symptoms

Symptoms related to aortic stenosis depend on the degree of stenosis (mild, moderate, severe or critical). Most people with mild to moderate aortic stenosis do not have symptoms. Symptoms usually present in individuals with severe and critical

aortic stenosis, though they may occur in those with mild to moderate aortic stenosis as well. The three main symptoms of aortic stenosis are loss of consciousness, anginal chest pain and shortness of breath with activity [31, 32, 41]

2.3.1 Angina

Angina in setting of heart failure also increases the risk of death. In people with angina, the 5-year mortality rate is 50 % if the aortic valve is not replaced [42].

Angina in the setting of aortic stenosis occurs due to left ventricular hypertrophy that is caused by the constant production of increased pressure required to overcome the pressure gradient caused by the aortic stenosis. While the muscular layer of the left ventricle thickens, the arteries that supply the muscle do not get significantly longer or bigger, so the muscle may not receive enough blood supply to meet its oxygen requirements [43].

2.3.2 Syncope

Syncope from aortic valve stenosis is usually exertional [32]. In the setting of heart failure it increases the risk of death. In people with syncope, the 3-year mortality rate is 50 % if the aortic valve is not replaced [42].

The causes of syncope with aortic stenosis remains unclear. One popular theory is that severe AS produces a nearly fixed cardiac output [44]. When a person with aortic stenosis is exercising, his peripheral vascular resistance will decrease as the blood vessels of the skeletal muscles dilate to allow the muscles to receive more blood. This decrease in peripheral vascular resistance is normally compensated for by an increase in the cardiac output. Since people with severe aortic stenosis cannot increase their cardiac output, the blood pressure falls and the person will faint due to decreased blood perfusion to the brain [42].

Sometimes, syncope may be operative. Due to the hypertrophy of the left ventricle in aortic stenosis, including the consequent inability of the coronary arteries to adequately supply blood to the myocardium, abnormal heart rhythms may develop [43].

In calcific aortic stenosis at least, the calcifications in and around the aortic valve can progress and extend to involve the electrical conduction system of the heart [45, 46]. If that occurs, the result may be heart block (a potentially lethal condition of which syncope may be a symptom).

2.3.3 Congestive heart failure

Congestive heart failure (CHF) carries a grave prognosis in people with aortic stenosis. People with congestive heart failure attributable to AS have a 2-year mortality rate of 50 % if the aortic valve is not replaced [42]. CHF in the setting of AS is due to a combination of left ventricular hypertrophy with fibrosis, systolic dysfunction (a decrease in the ejection fraction) and diastolic dysfunction (elevated filling pressure of the LV) [32].

2.4 Diagnosis

Aortic stenosis is most often diagnosed when it is asymptomatic and can sometimes be detected during routine examination of the heart and circulatory system [47].

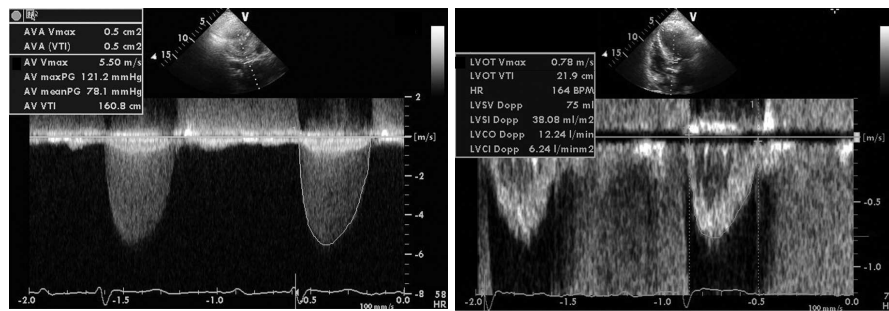
The severity of aortic stenosis, presented in table 2.1, can be measured accurately and reliably on the basis of antegrade velocity, mean pressure gradient and continuity equation of aortic valve area (AVA) (see equation 2.1) [36]. This equation requires the velocity time integral (VTI) of the LVOT and of the aortic valve (AoV) and the LVOT diameter. An echocardiography is used to measure the VTI (see figure 2.3).

Table 2.1: Recommendations for classification of aortic stenosis severity [48].

	Mild	Moderate	Severe	Critical
Mean gradient (mmHg)	≤ 20	20 – 39	40 – 59	≥ 60
Aortic jet velocity (m/s)	≤ 2.9	3.0 – 3.9	4.0 – 4.9	≥ 5.0
Aortic valve area (cm ²)	≥ 1.5	1.0 – 1.5	0.5 – 1.0	≤ 0.5

$$AVA = \frac{\pi \cdot \left(\frac{D_{LVOT}}{2}\right)^2 \cdot VTI_{LVOT}}{VTI_{AoV}}$$

(2.1)



(a) Transvalvular mean and peak gradients and the aortic valve VTI are obtained by continuous wave Doppler across the aortic valve. (b) The LVOT VTI is obtained from pulse wave Doppler in the LVOT.

Figure 2.3: Doppler of a calcified aortic valve used to measure the VTI [49].

Figure 2.4 shows the echocardiography of a non calcified aortic valve 2.4b and severely calcified aortic valve 2.4a.

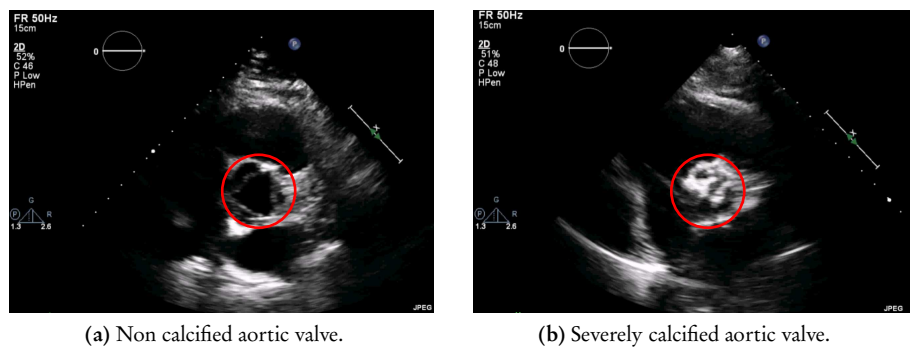


Figure 2.4: Echocardiography of open aortic valves (short axis). The valves are encircled in red.

A computed tomography scanner (CT Scan) can also be used to confirm the calcification of the aortic valve, as shown in figure 2.5.



Figure 2.5: CT Scan of a severely caclified aortic valve.

2.5 Prognosis

Without AVR, the prognosis is extremely poor, with a 3-year survival rate less than 30 %. However, 33 % of all patients aged over 75 years with severe AS are declined for surgery [38]. The mortality for untreated symptomatic severe AS is up to 60 % at 2 years in high-risk patients, and among such patients those who ultimately undergo surgical valve replacement, a proportion is at high risk of morbidity/mortality from the procedure [50, 51] (figure 2.6).

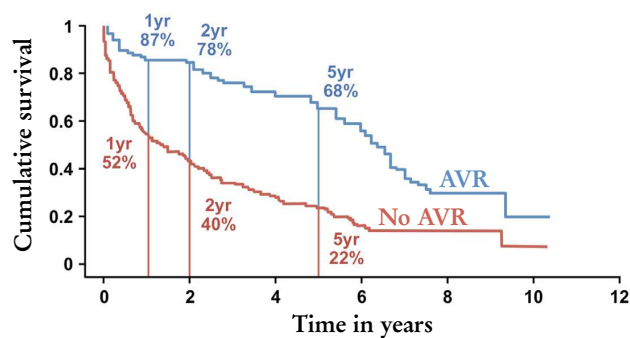


Figure 2.6: Severe AS patients not undergoing AVR have a shorter life expectancy than those receiving AVR (adapted from [52]).

Chapter 3

Medical treatment of aortic stenosis

The French surgeon Theodore-Marin Tuffier can be considered as a pioneer in thoracic and cardiovascular surgery in the field of clinical and experimental research. In 1912 he carried out the first clinical attempt to dilate a stenotic aortic valve through a transaortic approach using his finger [53]. In 1914, in collaboration at the New York Rockefeller Institute with Alexis Carrel, he published many cases of valve surgery with caval occlusion in animals: all died of cerebral anoxia, but the heart tolerated these procedures [54]. In 1913 he dilated the aortic valve by invagination of the aortic wall across the pathological valve. The improved patient survived for 10 years [55].

The advances in AVR have progressed over the last 60 years with developments in the heart lung machine (HLM), type of valve prosthesis and minimally invasive approaches.

3.1 Medication

The pathophysiology underlying aortic stenosis remains incompletely defined, and there are currently no effective medical treatments capable of altering its course [28, 56]. However, certain medications may help the symptoms, such as ones to reduce fluid accumulation, to slow heart rate or to control heart rhythm disturbances. Lowering blood pressure may prevent or slow the development of aortic stenosis.

3.2 Aortic valve replacement

With the development of cardiopulmonary bypass (CPB) and the HLM in the 1950s, it became possible to replace diseased heart valves in their native positions with a prosthetic valve. The first successful surgery with the HLM was performed

in June 1955 by Dr. Lyons. This was followed by what Dr. Edmunds described as the *great valve rush* [57].

In 1954, Hufnagel *et al.* reported the first attempts of valve replacement surgery dealt with aortic regurgitation with valves implanted in the descending aorta [58].

3.2.1 Surgical prostheses

Severely diseased heart valves that cause significant valvular disease, not amenable to be repaired due to extensive calcification, infection, or congenital malformation, have to be replaced by artificial or biological heart valves. Artificial mechanical heart valves (prostheses) are made from plastic materials, titanium or metallic alloys with the sewing ring from various fabrics. In biological valves the valve itself is mostly a biological tissue from other animal species that is mounted on a stent equipped with a sewing ring (bioprosthesis) [21].

Mechanical valves

Mechanical heart valves have been implanted since the beginning of the 1960s. They have been subject to continuous development and refinement of technical, hemodynamic, and biocompatibility parameters.

Hufnagel started the early clinical work on mechanical heart valve in 1958 [59]. Hufnagel's valve, shown in figure 3.1, was a silicon coated nylon poppet into a surrounding cage of lucent methacrylate Plexiglas. More than 200 Hufnagel's valves were implanted in the descending thoracic aorta for patients with aortic insufficiency; remarkably some of these valves functioned for as long as 30 years without significant wear [60].



Figure 3.1: Hufnagel artificial heart valve in the collection of the National Museum of Health and Medicine (from commons.wikimedia.org).

The first attempt to replace an aortic valve was performed by Dr. Starr in 1960 using a “ball and cage” mechanical valve, as shown in figure 3.2. The valve concept was a simple one: a design based on an 1858 patented wine bottle stopper [60].

Mechanical valves (see figure 3.3) are indicated in younger patients in whom a durable valve that can last decades is desirable. This decision must also be accompanied by the assessment of the patient's ability to tolerate anticoagulation because



Figure 3.2: Caged-ball valve Starr-Edwards [21].

clotting may occur with mechanical valves [61]. Due to the need for anticoagulation, these valves pose a problem in women in the childbearing age and in the pediatric population. In addition, the inability to expand with somatic growth during child development guarantees the need for reoperation if implanted in children [57].



Figure 3.3: Different types of mechanical prostheses [61].

Due to the mechanical nature of the valve, some patients can hear their valves “click” while opening-and-closing in their hearts. Moreover, due to its design, the only way to replace a mechanical valve with complications that occur years after implantation, is to perform an open heart surgery.

Biological valves

The rationale for development of biological valves was to reduce the risk of serious complications related to the mechanical heart valves (thrombosis, embolism, bleeding complications due to anticoagulation therapy, etc.) [21].

Bioprosthetic valves can be classified according to their species origin, nature of tissues used, whether or not they are mounted on a stent and the site of placement. Some bioprostheses are shown in figure 3.4.

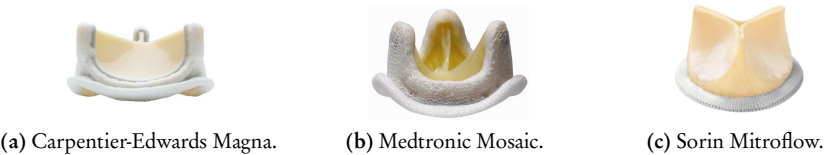


Figure 3.4: Different types of biological prostheses [62].

Sutureless valves

Sutureless aortic valve replacement has shown to produce similar efficacious outcomes as AVR, but with decreased hospitalization, reduction in sternal wound complications, reduced surgical trauma and improved cosmesis [63, 64]. The prostheses, as shown in figure 3.5, is made in shape memory alloys (SMA) and can be placed without any stitches which decreases the surgical procedure time.

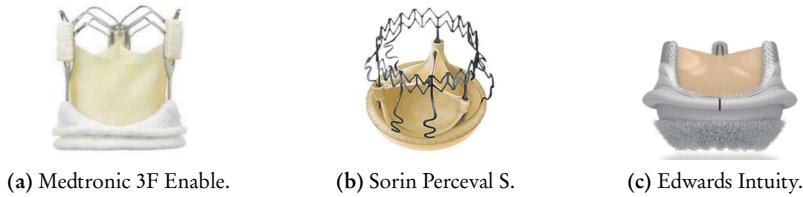


Figure 3.5: Different types of sutureless bioprostheses [63].

3.2.2 Surgical procedure

The AVR surgical procedure, performed under general anaesthesia, starts with a median sternotomy which consists on the incision of the skin and of the sternum. Then, the CPB is set in place with the insertion of a cannula in the right ventricle where the deoxygenated blood is pumped into the HLM and a cannula above the clamp, placed into the aorta which gives the oxygenated blood into the body, as shown in figure 3.6. Once the cannulae are firmly sutured, the heart is stopped thanks to a cardioplegic solution and emptied before opening it. Cardioplegic solution is the means by which the ischemic myocardium is protected from cell death. This is achieved by reducing myocardial metabolism through a reduction in cardiac work load and by the use of hypothermia.

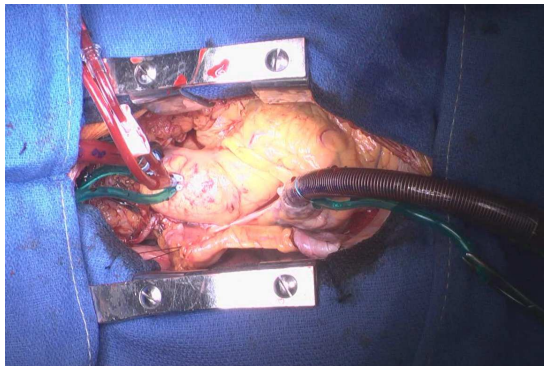


Figure 3.6: Cannulae for the CPB set in place into the heart.

To access the aortic valve, a transversal aortotomy is performed below the aortic clamp (see figure 3.7).

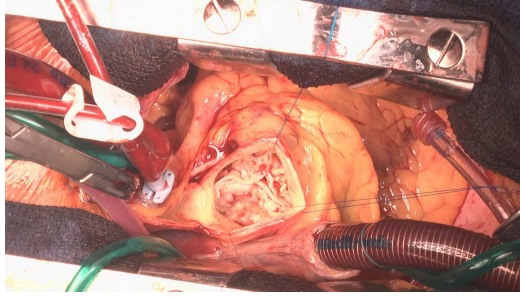


Figure 3.7: The aortotomy allows to easily access the aortic valve before its resection.

The aortic valve is resected and the aortic annulus is cleaned up with a surgical tweezers and a scalpel. In the same time, if calcifications are present onto the aorta, the surgeon removes the most as possible. Before the implantation of the valve, the aortic annulus is measured with a cusp sizer, as shown in figure 3.8. This measure allows to the surgeon to suture the right size of aortic prosthesis into the heart.

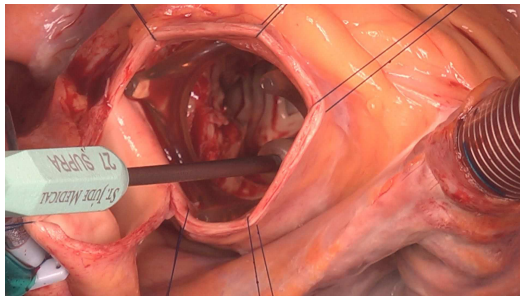


Figure 3.8: After the resection, a cusp sizer is used to measure the aortic annulus in order to implant the right prosthesis size.

As shown in figure 3.9, the next step consists on the suture of the aortic prosthesis into the aortic annulus with a dozen of stitches.

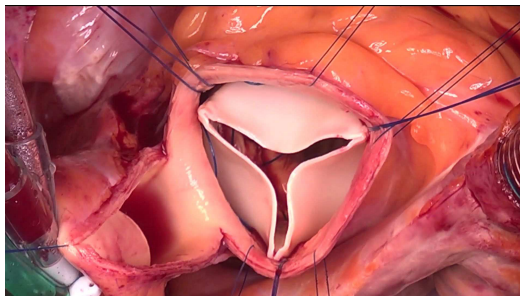


Figure 3.9: The bioprosthesis is sutured into the aortic annulus.

At the end of the procedure and before stopping the CPB, the aorta is closed (figure 3.10).

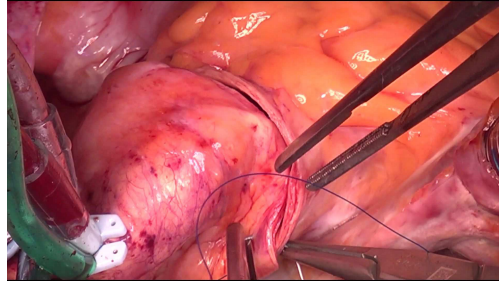


Figure 3.10: Before stopping the CPB, the aorta is closed.

Finally, the CPB is stopped, the sternum is closed with stainless steel wires and the chest is closed. The heart is stopped during about 45 minutes with a total procedure time of approximatively 3 hours. A post-operative CT Scan is shown in figure 3.11.

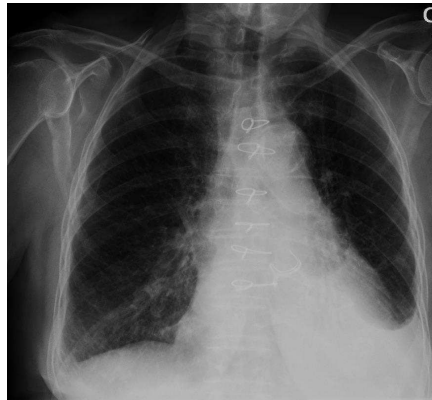


Figure 3.11: Post-operative CT Scan of the chest with the six stainless steel wires used to close the sternum and the structure of the prosthesis.

3.2.3 Advantages and disadvantages

To date, surgical aortic valve replacement is the only effective therapy, improving survival and ameliorating symptoms [38]. However, because the conventional AVR with CPB can be associated with an unacceptable risk of perioperative mortality and morbidity, almost one-third of patients with symptomatic severe aortic stenosis who could benefit most from intervention are declined for operative treatment because of end-stage disease, advanced age, and multiple comorbidities with subsequent short life expectancy [65, 66].

3.3 Percutaneous aortic balloon valvuloplasty

The initial attempts to treat non-surgical patients with advanced aortic stenosis have started with percutaneous aortic balloon valvuloplasty (PABV) [67]. In 1985, Cribier *et al.* performed the first percutaneous dilatation of an aortic valve degenerative stenosis [68]. Cribier later described the procedure in a documentary fashion: “*The patient was symptomatic for dyspnea and angina, she has a tight aortic stenosis and normal coronary arteries. At this time the surgical risk is considered too high because of her age and because she is a diabetic and obese. The procedure was performed through the ascending aorta to facilitate the crossing of the stenotic valve. The dilatation was performed with extreme caution. The gradient was decreased by 50 % in comparison to baseline. In the following days the clinical improvement was exciting.*”

In 1987, Cribier’s study involving 92 patients has generated a great enthusiasm [69]. Widespread interest was directed to PABV as a palliative treatment for elderly patients with calcified aortic stenosis [70, 71].

This technique was largely abandoned by clinicians as the benefits of valvuloplasty rarely lasted more than one year [72] in symptomatic patients who were at high risk of aortic valve replacement including very elderly patients, others with severe comorbidities or a severe depression in left ventricular function [73].

Nowadays, in some rare cases a bailout PABV performed through a subclavian or a humeral access prior to standard AVR can be taken into consideration. Similarly, for young patients in cardiogenic shock and multi-organ failure an urgent PABV for restoration of the patient’s hemodynamics, as a bridge to AVR, appears to be an option as long as no randomized trial is available. For these young patients, the use of CPB for urgent surgical AVR is at very high risk, so it is not encouraged [55].

3.4 Transcatheter aortic valve implantation

TAVI developed from implantation in a porcine model in 1992 by Andersen *et al.* [74] (see figure 3.12), to human experiments by Cribier *et al.* in 2002 [9], initially via an antegrade transvenous-transseptal-transmitral route was developed.

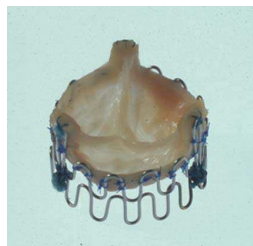


Figure 3.12: Andersen stent valve built for percutaneous transluminal catheter implantation. The stent valve consists of two folded metal rings and a porcine aortic valve mounted inside the stent [75].

Percutaneous techniques for AVR via, for example, transfemoral or transapical have become an alternative treatment option for high-risk patients during the last years [8, 76–78]. These methods minimize concomitant trauma and can be done in the beating heart situation: the native valve is crushed against the aortic wall and a stented biological prosthesis is implanted afterwards.

3.4.1 Endovalves prosthesis

To date, two types of transcatheter aortic valves are widely used in the clinical setting: the balloon-expandable valve Edwards Sapien XT from Edwards Lifesciences Corporation and the self-expandable CoreValve system from Medtronic CV Luxembourg S.a.r.l.

Balloon-expandable

The most implanted of balloon-expandable aortic valve prosthesis is the Edwards Sapien XT® (see figure 3.13) which consists of a trileaflet pericardial bovine valve mounted in a cobalt chromium frame. The frame design reduces the valve size, with no loss of radial strength. In addition, the scallop shape of the valve reduces leaflet volume and improves valve profile. The Sapien XT® valve is available in 20 mm, 23 mm, 26 mm, and 29 mm sizes, and is implanted using 18 French (for the 20 mm and 23 mm valves), 19 French (for the 26 mm valve), or 22 French (for the 29 mm valve) delivery catheter and sheath systems [79].

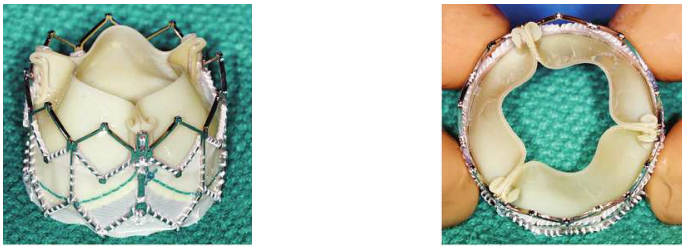


Figure 3.13: The Edwards Sapien XT® valve from Edwards Lifesciences Corporation [79].

Selfexpandable

The most implanted selfexpandable prosthesis is the CoreValve® aortic system (figure 3.14) made from a Nitinol frame and of three leaflets of porcine pericardium. The sealing skirt is fabricated from three separate pieces to facilitate uniform tissue thickness and improve the valve profile. The valve is available in 26 mm, 29 mm, and 31 mm sizes, and is implanted using an 18 French delivery catheter and sheath system [79].

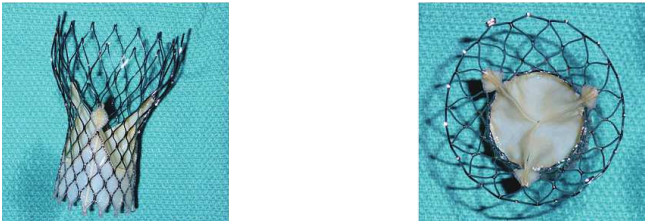


Figure 3.14: The third generation of the CoreValve® system from Medtronic CV [79].

3.4.2 Approaches used for TAVI

Currently, five approaches are used, or are under investigations, for the implantation of an aortic prosthesis through percutaneous access. These five approaches are shown in figure 3.15.

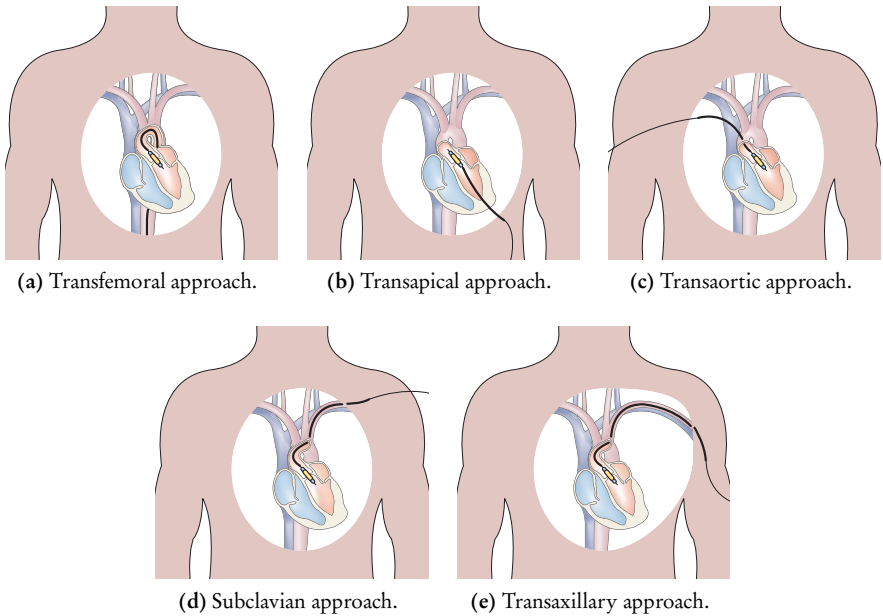


Figure 3.15: Approaches used for transcatheter aortic valve implantation [79].

Transfemoral approach

The transfemoral access (figure 3.15a) is the first choice in the majority of centers performing TAVI procedures. Before the procedure, the femoral artery needs to be accurately evaluated to be sure that the endo valve will be able to be routed from the groin to the heart. The endo valve will first pass through the femoral artery then

into the aorta and finally be placed into the native aortic valve. This strategy can be performed without the use of general anaesthesia.

Transapical approach

The transapical access (figure 3.15b) is the second approach used in the TAVI centers. In 2006, Lichtenstein *et al.* were the firsts to implant an endo valve through transapical access [80]. This access requires a small left lateral thoracotomy into the fifth intercostal space. The endo valve is inserted into the heart via an incision at the level of the apex, then is routed to the native valve through the left ventricle.

Advantages of this implantation route are the avoidance of using large catheters through the iliofemoral system, aortic arch, ascending aorta and aortic valve and the improvement of the coaxiality between the endo valve and the native aortic valve. The main disadvantages are the need of a thoracotomy and myocardial injury due to the apical perforation of the left ventricle [79, 81].

Transaortic approach

In 2009 and 2010, the transaortic approach (figure 3.15c) has been proposed [82–84]. This access requires a small right or mid sternotomy but avoids the use of large catheters through the iliofemoral system and aortic arch, and avoids puncture of the left ventricle apex [79].

Subclavian approach

In 2007, Ruge *et al.* implanted an endo valve through the left subclavian artery (figure 3.15d) as an alternative to the transfemoral approach [85]. The very short distance between the access and the native aortic valve might be associated with better control of the prosthesis during the positioning and the deployment. However, injuries of the subclavian artery would translate into a major intrathoracic bleeding that may be difficult to control [79].

Transaxillary approach

In 2009, De Robertis *et al.* [86] reported the first endo valve implanted by the transaxillary approach (figure 3.15e). 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 to 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 [79].

3.4.3 Transapical procedure

The transapical procedure is performed under fluoroscopy in a dedicated hybrid operating room. Before the beginning of the procedure, the fluoroscopy is positioned to visualize the aortic root and the aortic annulus in a perpendicular angle. All three aortic sinuses and aortic valve cusps should be in one plane.

The first step of the transapical procedure is to perform an anterolateral mini-thoracotomy in the fifth or sixth intercostal space (see figure 3.16a) in order to expose the left ventricular apex (figure 3.16b).

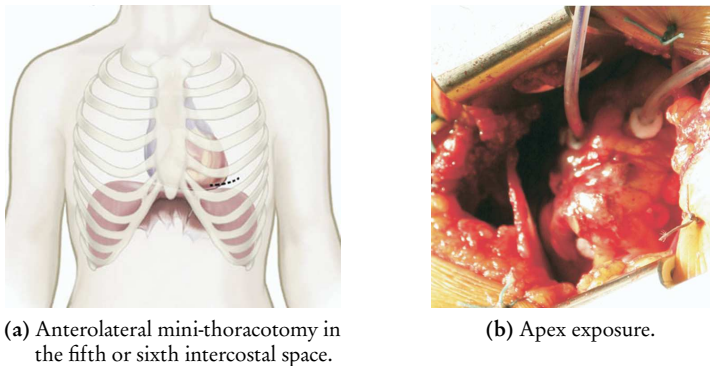


Figure 3.16: Access to the apex [87].

