The History of Heart Valves—An Industry Perspective: From Initial Designs to Today

Erin M. Spinner, PhD, Edwards Lifesciences

While heart valves themselves were documented by Leonardo da Vinci in some of his early sketches over 500 years ago, they have only been available for implantation since the 1950s. With the average heart beating 2.5 billion times in a human lifetime, the four valves of the heart must maintain unidirectional blood flow to maximize efficiency of the heart and provide oxygenated blood to the entire body. While valvular disease is usually associated with advanced age, congenital defects can also affect the valves since birth. Valves may lose functionality if they cannot maintain a proper seal or open completely. When any one of the valves is not working properly it may affect a person's ability to exercise or perform day to day tasks. Loss of these activities can result in a dramatic decrease in quality of life and ultimately lead to death. For these reasons, decades have been spent developing and perfecting devices to repair and replace the body's valves when they no longer function properly.

Innovation and development of replacement heart valves has largely focused on the aortic valve which directs oxygenated blood from the left ventricle to the rest of the body. The aortic valve and similar pulmonary valve structure is simpler than the other valves, making it an attractive target for early research. It has greater symmetry and lacks the subvalvular components characteristic of both the mitral and tricuspid valves. The aortic valve, like the pulmonary valve, consists of three leaflets of similar size and shape which are attached to the tubular vessel. In contrast, the mitral and tricuspid valves have leaflets which vary in number and size. These leaflets attach both directly to the wall of the ventricle at the annulus as well as indirectly through numerous chords (See figure 1). While past technologies have focused on the aortic valve, current technologies are being developed to create devices for the more complex valves of the heart.

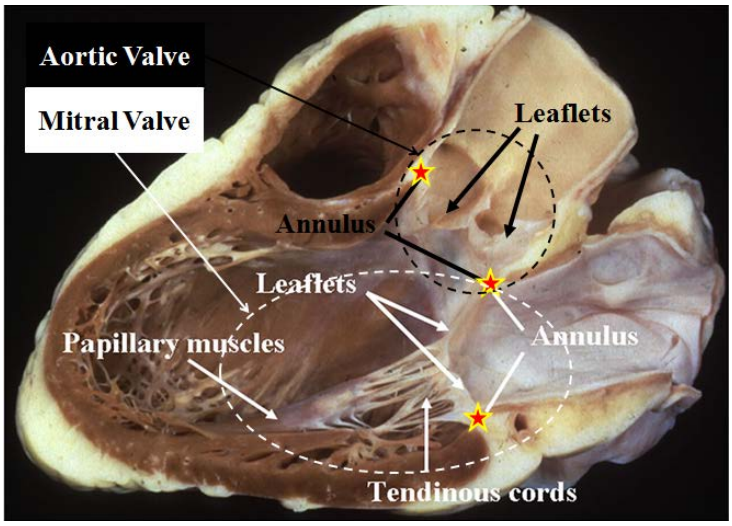

Figure 1: Anatomical comparison between the complexity of the aortic (black labels) and mitral valve (white labels). Note the subvalvular structure including the numerous chords and papillary muscles in the mitral valve. Modified from Andersen et. al (Anderson and Kanani 2007).

Past Technologies

Valve replacement devices can be classified into two categories: whole-valve and prosthetic valves. Whole valves consist of allografts and xenografts, while prosthetic valves are comprised of pericardial (tissue) and mechanical valves. While these valve designs vary in numerous aspects and have evolved over time, the overarching goal has remained the same. The ultimate goal of any replacement being to provide an easily implantable and durable solution which increases blood flow while decreasing the risk of associated complications such as thrombosis. Each type of valve has advantages and disadvantages which are taken into consideration when deciding which device is appropriate for an individual patient.

Allografts are valves transplanted from another human, whereas xenografts are from another species. Cow and pig valves are usually selected for transplant as they best mimic the size and structure of the human valves. Various attempts have been made to transplant mitral valves (Gulbins, Kreuzer et al. 2000, Kumar, Choudhary et al. 2000, Gulbins, Anderson et al. 2002) but the most successful and frequently used valves are pulmonary and aortic valves, which are often used interchangeably due to their similar geometry. Developments in transplanted valves have focused on improving structural support as is necessary when the valve is removed from its native surroundings (See figure 2). Additionally, vast strides have been made in cryopreservation of tissue which maintains high cell viability when thawed (O'Brien, Stafford et al. 1987). The appeal of allograft and xenograft valves suffers from their limited availability of size ranges and technically challenging procedure, in the case of stentless designs. As seen in figure 2 the stentless design requires the physician to remove the entire valve along with a portion of the aortic root and attach the replacement valve(See figure 2).