Then, the apex is punctured with a needle, and a soft guide wire is inserted antegrade across the stenotic aortic valve. A stiff guide wire is positioned across the aortic arch and into the descending aorta with the help of a catheter (figure 3.17). This guide wire will serve as an Ariadne's thread to be sure that implantation device is always into the aortic valve to earn time during the procedure.

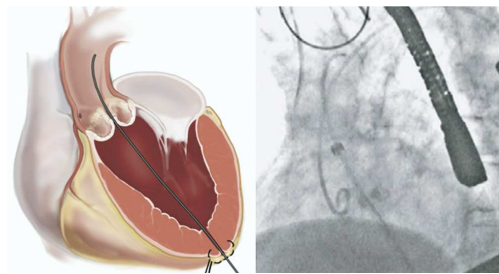


Figure 3.17: Apical wire insertion, schematic view (left) and fluoroscopic imaging (right) [87].

The next step, shown in figure 3.18, is to dilate the calcified aortic valve with a valvuloplasty balloon in order to break the calcification buds for an easier endovale insertion. This step is performed under rapid ventricular pacing (RVP) to stop the blood flow. The RVP is “effective” once there is no significant pulse pressure,

indicating a temporary cessation of left ventricular ejection and is performed at a rate between 170 bpm and 220 bpm.

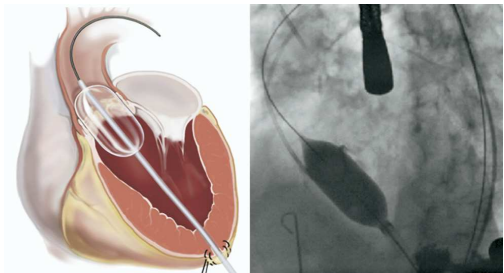


Figure 3.18: Balloon valvuloplasty of the aortic valve, schematic view (left) and fluoroscopic imaging (right) [87].

The endo valve is then introduced into the heart through the apex before its implantation (see figure 3.19).

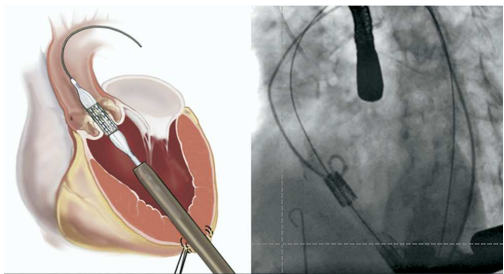


Figure 3.19: Valve positioning, schematic view (left) and fluoroscopic imaging (right) [87].

The exact valve positioning is the most critical step during TAVI. The proper valve positioning is performed under angiographic guidance (figure 3.20).

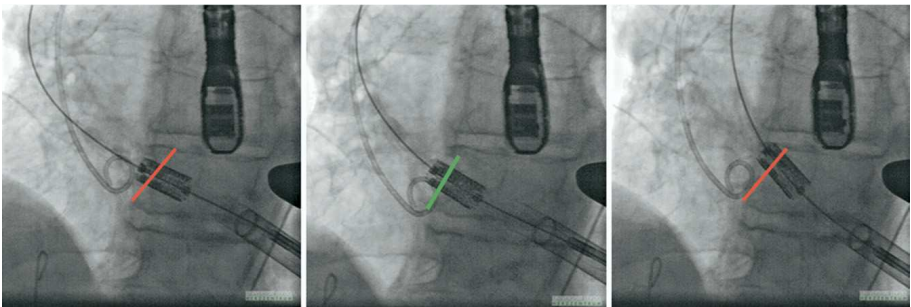


Figure 3.20: Valve positioning: (middle) correct position perpendicular to the aortic annulus, (left) rightward oblique position due to slack of the wire, and (right) leftward oblique position due to a tight wire [87].

The next step consists on the implantation of the endovalve, as shown in figure 3.21. The implantation is performed under RVP to stop the blood flow and avoid the migration of the valve during the inflation of the balloon. The implantation of the valve must not exceed 60 seconds to avoid any brain damages. For a self-expandable endovalve, the implantation is performed without RVP which allows more time for the implantation.

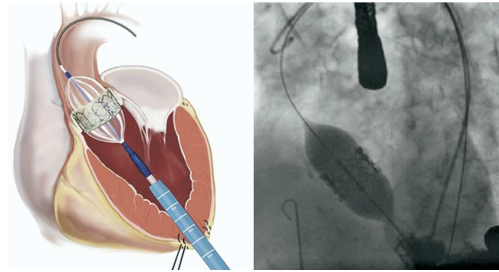


Figure 3.21: Valve implantation, schematic view (left) and fluoroscopic imaging (right) [87].

During the last step, before closing the apex and the chest wall, a valve function is assessed using angiography and echocardiography (figure 3.22). If big paravalvular leaks are observed then a new balloon dilatation is performed. This balloon dilatation can also be done for the self-expandable endovalves.

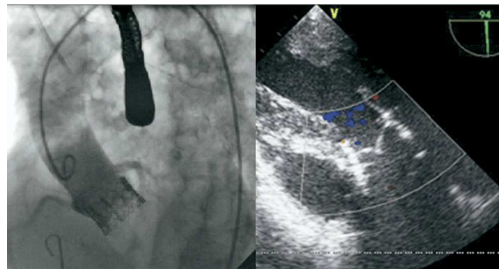


Figure 3.22: Final assessment after transapical aortic valve implantation, fluoroscopic imaging (left) and echocardiographic control (right) [87].

3.4.4 Potential complications from TAVI

This less invasive new technique is quite encouraging. The procedure is less traumatic for the patient undergoing AVR because it avoids the use of a full sternotomy and of a CPB. Moreover, the duration of the procedure is reduced to less than a minute and the revalidation time is shortened.

But, next to these benefits, there are known several complications: paravalvular leaks, vascular injuries, cerebral embolisation, annulus rupture and conduction abnormalities [88].

Paravalvular leaks

In contrast to surgical AVR, during TAVI the native valve is not removed but crushed instead, as shown in figure 3.23.

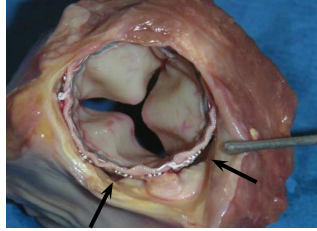
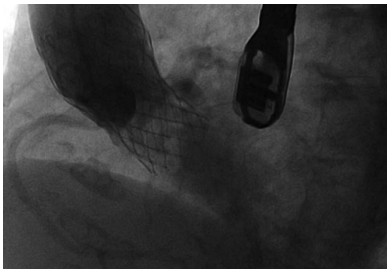
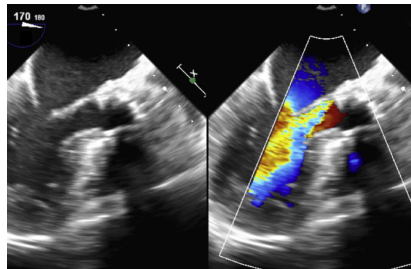


Figure 3.23: Paravalvular leak (PVL) (black arrows) can appear because the aortic valve prosthesis is implanted into the calcified native valve.

Slight aortic insufficiency is not uncommon and has been reported in about 70 % of patients for both available types of percutaneous valves [89–93]. Moderate regurgitation has been observed in up to 40 % of cases [90–92]. In open-heart surgeries, the occurrence of PVL has been reported in very few cases, being 2 % and 8 % after bioprosthesis and mechanical prosthesis respectively [94]. In most cases, such aortic insufficiency is clinically acceptable, however, severe insufficiency can occur (see figure 3.24). The current reports only briefly mention the treatment of such severe insufficiency. The discrepancies in the prevalence of valve regurgitation after TAVI [95, 96] are mainly due to the absence of standardized definitions and protocols to detect and score the leak.



(a) Angiography taken during the implantation.



(b) Transesophageal echocardiography (long axis). The normal blood flow is in blue, the regurgitations are in yellow, orange and red.

Figure 3.24: Significant PVL after implantation of a 26 mm aortic CoreValve prosthesis probably due to major focal calcification at the posterior site [97].

The aortic insufficiency after TAVI can be classified according to the type of regurgitation, its mechanism and its etiology. Paravalvular insufficiency may arise from patient-prosthesis mismatch due to under-sizing of the implanted device, incom-

plete expansion of the prosthesis stent frame or incorrect site of prosthesis implantation. Intravalvular insufficiency might be due to opening failure of the prosthesis' leaflets, leaflet damage occurring during the crimping manoeuvre or implantation phase, or again due to patient-prosthesis mismatch because of incorrect sizing of the valve [98].

In contrast to surgical procedure, direct sizing of the native aortic annulus is not possible during TAVI. The selection of the prosthesis that matches exactly with the native aortic annulus is paramount to the 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 plane 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, angiography, or CT Scan. There is no gold standard for annulus measurement, and a multimodal assessment is strongly recommended [99], since the aortic annulus is not always circular but might be oval shaped (figure 3.25).

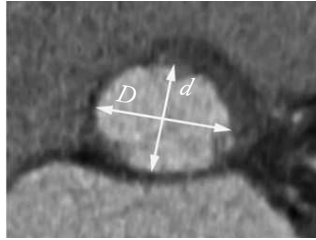


Figure 3.25: 50 % of the patients evaluated for TAVI have an oval shaped aortic valve. Coronal diameter $D = 26.5$ mm, Sagittal diameter $d = 20.6$ mm, Mean diameter 23.6 mm [100].

The annulus has 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 [100–102].

In most cases, aortic insufficiency is clinically acceptable and stable during follow-up [94, 103, 104], but 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 (see figure 3.26) [103]. When severe regurgitation is present, multimodal imaging for an accurate assessment of the underlying pathophysiology of the regurgitation is of utmost importance in selecting adequate therapy.

Atrioventricular block

The need for pacemaker implantation following TAVI ranges from 5.7 % to 39 % depending on the type of percutaneous prosthesis used [106, 107].

This complication may significantly affect the outcome of the patient, increase hospital stay, overall cost of treatment and may be associated with an increased risk of sudden death. The LBB exits 2 to 3 mm below the base of the triangle formed by the

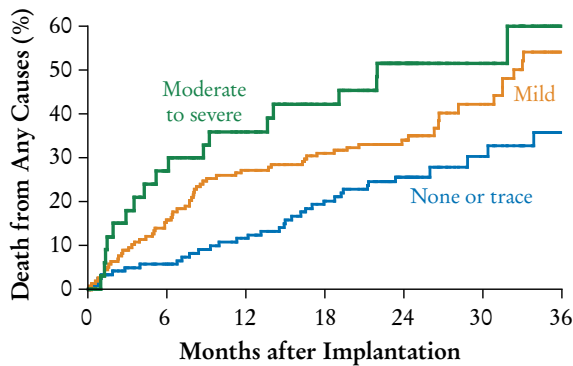


Figure 3.26: Severity of total aortic regurgitation (none or trace, mild or moderate to severe). Even mild PVL (or total) aortic regurgitation (occurring in approximately 40 % of patients) was associated with increased late mortality. Conversely, the absence of paravalvular aortic regurgitation or only trace regurgitation was associated with lower mortality [105].

non-coronary and right coronary cusps of the aortic valve, close to the annulus and LVOT. Therefore, aortic valve surgery and any cardiac catheterization procedure requiring crossing of the aortic valve with guide wires and catheters carries the risk of trauma to the septal conduction pathways and particularly to the LBB. Risk of atrioventricular block is subsequently higher in cases with pre-existing right bundle branch block (RBBB).

The reported incidence of atrioventricular block (AVB) requiring a pacemaker after CoreValve implantation ranges from 18 % to 39 % while the incidence of left bundle branch block (LBBB) is about 50 %. New onset conduction disorders and requirement for 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. For technical reasons, a deeper intraventricular insertion of the self-expanding CoreValve is generally observed. In the report by Piazza *et al.* [107], the length of stent below the non-coronary cusp was calculated to be on average 10.3 mm (range, 6.7 to 14.6 mm) in a series of 40 patients; the cutting distance being 6.7 mm. Indeed, the lower limit of the Edwards valve should not reach the upper part of the interventricular septum and in contrast to the CoreValve's Nitinol 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 abnormality and allowing safe retrieval of the temporary pacing lead at the end of the procedure [108].

Piazza *et al.*, in their series of CoreValve implantations, reported the occurrence of electrocardiographic changes during the procedure in 30 % of cases immediately after pre-implantation balloon valvuloplasty or guide wire crossing of the native aortic valve [107]. The large valves used in TAVI can also result in compression of the upper interventricular septum and impair atrioventricular conduction, as shown in figure 3.27. In their series of Edwards Sapien valve implantations, Sinhal *et al.* reported that 10 % of patients presenting with pre-existing RBBB needed pacemaker implantation [108]. Godin *et al.* reported similar outcome using similar Edwards

Sapien valve [109].

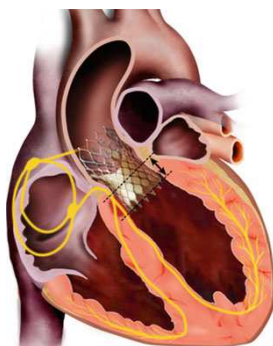


Figure 3.27: Diagram illustrating anatomic relation between a deep prosthesis implantation into LVOT affecting electrical conduction system [110].

Coronary ostia occlusion

A life-threatening complication is coronary artery stenosis or occlusion with a reported incidence of 0.6 % to 7 % [111, 112]. Rapid diagnosis and a staged management are mandatory to immediately save the life of the patient. Complete occlusion of the coronary ostium occurs at the time of valve deployment and is usually associated with hemodynamic collapse [113]. Any hemodynamic instability of a patient after or during TAVI should raise the suspicion of coronary artery obstruction or occlusion. The only treatment option after diagnosis is immediate reestablishment of blood flow by percutaneous techniques or coronary artery bypass grafting (CABG). Crimi *et al.* reported a case of a transapical aortic valve implantation complicated by acute left main occlusion, cardiac arrest, and hemodynamic collapse, successfully treated by balloon angioplasty and stent implantation [114]. In some cases, cardiopulmonary support of some sort is necessary.

Several patient and procedure related factors potentially associated with this event have been proposed and should be considered during the selection of the patients, though their predictive value has to be confirmed by additional data. A low-lying coronary ostium, bulky native leaflets, a narrow root, an excessively enlarged valve leaflet or the new valve prosthesis itself might result in coronary occlusion. The anticipation of coronary occlusion can allow the operator to establish measures such as positioning of a protective wire in the coronary artery at risk.

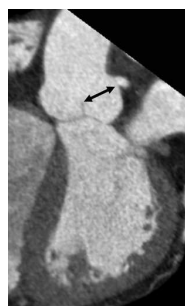
In all prior reports, the coronary occlusion has not been due to the endo valve itself but rather due to the native leaflets' calcium or native leaflets' height (see figure 3.28). Webb described it clearly in his report about a single patient in whom coronary obstruction by a displaced native valve was observed [113]. Until this is better understood, the presence of an unusually bulky left coronary leaflet appears to be a relative contraindication to percutaneous valve implantation.

As shown in figure 3.29, the distance between coronary ostia and the aortic annulus is crucial. Mean distance between the aortic annulus and the ostium of the right

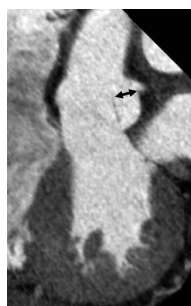


Figure 3.28: Coronary occlusion is due to the native leaflet length and not to the height of the prosthesis.

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 [101]. 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.



(a) Diastolic phase.



(b) Systolic phase.

Figure 3.29: Anatomical analysis: distance between left coronary ostium and leaflet tip [101].

Continuous embolisation of calcium debris

Neurological complication is a dramatic postoperative event, especially in this population with poor life expectancy. Indeed, cerebral event rates after conventional AVR range from 0.21 % to 2.0 % for neurological death and from 1.1 % to 6.6 % for clinical stroke [115]. Astarci *et al.* reported a rate of silent ischemic lesion of 90 % after transfemoral and 92 % after transapical implantation of Edwards Sapien valve [116].

The rate of stroke reported in the TAVI literature is an important topic. In the PARTNER trial, Smith *et al.* reported a rate of stroke that increases over the time [117]. Rates of all neurologic events were higher in the transcatheter group than in the surgical group at 30 days (5.5 % and 2.4 % respectively) and at 1 year (8.3 % vs. 4.3 %). Rates of major stroke were 3.8 % in the transcatheter group and

2.1 % in the surgical group at 30 days and 5.1 % and 2.4 %, respectively, at 1 year. Most strokes appeared to be procedure-related and embolic.

Patient-prosthesis mismatch

Transcatheter aortic valve implantation has emerged as an alternative to AVR in high-risk patients with aortic stenosis. However, no specific data exist on the results of TAVI in patients with a small aortic annulus. So far, only a few small series [118–123] have described the incidence of patient-prosthesis mismatch (PPM) after TAVI, and little is known about its impact on left ventricle performance and clinical outcomes in these patients.

The present observation demonstrates 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 one 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 [120]. In addition, the differences in prosthesis design may play a role. The Edwards Sapien valve has a 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.

Ewe *et al.* demonstrated that patients with PPM have less favorable changes post-TAVI compared with patients without PPM, displaying higher transvalvular gradients, limited left ventricle mass regression and left atrium volume reduction, and persistently elevated left ventricle filling pressures [120]. The effective orifice area of the valve is higher in patients without PPM than in patients with PPM. Finally, more patients reported a lack of clinical improvement in the group with PPM.

3.5 Conclusions

Since the development of TAVI, a greater number of patients can undergo surgery. However, the results can be worse than the open heart surgery because the native aortic valve is not removed. If a device was able to resect the native aortic valve prior the implantation of a stented valve in a mini-invasive way, the results of TAVI would be as good as the results of open heart surgery. Indeed, all the problems described in the literature and encountered with TAVI are due to the non-resection of the native aortic valve.

Usually, when a demand is requested by a client, the market is analysed to verify that the demand meets the need of several clients to be sure that it is the device to develop will be useful in order to be used by a great number of clients. Moreover, the developers discuss with different clients to completely understand the need and to target it. In this research, because of aspects of intellectual properties, only the demand of the surgeon at the base of the project has been taking into account.

No discussions with other clients have been done. Only a market analysis has been performed to have an idea of the potential of the usage of the future device. Develop a device with a single client is restrictive because the developers will only have the point of view of one person.

Part II

Design method

Chapter 4

Functional analysis

As seen in chapter 3, if the aortic valve is kept in place before the implantation of the endo valve, the results may be worse than the AVR in open heart surgery. To achieve the same results in TAVI than in AVR, a new medical device has to be designed. This medical design will allow to resect the valve and to implant an aortic endo valve in a minimally invasive way.

Before going further, the question *is the problem correctly stated?* must be answered. Indeed, as defined by the Soviet inventor Genrich Altshuller in its method teoriya resheniya izobretatelskikh zadach (TRIZ) (or theory of inventive problem solving (TIPS) in English), *a real problem can be described as a contradiction* [124]. This method is a problem-solving, analysis and forecasting tool derived from the study of patterns of invention in the global patent literature [125].

The figure 4.1 presents the contradiction of the aortic valve replacement. Both current solutions to replace the aortic valve have different advantages and disadvantages. For the surgical AVR, the advantages are the resection of the aortic valve, very limited PVL and a good match between the patient and the implanted prosthesis. These advantages are the disadvantages of TAVI. The advantages of TAVI, which are the disadvantages of surgical AVR, are no CPB nor sternotomy necessary and a faster surgical procedure.

The problem to be solved is a contradiction with the current available solutions. A new device to replace the valve needs to be designed.

4.1 Design method

To develop the best solution as possible for the medical device, a systematic and iterative design method, described in [14, 126], has been followed. This method consists in seven steps:

1. The **objectives are clarified** thanks to the analysis of the need. This first step aims to clarify the design objectives and sub-objectives and the relationships between them.

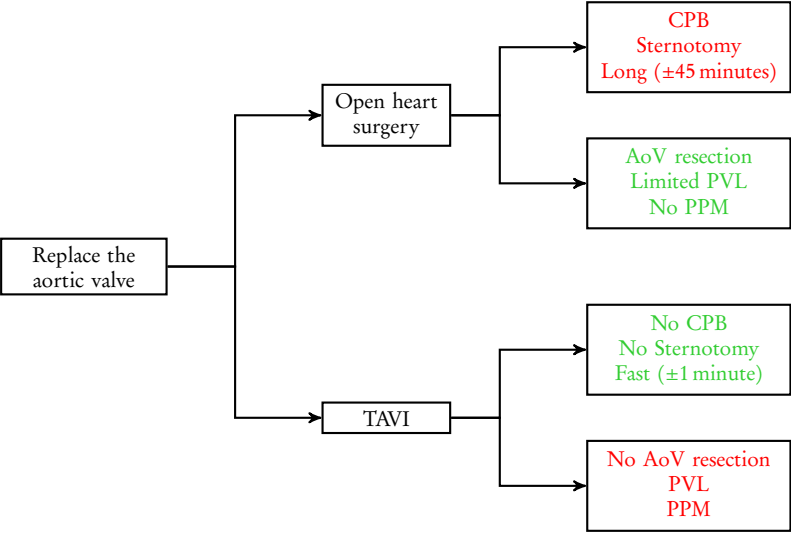


Figure 4.1: AVR described as a contradiction. In red, the disadvantages of each solution and in green, the advantages.

2. **Establishing functions** consists in the functional analysis of the need with the establishment of the required functions, and the new boundary, of a new design.
3. The **requirements are set** with the functional specifications which aim to make accurate specifications of the performances required of a design solution.
4. The comparison criteria **determine the characteristics** and set targets to be achieved for the engineering characteristics of a product, such that they satisfy the customer requirements.
5. **Alternatives are generated** in the technical functional analysis in order to have the complete range of alternative design solutions for a product, and hence to widen the search for potential new solutions.
6. During the technical functional analysis, the **alternative are evaluated** each other thanks to the comparison criteria. The aim of this step is to objectively compare the utility values of alternative design proposals, on the basis of performance against differentially weighted criteria.
7. The last step is the device development with the **improvement of the details** to increase or maintain the value of a product to its purchaser while reducing costs to its producer.

4.2 Analysis of the need

Before starting the brainstorming and find the best solution for a given problem, a tasks clarification has to be done to be sure that all the needs and constraints will be taken into consideration. A misstated problem can lead to very good results at the

expense of a long process of research and exorbitant development costs.

Following the norm Association française de normalisation (AFNOR) NF X50-151, the first step is to analyse the need. The norm define the need as follow: *A need is a desire (or a necessity) experienced by the user of a system* [127].

There are two primary forms of need: the need expressed and the latent need. For example, the main human needs are: food, resting, protection, healing, communication, movement, entertainment, education, etc. Each of these primary needs can be decomposed into other needs. For example, “protection” can be expressed by “housing”, “wearing clothes”, “respect of the environment”, etc. It is to be noticed that the needs of the humans are evolving with time [127].

The first step to clarify the need is to verbalise it. To achieve this verbalisation, the method of need analysis is based on two hypothesis:

- the satisfaction of the need is performed by using the product to design;
- the need is met by the state change of a field of work.

To verbalise the need, three questions have to be asked (... and answered):

1. **To whom** does the product serve? To the **customer**.
2. **On what** does the product act? On the **field of work**.
3. **In what purpose?** To satisfy the **need**.

This verbalisation can also be presented thanks to a graphical tool from the *application aux techniques d'entreprise (APTE)* method (in English: application to the corporation methods): “The horned beast”, as shown in figure 4.2. The need can finally be expressed in the following way: *the product serves the customer by acting on the field of work to satisfy the need*.

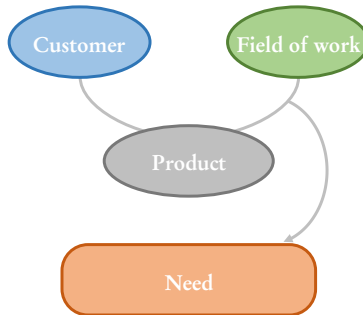


Figure 4.2: “The horned beast” from the APTE method.

For the development of the assistance to the replacement of the native valve, there are two needs: (1) resect the aortic valve and (2) implant an aortic endo valve. The first need, schematically represented as a horned beast form in figure 4.3a, is a *medical device serving the surgeon to resect the native aortic valve from the heart*. The second need, schematically shown in figure 4.3b, is a *medical device serving the surgeon to implant an endo valve into the heart*.

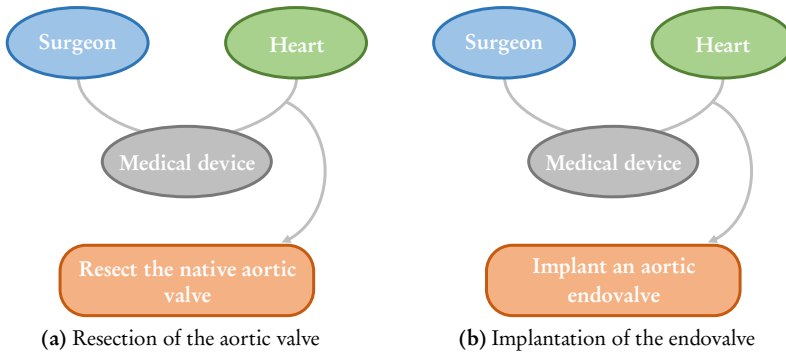


Figure 4.3: Need diagrams for the assistance to the replacement of the native aortic valve.

4.3 Functional analysis of the need

Now that the need analysis is finished, the next step is to performed the functional analysis of the need. This step is so called because it will allow to translate the need into functions to achieve: the service functions. Moreover, the step will allow to elaborate the specification of the device which has to be designed by identifying the relation between the product and its context of use, in order to get the functions suitable to meet the need. The functional analysis of the need is based on two hypothesis:

- the need is satisfied by the usage of the product;
- the product is a services generator.

The norm defines a service function as *an action of a product or of one of its components exclusively expressed in terms of finality*. This implies that the functions can only be identified and characterised if the external environment of the product has been identified and characterised. The external environment of the product to be designed depends of the moment it is considered. Because the life cycle of the product consists in a lot of steps, the external environment of each life phase of the product has to be determined.

To perform the functional analysis of the need, and determine the service functions, two steps have to be followed:

1. identification of the life phases of the product;
2. for each life phase, identification and characterisation of the elements of the external environment.

4.3.1 Life phases of the product

Depending on the design objectives and the desired level of precision, a lot of life phases for a product can be identified. The life phases of a product can be, for

example, the mechanical design, the manufacturing, the packaging, the marketing, the maintenance, the usage, the storage, etc.

In practice, a product is designed to satisfy a need corresponding to its usage. However, each life phase of the product adds new constraints and its design becomes more and more complex. To design the best product as possible, compromises have to be done between satisfied need and dreamed need.

For the medical device to design, three life phases have been identified:

- the mechanical design;
- the manufacturing;
- the use of the product.

4.3.2 Elements of the external environment

To identify the functions of the product, its environment must be correctly characterised. This characterisation has to be done for each life phase of the product to design. Two rules must be respected during this identification. Firstly, an element of the external environment must be defined in an objective way for all the designers. If an element cannot be entirely defined by objectives criteria, then this element is not an element of the external environment. Secondly, if an element is a solution for the product, this element is not an element of the external environment, unless this solution must be integrated into the design and so will become a constraint.

The elements of the external environment for each of the three life phases of the medical device are presented in figure 4.4 for the mechanical design, in figure 4.5 for the manufacturing life phase and in figure 4.6 for the use of the product.

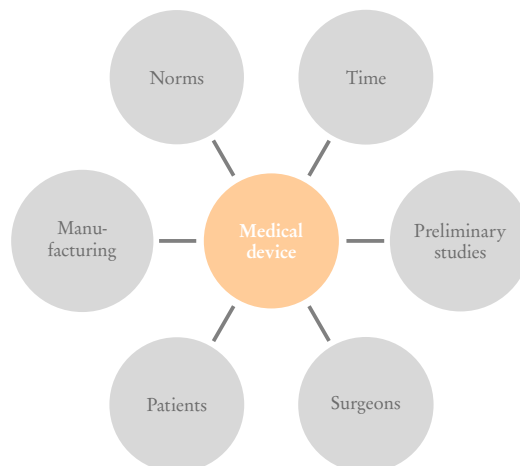


Figure 4.4: Identification of the elements of the external environment for the mechanical design life phase of the medical device.

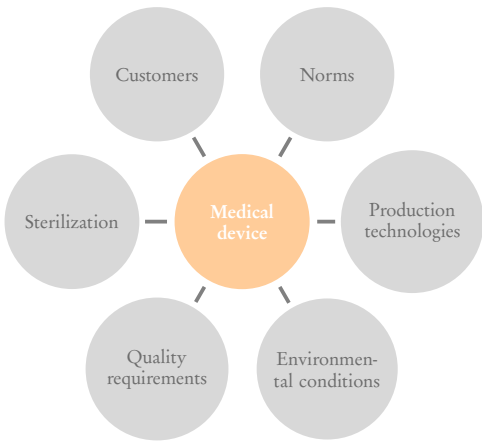


Figure 4.5: Identification of the elements of the external environment for the manufacturing life phase of the medical device.

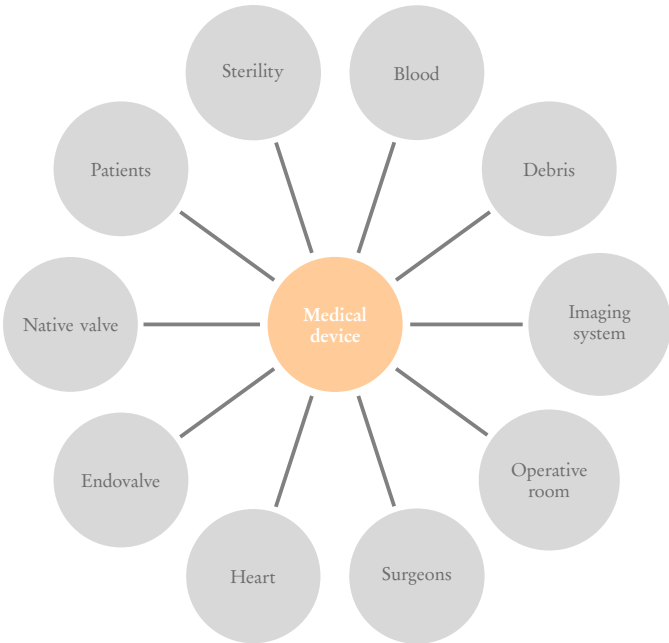


Figure 4.6: Identification of the elements of the external environment for the usage life phase of the medical device.

4.4 Functional specifications

Based on the analysis of the need and on the functional analysis of the need, the service functions can now be determined. There are two kinds of service functions: the functions and the constraints. A function is a service function which connects,

through the product, two or more elements of the external environment and a constraint is a service function which connects the product with one element of the external environment. The constraints reflect most of the time an adaptation of the product to its external environment.

The figure 4.7 shows the relations between different elements form the eternal environment of the usage life phase in order to determine the service functions. As shown in this figure, three service functions emerge for this life phase. The other elements of the external environment are the constraints to take into account during the development of the device. For the two others life phases, no relations between two or more element from the external environment could not be established meaning that these life phases only impose some constraints to the medical product to be designed.

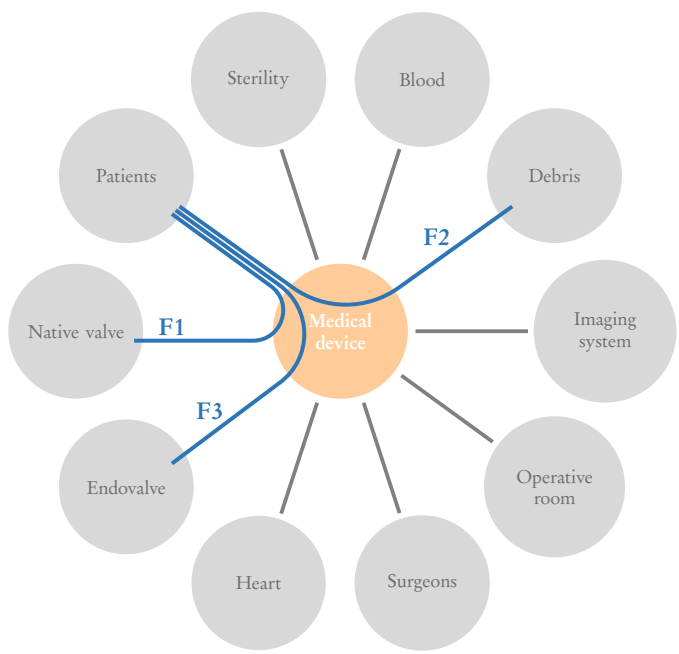


Figure 4.7: Octopus diagram to identify the service functions and the constraints for the usage life phase of the medical device.

To be relevant, the functions and the constraints must be set in accordance with different rules. The expression of the functions and of the constraints is standardised by the AFNOR: *a function consists of a verb or a verbal group characterising the action and of complements representing the elements of the external environment involved in the function.* The subject of the sentence does not appear in the function or in the constraint but always refers to the product.

Beside this formal definition, some usage rules must be respected:

1. passive and negative forms are to be avoided (passive form can be admitted for the constraints);

2. the expression of the function must be independent of any solution;
3. the expression must be as concise and as clear as possible.

The functional specifications with the functions and the constraints for the medical device to design are given in table 4.1. These specifications, based on the model proposed in [126, 127], have been established in collaboration with the surgeon and a team of engineers. The establishment of the specifications requires a lot of time in order to be the most complete as possible and earn time during the technical functional analysis.

The medical device to design will achieve three functions: (1) resect the native aortic valve, (2) collect the debris of the resected valve and (3) implant the endo valve. Those functions imply that the device must be integrated to be as effective as possible. The functional requirements of each function give the level of performance that the function needs to achieve to be satisfied.

For the function *resect the native aortic valve*, four functional requirements need to be taken into account. First, the resection needs to be performed despite the presence of calcification buds. Indeed, the valve to be resected will be at least severely calcified (see table 2.1). Secondly, in order to avoid an oval shape of the implantation site, as described in section 3.4.4, the resection needs to be the most circular as possible. Thirdly, to be as safe as possible for the patient, the resection will be centred relative to the aortic valve to be sure that the aorta and all the peripheral tissues will not be damaged during the resection. Finally, the fourth functional requirement for the resection of the valve will also allow to maximise the safety for the patient because the diameter of the resection will be adapted to the diameter of the aortic annulus of the patient. Moreover, the resection diameter will be smaller than the diameter of the aortic annulus to avoid damages on peripheral tissues of the aortic valve.

The function *collect the resected debris* requires only one functional requirement: the minimal size of the debris to collect. If a big part of the resected aortic valve is not collected during (or after) the resection and goes into the blood circulation, irreversible complications as embolism or stroke could occur. Ideally, all the debris, regardless their size, should be collected, but if only tiny debris (smaller than $100\text{ }\mu\text{m}$) are not collected, the damages will be limited. The new device needs to be as effective as the open heart surgery, and better than TAVI, to expect that surgeons will use it to replace aortic valves.

Implant an aortic endo valve implies two functional requirements. The first one is the precise position into the implantation site. Malpositioning of the valve, which occurs when it is deployed too high or too low in relation to the aortic annulus, may be associated with adverse outcomes such as arrhythmias, coronary occlusion, mitral insufficiency and aortic injury. Transcatheter valves can embolize into the aorta if the valve is malpositioned too high or, less commonly, migrate into the left ventricle when the valve is malpositioned too low [128]. And the second functional requirement is the type of the endo valve (self-expandable or balloon-expandable) which will change the implantation system.

Finally, the constraints have been grouped in three categories. The first constraint implies that the procedure will be performed off-pump, *i.e.* without CPB. It requires

Table 4.1: Functional specifications for the assistance to the replacement of the native aortic valve through minimally invasive beating heart surgery.

Date	Origin	Specifications
		Functions
9 th Nov. 2011	P. Astarci	F1. Resect the native aortic valve
9 th Nov. 2011	P. Astarci	F2. Collect the resected debris
9 th Nov. 2011	P. Astarci	F3. Implant an aortic endovalve
		Functional requirements
9 th Nov. 2011	P. Astarci	FR1.1. Resection of the aortic valve despite calcification buds
9 th Nov. 2011	P. Astarci	FR1.2. Circular resection of the aortic valve
9 th Nov. 2011	P. Astarci	FR1.3. Resection centred relative to the aortic valve
9 th Nov. 2011	P. Astarci	FR1.4. Resection to a diameter between 18 and 26 mm
9 th Nov. 2011	P. Astarci	FR2.1. Collection of all the debris bigger than 100 μ m to avoid embolism
9 th Nov. 2011	P. Astarci	FR3.1. Precise position of the endovalve in the anchoring site ($\pm$ 1.5 mm)
9 th Nov. 2011	P. Astarci	FR3.2. Implantation of a balloon-expandable or a self-expandable endovalve
		Constraints
9 th Nov. 2011	P. Astarci	C1. Perform the procedure off-pump
9 th Nov. 2011	P. Astarci	C2. Ensure patient safety during the procedure
9 th Nov. 2011	X. Bollen	C3. Respect of the norms relative to medical devices
		Constraint requirements
9 th Nov. 2011	P. Astarci	CR1.1. The heart cannot fibrillate for more than 60 seconds
9 th Nov. 2011	P. Astarci	CR1.2. The surgery is performed under fluoroscopy
9 th Nov. 2011	B. Raucent	CR1.3. The materials used for the device must limit the artifacts to ensure the best visibility as possible
9 th Nov. 2011	P. Astarci	CR2.1. The diameter of the device should be smaller than 11 mm
9 th Nov. 2011	P. Astarci	CR2.2. The device must be able to be slipped on a guide wire of 0.89 mm
9 th Nov. 2011	P. Astarci	CR2.3. The device must be adaptable to any geometries of the heart or of the vessels
9 th Nov. 2011	X. Bollen	CR3.1. The device must be manufactured with biomaterials
9 th Nov. 2011	X. Bollen	CR3.2. The mechanical design and the production procedures must be conform to the directive MDD 93/42/EEC
9 th Nov. 2011	X. Bollen	CR3.3. The device must be sterilized by following an autoclave cycle of 18 minutes at 134 °C at 3 bar
9 th Nov. 2011	X. Bollen	CR3.4. The non sterilizable parts shall be isolated from the operative field with a plastic film

that the heart cannot be stopped for more than 60 seconds in order to avoid a lack of brain oxygenation and prevent irreversible brain damage or death. The second group will allow to ensure the safety of the patients. For example, the hole to insert the device into the body will be limited to a diameter of maximum 11 mm. Finally, the last one is related to the medical field: compliance with the directives and

norms, sterility assurance, biocompatibility of the materials used to manufacture the device, etc.

4.5 Comparison criteria

The fourth step of the conception method is *determining characteristics* to evaluate all the generated alternatives for each function. These characteristics are based on the function and constraints requirements of the functional specifications. Five criteria have emerged to evaluate each solution comparatively to the others:

The safety for the patient is an important criterion. If a function does not ensure enough safety for the patient, some possible complications could appear with eventual irreversible damage.

The speed of resection or deployment of each system allows to limit the duration of the procedure. As a reminder, the duration of the procedure cannot exceed 60 seconds, and therefore every second that can be earned is very precious.

The size of the solutions for each function has to be limited to have the biggest space as possible for the resected aortic valve. For a same trocar diameter, a too bulky system will not let a lot of space for the debris and all the resected debris must be removed from the body to avoid embolism or stroke.

A complex solution may cause failure to the system and the learning curve of the surgeons will be longer. For this criterion, a complex solution has a lower score than a simple solution.

The actuation system needs to be the most simple as possible. Each degree of freedom (DOF) needs to be actuated by one actuator. If there is only one actuator for a function, the risk of failures will be less important than if there are two or three actuators.

Chapter 5

State of the art of resection systems

Since the apparition of TAVI, three different groups have worked on systems to resect the native aortic valve prior to the implantation of the endo valve. Various solutions have been imagined and tested [129]. The key element of TAVI is the resection system and will therefore be focused on in this chapter. The state of the art of the resection system will allow to exclude solutions which do not properly meet the functional specifications.

The first research team, from the University of Kiel in Germany, has developed three different resection solutions: a resection systems using laser, a resection using high pressure water stream scalpel and a stapler-based aortic valve replacement (StapAVR) system. In order to avoid any damage during the procedure, aortic valve isolation chamber (AVIC) were developed in the same time.

The second research team, from the University of Pittsburgh Medical Center in the United States of America, worked on a resection system comprising two sliding tubes to cut the valve. Due to the resection time of about 4 minutes and to avoid a CPB, a temporary valve was designed and implanted during the tests [130].

Finally, the third group, from the University Hospital of Essen in Germany, developed a resection system using a foldable and rotating Nitinol blade to remove the valve.

All the resection systems are coupled with a collection system and no specific state of the art will be studied. About the implantation system, no state of the art will be studied because there are currently only two solutions (a stent implanted thanks to a balloon or a self-expandable stent made of SMA) which have already been described in chapter 3.

5.1 Laser devices

The concept of endovascular resection of the aortic valve before TAVI was first reported in 2002 by Lutter *et al.* [131]. In this study, the authors present the initial experience of aortic valve resection using different laser technologies as CO₂, Holmium YAG (Ho:YAG) and Erbium YAG (Er:YAG). The complete ablation of each aortic cusp took from 1 hour to 2.5 hours, depending on the technology.

In 2008, the same group reported their results using a Tm:YAG laser resection system with a 20 W power rating [132, 133]. They demonstrated the feasibility of endovascular resection of stenotic aortic valves *in situ* in human cadavers.

To avoid debris escape during the valve resection, they developed a system to seal the aortic valve, called AVIC, consisting of a supra-ventricular balloon and two sub-ventricular balloons (see figure 5.1). The deployment of the AVIC took 7.3 ± 5.8 minutes and the resection time for the three leaflets took 6.0 ± 3.6 minutes.

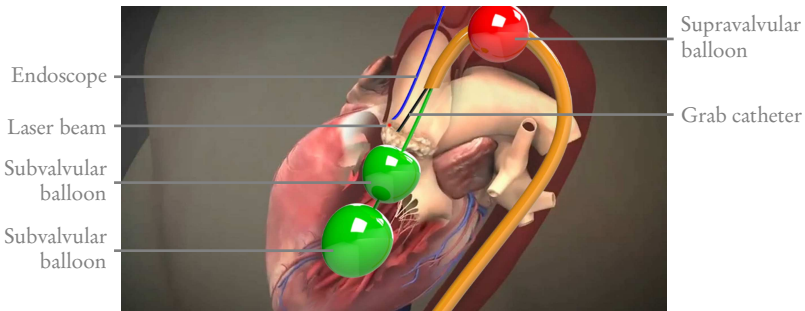


Figure 5.1: Experimental set-up with a retrograde deployed AVIC system with its supra-ventricular and sub-ventricular balloons, the endoscopic guided laser fibre with the aiming laser beam (red dot) and the grab catheter [133, 134].

The leaflets were excised 2 to 3 mm from the insertion of the annulus. As shown in figure 5.2, macropathology and micropathology demonstrated superficial lesions and one complete perforation of the aortic wall.

In 2010, the same team published a new study of aortic valve resection using a similar Tm:YAG laser with different endovascular and intracardiac tractability methods [135].

Four resection systems were designed and analysed. The experimental set-up for the two first resection systems is approximately the same as the set-up shown in figure 5.1. In the first system (group A), the laser fibre is controlled by a free in-lying flexible endoscope. Its distal part was moved in one plane by proximal manual control with three DOF. The second system (group B) is the same than the first but with the grab catheter having its own chain guide. The third resection system (group C) is a mechanical microactuator carrying the laser fibre with three DOF (see figure 5.3). Finally, the last system (group D) contains a rotatable inlay with defined rooms and a newly design Nitinol (a SMA) microactuator that controlled the laser fibre with four DOF.

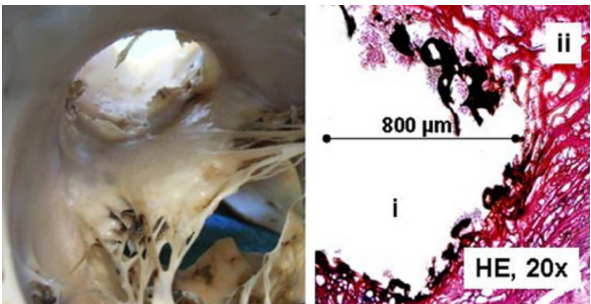


Figure 5.2: Resected aortic valve from the ventricular side and micropathology of a lesion due to resection into the aortic annulus (i, aortic side; ii, annulus tissue) [133].

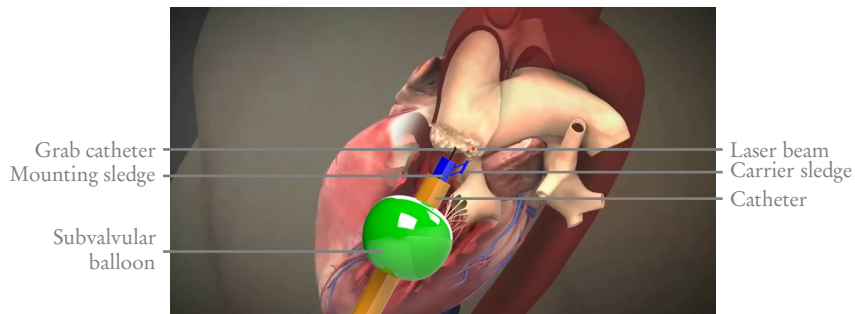


Figure 5.3: Experimental set-up with the AVIC transapically inserted. The mechanical microactuator consists of two sledges that are connected with siwel joints. One sledge is mounted on a catheter (mounting sledge), and the second one carries the surgical resection instrument (carrier sledge) [135].

The results of the resection are shown in table 5.1.

Table 5.1: Results of the resection of aortic valve using a Tm:YAG laser. Resection times are given for the resection of one leaflet [135].

Group	Type of valve	Resection time (in minutes)	Injuries
A	Retrograde human calcified aortic valve	5.5 ± 2.3	Yes
B	Retrograde healthy porcine aortic valve	7.4 ± 2.7	Yes
C	Antegrade healthy porcine aortic valve	19.0 ± 6.6	Yes
D	Antegrade healthy porcine aortic valve	2.3 ± 1.2	Yes

For the group A, the endoscopic guidance of the laser fibre was acceptable but not reproducible. Several pre-try-outs were necessary to ensure an exact resection in the annulus before resecting the valve and superficial lesions were found on the aortic

annulus and the ascending aorta.

In group B, the endoscopic guidance was affected by the separate chain guides in the AVIC, the resection instruments couldn't be geared perpendicularly toward one leaflet. The gross anatomy and histology observed lesions on the annulus and the ascending aorta.

The procedure in group C could not be performed with precision. Difficulties occurred mainly in steering the actuator with the laser fibre. In three cases, the resection was interrupted. Significant damages of the aortic wall and the aortic annulus were observed.

Finally, for the group D, the combination of the SMA microactuator and the rotatable AVIC inlay offers a good handling and reproducible guidance of the laser. The infinitely variable diameter of the cutting and the perpendicular way to the leaflet offers a safe and fast resection. Only one superficial lesion in the aortic annulus occurred.

5.2 High pressure water stream scalpel

In 2005, Quaden *et al.* described the initial experience of aortic valve resection in three different *in vitro* models (human calcified aortic valve, healthy isolated porcine valve and healthy *in situ* porcine valve) using a high-pressure water stream scalpel with a maximal pressure of 150 bar [136].

The set-up used for the resection of the healthy isolated and *in situ* porcine valves is shown in figure 5.4. The set-up used for the resection of the human calcified aortic leaflets consists in cusps fixed in a rubber band and placed into an acrylic tube.

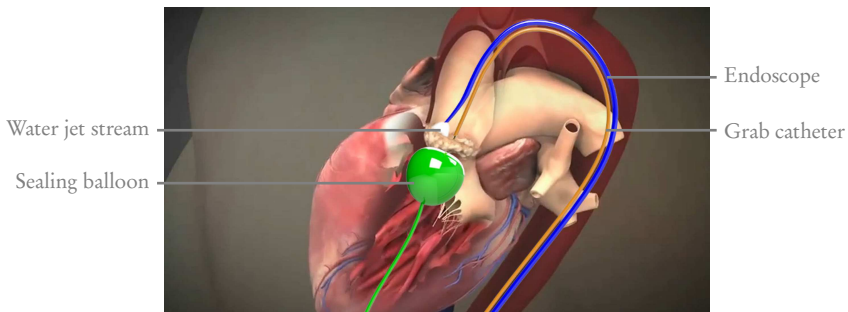


Figure 5.4: The endoscope with resection tools inside were inserted via the descending aorta to excise the valve. A polyethylene balloon was placed directly beneath the aortic valve to protect the subvalvular structures [136].

The resection device was manually controlled by a flexible endoscope and was positioned *in situ*. The endoscope was inserted into the ascending aorta, pushed forward through the arch and the ascending aorta and placed directly above the aortic valve. During the resection, the leaflets were held in place with the grab catheter and a

balloon was positioned directly beneath the aortic valve to protect the subvalvular area.

The results of the aortic resection for the three different models are given in table 5.2.

Table 5.2: Results of high-pressure water stream scalpel for aortic valve resection. Resection times are given for the resection of the three leaflets.

Type of valve	Pressure	Resection time (in minutes)	Injuries
Human calcified aortic valve	150 bar	6.0 ± 2.4	N/A
Healthy isolated porcine valve	60 bar	2.3 ± 0.3	Yes
Healthy <i>in situ</i> porcine valve	60 bar	12.2 ± 0.8	Yes

The procedure was easily performed and leaflets were ablated correctly. Due to the set-up used for the resection of the human calcified aortic valve, no injuries were detected. In the healthy isolated porcine valve group, the aortic annulus was moderately affected in six cases, whereas the mitral valve and coronary ostia remained untouched. Micropathology of the affected aortic annuli demonstrated superficial lesion depth of 1,400 and 1,600 μm on two cases, and an average of $460 \pm 215 \mu\text{m}$ in the other four specimens. In the *in situ* group, macroscopic examination revealed four superficial lesions in the aortic wall and one on the aortic annulus and coronary ostium. Microscopic analysis demonstrated superficial lesions with a maximum lesion depth of 1,200 μm in one case, and an average of $580 \pm 145 \mu\text{m}$ in subsequent specimens (see figure 5.5). No dissection or penetration occurred.

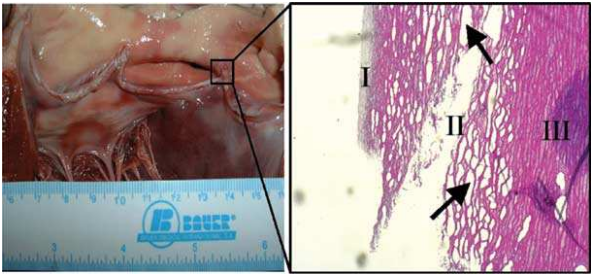


Figure 5.5: Macropathology and micropathology of a lesion due to resection into the aortic annulus (depth = 700 μm). The micropathology shows the endothelium (I), the resection lesion (II), the myocardial layer (III) and vacuolization due to high water pressure (arrows) [136].

5.3 Mechanical devices

To date, three different researchers teams have worked on blade-based mechanical devices for the resection of the aortic valve through minimally invasive access.

5.3.1 Sliding tubes

In 2009, Salizzoni *et al.* developed a cutting device for transapical off-pump removal of the native aortic valve [130]. The cutting device, as shown in figure 5.6, is composed by an inner tube sliding into an outer tube. One extremity of the inner tube is sharpened to a knife edge for cutting and slide freely inside the outer tube, which has a sharpened notched section close to the distal end.

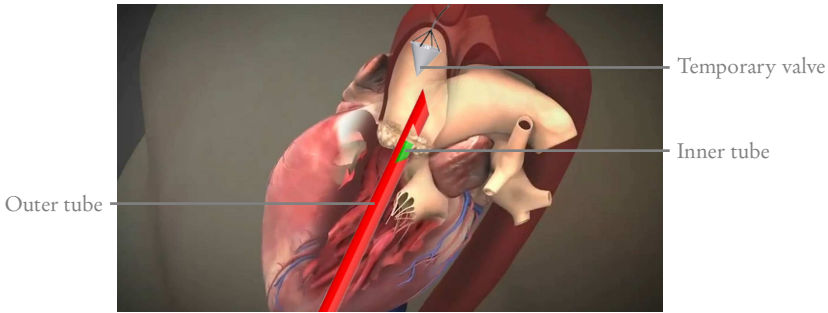


Figure 5.6: Set-up for transapical removal of aortic cusps using the cutting device. The inner tube has a sharpened end and the outer comprises a sharpened notch section. The temporary valve is closed during systole to permit blood flow and is opened in diastole to prevent aortic regurgitation [130].

To perform the resection, the cutting device is inserted into the LV of a pig through the apex and the three aortic cusps are sequentially removed one by one. When the healthy cusp is captured in the notch of the outer tube, the inner tube is moved forward to cut the cusp, which remained trapped inside the device and is removed. At most two attempts were needed to grab and cut each cusp. The removal of all three leaflets took less than 4 minutes in all cases ($n = 10$). A temporary valve was inserted in a retrograde position through the right carotid artery and advanced to the ascending aorta. This temporary valve restores the hemodynamic stability during the off-pump resection of the three leaflets.

In all cases, cusp removal and insertion of the temporary valve caused neither anatomic abnormalities nor damage to the mitral subvalvular apparatus, aortic root and annulus or aortic wall (see figure 5.7).

5.3.2 Foldable Nitinol blade

In the same period, Wendt *et al.* reported a new aortic valve resection tool for endovascular and minimally-invasive surgery, based on a foldable and rotating Nitinol blade [137]. The concept, shown in figure 5.8, was totally different compared to previous reported studies. In their works, the authors tested their prototype on stented bioprosthesis, artificially calcified by cementing different calcified fragment on the leaflets [123]. In a subsequent work [138] they equipped the prototype with a linear motor drive to decouple feed motion and manual rotation during the valve resection.

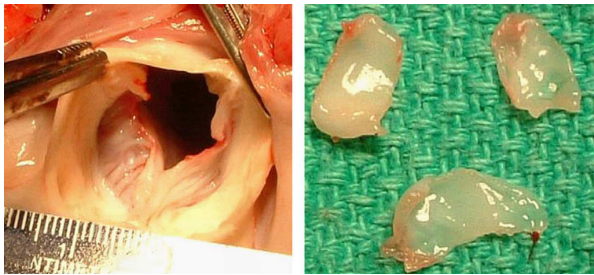


Figure 5.7: The aortic root and cusps after the resection procedure [130].

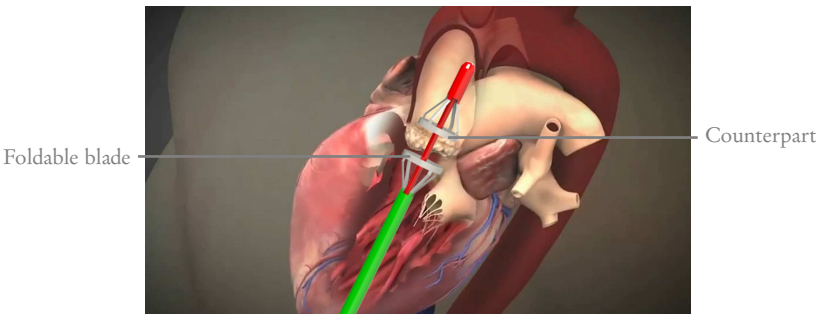


Figure 5.8: Set-up for transapical removal of aortic cusps using two circular foldable Nitinol blades [78, 123].

Three types of models have been tested with this device. The two first models consists of an aortic bioprosthesis artificially calcified by cementing different calcified fragment on the leaflets. The first group received one fragment per leaflets (total weight of 1.19 ± 0.03 g) and the second group received two fragments per cusps, with a total weight of 2.09 ± 0.03 g [123]. The last model was composed of porcine aortic valve artificially stenosed by fusing the three unrestricted leaflets and additionally, the aortic valve was freezed by a cooling spray prior the resection process [138]. The cutting results of each group are given in table 5.3.

Table 5.3: Results of circular foldable Nitinol blade resection. Resection times are given for the resection of the three leaflets.

Type of valve	Resection time (in seconds)
Moderate artificially calcified aortic bioprosthesis	15.5 ± 3.0
Severely artificially calcified aortic bioprosthesis	34.9 ± 15.0
Artificially calcified porcine aortic valve	49.7 ± 15.0

All valves were correctly cut and no signs of complications occurred during the resection. Neither the resection tool nor the linear motor drive system showed any signs of malfunction during the experiments. A resection result is shown in

figure 5.9.

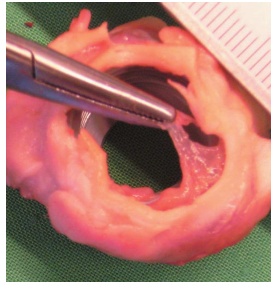


Figure 5.9: Resection result of an artificially calcified porcine aortic valve. Forceps indicating residue of non-coronary cusp [138].

5.3.3 Stapler based instrument

In 2013, Brecht *et al.* [139], described a new prototype, a StapAVR for transapical aortic valve replacement (see figure 5.10). This device consists of a resection system, a transventricular valve isolation chamber (TVIC) and a valve implantation system (not represented on the figure). The resection system comprises a circular blade and a tiltable cap. This tiltable cap allows an easier passage through the aortic valve and serves as thrust block. The resection is performed by translating the blade against the tiltable cap.

The prototype also comprises a TVIC, which includes a ventriculoarterial bypass system, to isolate the valve using a supralvalvular balloon and a subvalvular sealing balloons by maintaining blood flow from the ventricle to the artery. The blood flow is obtained by using a microaxial pump which pumps the blood from the ventricle to the artery.

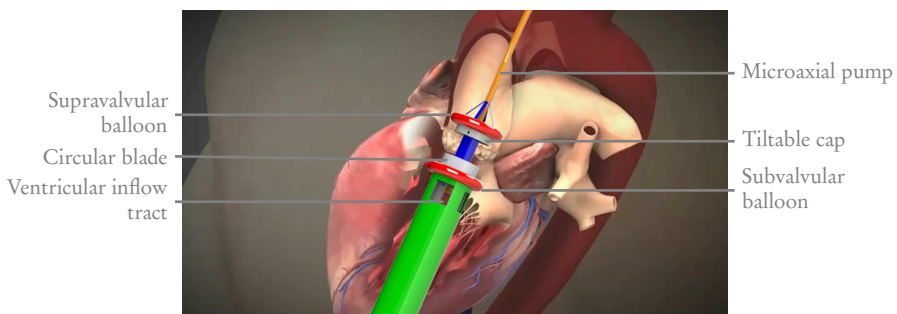


Figure 5.10: The StapAVR with the TVIC. The inlet of the microaxial pump is placed in the left ventricle and its outlet is located above the aortic valve. The aortic valve is isolated between the two balloons [139].

The prototype has been built and tested in two separated parts: the resection system and the TVIC system. First, the resection system has been tested on silicon-based

artificial aortic valves containing fluorescent granules to simulate calcified particles. An artificial valve, before and after resection, can be seen in figure 5.11. A total of 20 tests have been performed. The deployment of the resection system in the correct position and the valve resection time took a mean of 90.1 ± 18 seconds. The tests with the TVIC system confirm the sinus rhythm of the heart during the isolation of the valve.



Figure 5.11: Artificial heart valve with fluorescent debris before and after resection with the StapAVR [139].

5.4 Comparison with the functional specifications

To confirm the need of a new medical device to resect the native valve and implant an endo valve off-pump, the state of the art has to be compared with the functional specifications (see table 4.1) given in the functional analysis from chapter 4. This comparison is given in table 5.4.

All the devices from the state of the art were compared with the required functions and constraints. Obviously, all the systems can resect the aortic valve. For the debris collection, it is supposed that all the systems were able to evacuate the resected leaflets even if it is not clearly specified in the papers. For example, for the StapAVR study, the debris occurrence during the valve resection was measured but the size of the debris was not reported. Only the StapAVR has an implantation part integrated in the device.

The durations given in the table are the durations of the resection only. The duration of the whole procedure (resection and then implantation of the endo valve) for each device is not specified in the different studies.

This comparison shows that none of the existing devices do exactly meet all the specifications. Moreover, the state of the art proves that mechanical devices are the safest and fastest implementations for the resection devices.

Since each solution of the state of the art integrates both collection and resection systems, no specific state of the art for the collection system will be studied. It will be the same for the placement of the aortic prosthesis because two systems are currently used for the implantation: a balloon-expandable stent crimped onto a surgical balloon and a self-expandable stent crimped into a capsule.

Table 5.4: Comparison of the resection systems from the state of the art with the functional specifications.

	Laser [131–135]	Water stream [136]	Sliding tubes [130]	Nitinol blades [78, 123, 137, 138]	StapAVR [139]
F1. Resect the aortic valve	✓	✓	✓	✓	✓
F2. Collect the resected debris	✓	✓	✓	✓	✓
F3. Implant an endo valve	✗	✗	✗	✗	✓
C1. Off-pump procedure	✗	✗	✓ ^a	✗	✓ ^b
C2. Ensure patient safety	✗	✗	✓	✓	✗
Expandable system	✓	✓	✓	✓	✗
Duration of the resection (in seconds)	330 ± 138 ^c	360 ± 144	< 240 ^d	49.7 ± 15.0	90.1 ± 18 ^e

^a A temporary valve was implanted during the procedure.

^b A TVIC system was used during the resection.

^c The resection time is given for one leaflet.

^d The resection time is given for non calcified porcine aortic valve.

^e The resection time is given for silicone-based artificial aortic valve.

Chapter 6

Technical functional analysis

The technical functional analysis allows to make the transition from the functional analysis of the need and the detailed design, which takes into account the technological considerations. After the functional analysis and the state of the art and at the beginning of the development of the device, the functional specifications raise several questions:

- what percutaneous approach use to access the aortic valve?
- what movement give to the resection system?
- how to deploy the resection system?
- what kind of abutment support use?
- what system use to center the device relative to the aorta?
- how to collect the resected debris?
- how to implant the endo valve after the resection?

Each of these questions will be answered by finding different solutions and by comparing them with each other according to different criteria. These criteria have been defined in section 4.5.

The brainstorming for the different solutions and the filling of the different tables have been done by several persons in order to respectively generate a lot of solutions and to be the most objective as possible. Different methods to find solutions for each sub-functions exist and are given in [140, 141].

No solutions will be found for the question *how to implant the endo valve after the resection?* because the endo valve implanted after the resection is either a balloon-expandable or either a self-expandable valve. The current implantation systems used by the surgeons will be implemented on the device.

6.1 Percutaneous approach

The final solution essentially depends on the percutaneous access chosen to perform the resection of the native valve and the implantation of the endo valve. That is

why the percutaneous approach is studied first. As described in chapter 3, five routes, shown in figure 3.15, are currently used to implant an aortic prosthesis: transfemoral, tansapical, transaortic, subclavian and transaxillary.

The five access routes are relevant for the application. In order to find the best access route, they must be compared with each other according to several criteria coming from the functional analysis of the need. The comparison criteria for the percutaneous approach are different from those presented in section 4.5 because the percutaneous approach will set the basis of the whole device and not the details.

The safety for the patient is one of the most important criterion for the choice of the access route. The bleeding can be more easily managed in case of complication if the access point is closer from the heart. With the exception of the transfemoral route which is the most currently used and so the management of any complications is well known.

The maximal diameter of the catheter which can be used for the device is also quite important because if the catheter is large, a bigger amount of resected leaflets will be removed from the body. Moreover, a bigger catheter allows to resect more calcified valves because the calcifications are incompressible.

The torque transmission has a an important influence. As shown in the state of the art, a mechanical system to resect the aortic valve is more efficient, faster and safer than the use of a laser or a high pressure water stream jet. So, transmit a torque for the resection of the aortic valve is mandatory.

Center the device during the resection will increase the safety for the patient but also the quality of the resection. If the resection is not correctly centered relative to the aortic valve, the risks of damaging the aorta, the mitral valve or the cardiac muscles are bigger. A centering made into the aorta which have a cylindrical shape is better than a centering made into the left ventricle.

The space needed for the centering system and for the endovalve is bigger into the aorta than into the left ventricle. An antegrade approach allows to place these two systems into the aorta during the resection.

The table 6.1 presents the evaluation of each access route according to these weighted criteria. For each criterion, a score is assigned based on the comments made here above. A scale ranging from 0 (*inadequate solution*) to 4 (*excellent*), through *weak*, *satisfactory* and *good* was chosen as recommended in [14, 126].

Table 6.1: Choice of the access route.

Criterion	Weight	Transfemoral	Transapical	Transaortic	Subclavian	Transaxillary
Safety	1.00	4	3	4	1	2
Torque transmission	1.00	1	4	4	1	1
Diameter	0.75	2	3	4	1	1
Centering	0.50	1	4	1	1	1
Space	0.25	1	4	1	1	1
Total (weighted)	14.00	7.25	12.25	11.75	3.50	4.50
SD (unweighted)	—	1.30	0.55	1.64	0.00	0.45

Because of the distance between the vascular access and the heart and of the aortic vasculature, the transfemoral, the subclavian and the transaxillary approaches are not a good choice. Moreover, the diameter of the subclavian artery (used for the subclavian and the transaxillary accesses) and of the femoral artery (used for the transfemoral access) can be very small and does not allow to use large catheters to remove the resected debris from the body.

Between the transapical and the transaortic approaches, the **transapical route** has the best weighted total with the lowest standard deviation (SD) which indicates its homogeneity compare to the different criteria. It is the best choice because the centering of the device will be easier due to the cylindrical shape of the aorta. Furthermore, the integrated aspect of the device to design imposes to place the endo valve into the ascending aorta and into the arch of the aorta during the resection and then be moved back into the anchoring site for the implantation. If the transaortic route is chosen, the small space into the ventricle does not allow to contain both the endo valve and the centering system. This last system will also be less efficient into the ventricle due to the non cylindrical shape of the ventricle and due to the presence of the mitral valve close to the aortic valve.

6.2 Resection system

The resection system is composed of four different subfunctions: the resection movement to cut the valve, the deployment system to pass from a diameter of maximum 11 mm to a resection diameter of approximately 20 mm, an abutment support to make an efficient cut and a centering part ensuring a resection centered relative to the aortic valve. Each solution for the different functions will be compared thanks to the criteria presented in section 4.5.

As seen in chapter 5, a mechanical system to resect the aortic valve is probably safer, faster and more efficient than other systems like a laser or a high pressure water stream jet which may imply a lot of damages on the aorta, on the peripheral tissues of the aortic valve and on the cardiac muscle. So, only mechanical solutions for the resection system will be retained during the brainstorming to try finding the safest and fastest solution as possible.

6.2.1 Resection movement

Four solutions have been imagined during the brainstorming for the resection movement: an axially rotating blade (see figure 6.1a), a punching blade (figure 6.1b), a vibrating blade (figure 6.1c) and a radially rotating blade (see figure 6.1d).

The axially rotating blade needs two DOF, one for the rotation of the blade and one for the translation of the blade for its movement from the ventricle to the aortic valve. This solution also allows to make oscillations during the resection.

Only one DOF is required for the punching blade. An axial translation moves the blade from the vascular access to the native aortic valve and cuts it.

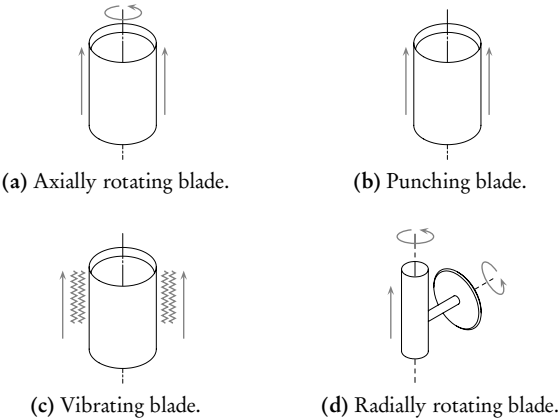


Figure 6.1: Morphological matrix for the resection movement.

The third solution uses ultrasound for the vibration of the blade. As for the axially rotating blade, a second DOF is needed two axially translate the blade to resect the valve and to move the system into the ventricle.

Finally, the last solution has three DOF: one for the translation of the system from the access to the aortic valve, one axial rotation and one radial rotation. This last DOF does not necessarily require a dedicated actuator for its movement because, if the radial rotation is free along its axe, the movement will be induced by the axial rotation of the system.

The results of the comparison of these four solutions according to the different criteria are given in table 6.2.

Table 6.2: Choice of the resection system movement.

Criterion	Weight	Rotating (axially)	Punching	Vibrating	Rotating (radially)
Safety	1.00	4	4	4	2
Speed	1.00	4	4	3	2
Size	0.75	4	4	4	1
Complexity	0.50	3	3	2	1
Actuation	0.25	3	4	2	1
Total (weighted)	14.00	13.25	13.50	11.50	5.50
SD (unweighted)	—	0.55	0.45	1.00	0.55

The best solution for the resection movement is a **punching blade** (it has the best total and the lower SD). However, the use of an axially rotating blade may also be a good solution. The weighted total and the unweighted SD are almost the same than to those of the punching blade. Only the number of actuators changes between the two solutions. Performing tests of both solutions with a manually actuated demonstrator will not ask big modifications on the device and will allow to show

which movement is the most efficient to resect the valve.

6.2.2 Deployment of the blade

A deployment system of the blade is mandatory to be able to resect the valve at a diameter of about 20 mm with a vascular access of maximum 11 mm of diameter. Moreover, the deployment system needs to be reversible (*i.e.* it must be able to be deployed once into the heart and then to be folded up again to be removed from the heart).

Three solutions have emerged from the brainstorming: a *foldable cone*, a *circular blade attached on a surgical balloon* and a *stent* made from SMA.

The conical blade, as shown in figure 6.2, has two states: an open state having a frustoconical shape and a closed state having a cylindrical shape. The opening and the closing of the blade is made with a catheter sliding on the cone.

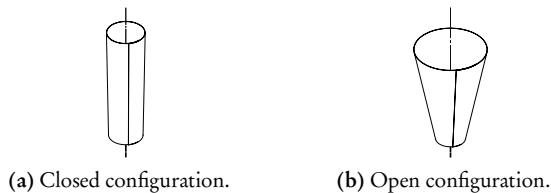


Figure 6.2: Conical blade deployment.

The second solution consists of a circular blade attached on a surgical balloon (see figure 6.3). To open the blade, a saline solution is injected with a syringe, through a lumen of a catheter, into the balloon to inflate it. When the blade needs to be closed, the balloon is deflated by removing the saline solution.

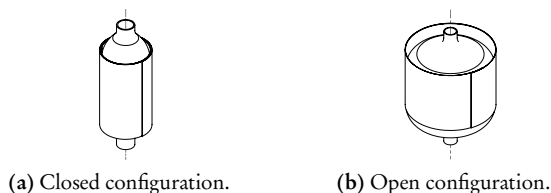


Figure 6.3: Deployment of the blade mounted on a balloon.

The last solution comprises a stented blade (figure 6.4). The stent is manufactured from SMA as Nitinol, which is a biomaterial. The main advantage of this kind of alloys is that the manufactured parts can have two configurations. To obtain one of the desired configurations, the part has to be heated up or cooled down. To increase the temperature an electric current resulting in Joule heating can be used. Decreasing the temperature to change the shape of the part is obtained by free convective heat transfer to the ambient environment [142]. Because of the free convective heat transfer, the cooling down takes more time than the heating up.

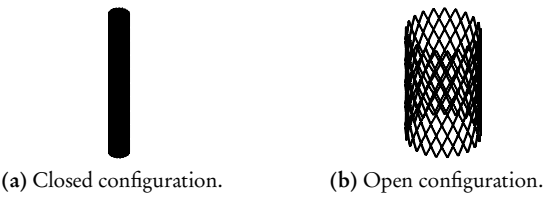


Figure 6.4: Deployment of the stented blade.

The table 6.3 shows the results of the evaluation of each solution according to the different criteria.

Table 6.3: Comparison of the different systems for the deployment of the resection blade.

Criterion	Weight	Cone	Balloon	Stent
Safety	1.00	4	4	2
Speed	1.00	4	3	2
Size	0.75	4	3	2
Complexity	0.50	4	3	1
Actuation	0.25	3	4	2
Total (weighted)	14.00	13.75	11.75	6.50
SD (unweighted)	—	0.45	0.55	0.45

The **conical blade** is the solution with the highest weighted total and the smallest unweighted SD. This solution is better than the others, because it is safer, faster, less bulky and less complex to implement. Only the actuation is a little bit more complicated than the blade attached on the balloon. Indeed, to actuate the inflation and the deflation of the balloon, only a syringe with saline solution is required.

6.2.3 Abutment support

If you want to efficiently cut slices in a roast beef with a knife you need a cutting board. Without this cutting board, cutting slices is hard. So, as for your roast beef, an abutment support is needed to mechanically resect the aortic valve. With a laser or a water stream, the abutment would not have been necessary.

For the abutment support, two solutions have been imagined: a foldable cone (see figure 6.5a) and a surgical balloon (figure 6.5b). Both of the solutions have, as for the resection system, an open state and a closed state.

The foldable counter cone has the same shape when closed or open than the resection cone. The counter cone will be open and closed thanks to the resection cone. To close the counter cone, the resection cone will be larger in order to encompass it and close it.

Concerning the chopping balloon, a third lumen will be added into the catheter to implant the endovalve (the first lumen is used for the guide wire and the second is

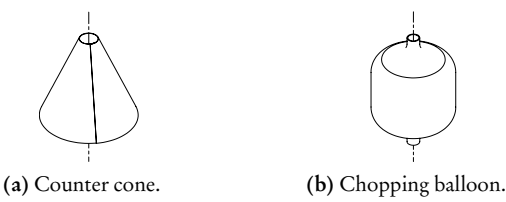


Figure 6.5: Solutions for the abutment system.

used to implant the endovalve). The chopping balloon will also be strengthened to avoid being pierced by the blade during the resection.

The two solutions have been compared according the different criteria and the results are presented in table 6.4.

Table 6.4: Choice of the abutment support.

Criterion	Weight	Cone	Balloon
Safety	1.00	4	4
Speed	1.00	4	3
Size	0.75	4	4
Complexity	0.50	2	4
Actuation	0.25	2	4
Total (weighted)	14.00	12.50	13.00
SD (unweighted)	—	1.10	0.45

The best solution for the abutment support is the **chopping balloon**. It will pass more easily through the aortic valve and will be easier to actuate. Only a lumen on a catheter and a syringe with saline solution are necessary for its inflation and its deflation.

6.2.4 Centering systems

The last question for the resection system to answer is *what system use to center the device relative to the aorta?* This system is very useful to ensure a good centering of the resection blade relatively to the aortic valve to avoid damage on the aortic wall or on the peripheral tissues.

The brainstorming highlighted three solutions: a *surgical balloon*, actuated *rigid cams* and *SMA wires*.

The surgical balloon is based on the same principle as the chopping balloon. The main advantage to use a balloon for the centering system is that it can be the same as the chopping balloon. If this solution is the best, the both system of centering and abutment support will be merged.

The second imagined solution is actuated cams. During the procedure, the four rigid cams (see figure 6.6) expand to exert a pressure on the aortic wall to centre the device relative to the aortic valve.

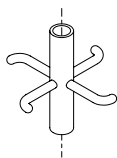


Figure 6.6: Rigid cams in open position.

As for the stent for the resection blade, the wires to centre the device are made of SMA with two configurations: closed (see figure 6.7a) and open (figure 6.7b). A large diameter for the wires should be used to be rigid enough to firmly centre the device relative to the aortic valve.

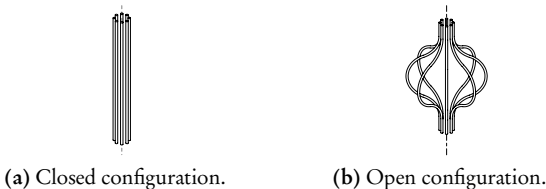


Figure 6.7: Solution for the centering system using SMA wires.

The comparison of these three solutions according to the different criteria is presented in table 6.5.

Table 6.5: Choice of the centering system.

Criterion	Weight	Balloon	Rigid cams	Wires
Safety	1.00	4	3	2
Speed	1.00	3	3	3
Size	0.75	4	2	4
Complexity	0.50	4	1	1
Actuation	0.25	4	2	2
Total (weighted)	14.00	13.00	8.50	9.00
SD (unweighted)	—	0.45	0.84	1.14

The comparison shows that the **surgical balloon** has the highest total and the lowest SD. This solution allows to merge both abutment and centering systems in a single reinforced balloon to limit the components of the final device in order to limit failures during the procedure and to earn space for the resected debris.

6.3 Collection systems

The second function from the functional analysis is *collect the resected debris*. After the brainstorming, four potential solutions have been imagined, shown in figure 6.8. As for the resection system, these solutions have been compared between each other according weighted criteria (see section 4.5).

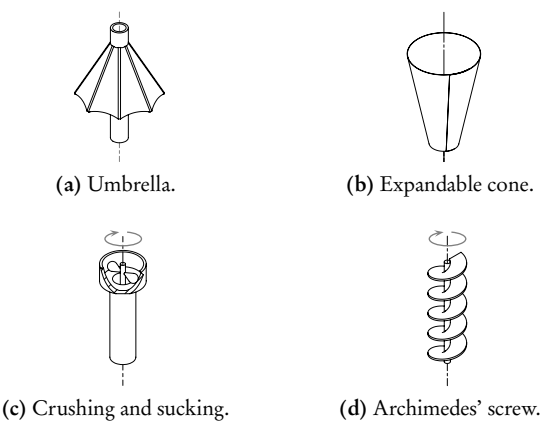


Figure 6.8: Morphological matrix for the collection system.

The first solution consists in a umbrella (see figure 6.8a). Umbrellas are already used for patients undergoing minimally invasive cardiac surgery to prevent embolisms or strokes during the procedure [143].

The second solution is to use the resection cone as a collection chamber. As for the chopping balloon merged with the centering system, using the resection cone as collection chamber allows to decrease the number of components of the final device and reduce failures.

The third solutions comprises a crushing system coupled with a sucking catheter (figure 6.8c). The resected debris are crushed with a helix and then sucked up into the catheter to be removed from the body.

Finally, the last solution is an Archimedes' screw, as shown in figure 6.8d. The debris are pushed down the catheter by the rotating helicoid until finally they're poured out from the bottom of the catheter.

The table 6.6 presents the results of the comparison of the four solutions for the collection system according to the different criteria.

Table 6.6: Choice of the collection system.

Criterion	Weight	Umbrella	Cone	Crushing	Screw
Safety	1.00	4	4	2	2
Speed	1.00	3	4	2	1
Size	0.75	4	4	1	1
Complexity	0.50	1	3	1	1
Actuation	0.25	2	4	1	1
Total (weighted)	14.00	11.00	13.50	5.50	4.50
SD (unweighted)	—	1.30	0.45	0.55	0.45

The cone appears to be the best solution. Moreover, the main advantage of using a cone for the collection system is that it can be merge with the conical blade. The

empty space within the resection cone, made from a sheet of metal of some hundredths of a millimeter, will allow to store the resected valve before being removed from the heart of the patient.

6.4 Conclusion

This chapter presents different solutions for the systems that will compose the device. To chose the best solution as possible for each system, weighted comparison criteria have been established. These criteria were used to objectively evaluate the different solutions of each function. It is clear that these solutions are may be not the best solutions in the absolute sense, such perfection does not exist. However, among the solutions for each system, the analysis and the comparison allowed to identify, with the greatest possible objectivity, those which best meet the expectations expressed in the functional analysis.

Part III

Device development

Chapter 7

Preliminary project

Thanks to the technical functional analysis from chapter 6, all the functions and the sub-functions of the device have now a solution. A preliminary project of the device can be sketched before being studied. After a first and quick study of the device and of its functioning, a demonstrator of the resection system will be designed and manufactured. Only the resection mechanism to cut the aortic valve will be tested thanks to the demonstrator because it is the bottleneck of the entire device. Indeed, the placement system is well known and does not need to be tested to be sure that it's working and the deployment system is not as challenging as the resection system and will not be implemented onto the demonstrator.

The distal part of the device comprises, as shown on figure 7.1, seven main parts. Arbitrarily, all the figures and the explanations of this chapter are given for a balloon-expandable aortic prosthesis. The device can be easily transposed for a self-expandable prosthesis by adapting the placement system.

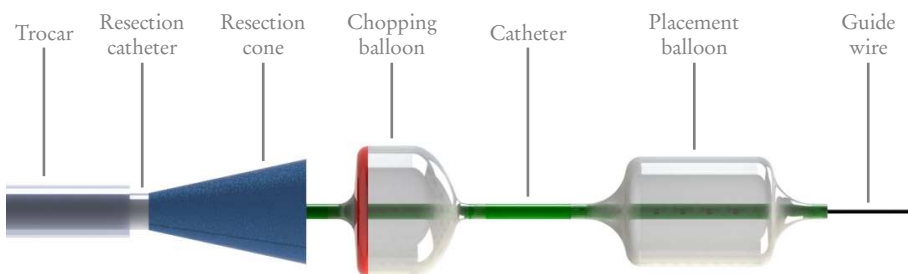


Figure 7.1: Components of the distal part of the device.

The guide wire, having a diameter of 0.89 mm, is used like a Ariadne's thread. As the guide wire used during the current TAVI procedures for the implantation device, the new device will be threaded over the guide wire to be sure that it will always be into the aortic valve to earn time during the procedure.

The catheter, with a diameter of 3 mm, has one lumen for the passage of the guide wire, one lumen for the actuation of the chopping balloon and one last lumen to inflate and deflate of the endovalve balloon-expandable. The placement balloon is the same than the balloons currently used in the devices manufactured by Edwards Lifesciences. The chopping balloon has different functions: center the device relative to the aortic valve, support the blade during the resection and close the resection cone to contain the resected leaflets like a cap. The red part of the chopping balloon in figure 7.1 is the reinforcement needed to avoid that the blade pierces the balloon during the resection.

The cone, attached on the resection catheter, is used to resect the valve and to contain the resected debris. At the beginning of the procedure, the cone is closed by the trocar to a diameter smaller than 11 mm. When the device is inserted into the heart, the cone is open and moves along the catheter near the aortic valve in order to resect it. After the resection, the debris are kept into the empty space inside of the resection cone. At the end of the procedure, when the endovalve is placed, the trocar closes the cone to compact the resected leaflets in order to remove them from the heart through the 11 mm hole.

7.1 Surgical procedure

The resection of the native valve and the implantation of the endovalve are performed under fluoroscopy. The beginning of the surgical procedure using this new device is to prepare the apex, like in the current transapical procedure. Then, the guide wire is inserted into the heart and into the aortic valve.

The first step of the procedure, shown in figure 7.2, is to insert the device over the guide wire and to push it until the chopping balloon and the prosthesis crimped over the placement balloon are into the aorta. During this first step, the trocar contains the chopping balloon and the resection cone to facilitate the passage of the chopping balloon through the aortic valve.

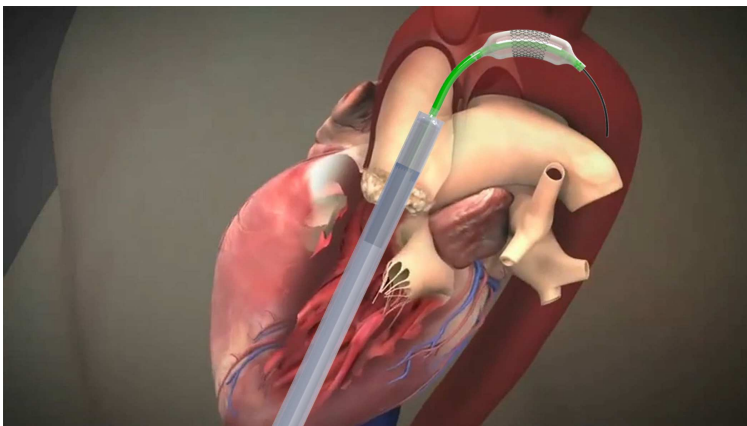


Figure 7.2: Insertion of the device into the heart through the apex.

After the first step, the resection cone, within the trocar, is moved back into the ventricle. Afterwards, the chopping balloon is pre-inflated into the aorta (see figure 7.3). This allows to still have the possibility to move the balloon and be sure that it is correctly placed against the aortic valve before is complete inflation to center the device.

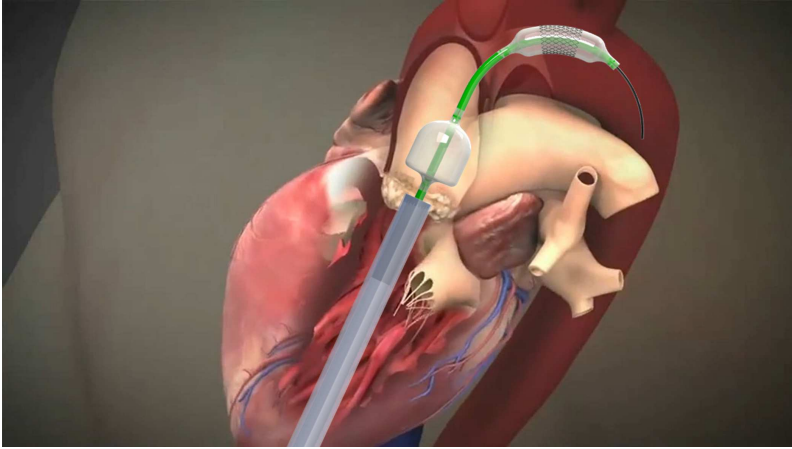


Figure 7.3: Pre-inflation of the chopping balloon.

After its pre-inflation, the chopping balloon is moved back against the aortic valve and the resection cone is deployed into the left ventricle, as seen figure 7.4. The rapid pacing is started during this step in order to fibrillate the heart to cancel the blood flow. As for the current implantation procedure, the fibrillation is mandatory to avoid the migration of the prosthesis to an unwanted anchoring site during the inflation of the placement balloon.

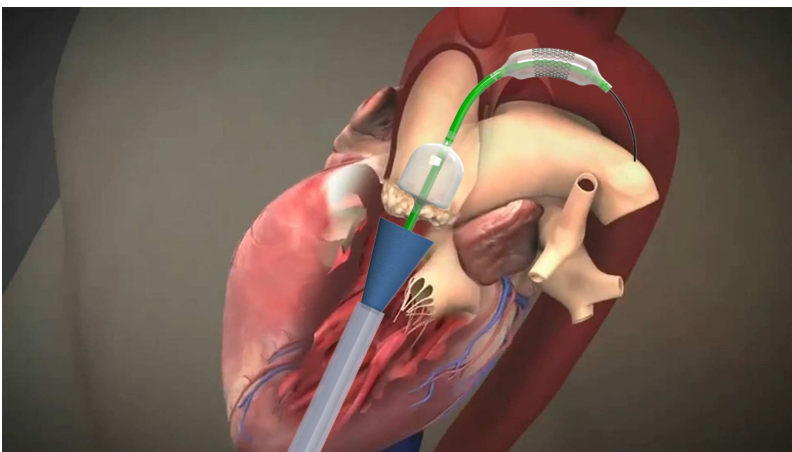


Figure 7.4: Deployment of the resection cone and translation of the chopping balloon against the aortic valve.

The next step is to completely inflate the chopping balloon to center the device relative to the aortic valve (see figure 7.5).

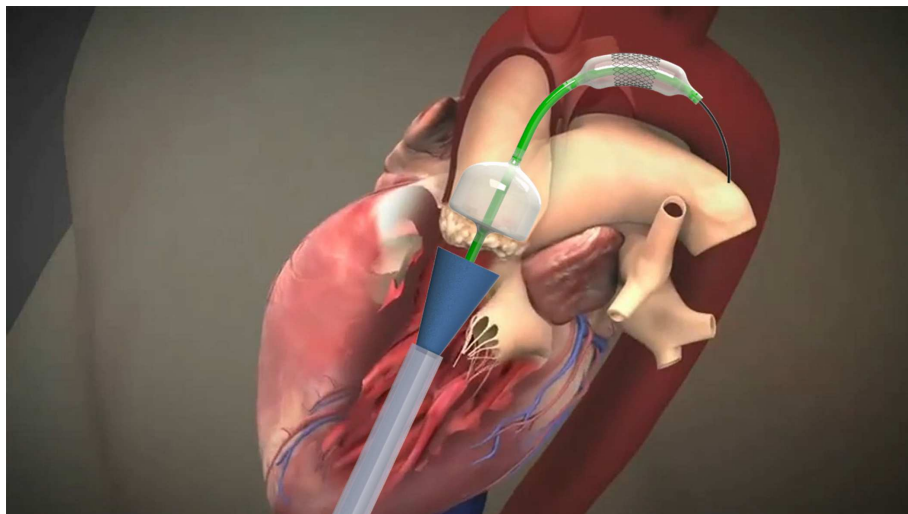


Figure 7.5: Complete inflation of the chopping balloon.

The fifth step (figure 7.6) consists in the resection of the aortic valve by moving the resection cone and its catheter. The resection is complete when the cone is in total contact with the chopping balloon.

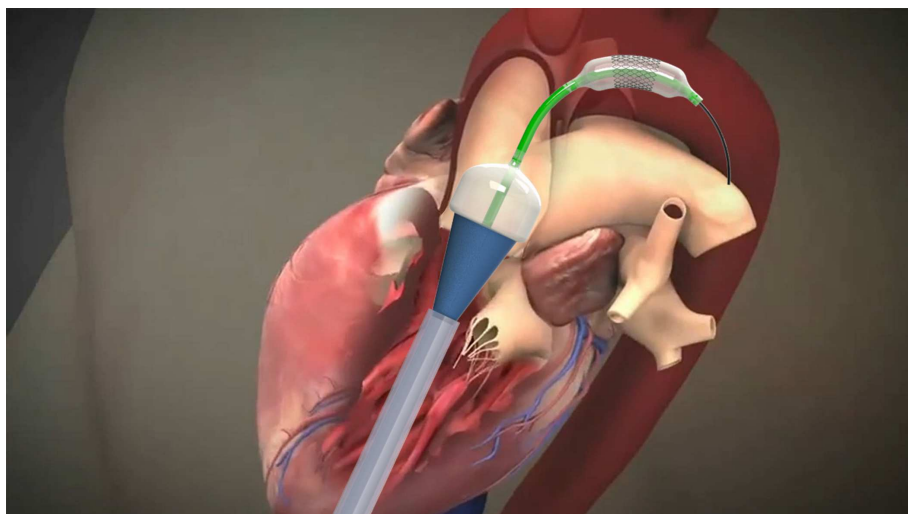


Figure 7.6: Aortic valve resection.

As shown in figure 7.7, when the aortic valve is resected, the chopping balloon is pre-deflated to be able to be moved back into the ventricle before the implantation of the aortic prosthesis.

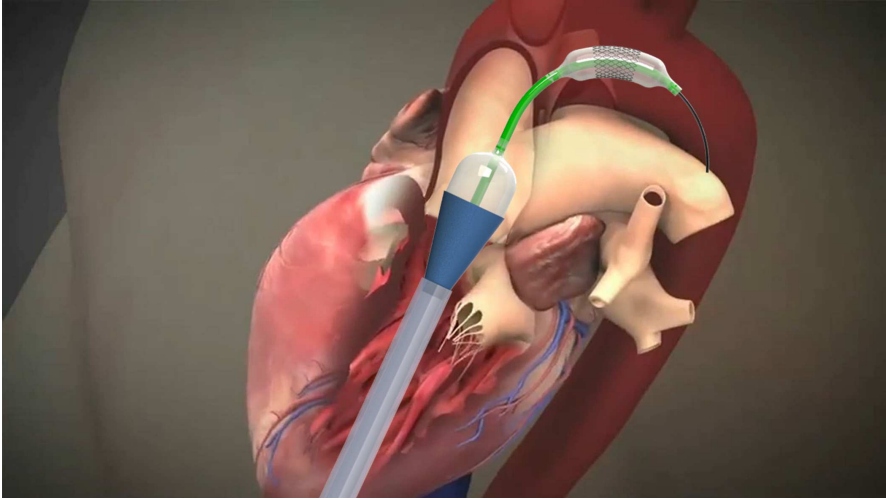


Figure 7.7: Pre-deflation of the chopping balloon.

The device is moved back to bring the prosthesis into the implantation site (figure 7.8). During this step, the chopping balloon should move remaining against the resection cone to seal the collection chamber and prevent small debris from escaping it.

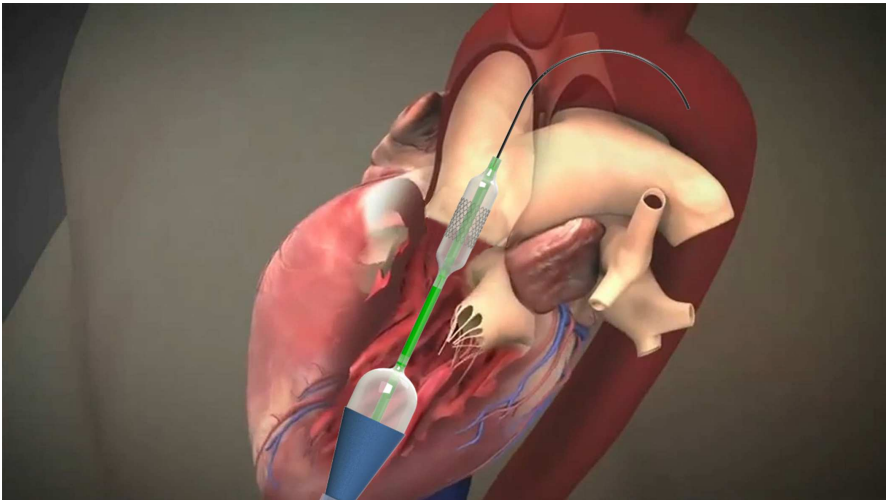


Figure 7.8: Translation of the device until the prosthesis is into the aortic annulus.

Once the prosthesis is into the anchoring site (see figure 7.9), the placement balloon is inflated following the procedure currently used for TAVI. The position of the placement site is not chosen automatically. Indeed, the device is automatically moved back into the anchoring site but the surgeon can manually adjust the position of the stent.

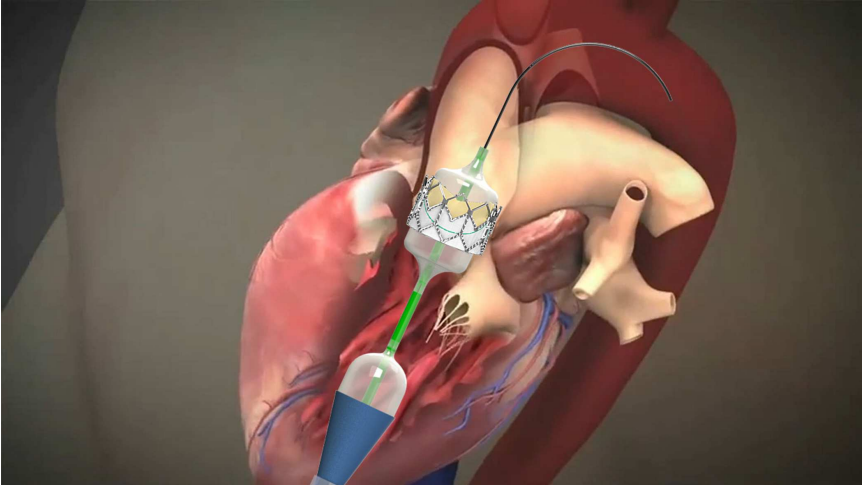


Figure 7.9: Inflation of the placement balloon.

Before deflating of the placement balloon, as shown in figure 7.10, it must remain fully inflated for at least 5 seconds to ensure a symmetric deployment and prevent stent recoiling [144]. After the implantation of the endo valve, the rapid pacing is stopped. Once the heart begins to beat normally, the compaction of the resected leaflets can be performed. This compaction is done by closing the resection cone with the trocar. During the closure of the resection cone, the trocar translates and rotates to decrease the efforts required to compact the debris.

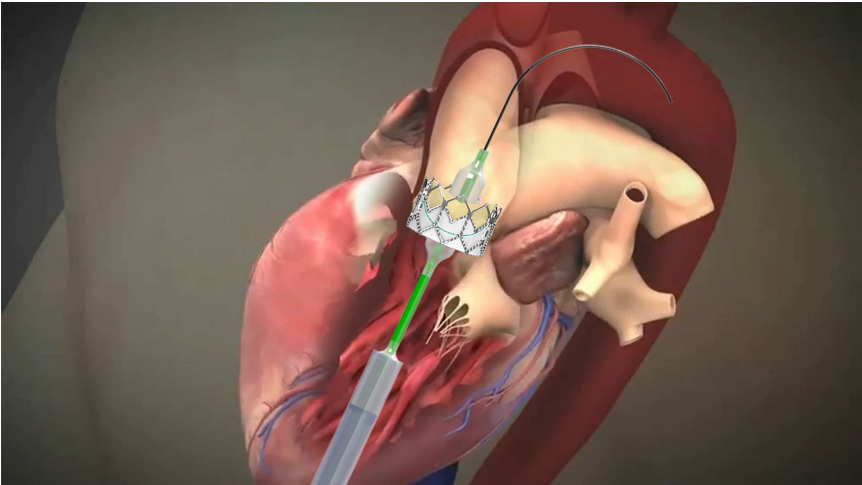


Figure 7.10: Deflation of the placement balloon and compaction of the resected debris.

Before closing the apex and the thoracotomy performed on the patient, the last step consists in the withdrawal of the device (see figure 7.11) from the heart.

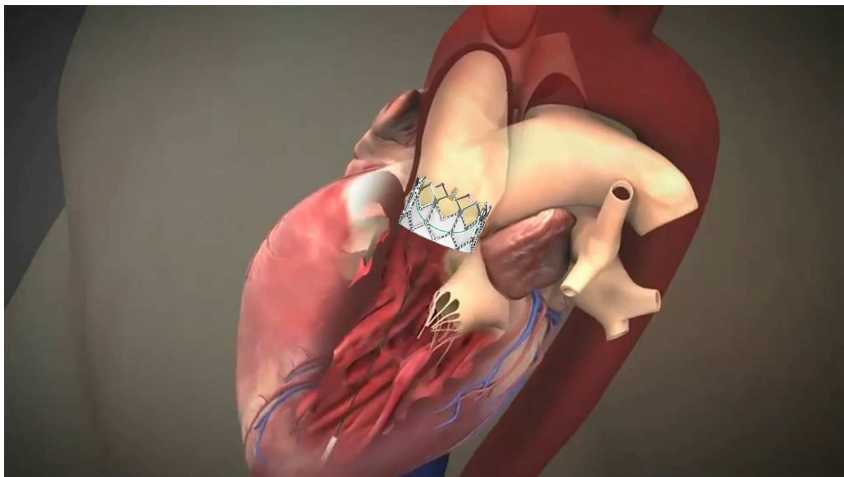


Figure 7.11: Withdrawal of the device from the heart.

The device has been patented on the 19th September 2013 under the reference WO2013/135792 [11]. The first page and the claims of the patent are given in Appendix A.

7.2 Demonstrator of the resection system

As recommended in [145–147], before going further in the development of the device, the concept of the resection system will be verified thanks to a demonstrator. This demonstrator will allow to show the relevance of the design choices made for the resection system and detect the design defaults which should be corrected during the next iteration. The iterative approach of design and verification is represented by the *Waterfall model* recommended by the Food and Drug Administration (FDA) (see figure 7.12).

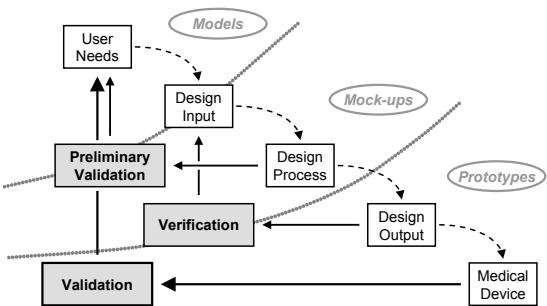


Figure 7.12: *Waterfall Model* with successive use of models, mock-ups and prototypes during the design process and the verification and validation steps [145].

Besides these recurring *verification* steps during the design, which serve to verify if the suggested design correctly answers to the functional specifications, a final *validation* is necessary to ensure that the device correctly meets the initial demand. The verification steps must answer to the question *Are we building the thing right?* and the validation step must answer to the question *Have we built the right thing?* [146].

The materialization of the solution is of particular importance for the surgeons. If engineers are quite familiar with virtual representations of a solution by modeling softwares, the surgeons need to have a manufactured demonstrator to see it, test it and try it. The manufactured demonstrator will help them to have an informed opinion on the merits of the solution and to criticize it in order to make improvements. If the demonstrator arrives late in the design process, then the problems will be more consequent if the solution is not adequate, despite the precautions taken during its design by following an optimized systematic approach.

To easily manufacture the demonstrator, several simplifications are made. First of all, the demonstrator is manually actuated to decrease the costs and the time of development because no programming will be required to move the device. Due to this kind of actuation, it is also easier to implement the translation and the rotation for the resection movement. Secondly, the device is not deployable. The prosthesis implantation system is not necessary to perform the tests of the resection system and has not been developed nor manufactured. To simplify the manufacturing of the catheter, a solid shaft of 4 mm of diameter and with no lumina, is used. Finally, a hard chopping board is used to mimic the chopping balloon. The virtual modelling of the demonstrator is shown on figure 7.13.

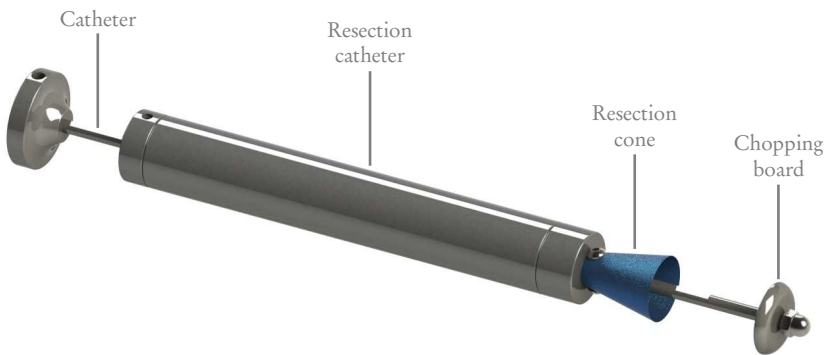


Figure 7.13: SolidWorks modeling of the demonstrator.

Except the blade, all the different parts of the demonstrator (figure 7.14) have been manufactured in stainless steel. Using stainless steels will allow to easily clean the device after testing it on cadavers.

The blade has a distal diameter of 20 mm, a thickness of 0.003 inch or 76 μm and is made of Nitinol. The distal end of the blade is straight and sharpened.

Nitinol is a biomaterial metal alloy of nickel and titanium, where the two elements are present in roughly equal atomic percentages. The advantage of the Nitinol is its superelasticity property which is the direct result of the formation of martensite (a



Figure 7.14: Manufactured demonstrator.

very hard form of crystalline structure) by applying a stress as well as by cooling. In a certain temperature range, a stress can be applied to austenite (a solid solution of iron with an alloying element), causing martensite to form while at the same time changing the shape. In this case, as soon as the stress is removed, the Nitinol will spontaneously return to its original shape. In this mode of use, Nitinol behaves like a super spring with an elasticity up to 30 times greater than a normal spring material. For the final device, Nitinol will be used for the conical blade to allow it to deploy itself into the heart once removed from the trocar.

In the demonstrator, the resection is performed by translating the resection catheter. To avoid the rotation of the blade during the resection, a meplat has been made on the solid shaft and one set screw is used to block the rotation (see figure 7.15). To use the device with a translation, the set screw just has to be removed.

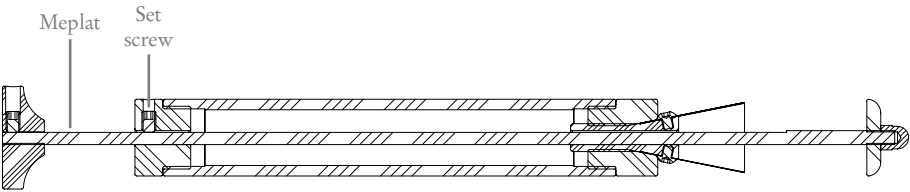


Figure 7.15: Sectional view of the demonstrator.

7.3 Resection tests

To verify that the resection system works on aortic valve, several tests have been performed with the demonstrator on calcified aortic leaflets excised from an open heart surgery. These leaflets, as shown in figure 7.16, were severely calcified.

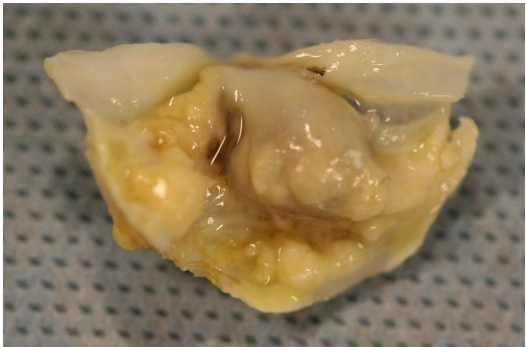


Figure 7.16: One aortic leaflet used to perform a verification test.

The first step of the tests is to place the leaflet between the chopping board and the resection cone (see figure 7.17).

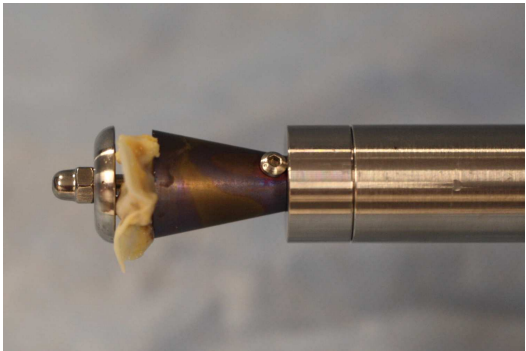


Figure 7.17: Placement of the leaflet into the demonstrator.

Then, the resection catheter is translated, while the chopping board is held in place in order to resect the leaflet (figure 7.18).

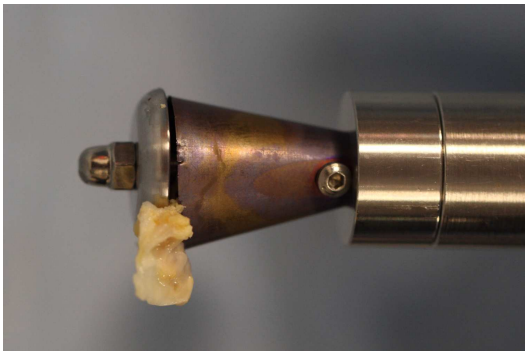


Figure 7.18: Demonstrator and leaflet during the resection test.

If the resection is performed without rotation, *i.e.* just a translation of the resection cone, the resection is completely ineffective. With the rotation of the resection cone, the leaflet is not resected (see figure 7.19) but it is easier to cut the hard tissues.

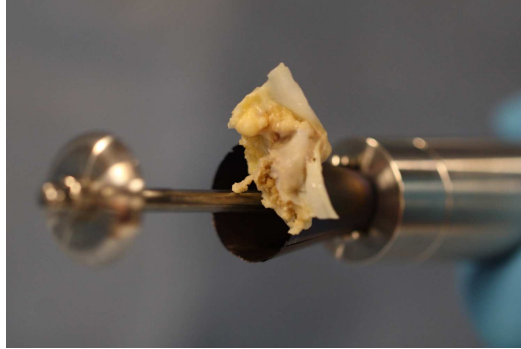


Figure 7.19: Aortic leaflet into the demonstrator after the test.

The tests show that only the calcifications were cut with the developed design, as shown in figure 7.20.

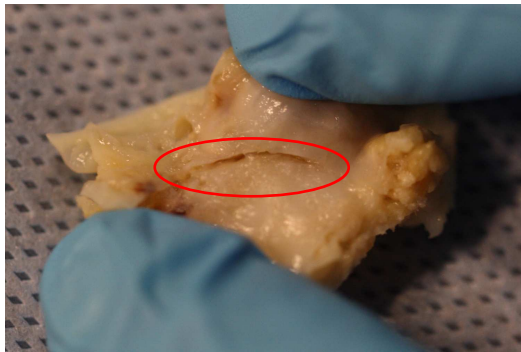


Figure 7.20: Aortic leaflet after the resection test. Circled in red, a notch made by the blade into a calcification.

7.4 Conclusion

The tests performed with the demonstrator in order to verify the designed device have shown that the concept is not able to resect the aortic valve. Indeed, the soft tissues which compound the aortic valve are not cut whereas the calcifications are cut. A new concept needs to be developed to be able to resect both hard and soft tissues.

The performed tests have also shown that only a translation to move the resection cone is not efficient. To resect the aortic valve, the resection cone needs to rotate and translate.

Chapter 8

First iteration

The tests, presented in chapter 7, have shown that the designed resection system was not able to resect the aortic valve. The hard tissues, *i.e.* the calcifications, were easily cut while the soft tissues, *i.e.* the rest of the valve, were not cut at all. A new device needs to be designed to find a solution which is able to cut both tissues types. The main idea of the concept will not be changed, only the resection system needs to be redesigned.

To find a new solution for the resection system, the TRIZ method has been applied. The usual approach used to solve a problem is to find a specific solution for a specific problem, as shown in figure 8.1. This approach, applied to find the previous resection system, often leads to find a good solution to the wrong problem instead of finding a wrong solution to the right problem. A precise definition of the problem will help to find the best solution as possible.

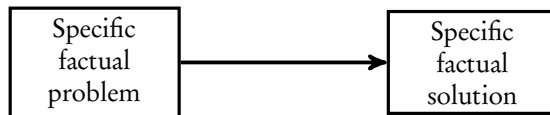


Figure 8.1: Usual approach to solve a problem.

The systematic approach used in TRIZ, is the same as the approach for solving mathematical problems: find a generic solution for a generic problem (see figure 8.2). This approach allows to limit the trials, the errors and the adjustments of the specific solution to the specific problem.

The TRIZ' philosophy of action is summed up in four steps:

1. identify the most important specific factual problem to solve;
2. generalise the specific factual problem into a conceptual problem;
3. apply to this conceptual problem a set of solving principles belonging to TRIZ to determine a conceptual solution;
4. derive, from this conceptual solution, the specific factual solution.

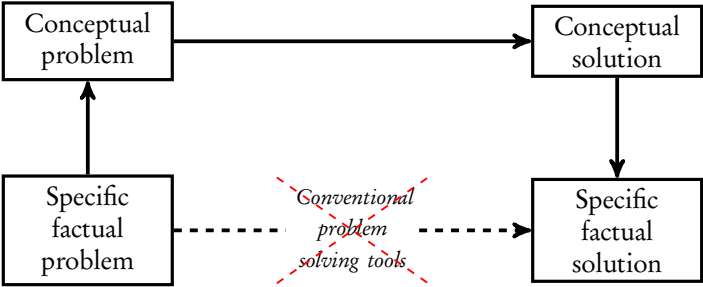


Figure 8.2: TRIZ systematic approach to problem solving (adapted from [124]).

8.1 New resection system

The most important specific factual problem to solve for the device is *resect the native aortic valve*. Because the calcified aortic valve is composed of both hard and soft tissues, instead of finding a specific factual solution for the resection of the aortic valve, a conceptual solution needs to be developed for the generalised problem *cut hard and soft tissues*. All the other functions, functional requirements, constraints and constraint requirements from the functional specifications must be respected for this new resection system.

In surgery, two kinds of mechanical blades are currently used: straight blades and toothed blades. The straight blades, mounted on a scalpel, are used to cut the soft tissues or to perform anatomical dissections whereas toothed blades are mainly used for cutting hard tissues such as bones (as hard as calcifications). Soft tissues can also be cut with toothed blades. Indeed, to cut a meat you can use either a toothed knife or either a sharp flat knife. If a toothed blade is used to cut the soft tissues, the teeth will pierce the tissues to resect them.

Using a toothed blade involves a piercing risk of the chopping balloon. The abutment support needs to be redesigned to fit with this new blade. Starting from the results of the technical functional analysis and the imagined solutions for the abutment system (see section 6.2.3), the use of a counter cone instead of a chopping balloon is a good choice. Moreover, the comparison of the two abutment supports (see table 6.4) shows that the counter cone was almost as good as the chopping balloon with the big advantage to increase the free space to collect the resected leaflets.

With this new resection system, a centering balloon should be added to center the device relative to the aortic valve. Therefore, the chopping balloon is replaced by a centering balloon and a counter cone. The new resection system is shown in figure 8.3.

The new surgical procedure is almost the same as the procedure with the first designed device. For this new iteration of the device, the main difficulty lies in the closure of the device before its withdrawal from the heart. Indeed, when the trocar will slide to close the resection cone, it will not close the counter cone due to its larger diameter. This issue will be addressed later when the new concept will be verified thanks to a demonstrator.

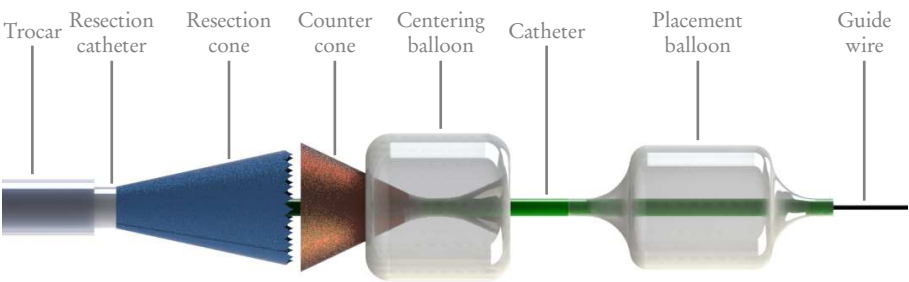


Figure 8.3: New resection system with the toothed resection blade.

Resect the aortic valve with this system implies that the aortic valve will not be entirely removed. A circular neo-annulus will be created. This neo-annulus, which is *a priori* a disadvantage is an advantage for two reasons: (1) it will decrease the risk of cutting into the peripheral tissues of the aortic valve which may cause hardly manageable blood leakages and (2) it may overcome the present problems of paravalvular leakage if the endovalves are redesigned with a “c-shaped” annulus covering this neo-annulus [123, 138, 148].

8.2 Tests of the resection system

To verify that this new resection system is able to resect the aortic valve, a demonstrator has been designed and manufactured and two different tests have been performed: (1) verification of the ability of the blade to pierce soft tissues and (2) resection tests using the toothed resection conical blade with the counter-cone.

8.2.1 Test of the toothed blade

The first test that needs to be performed is to verify that a toothed blade (figure 8.4) is able to pierce the soft tissues. The teeth were designed in order that their tops pierce the soft tissues and their bases act like scissors when combined with the counter cone. The blade has been manufactured in Nitinol of 72 μm thick.

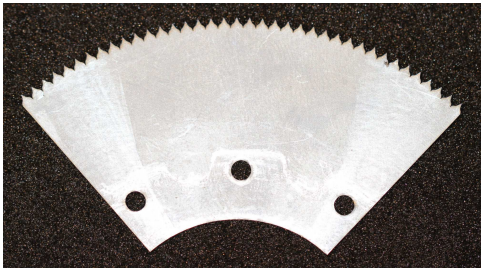


Figure 8.4: Blade used during the test.

For this test a bovine pericardium has been used. The bovine pericardium is a good soft tissue to mimic the aortic leaflets because some aortic bioprosthesis are made with this biomaterial.

To verify the design of the blade, the test consists in pushing the unfolded blade on the biomaterial in order to pierce it (figure 8.5). The force required to pierce the biomaterials has not been measured during the test.



Figure 8.5: Test set-up.

As shown in figure 8.6, the new designed blade can pierce the soft tissues. Therefore, the new design of the device should be able to completely resect the calcified aortic valve.



Figure 8.6: Results of the piercing of the bovine pericardium. Encircled in red, teeth of the blade that passed through the tissue sample.

8.2.2 Demonstrator of the resection system

As for the first version of the device, a demonstrator, shown in figures 8.7 and 8.8, has been designed and manufactured to verify the resection system.

The design of this new demonstrator looks like the first version and the simplifications operated in the first demonstrator have also been made in this one (*i.e.* non-deployable system, manually actuated demonstrator, etc.). The resection is performed by rotating and translating the resection cone while the counter cone stays fixed. All the parts, excepted the cones made in Nitinol, have been manufactured in stainless steel.

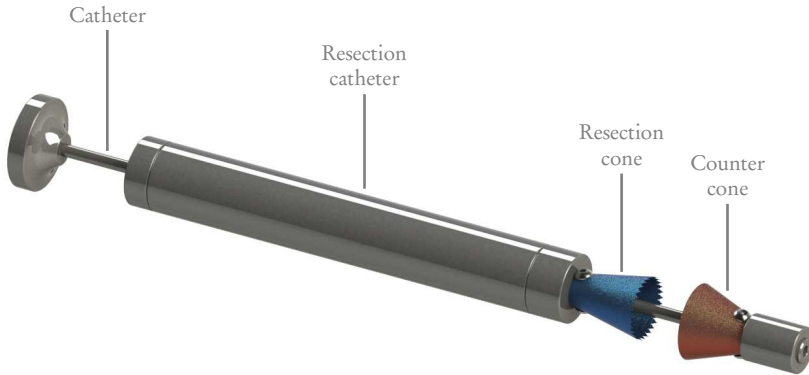


Figure 8.7: SolidWorks modeling of the second demonstrator.



Figure 8.8: Manufactured demonstrator.

8.2.3 Resection tests

Like for the first demonstrator, resection tests have been performed to verify that the new resection system is working and can resect both soft and hard tissues. The same procedure described in section 7.3 has been applied.

The aortic leaflets, heavily calcified (see figure 8.9), used during this tests have been excised from patients undergoing surgical AVR.

The first step of the verification tests is to place the aortic leaflet into the device, between the resection cone and the counter cone, as shown in figure 8.10.

The next step is the resection of the aortic leaflet using the demonstrator (figure 8.11). The resection is performed with a rotation and a translation of the resection cone.

The tests show that both soft and hard tissues are cut but also that the resection is not complete, even after a lot of rotations of the resection cone (see figure 8.12).



Figure 8.9: One of the aortic leaflets used to test the resection system.



Figure 8.10: Leaflet placed between the resection cone and the counter cone.

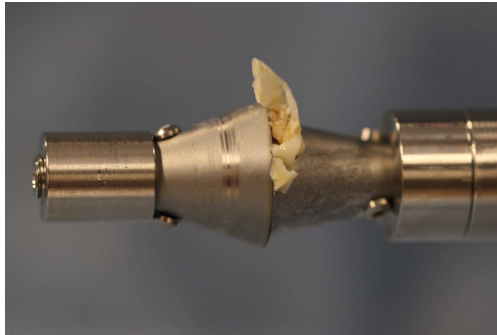


Figure 8.11: Leaflet being resected during the test.

During the tests, it has been noticed that the leaflet was not correctly held in place between both cones and was rotating with the resection cone. If this problem is not solved in the device, it will be very dangerous for the patient. Indeed, if the heart rotates with the resection blade, a risk of cardiac tissues tearing is possible resulting in blood leakages with difficulties to control them because of the endovascular access and the absence of CPB.

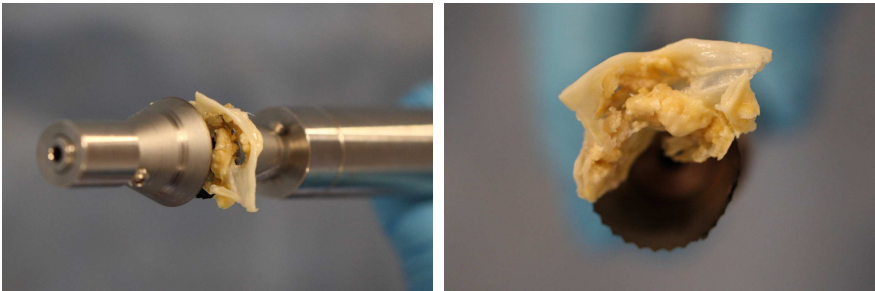


Figure 8.12: Leaflet in the demonstrator of the verification test.

8.3 Conclusion

The tests have shown that the new design was able to cut both soft and hard tissues but was not able to completely resect the aortic valve. Moreover, it has been noticed that the leaflets were rotating with the resection cone involving potential damages for the patient during the future procedure. Indeed, a torque is applied by the device on the peripheral tissues of the aortic valve during the resection, as shown in figure 8.13.

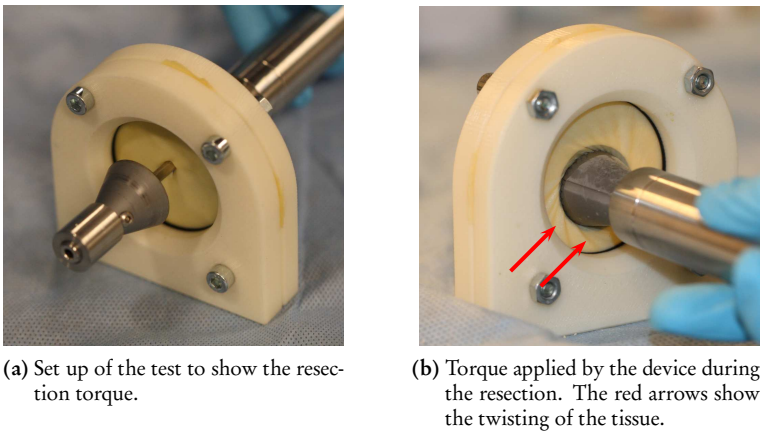


Figure 8.13: The torque applied by movement of the resection cone results in rotation of the tissue sample.

A new device has to be designed taking into account this new function *firmly hold the aortic valve during the resection*. Solutions for this function will be imagined to increase the patients safety. The functional specifications from table 4.1 have been updated with this new function (see table 8.1).

Table 8.1: Second version of the functional specifications for the assistance to the replacement of the native aortic valve through minimally invasive beating heart surgery.

Date	Origin	Specifications
		Functions
9 th Nov. 2011	P. Astarci	F1. Resect the native aortic valve
9 th Nov. 2011	P. Astarci	F2. Collect the resected debris
9 th Nov. 2011	P. Astarci	F3. Implant an aortic endovalve
12 th Dec. 2013	X. Bollen	F4. Hold the native aortic valve during the resection
		Functional requirements
9 th Nov. 2011	P. Astarci	FR1.1. Resection of the aortic valve despite calcification buds
9 th Nov. 2011	P. Astarci	FR1.2. Circular resection of the aortic valve
9 th Nov. 2011	P. Astarci	FR1.3. Resection centred relative to the aortic valve
9 th Nov. 2011	P. Astarci	FR1.4. Resection to a diameter between 18 and 26 mm
9 th Nov. 2011	P. Astarci	FR2.1. Collection of all the debris bigger than 100 μ m to avoid embolism
9 th Nov. 2011	P. Astarci	FR3.1. Precise position of the endovalve in the anchoring site (± 1.5 mm)
9 th Nov. 2011	P. Astarci	FR3.2. Implantation of a balloon-expandable or a self-expandable endovalve
12 th Dec. 2013	X. Bollen	FR4.1. Torque applied on the aorta and/or the cardiac muscle lower than 1 mNm
		Constraints
9 th Nov. 2011	P. Astarci	C1. Perform the procedure off-pump
9 th Nov. 2011	P. Astarci	C2. Ensure patient safety during the procedure
9 th Nov. 2011	X. Bollen	C3. Respect of the norms relative to medical devices
		Constraint requirements
9 th Nov. 2011	P. Astarci	CR1.1. The heart cannot fibrillate for more than 60 seconds
9 th Nov. 2011	P. Astarci	CR1.2. The surgery is performed under fluoroscopy
9 th Nov. 2011	B. Raucourt	CR1.3. The materials used for the device must limit the artifacts to ensure the best visibility as possible
9 th Nov. 2011	P. Astarci	CR2.1. The diameter of the device should be smaller than 11 mm
9 th Nov. 2011	P. Astarci	CR2.2. The device must be able to be slipped on a guide wire of 0.89 mm
9 th Nov. 2011	P. Astarci	CR2.3. The device must be adaptable to any geometries of the heart or of the vessels
9 th Nov. 2011	X. Bollen	CR3.1. The device must be manufactured with biomaterials
9 th Nov. 2011	X. Bollen	CR3.2. The mechanical design and the production procedures must be conform to the directive MDD 93/42/EEC
9 th Nov. 2011	X. Bollen	CR3.3. The device must be sterilized by following an autoclave cycle of 18 minutes at 134 °C at 3 bar
9 th Nov. 2011	X. Bollen	CR3.4. The non sterilizable parts shall be isolated from the operative field with a plastic film

Chapter 9

AVATAR² system

The two first developed concepts are not able to resect the aortic valve because the leaflets are not firmly held during the resection. To resolve this issue, solutions have been imagined for this new function. After the evaluation of the different solutions with the comparison criteria (from section 4.5), a demonstrator will be designed and manufactured before to test it on embalmed hearts explanted from cadavers.

9.1 Solution for the holding system

During the brainstorming for the holding system, three different solutions have emerged. Using the results of the previous iteration, all the solutions have a toothed resection cone.

The first imagined solution consists in three cones (see figure 9.1): a resection cone, a counter cone and a holding cone. The idea is that the aortic valve will be held between the holding cone and the counter cone while the resection cone, comprises between both cones during the resection, cut the aortic valve.

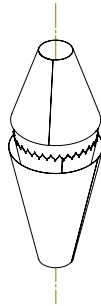


Figure 9.1: Solution using three cones.

The second solution is two toothed cone (figure 9.2): one counter cone and one

resection cone. The toothed counter cone will be anchored into the aortic valve to hold it during the resection.

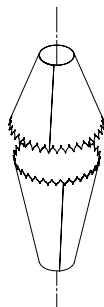


Figure 9.2: Solution with two toothed cones.

The last solution, shown in figure 9.3, is composed of two cones and three pliers. The pliers will grip the aortic valve during the resection and the counter cone serves like a chopping board and ensures the sealing of the whole device.

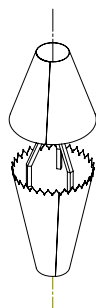


Figure 9.3: Solution using two cones and three pliers (one per leaflet).

The table 9.1 presents the comparison results of each solution of the holding system relative to the others.

Table 9.1: Comparison of the different systems to hold the aortic valve during the resection.

Criterion	Weight	Three cones	Two toothed cones	Two cones and pliers
Safety	1.00	4	1	2
Speed	1.00	4	4	1
Size	0.75	3	4	2
Complexity	0.50	3	4	1
Actuation	0.25	3	4	2
Total (weighted)	14.00	12.50	11.00	5.50
SD (unweighted)	—	0.55	1.34	0.55

It appears that the best solution (with the highest weighted total and the smallest SD), for the holding system, is the use of **three cones**. The biggest advantage of

this solution is the holding of the valve close to the resection site. This is not the case for the solution with the two cones and the pliers where the valve is held in its center without reducing the applied torque. For the two toothed cones solution, the teeth on the counter cone can be very dangerous for the patient because they may pierce the aorta and/or the cardiac muscle and engendered hardly manageable blood leakages.

Starting from these results, a new device has been designed. This device, called Aortic Valve TransApically Resected and Replaced (AVATAR²) and shown in figure 9.4, is an evolution of the device from the second iteration. It comprises a holding cone, a toothed resection cone, a counter cone, a centering balloon and a placement balloon on which the endo valve is crimped. The resection cone has a smaller diameter than the counter cone which has a smaller diameter than the holding cone.

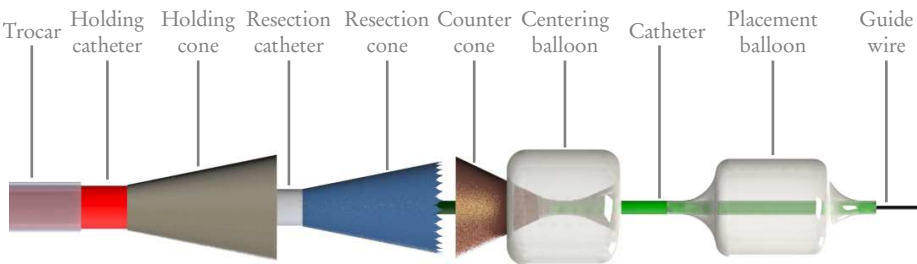


Figure 9.4: Components of the AVATAR² system.

Before its withdrawal from the heart, the device will be closed by sliding the trocar onto the holding cone which will close the counter cone and the resection cone thanks to its bigger diameter.

9.2 Demonstrator

As for the previous versions, a first demonstrator of the AVATAR² device has been designed (see figure 9.5) and manufactured (figure 9.6).

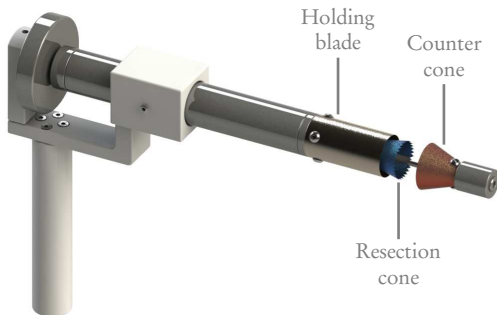


Figure 9.5: Solidworks modeling of the first version of the AVATAR² system.



Figure 9.6: First version of the AVATAR² system manufactured.

All the simplifications made for the previous versions have also been applied in this demonstrator during the design and the manufacturing processes to decrease the development time and speed up the manufacturing. Another simplification was made for the holding cone which was replaced by a cylindrical blade with a smaller diameter than the counter cone to manufacture more simple parts.

The parts of the demonstrator have been manufactured either in stainless steel (as the holding catheter, the catheter, etc.), either in Nitinol (for the three cones) either were 3D printed in acrylonitrile butadiene styrene (ABS) or in polyamide 2200 (PA2200) (the handles and the resection catheter). The resection cone, the holding cone and the counter cone have a diameter of 20 mm, 22 mm and 24 mm respectively.

9.3 Resection tests

To verify that the concept works for the resection of the aortic valve, the AVATAR² system has been tested on calcified heart embalmed (see figure 9.7) with zinc chloride (ZnCl_2) in the Laboratory of Anatomy of the Cliniques Universitaires Saint Luc, Bruxelles. The heart used for the tests was moderately calcified.

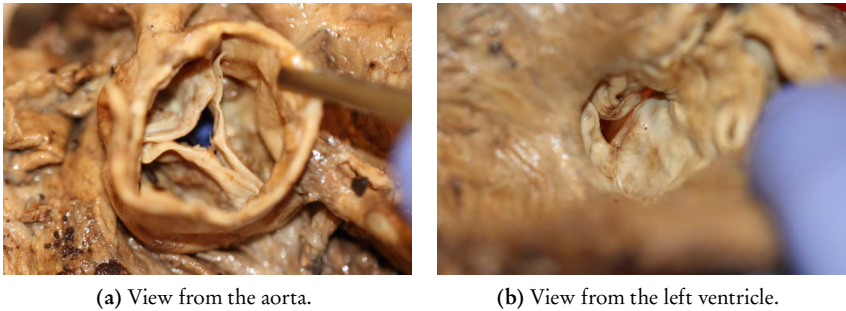


Figure 9.7: Embalmed heart used for the resection test of the first version of the AVATAR² device.

The first step of the test is the insertion of the device into the heart via the ventricle side. Then, the device is moved until the counter cone is entirely into the aorta (passing through the aortic valve). The third step is the holding the aortic valve by moving the holding cone and the counter cone (figure 9.8).

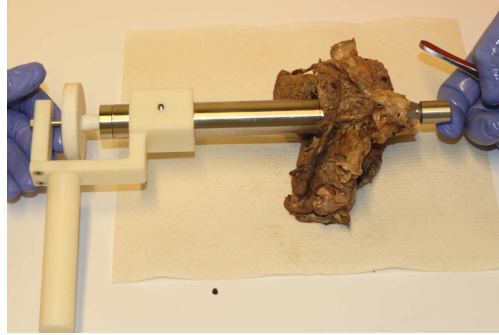


Figure 9.8: Device inserted into the embalmed heart.

Once the aortic valve is firmly held thanks to the holding cone and the counter cone, the resection is performed by rotating and translating the resection catheter with the dedicated handle. During the resection, the heart did not rotate, meaning that the holding system is working fine and drastically reduces the applied torque to the heart and the aorta.

After the resection, and for an easier removal of the device due too its big diameter, the counter cone has been unscrewed from the catheter, as shown in figure 9.9.



Figure 9.9: Device before its withdrawal from the heart.

Figure 9.10 shows that neo-annulus is perfectly circular and is ready to receive an endovalve. The figure also shows that the resected leaflet were entirely located into the resection cone. The little parts of the aortic valve left into the neo-annulus were still attached on it and did not risk to cause stroke because the endovalve would have crushed them onto the aortic annulus.



Figure 9.10: Aortic neo-annulus after the resection of the aortic valve.

The leaflets (see figure 9.11) were resected in approximatively 10 seconds (this time was not measured during the test but has been approximated after).



Figure 9.11: Resected leaflets at the end of the test.

The heart has been inspected after the test and it appears that a part of the aorta was cut during the resection (figure 9.12). This problem occurred because of the too big diameter of the device relative to the tested heart and of the muscles contraction due to the embalming process.

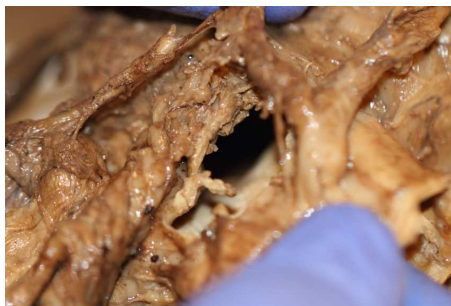


Figure 9.12: The aorta has been cut during the test because of the embalming process and the mismatch between the device diameter and the aortic valve diameter.

9.4 Conclusion

The first tests performed on an embalmed heart with this new three cones concept allow to verify that the aortic valve is entirely resected. The only problem that has occurred during the tests is the damage caused on the aorta due to the the embalming process which contracts the muscles and to the too big diameter of the device relative to the diameter of the aortic valve. In order to validate the resection of the aortic valve, clinical trial has to be performed on patients undergoing open heart surgery.

Part IV

Experimental validations

Chapter 10

Development of the AVATAR² device

To verify the AVATAR² concept, a preliminary test on embalmed cadavers has been performed. The main problem of the embalmed tissues is their retraction due to the use of ZnCl_2 . Thus, to validate the concept, clinical trials on patients undergoing open heart surgery need to be performed. For these clinical trials, the demonstrator has to be redesigned to be fully biocompatible and as safe as possible for the patient. Once the demonstrator will be designed and manufactured, new tests on cadavers will be performed to verify that everything is working fine before to be used in operating rooms.

10.1 Second version of the demonstrator

Because of the big diameter of the first demonstrator (overall diameter of 24 mm), a new device with a smaller diameter needs to be designed.

Several simplifications and improvements have to be implemented on this new version of the demonstrator to ensure the safety for the patients.

- the resection cone diameter will pass from 20 mm to 18 mm, the counter cone diameter from 24 mm to 22 mm and the holding blade from 22 mm to 20 mm in order to be able to use the device on a wider portion of the population to avoid damage in the aorta or on the peripheral tissues of the aortic valve due to a too big resection diameter;
- the counter cone and the holding blade will be made in stainless steel instead of Nitinol to avoid their deformation during the resection;
- the handle will be designed in one piece instead of three to reduce the number of screws and will be 3D printed in PA2200, a biocompatible material;
- the shaft supporting the counter cone will be able to slide and to be blocked to hold the aortic valve.

All the other parts will not be redesigned and will be manufactured in stainless steel. The demonstrator is used like the first version. The main difference is the blocking of the counter cone: to block it, the surgeon will need to screw the hexagonal part located on the handle (see figure 10.1).



Figure 10.1: Solidworks modelling of the new version of the demonstrator.

10.1.1 Resection tests on cadavers

Several test campaigns were conducted in the Anatomy Laboratory of the Cliniques Universitaires Saint Luc to verify and to eventually improve this new version before to use it on open heart patients.

One of the first performed tests on a calcified embalmed heart has shown the resection blade was not really well designed. Indeed, the bases of the teeth create a notch where cracks propagation can occur. During the resection test, and because of the contraction of the muscles which has hardened them, too high efforts have been applied on the resection blade causing its fracture (figure 10.2).



Figure 10.2: Because of the muscles contraction due to the embalming process and of the design of the blade, a too high effort was applied on the resection cone resulting in its fracture.

Because of this too fragile design of the blade a flashback has been made. For the next tests, a straight blade, as the one presented in the chapter 7 will be used. This blade was not able to resect the aortic valve in the first concept of the medical device and has not been tested in the other iterations. If a straight resection cone can resect the aortic valve, the risks of crack propagation will be reduced to almost zero resulting in an increasing of the safety for the patients. Wendt *et al.* reported that the cutting results with a toothed blade was of less quality and results in huge amounts of particles than a straight blade [137]. Moreover, the results with the straight blade were superior because of a simpler grinding process.

A new test was performed with this new blade on embalmed calcified aortic valve. This valve, shown in figure 10.3, was heavily calcified and had a diameter fitting with the demonstrator.



Figure 10.3: Aortic valve with big calcifications buds used for the resection test with a straight blade.

The device is inserted via the ventricle side until the counter cone passes the aortic valve (see figure 10.4).

Then, the resection is performed once the aortic valve is firmly held between the counter cone and the holding blade. The holding of the aortic valve is done by moving back the counter cone until the holding blade and by blocking it with the hexagonal screw. As seen on figure 10.5, the resected leaflets are located into the counter cone and are sharply cut.

The result of the resection is shown in figure 10.6. If a endo valve was implanted after the resection, the small part left on the aortic annulus will be crushed against the aortic wall with the stent.

The resection is perfectly circular and the soft tissues and even the big calcifications were cut with the straight blade. However, some improvements need to be made on the demonstrator before to be used in open heart patients.



Figure 10.4: Device inserted into the heart.



Figure 10.5: Resected leaflets into the counter cone after the resection.

10.1.2 Improvements to implement

Following the resection tests on cadavers, and before to use the device on open heart patients, the surgeon asked to modify the device with several improvements.

First, the handle which allows to translate and rotate the resection cone is too smooth and the gloved hands slip on it. So, the handle needs to be grooved to solve this issue.

Secondly, the hexagonal screw that blocks the counter cone cannot easily be used by only one person. Indeed, the blocking of the counter cone requires three hands: two to maintain the effort to hold the valve and one to screw the hexagonal screw. A simpler system, as the trigger and the spring to release a caulk tube from a caulk gun, needs to be designed on the handle.

The nut, next to the counter cone, needs to be removed to avoid any falling into the heart during the resection. It means that the counter cone must be redesigned to



Figure 10.6: Result of the resection of the aortic valve with a straight resection cone.

limit its unscrewing. A fine left-handed screw thread will be implemented and the counter cone will be glued onto the shaft.

The resection blade must have a bigger diameter (20 mm) and the holding of the aortic valve must be closer from the resection site. Moreover, the device must be designed like the AVATAR² system, *i.e.* the counter cone having a smaller diameter than the holding cone. The holding cone will have a diameter of 22 mm and the counter cone, a diameter of 21 mm.

10.2 Demonstrator for the open heart surgeries

All the improvements have been implemented on a third version of the AVATAR² device (see figure 10.7). As for the second version, all the parts of this device are entirely made with biomaterials.



Figure 10.7: Solidworks modelling of the new version of the demonstrator.

The new manufactured demonstrator, shown in figure 10.8, has to be verified on cadavers before to be used on open heart patients. This will allow to be certain that all the modifications implemented on the device are useful and efficient and do not damage the heart during the resection.

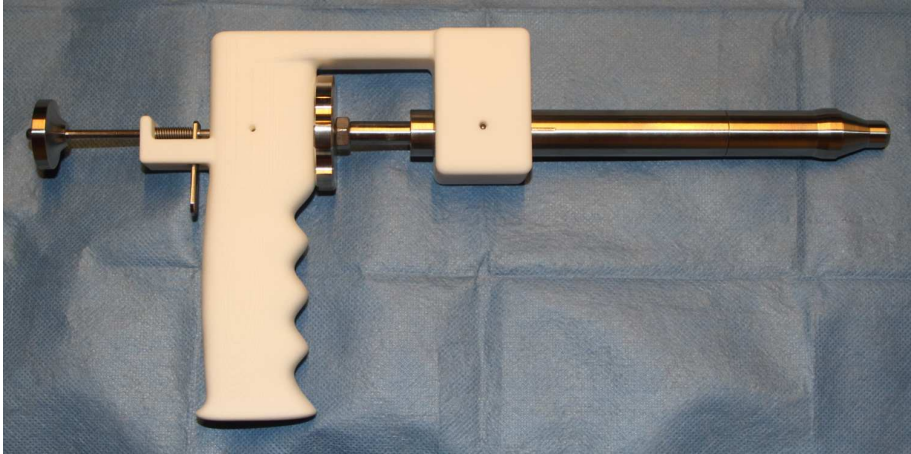


Figure 10.8: Manufactured AVATAR² device that will be used for patients undergoing open heart surgery.

To test the device, several resections were performed on embalmed hearts (figure 10.9) in the Anatomy Laboratory of the Cliniques Universitaires Saint Luc.



Figure 10.9: One of the calcified embalmed heart used during a resection test with the third version of the AVATAR² device.

During the open heart surgeries, the resections will be performed through a transaortic access. Indeed, the device cannot be deployed, if it is passed through the apex, a hole of at least 22 mm should be made which is too risky for the patients. All the tests on embalmed cadavers were done using this same approach (see figure 10.10).



Figure 10.10: Insertion of the device through a transaortic approach.

Once the counter cone is into the ventricle, the aortic valve is held by moving back the counter cone against the holding cone. The trigger which is on the handle only serves to release the valve after the resection. The spring pushes on the trigger to block the shaft to avoid that it moves and release the aortic valve during the resection. The aortic neo-annulus, created by the resection, is shown in figure 10.11. If an endo-atrial valve had been implanted after the resection, a lot of the known problems of TAVI, described in chapter 3, would have been limited thanks to this neo-annulus.

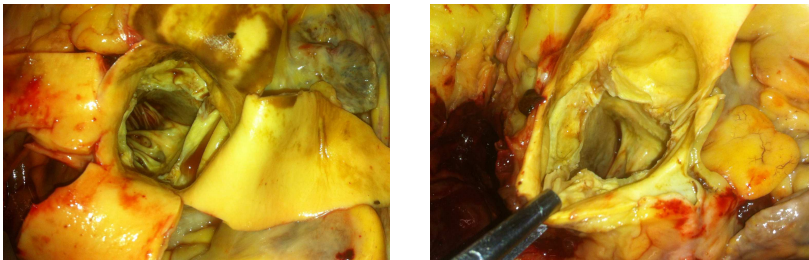


Figure 10.11: Aortic annulus after the resection of the calcified aortic valve.

All the three leaflets were sharply cut without any small debris of soft or hard tissues (see figure 10.12).

10.3 Conclusion

The different tests performed on embalmed hearts have allowed to verify that the third version of the AVATAR² device was ready to be tested on patients undergoing open heart surgery. Indeed, the leaflets were systematically sharply cut and, if the aortic valve was with a diameter of at least 24 mm, the aorta and the peripheral tissues were never damaged. Moreover, all the improvements implemented on the last version of the device have been approved by the surgeon during the resection tests on cadavers. Only two modifications were asked by the surgeon:



Figure 10.12: Aortic leaflets after the resection.

1. a blocking piece to let the resection cone in position when the counter cone passes the aortic valve to prevent any damage on the heart or the aorta;
2. a blocking piece to limit the opening of the counter cone before the withdrawal of the device at the end of the resection in order to avoid any falling off resected debris into the left ventricle.

The figure 10.13 shows the device that will be used during the clinical trials on open heart patients.

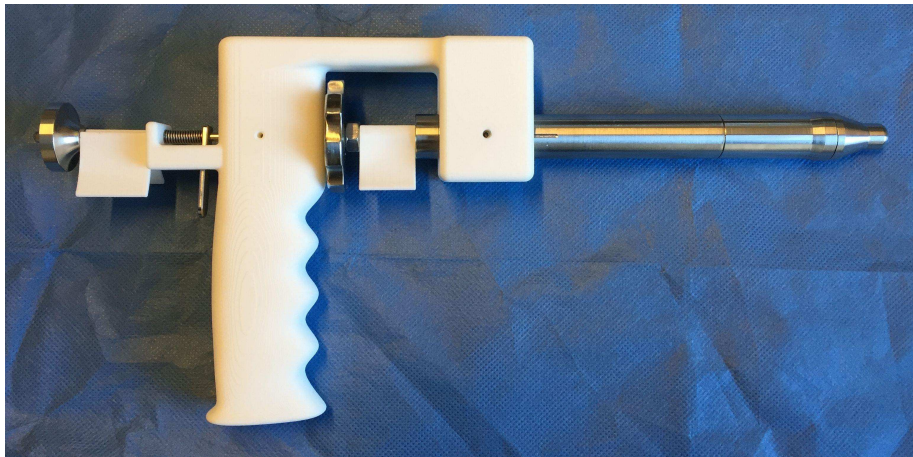


Figure 10.13: AVATAR² device that will be used during the clinical trials.

Chapter 11

Clinical trials

In Belgium, and more generally in European Union, a clinical trial can only start after receiving a favourable opinion from the Ethics Committee (from the hospital where the clinical trials will be performed) and if the relevant authority, the FAMHP, has not indicated any major insufficiency within the legal timeframe (*i.e.* 28 days) provided for in the law dated 7th May 2004 related to experiments on human people [149].

Therefore, a file has been written and filed to the FAMHP and to the Ethics Committee of the Cliniques Universitaires Saint Luc in order to get the authorization before to start the clinical trials. This file contains, *inter alia*, the user manual, the assembly instructions, all the reports of the resection tests on cadavers, the case report form (CRF), etc.

11.1 Patients selection

The surgeon has defined criteria to include or exclude patients for the clinical trials. The subject must match all these criteria to be part of the study.

Inclusion criteria:

1. Severe aortic stenosis defined as one or more of the following by Doppler echocardiography: mean gradient > 40 mmHg, max velocity > 4 m/sec and $AVA \leq 0.8$ cm².
2. Symptoms related to aortic valve disease, and New York Heart Association (NYHA) Functional Class II or greater.
3. Subject is indicated for aortic valve implantation with a biological prosthesis.
4. Age ≥ 65 years.
5. Echocardiographically determined aortic annulus diameter ≥ 24 mm and ≤ 30 mm in a long-axis view.
6. Subject understands the implications of participating in the study and provides informed consent.

Exclusion criteria:

1. Congenital unicuspid or bicuspid aortic valve.
2. Severe eccentricity of calcification, defined as calcium deposits larger than 6 mm in diameter.
3. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
4. Left ventricular ejection fraction < 25 % as determined by contrast ventriculography, or echocardiography or radionuclide angiography if contrast ventriculography not available.
5. Hypertrophic obstructive cardiomyopathy.
6. Subjects with life expectancy less than 12 months due to an underlying non-cardiac co-morbid disease.
7. Known hypersensitivity or contraindication that cannot be adequately controlled with pre-medication to any study medication or material, such as contrast medium or Nitinol.
8. Blood dyscrasia such as acute anemia, leucopenia, or thrombocytopenia; bleeding diathesis, or coagulopathy.
9. Renal insufficiency assessed by creatinine > 2.5 mg/dl and/or end stage renal disease requiring chronic dialysis.
10. Poor lung function that in the investigator's opinion is prohibitive for thoracotomy.
11. Active peptic ulcer or gastrointestinal bleeding within 3 months from the planned index procedure.
12. Cardiogenic shock, suspected cardiogenic shock, or hemodynamic instability requiring inotropic support or mechanical heart assistance.
13. Peripheral vascular disease, including abdominal and thoracic aortic disease, that could pose a problem for eventual transarterial mechanical support (e.g. intraaortic balloon pump).
14. History of myocardial infarction in the last 6 weeks.
15. History of transient ischemic attack (TIA) or cerebrovascular accident (CVA) in the last 6 months.
16. Subject refuses to have a blood transfusion.
17. Subject is currently enrolled in another investigational device or drug trial that may influence the outcome of this trial.

If the patient matches with all the criteria and agrees to be part of the study, he must sign an informed consent. Then, several informations about the patient are collected before the surgery. These informations are, for example, his gender, his height, his weight, his European System for Cardiac Operative Risk Evaluation (EuroSCORE) which allows the calculation of the risk of death after a heart operation, his Society of Thoracic Surgeons (STS) Score which allows to calculate a patient's risk of mortality and other morbidities, such as long length of stay and renal failure. Other echocardiographically determined data will also be collected in order to be compared with the results determined after the surgery. These data are the diameter of the aortic annulus, the aortic peak and mean gradients, the AVA, etc.

11.2 Procedural data

Different data will be collected during each surgery. The data, scored from 0 (*inadequate*) to ten (*excellent*), are essentially an assessment by the surgeon on the usability of the device during the resection (like the handling of the device through the aortic valve or the deployment of the system); the eventual damages caused by the device (on the the aortic wall, on the cardiac muscle, on the mitral valve or on aortic annulus); the visual aspect of the resection edge on the aortic annulus, of the resection cone and of the resected and collected leaflets and the global satisfaction of the surgeon.

The diameter of the aortic valve measured, in the operating room, with the echocardiography just before the aortotomy and with the cusp sizer are also collected for the clinical trials file.

The resection time will also be measured during the procedure and will be considered from the start of the rotation of the resection cone until the opening of the holding cone and the counter cone (before the withdrawal of the device from the heart).

11.3 Surgical procedure

During the surgical procedure, the patient is placed under general anaesthesia. From the skin incision to the transversal aortotomy, the surgical procedure performed during the clinical trials is the same as the conventional surgical procedure for the AVR, described in section 3.2.2.

Once the transversal aortotomy has been performed, the valve is exposed to facilitate its resection (see figure 11.1).

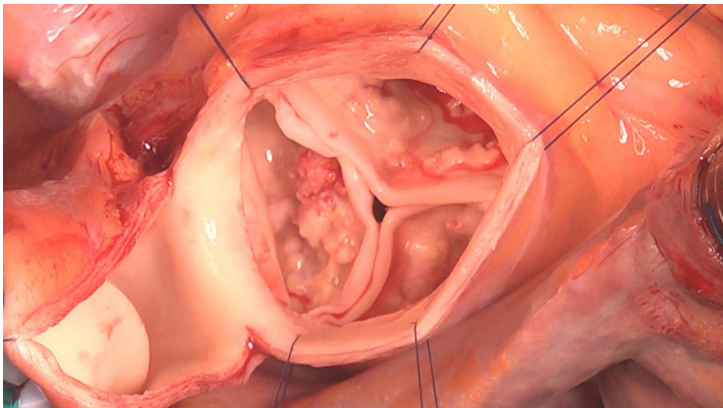


Figure 11.1: Exposition of the aortic valve.

Then, the diameter of the aortic valve is verified with a cusp sizer (figure 11.2) to confirm the diameter echocardiographically determined, which is an estimation of the actual diameter.

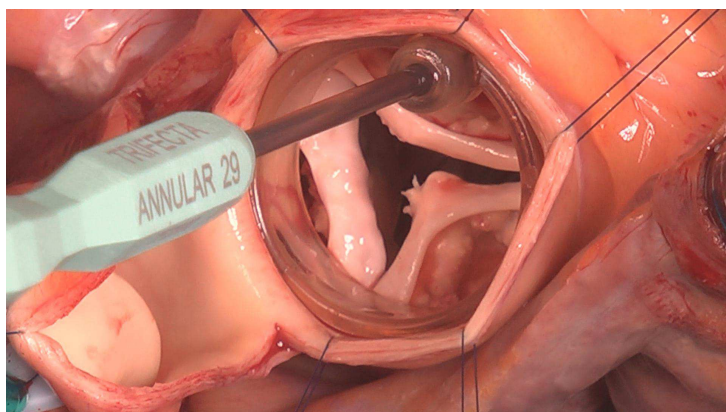


Figure 11.2: Measure of the aortic valve with a cusp sizer.

If the measure confirms that the diameter of the aortic valve matches with the inclusion criteria specified in section 11.1, *i.e.* between 24 mm and 30 mm, then the AVATAR² device is assembled in the operating room. After its assembly and its verification, the device is given to the surgeon for the resection (figure 11.3).

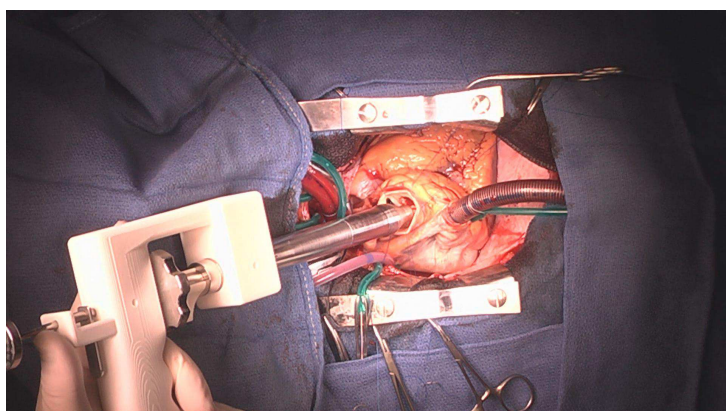


Figure 11.3: Device, in its closed configuration, placed into the operative field before to start the resection.

The first step of the resection is the opening of the device (see figure 11.4) in order to introduce the counter cone into the left ventricle through the aortic valve, as shown in figure 11.5.

After the insertion of the counter cone into the left ventricle, the counter cone is moved back against the holding cone to hold the aortic valve (see figure 11.6). Once the valve is correctly held, the resection is performed. If the heart starts to rotate during the resection, the counter cone is moved back again for a better holding of the aortic valve.

The resection is complete when the surgeon does no longer feel any resistance dur-

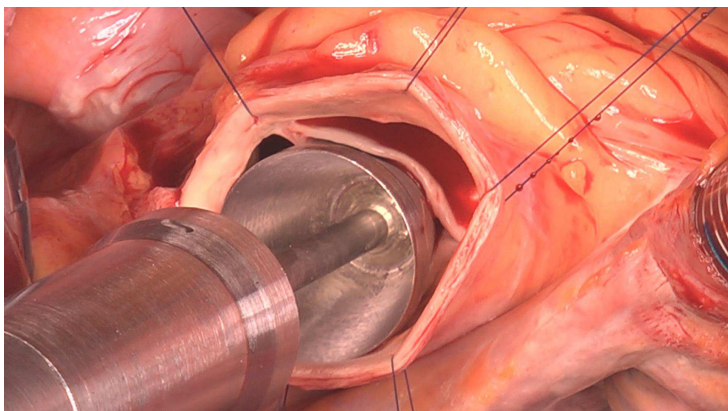


Figure 11.4: Insertion of the counter cone through the aortic valve.

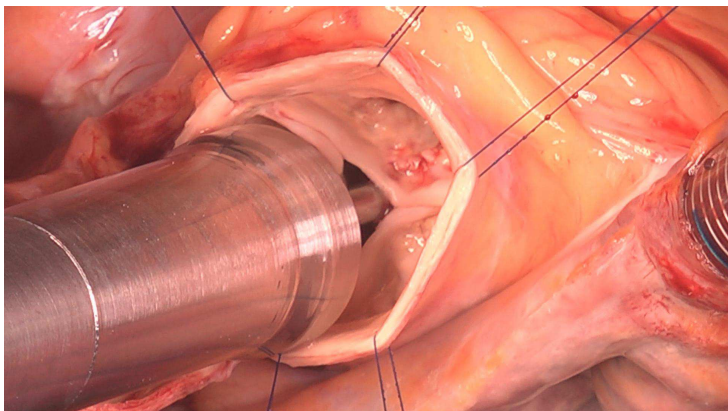


Figure 11.5: Counter cone inside the left ventricle.

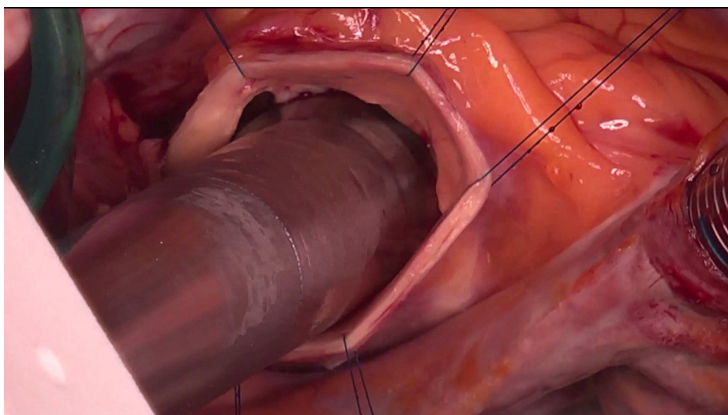


Figure 11.6: Holding and resection of the aortic valve.

ing the rotation of the resection cone. The resulting aortic annulus after the resection with the AVATAR² device is shown in figure 11.7. As seen on the figure, the neo-annulus created with the device is perfectly circular and would be ready to receive an endovalve.

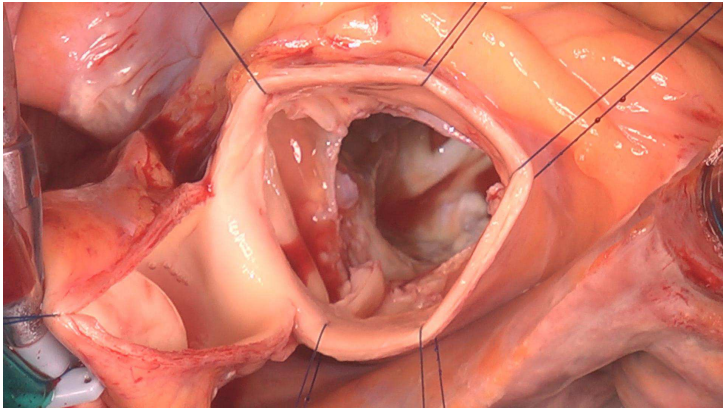


Figure 11.7: Aortic annulus after the resection of the aortic valve.

After the resection with the AVATAR² device, the aortic annulus is cleaned up with a scalpel and tweezers to be ready to receive the aortic prosthesis. Then, the conventional surgical AVR, described in section 3.2.2, is followed again till the end of the operation.

11.4 Results

Once the resection is performed, the resected aortic leaflets are removed from the device to examine their integrity and their resection edges, as seen in figure 11.8.



Figure 11.8: Leaflets resected with the AVATAR² device.

After the examination of the resected leaflets, the surgeon gives his assessment for each procedural data. To date, eight resections using the AVATAR² device have

been performed in the operating room of the Cliniques Universitaires Saint Luc. The procedural data of these eight surgeries are given in the appendix C and their mean and SD are given in table 11.1.

Table 11.1: Means and SD of the procedural data for the eight resections. Data are scored from 0 (*inadequate*) to 10 (*excellent*).

Criteria	Mean	SD
Handling of the device through the aortic valve	9.50	1.41
Setting of the device	10.00	0.00
Deployment of the system	9.50	1.41
Visual aspect of the aortic annulus after resection	8.75	1.49
Debris collection	9.75	0.71
Aortic wall damage	10.00	0.00
Mitral valve damage	10.00	0.00
Myocardial damage	9.75	0.71
Aortic annulus damage	10.00	0.00
Visual aspect of the resection edges	8.63	1.41
Visual aspect of the resection cone and blade	7.75	2.19
Visual aspect of the resected and collected leaflets	10.00	0.00
Global satisfaction of the surgeon	9.00	1.20

As seen on the table, the results of the surgeries are encouraging. Indeed, the assessment of the surgeon for the use of the device is almost excellent and he is globally satisfied with the device. The resection edges and the visual aspect of the aortic annulus after the resection were globally satisfactory for the surgeon.

The passage of the counter cone through the valve was sometimes complicated due to big calcifications buds or to the fusion of the commissures.

The device does almost not damage the heart and its peripheral tissues. Only a small part of the interventricular septum was removed during the first resection test with no consequences for the patient (who had a small hypertrophic cardiomyopathy).

The Achilles' heel of the AVATAR² device is its resection cone. The Nitinol blade was often damaged, as shown in figure 11.9, because of the rigid counter cone. If the counter cone was made of Nitinol, it would be able to be deformed by the calcifications in order to encompass the resection cone and avoid its damage.

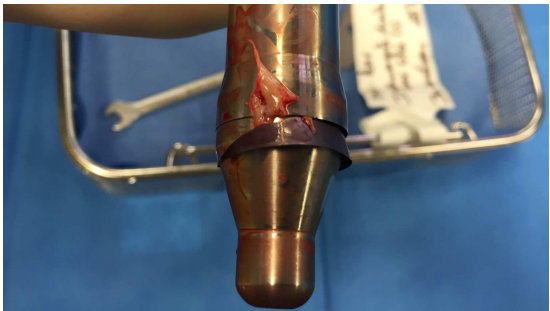


Figure 11.9: Damage resection cone due to the rigidity of the counter cone.

The table 11.2 presents the results of the clinical trials. At the end of the procedure, the resection times have been measured with the video taken during the surgery to have the most accurate duration of the resection. The resection ratio has been measured by comparing the volume of the leaflets resected with the device and the volume of the whole valve (the resected leaflets with the device and the debris removed to clean the aortic annulus).

Table 11.2: Results of the clinical trials.

Patient	Valve diameter (in mm)	Resected volume (in ml)	Resection ratio (in %)	Resection time (in seconds)
1	29	1.00	38.46	25.16
2	25	1.20	42.11	12.24
3	27	2.20	70.97	26.00
4	29	1.00	27.78	9.00
5	27	1.00	38.46	23.24
6	27	0.70	53.85	10.24
7	27	0.80	72.73	15.03
8	27	1.20	66.67	11.24
Mean	27.25	1.14	51.38	16.52
SD	1.28	0.46	17.14	7.11

The resection time, 16.52 ± 7.11 seconds, is better than the fastest resection system from the state of the art (see table 5.4). The device resects around half ($51.38 \pm 17.14\%$) of the aortic valve volume (see figure 11.10).

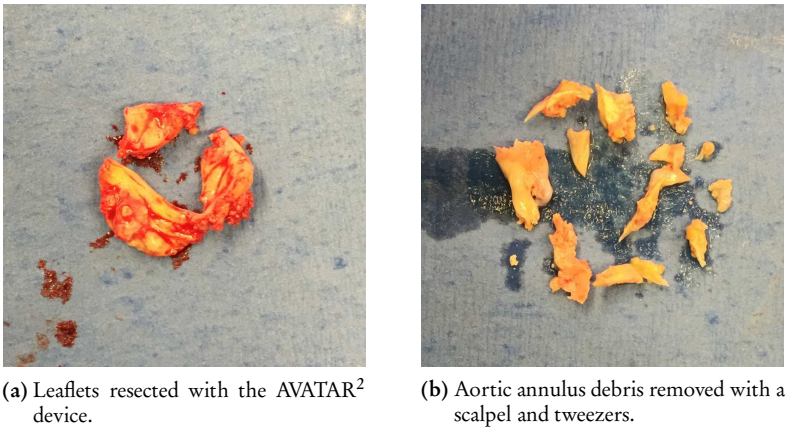


Figure 11.10: Complete aortic valve resected during a clinical trials.

11.5 Conclusion

After the verification of the AVATAR² system on embalmed hearts, the system has been validated on eight patients undergoing open heart surgery. The device

allow to safely (only one small damage on the interventricular septum) and quickly (16.52 ± 7.11 seconds) resect the calcified aortic valve.

During the clinical trials, a second collection chamber (see figure 11.11) formed between the resection cone and the holding cone has been discovered. This new collection chamber increase the safety of the device because it allows to collect more small debris and therefore limit CVA.

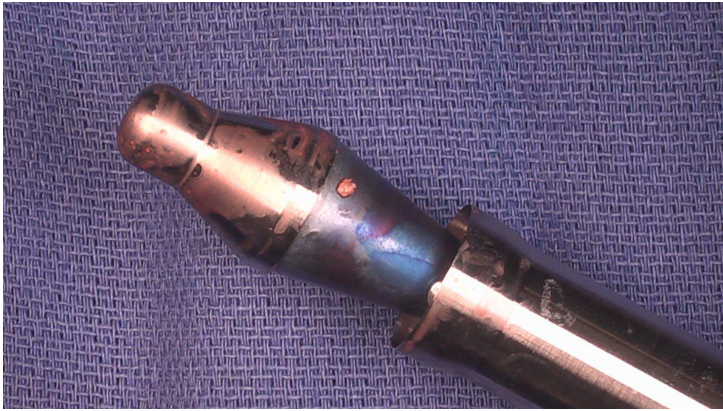


Figure 11.11: Small debris collected into the second collection chamber formed between the resection cone and the holding cone.

To increase the satisfaction of the surgeon, two improvements should be implemented on the AVATAR² device: (1) the counter cone should be deployable to facilitate its passage through the calcified aortic valve and (2) the three cones should be manufactured in Nitinol to allow small deformations due to the calcifications and limit the damage on the resection cone.

In the future, if the AVATAR² device is used in operating rooms for open heart aortic valve replacement surgery, the global procedure time will drastically decrease. Currently, the heart is stopped for approximately 45 minutes due to the resection time and the suture time. With the AVATAR² device, this time can be reduce to less than 15 minutes if a sutureless valve is implanted. Indeed, the resection takes a maximum of 30 seconds with the developed device. And if a modified suturless valve is implanted in the aortic neo-annulus without any stitches than the aortic annulus does not need to be cleaned up which will result in a faster surgical operation.

Thanks to the good results of the clinical trials, a second patent of the AVATAR² concept was filed in the European Patent Office under the reference EP16160156.2 on the 14th of March 2016 [12]. The first page and the claims of the patent are given in Appendix B.

Conclusions and prospects

The initial objective of this thesis was to design an assistance to the replacement of the aortic valve through a minimally invasive beating heart surgery. To achieve this multidisciplinary study, a systematic effectual approach has been applied from the initial need to the experimental validation of the final solution on patients undergoing open heart surgery.

The approach

The effectual approach used for this research and based on the approach developed by Sarasvathy [150], contradicts the casual approach usually used. The casual approach first emphasizes the specific purpose before to focus on the means to achieve them, while the effectual logic starts to focus on the means and then on the achievable effects. This effectual approach, used for a situation of total incertitude but where a solution is still possible, has allowed to develop a breakthrough innovation.

Starting from the initial need, the heart, the calcific aortic stenosis and the current medical treatment of this pathology have been studied in details to *identify the key challenges*. This study has allowed to meet the surgeons and to attend open heart and minimally invasive surgeries in order to better understand the initial need and the expectations of the surgeons.

Once the medical context was studied and well understood, the design method has been started with *the analysis of the need*. Two needs were identified: (1) *design a medical device serving the surgeon to resect the native aortic valve from the heart* and (2) *design a medical device serving the surgeon to implant an endo valve into the heart*.

Then, *the functional analysis of the need* was undertaken to highlight the life phases of the device and its elements from the external environment. This functional analysis has allowed to establish the *functional specifications* and the three main functions to achieve: (1) *resect the native aortic valve*, (2) *collect the resected valve* and (3) *implant an endo valve*. Based on the functional specifications, *comparison criteria* were identified to objectively evaluate the generated alternatives of each function.

A study of *the state of the art of resection systems* was done to have an idea on how an aortic valve can be resected. Then, a comparison between the functional specifications and the different systems from the literature was performed to verify that none of the systems did respond to the initial need of the surgeon.

The next step of the design method was to perform *the technical functional analysis* in order to find and objectively evaluate several solutions for the different main functions (percutaneous approach, resection systems and collection systems) of the device.

After to have found the best solution for each function, the development of the device was initiated. A first demonstrator without deployment and implantation system was designed, manufactured and tested on a calcified aortic valve to verify that the concept of a resection cone coupled to a chopping balloon was able to resect the valve. The results were inconclusive because only the hard tissues (*i.e.* the calcifications) were cut while the soft tissues remained uncut.

A new toothed blade was then designed to allow cutting of the soft tissues implying a new combination of solutions for the entire device. Using a toothed blade on a chopping balloon risks to engender a piercing of the balloon. After the test of the new blade and the combination of the solutions, a demonstrator with a resection cone and a counter cone used as abutment support was designed and manufactured before to be tested on calcified aortic cusps. The results were better than the first demonstrator but the resection was not complete. Moreover, a new main function was identify: *hold the valve during the resection*. Indeed, during tests with the demonstrator, it appeared that the heart was rotating with the resection blade implying high torque on the peripheral tissues of the aortic valve.

The new function resulted in a new brainstorming to find the best solution to hold the aortic valve during the resection. The new concept, two cones to hold the valve while a third cone is used to resect it, was developed. As for the previous concepts, a demonstrator was designed, manufactured and tested on embalmed heart in the Anatomy Laboratory of the Cliniques Universitaires Saint Luc. The tests were totally satisfactory and the device, called AVATAR², has been improved to be used and validated during open heart clinical trials.

Eight resections with the AVATAR² device were performed on patients undergoing open heart surgery. The resection took 16.52 ± 7.11 seconds which is better than the fastest resection system from the state of the art with a resection time of 49.7 ± 15.0 seconds [138]. No big damages on the peripheral tissues of the aortic valve (aorta, cardiac muscle and mitral valve) occurred during the clinical trials. Only a tiny part from the interventricular septum was removed once. During the clinical trials, a second collection chamber formed between the resection cone and the holding cone was discovered. This new collection chamber drastically increases the safety of the device by allowing to collect more debris from the resection resulting in lower risk of CVA.

The clinical trials allowed to *validate the device* that was developed during this thesis. The device meets the expectations formulated at the beginning of the research by the surgeons. Finally, thanks to the very good results during the clinical trials, a patent has been filed [12] to protect the invention.

In the future, the AVATAR² device designed and tested during this thesis will be used during open heart surgery coupled to a sutureless aortic bioprosthesis. This combination will allow to decrease the procedure time from about 45 minutes to less than 15 minutes. Indeed, the resection with the device will be faster than a

resection using a scalpel and tweezers and the sutureless prosthesis will take less time to be implanted than a conventional prosthesis which requires a dozen of stitches to be attached on the aortic annulus. Because of the quicker surgery procedure, the surgery will be less traumatic for the patients. Moreover, thanks to an easier way to remove the calcified aortic valve, a mini-sternotomy can be performed and will decrease the hospitalization stay, reduce the sternal wound complications and improve cosmesis [63, 64].

The solution

The AVATAR² device developed during this research project has the following sub-sets:

- a **rotating and translating resection cone** to cut the aortic valve;
- a **counter cone** used as an abutment support to facilitate the resection;
- a **holding cone** which when coupled to the counter cone firmly holds the aortic valve to increase the safety for the patient and allow to efficiently resect the aortic valve.

To resect the valve, the device is introduced, once the heart is stopped and the aortotomy has been performed, into the heart through a transaortic access. Once the counter cone is into the left ventricle, after passing through the aortic valve, it is moved back to be against the holding cone. This movement will allow to firmly hold the aortic valve during its resection. Then the resection is performed by rotating the straight resection cone. Once the resection is complete, the surgeon removes the device from the operating field and continues the AVR surgery like in the conventional surgery.

The best way to *cut a leaflet* is to hold it during its resection. In the conventional open heart surgery, the leaflet is held with tweezers while the surgeon use a scalpel for the resection. This method has been transposed into the AVATAR² system. Indeed, the counter cone and the holding cone act like tweezers and the resection cone mimics the scalpel. This allow to efficiently and rapidly resect the aortic valve.

This solution is working fine in the operating room but can be improved thanks to the lessons learned during its development. Indeed, a lot of choice have been made during the different steps of the design method and, like it is well known, to choose is to forsake. It means that some of the choices, even if there were made with the most objectivity as possible, may not be the best ones.

The use of a balloon as the chopping board in the device was abandoned due to the use of a toothed blade to be able to resect both soft and hard tissues. In order to avoid to pierce the chopping balloon with the teeth of the blade, it was replaced by a counter cone made of Nitinol. Finally, because of the flashback made with the use of a straight blade instead of a toothed one, replace the counter cone by a reinforced chopping balloon into the final AVATAR² device can be a good choice. It will simplify the actuation of the entire system and facilitate the passage of the device through the aortic valve.

The contributions

The *technical contributions* of this thesis can be summed up in two points:

- a realisation of an innovative medical device for the resect of calcified aortic valves;
- a validation of the device during clinical trials on patients undergoing open heart surgery.

The *scientific contributions* of this thesis are a rational and systematic study of an innovative mechanical device aiming to answer to the initial need of the surgeon with two international patent applications [11, 12] (see appendices A and B). The rational and systematic study includes a need analysis of the minimally invasive AVR, based on the problems of the surgical AVR and of TAVI and on a review of the existing resection systems.

During the rational and systematic study of the medical device, key milestones (with some vigilance points) for the development of future medical devices have been identified.

The functional analysis is the most important step of the design method. If the task is not sufficiently clear for the designer, then the designer will develop a good solution to the wrong problem instead of a wrong solution to the good problem. This step, which can take time, needs to be done in close collaboration between the surgeons and the designers in order to earn time during the next steps of the design method. If designers need to develop a medical device, we recommend them to study and understand the environment in which the device will be used (the anatomy of the organ, its physiology, etc.), the pathology to treat and how it is currently treated. If the problem is correctly stated, the development of the device will be quicker and more efficient with fewer trials and errors.

Another vigilance point to earn time and to develop a more efficient device is to test, a lot of times and on different models, each system of the device separately thanks to demonstrators. The demonstrators will help the designers to discuss with the surgeons during the tests and will allow to rapidly verify, iterate and improve a concept before its final implementation into the entire device.

If we had to redo it...

If we had to redo the research, a lot of things would be done on the same way. Indeed, the work performed during this research has allowed to achieve good results in a short period of time (3 years between the start of the project and the designed device ready to be tested during open heart surgeries). Ideally, to be even faster, discussions with several surgeons would have helped to have different point of views on the device to be designed. It would have maybe allowed to find the final resection system solution faster. Nothing about the way on how the tests were performed would be changed because if a lot of tests are realized, then more problems can be detected and managed before the use of the device on patients.

The prospects

Several aspects of the final device have not been explored during this thesis but are mandatory for the final version of the minimally invasive device.

The deployment of the system has not been studied in details. The principle of the closing and the opening of the cones has been tested with a simple demonstrator to verify its functioning.

The attachment of a cone on a catheter is a tricky problem and has not been studied. There are many constraints on the attachment system (*e.g.* deployment, torque transmission, concentricity between the cone and the catheter, etc.). Find a solution was beyond the scope of this doctoral research but is mandatory before to be able to use the device in a minimally invasive way.

The required space to collect the resected aortic leaflets before their withdrawals from the heart needs to be optimized in order to increase the device safety and avoid any embolisms of a resected debris with irreversible effects for the patient. The length of the resection system and the diameter of the transapical access need to be as limited as possible with the biggest volume in the collection chambers for the resected aortic valve.

The clinical trials were performed in only one hospital and by only one surgeon. The results of the clinical trials, and in particular the global satisfaction of the surgeon, are maybe too enthusiastic and should be used with caution. To have more objective results, a multicenter clinical trial needs to be organised prior to any marketing.

The next steps of the research project will be to have a fully expandable device to be used in a transapical way. The imagined procedure will require about ten different steps after the exposure of the apex.

The first step will be the insertion of the device through the apex and through the aortic valve, as shown in figure 1. Once the device is inside the left ventricle, the RVP is started to limit the blood flow and avoid a migration of the device during the inflation of the centering balloon.

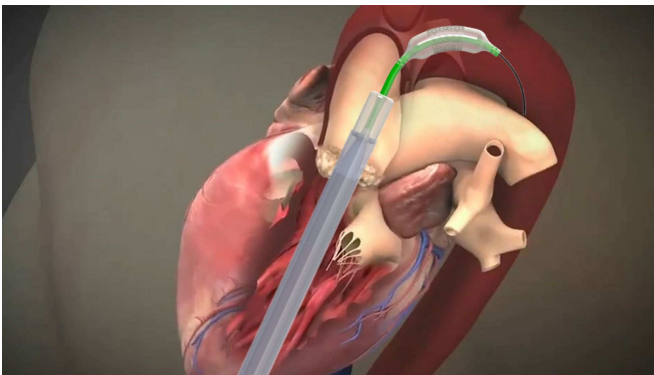


Figure 1: Insertion of the device into the heart through the apex.

The next step (see figure 2) consists in the deployment of the counter cone and of the inflation of the centering balloon while the rest of the device is moved back into the left ventricle.

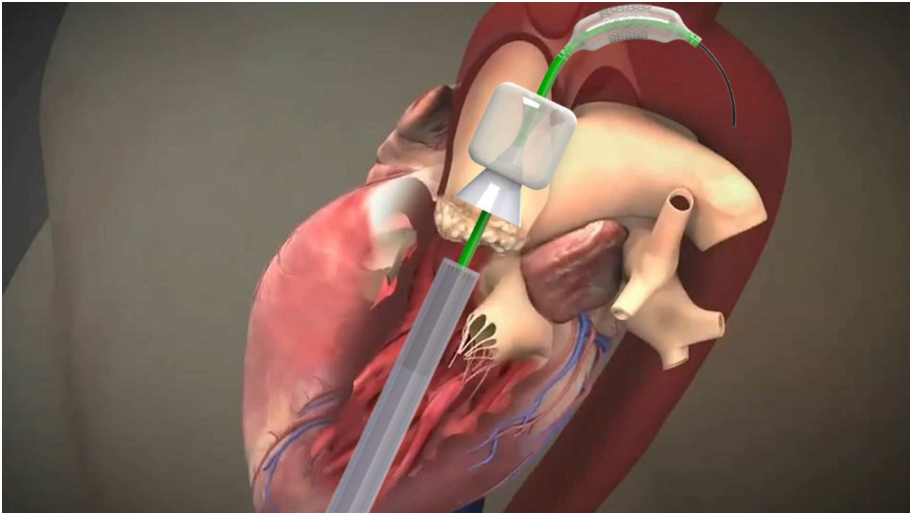


Figure 2: Inflation of the centering balloon and deployment of the counter cone.

When the rest of the device is located into the left ventricle, the trocar is pulled back to deploy the holding cone and the resection cone (figure 3).

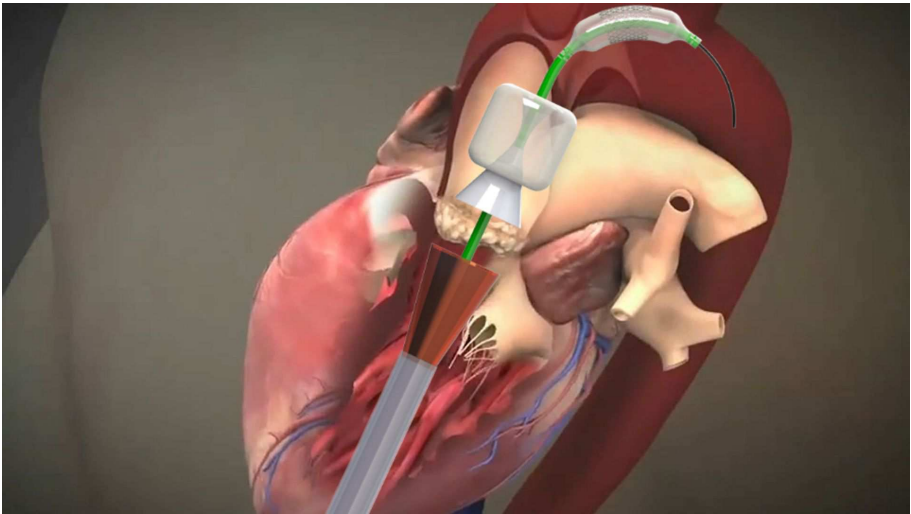


Figure 3: Deployment of the holding cone and of the resection cone.

After the deployment of the two cones, the device is moved to hold the aortic valve before its resection (see figure 4).

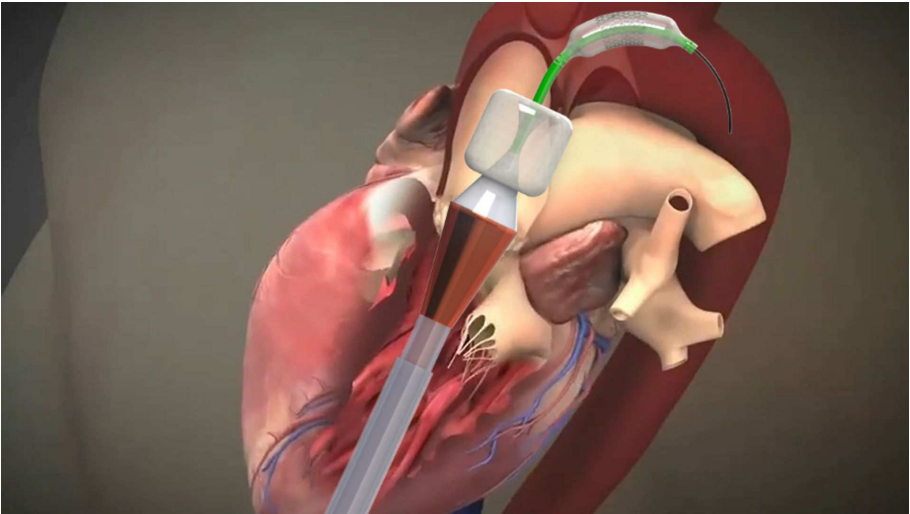


Figure 4: Holding and resection of the aortic valve.

Then, as shown in figure 5, the centering balloon is deflated.

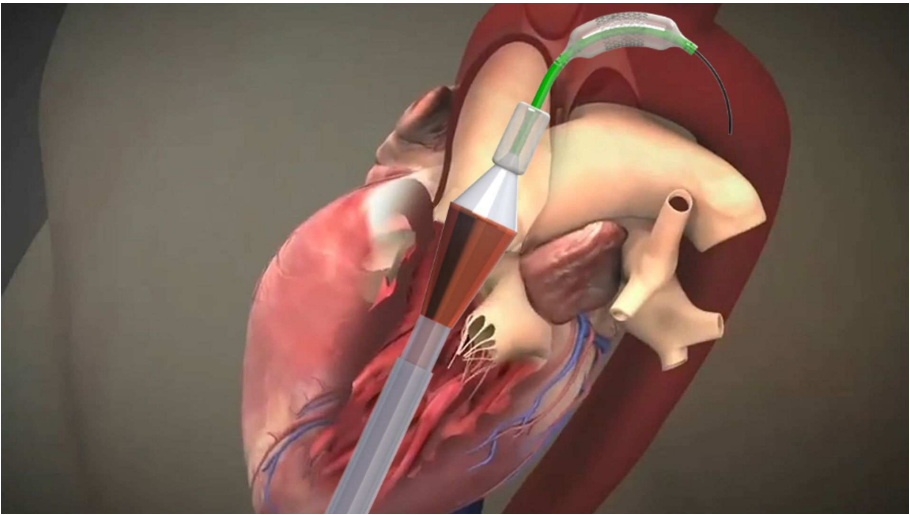


Figure 5: Deflation of the centering balloon.

The next step is the translation of the whole device until the placement system is at the aortic annulus level (figure 6).

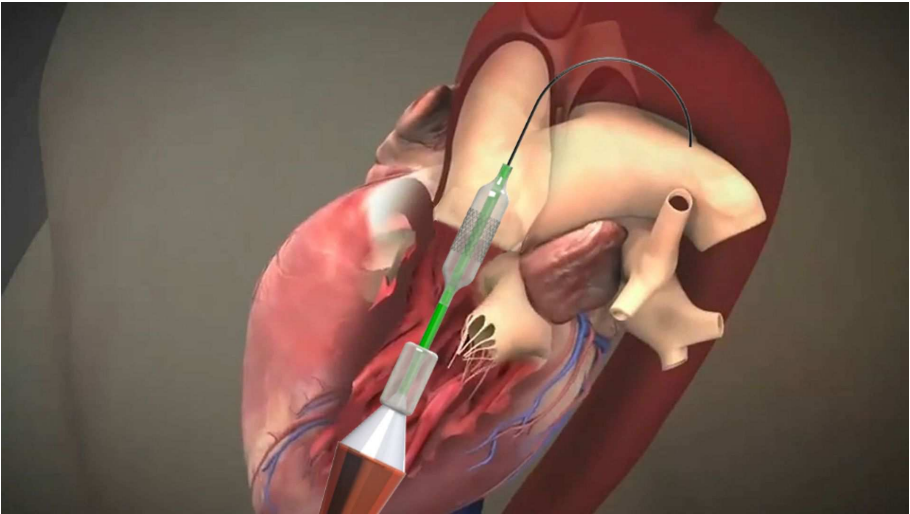


Figure 6: Translation of the device until the endovalve is into the aortic neo-annulus.

The placement balloon is then inflated during at least 5 seconds in order to release the aortic endovalve into the anchoring site (see figure 7).

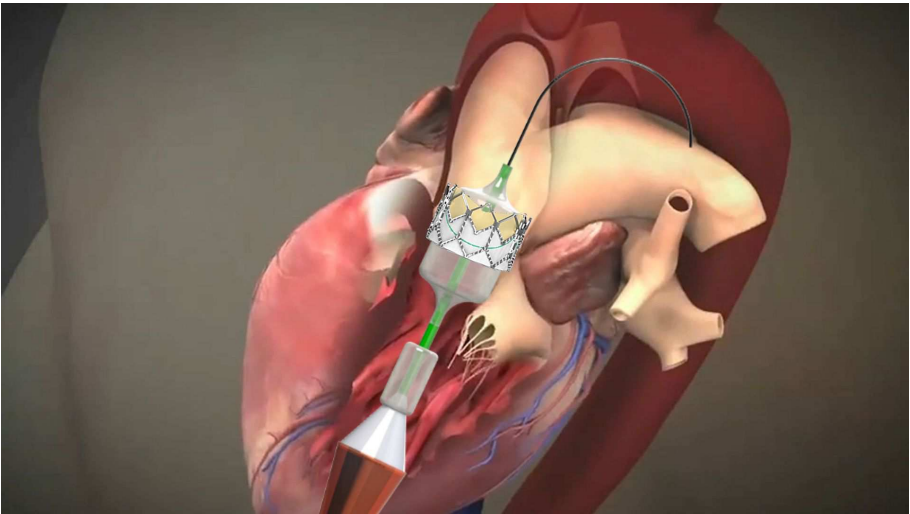


Figure 7: Inflation of the placement balloon during at least 5 seconds.

After the 5 seconds, the placement balloon is deflated, as shown in figure 8.

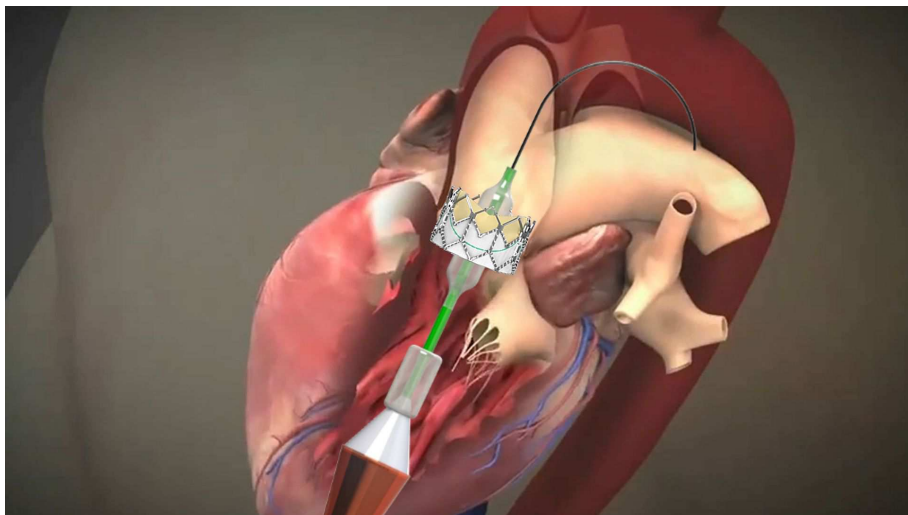


Figure 8: Deflation of the placement balloon.

At this moment of the procedure, the RVP is stopped. After the heart starts to beat again, the device is closed to prepare its withdrawal. To close the device, the resected leaflet are compacted (figure 9).

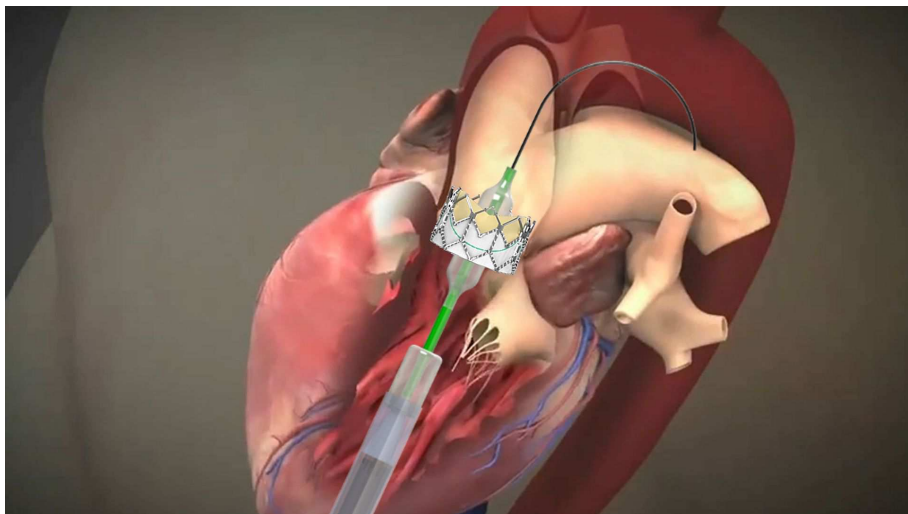


Figure 9: Compaction of the resected debris.

The final step of the procedure is the withdrawal of the device and the verification of the good placement of the endo valve (see figure 10).

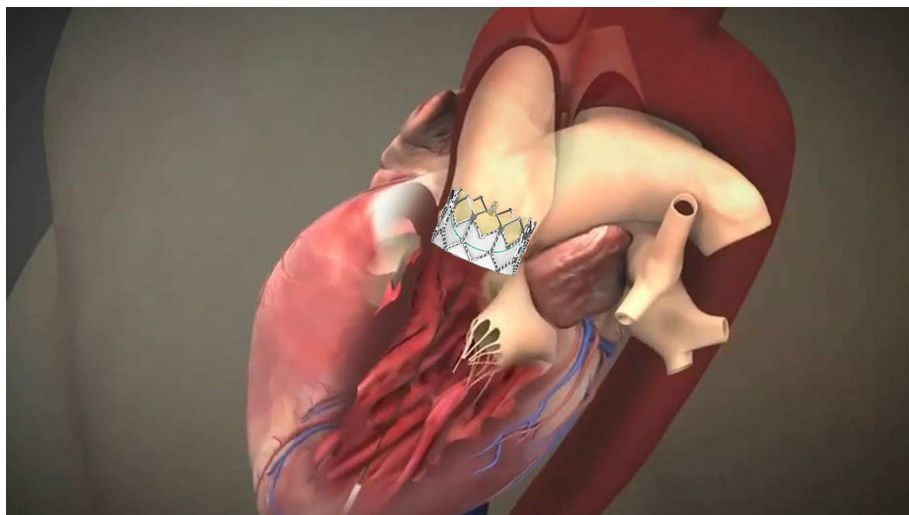


Figure 10: Withdrawal of the device from the heart.

The table 1 presents the comparison of the mini-invasive AVATAR² device and of the resection systems form the state of the art with the functional specifications from chapter 8.

As presented in the table, the AVATAR² device is the only system that meets all the functional specifications. Moreover, it is the fastest resection system to resect the aortic valve.

In 2013, during the development of the AVATAR² device, Edwards Lifesciences Corporation put on the market its new generation of transcatheter heart valve, the Sapien 3, shown in figure 11. In 2013, Binder *et al.* reported that the low-profile of the Sapien 3 valve and its delivery system facilitate fully percutaneous implantation in a broader range of patients with the potential for more accurate positioning and less paravalvular regurgitation.



Figure 11: Edwards Sapien 3. The inflow of the valve is covered by an outer polyethylene terephthalate cuff, which enhances paravalvular sealing [151].

Table 1: Comparison of the resection systems from the state of the art and of the AVATAR² device with the functional specifications.

	Laser [131–135]	Water stream [136]	Sliding tubes [130]	Nitinol blades [78, 123, 137, 138]	StapAVR [139]	AVATAR ²
F1. Resect the aortic valve	✓	✓	✓	✓	✓	✓
F2. Collect the resected debris	✓	✓	✓	✓	✓	✓
F3. Implant an endo valve	✗	✗	✗	✗	✓	✓
F4. Hold the aortic valve	✓	✗	✗	✗	✗	✓
C1. Off-pump procedure	✗	✗	✓ ^a	✗	✓ ^b	✓
C2. Ensure patient safety	✗	✗	✓	✓	✗	✓
Expandable system	✓	✓	✓	✓	✗	✓
Duration of the resection (in seconds)	330 ± 138 ^c	360 ± 144	< 240 ^d	49.7 ± 15.0	90.1 ± 18 ^e	16.52 ± 7.11 ^f

^a A temporary valve was implanted during the procedure.

^b A TVIC system was used during the resection.

^c The resection time is given for one leaflet.

^d The resection time is given for non calcified porcine aortic valve.

^e The resection time is given for silicone-based artificial aortic valve.

^f The resection time is given for the manually actuated device used during open heart surgery.

Because of this new valve, designed to drastically improve or eliminate the current known issues of TAVI, the initial demand from the surgeon, *develop an integrated device to resect the aortic valve and to implant an endoprosthesis through a minimally invasive beating heart surgery*, is partially answered. Indeed, the aortic valve is not resected, but the PVL are decreased and a fewer number of pacemakers is implanted after the implantation of the Sapien 3 valve. But, the use of the open heart surgery AVATAR² device stays relevant because it decreased the duration of the CPB and is less traumatic for the patients.

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Part V

Appendices

Appendix A

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A first patent has been filed on the 19th of September 2013 with the reference WO 2013/135792 [11]. The front page and the claims are given hereafter.

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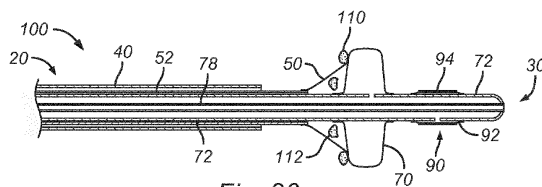


Fig. 36

(57) Abstract: A device (100) for the excision of a heart valve via a percutaneous route having a proximal (20) and distal (30) end, comprising an expandable cutting instrument, ECI, that forms a receptacle in the open configuration for receiving, compacting and containing the excised heart valve, an expandable cutting block, ECB, and a displacement mechanism (5, 6) for adjusting the distance between the ECI and the ECB (70).

CLAIMS

1. A device (100) for the excision of a heart valve *via* a percutaneous route having a proximal (20) and distal (30) end, comprising:
 - 5 - a radially expandable cutting instrument, ECI, (50, 50') capable of radial expansion from a closed (50') to an open (50) configuration,
 - wherein the open configuration provides a receptacle with a void (64) having an aperture (65) at one end,
 - 10 the distal edge of the aperture (65) forming a cutting edge (66) for excision of the heart valve,
 - which receptacle is configured to receive and contain the excised heart valve,
 - wherein the ECI (50') in the closed configuration, is configured for passage through the lumen (42) of a delivery catheter (40),
 - 15 - wherein the ECI (50) is at least partly conical in the open configuration, and
 - wherein the receptacle is configured to compact and store the excised heart valve by contraction of the ECI from the open (50) to the closed configuration (50');
 - an expandable cutting block, ECB, capable of expansion from a closed (70') to an open
 - 20 (70) configuration, disposed adjacent to the cutting edge (66),
 - wherein the ECB in the open configuration (70) provides a support surface (77) to support the heart valve under excision by the ECI (50),
 - wherein the ECB in the closed configuration (70'), is configured for passage through the lumen (42) of the delivery catheter (40);
 - 25 and
 - a displacement mechanism (5, 6) for adjusting the distance between the cutting edge (66) and the ECB (70).
2. A device according to claim 1 wherein the displacement mechanism comprises a first
 - 30 elongate member (52) and a second elongate member (72), wherein the ECI (50) is attached to a distal end (30) of the first elongate member (52) and the ECB (70) is attached to a distal end (30) of the second elongate member (72), which first and second members are slidable relative to each other.

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3. A device according to claim 1 or 2, wherein the first elongate member (52) is provided with a lumen (54) extending between the proximal end (20) and the distal end (30) and is open at both ends, configured for the passage of the second elongate member (72).
- 5 4. Device according to any of claims 1 to 3, wherein the second elongate member (72) is provided with a guidewire lumen extending between the proximal end (20) and the distal end (30) and is open at both ends, configured for the passage of a guidewire.
- 10 5. Device according to any of claims 1 to 4, wherein the ECB (70) comprises an expandable balloon, and the second elongate member (72) is provided with an inflation lumen in fluidic connection with an inflation lumen of said expandable balloon.
- 15 6. Device according to any of claims 1 to 4, wherein the ECB (72) comprises two expandable balloons, an outer expandable balloon (71) and an inner expandable balloon (71') provided within a lumen of the outer expandable balloon (71), and the second elongate member (72) is provided with an inner-balloon inflation lumen (74) in fluidic connection with an inflation lumen of said inner-expandable balloon, and with an outer-balloon inflation lumen (73) in fluidic connection with an inflation lumen of said outer-expandable balloon.
- 20 7. Device according to any of claims 1 to 6, wherein the cutting edge (66) points in a distal (30) direction and the support surface (77) points in a proximal (20) direction.
- 25 8. Device according to any of claims 1 to 7, wherein the ECI (50) comprises an expandable cone (500) having a sheet of material comprising a geometric shape of an annulus segment.
- 30 9. Device according to claim 8, wherein the ECI (50) comprises an expandable cone (500) having a sheet of material comprising a geometric shape of an annulus segment wherein the expandable cone is configured to transition from the open to closed configuration by rolling the annulus segment into essentially a cylindrical shape.
- 35 10. Device according to claim 9, incorporating the features of claim 2, wherein said rolling actuated by the rotation and proximal displacement of the first elongate member (52) relative to the delivery catheter (40).

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11. Device according to any of claims 1 to 10, wherein the ECI (50) and ECB (70) in mutual contact form a closed debris-impermeable receptacle formed by the support surface (77) of the ECB co-operating with the receptacle aperture (66).

- 5 12. Device according to any of claims 1 to 11, further comprising an implant deployment unit, IDU (90), comprising a replacement heart valve, which IDU (90) configured to deploy the replacement heart valve upon actuation.

- 10 13. Device according to claim 12, wherein the IDU (90) is operatively attached to the second elongate member (72), distal (30) to the ECB (70).

14. Device according to claim 12 or 13, wherein the IDU (90) comprises an expandable balloon around which the replacement heart valve is disposed, and the replacement heart valve is balloon deployable.

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15. Device according to any of claims 12 to 14, wherein the distance between the IDU (90) and the ECB (70) is fixed.

Appendix B

Patent EP16160156.2

A first patent application has been filed on the 14th of March 2016 with the reference EP 16160156.2 [12]. The claims are given hereafter.

Claims

1. A device (100) for excision of a heart valve comprising:
 - a first (120) and second (140) clamping element in mutual sliding relation, each having an annular clamping surface (122, 142) which annular clamping surfaces (122, 142) mutually co-operate to form an annular clamping region (166) configured for clamping a heart valve annularly, and
 - a slidable cutting element (160) slidable with respect to the annular clamping region (166) configured to circularly excise the heart valve, wherein the slidable cutting element (160) is displaceable within an annulus of the annular clamping zone region (166).
2. The device (100) according to claim 1, wherein the second clamping element (140) comprises a cap (146), which cap (146) comprises a void space configured for retention of tissue debris.
3. The device (100) according to claim 1 or 2, wherein the first clamping element (120) comprises a hollow tubular member (121).
4. The device (100) according to any of claims 1 to 3, wherein the slidable cutting element (160) and second clamping element (140) mutually co-operate to form a first closed container for retention of tissue debris.
5. The device (100) according to claim 4, wherein the first (120) and second (140) clamping elements mutually co-operate to form a second closed container for retention of tissue debris, wherein the first container is disposed within the second container.
6. The device (100) according to any of claims 1 to 5, wherein one of the first (120) or second (140) clamping elements is configured to fittingly receive at least part of the other of the first (120) or second (140) clamping elements.
7. The device (100) according to any of claims 1 to 6, wherein the slidable cutting element (160) is disposed on a circular edge of a cup-shaped body configured for retention of tissue debris.
8. The device (100) according to any of claims 1 to 7, wherein the first clamping element (120) is attached to a first elongated tube (124), the slidable cutting element (160)

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is attached to a second elongated tube (164) arranged within a lumen of the first elongated tube (124), and the second clamping element (140) is attached to a longitudinal member (144) arranged within a lumen of the second elongated tube (164).

- 5 9. The device (100) according to any of claims 1 to 8, further comprising a heart valve balloon catheter (240) for deployment of an expandable heart valve (260).
- 10 10. The device (100) according to claim 9 further comprising the features of claim 8, wherein the heart valve balloon catheter (240) is substantially disposed within a lumen of the longitudinal member (144).
- 15 11. The device (100) according to any of claims 1 to 10, wherein the first (120) and second (140) clamping elements and the slidable cutting element (160) are each expandable in a radial dimension.
- 20 12. The device (100) according to claim 11, wherein the first (120) and second (140) clamping elements and the slidable cutting element (160) are each radially expandable compliant members biased in an open configuration.
- 25 13. The device (100) according to claim 11 or 12, further comprising a deployment catheter (180), wherein the first (120) and second (140) clamping elements and the slidable cutting element (160) are retractable into a lumen of the deployment catheter (180).
- 30 14. The device (100) according to any of claims 1 to 10, wherein the first (120) and second (140) clamping elements and the slidable cutting element (160) are each radially non-expandable.
15. The device (100) according to any of claims 1 to 10, wherein the first (120) and second (140) clamping elements and the slidable cutting element (160) are controllably radially expandable, optionally the respective radii being lockable.

Appendix C

Procedural data of the clinical trials

All the collected procedural data for the eight resections are given in table 1.

Table 1: Procedural data for the eight resections.

Criteria	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Mean	SD
Echocardiographically aortic annulus diameter (in mm)	28	24	25	26	28	27	25	26	26.13	1.46
Aortic annulus diameter measured with cusp sizer (in mm)	29	25	27	27	27	27	27	27	27.00	1.07
Handling of the device through the aortic valve	10	10	10	10	10	6	10	10	9.50	1.41
Setting of the device	10	10	10	10	10	10	10	10	10.00	0.00
Deployment of the system	10	10	6	10	10	10	10	10	9.50	1.41
Visual aspect of the aortic annulus after resection	10	8	8	8	6	10	10	10	8.75	1.49
Debris collection	10	10	8	10	10	10	10	10	9.75	0.71
Aortic wall damage	10	10	10	10	10	10	10	10	10.00	0.00
Mitral valve damage	10	10	10	10	10	10	10	10	10.00	0.00
Myocardial damage	8	10	10	10	10	10	10	10	9.75	0.71
Aortic annulus damage	10	10	10	10	10	10	10	10	10.00	0.00
Visual aspect of the resection edges	10	8	8	9	6	8	10	10	8.63	1.41
Visual aspect of the resection cone and blade	10	8	8	8	7	10	3	8	7.75	2.19
Visual aspect of the resected and collected leaflets	10	10	10	10	10	10	10	10	10.00	0.00
Global satisfaction of the surgeon	10	8	8	10	7	9	10	10	9.00	1.20
Resection time (in seconds)	25.16	12.24	26.00	9.00	23.24	10.24	15.03	11.24	16.52	7.11