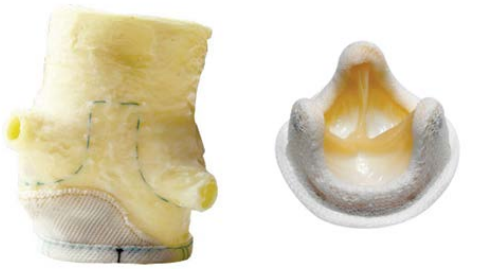

Figure 2: Examples of both a) stentless and b) supported xenografts.

While transplanted whole-valves remain a viable option, prosthetic valves including both mechanical and pericardial tissue valves hold the largest share of the market. The majority of valves implanted today are pericardial tissue valves with approximately 60,000 pericardial valves implanted in the US while only 10,000 mechanical valves were implanted in 2013 (Millennium Research Group 2013). This is ever changing as new improvements are made to designs minimizing or often eliminating the disadvantages.

Both the pericardial and mechanical valves consist of a sewing ring for securing in place, a support structure and leaflets. Mechanical valves are similar in structure to tissue valves, where they differ is the

leaflet design (See figure 3). Mechanical valves have seen the greatest variety in designs including: ball and cage, floating/tilting disc and bi-leaflet.

a) St. Jude Medical Regent b) Carpentier-Edwards PERIMOUNT Magna Ease

Figure 3: Examples of both a) bi-leaflet mechanical and b) tissue prosthetic valves.

While these designs were optimized through geometry, hinge mechanisms and materials, the leading design in today's industry is the bi-leaflet valve. These valves typically outlive the patient and do not need to be replaced; however, they require the constant use of anti-coagulants. This is not appealing to most and not an option for some. This is in contrast to tissue valves which lack the longevity of mechanical valves, but do not require anti-coagulation. Thus tissue valves are often a preferred choice.

In contrast to mechanical valves, pericardial tissue, the sac which lines the heart, is used to construct the leaflets of a tissue prosthetic valve as it has shown to be highly durable. The leaflets are then sewn to the stent support structure which attaches to the sewing ring. This process requires each valve to be hand assembled and sewn as the attachment of the tissue to the structure is crucial to ensure durability. The sewing ring may consist of a silicone band and cloth, which supports tissue ingrowth to the surrounding anatomy to provide future fixation support. While the overall design of the tissue valve has remained relatively unchanged throughout the years and mimics the design of the native aortic and pulmonary valves, the fixation process for the leaflets has been optimized. Various solutions are used to crosslink the collagen fibers and ensure durable leaflet structure. To this day, the process by which tissue is fixed and preserved is a proprietary process guarded by each respective company. As with any design, tissue valves also have limitations with the main issue of tissue valves being durability. Typical tissue valves on the market today can last up to 20 years before the leaflets lose functionality and experience structural deterioration, mainly attributed to calcification of the leaflets (Schoen and Hobson 1985, Schoen and Levy 2005). For this reason a physicians may choose to implant a mechanical valve, although recent studies show no difference in mechanical and tissue valves after 20 year follow-up (Ruel, Chan et al. 2007).

Current Technologies

Over the last 10 years, non-invasive implantation of next-generation heart valves has revolutionized and brought new excitement to the field. Heart valves have traditionally been implanted with direct access and visualization by the surgeon which requires the chest to be splayed open, allowing access to the heart. New advancements can replace a valve with an incision as small as an inch accessing the valve through the femoral vein. This non-invasive approach can be used for patients who are not candidates for open-heart surgery and offer a faster recovery period. The first transcatheter delivery of a valve was

attempted in the 1960s, but it has only recently become accepted into the marketplace as a viable product. Transcatheter technology has been aided by advancements in stent design and non-invasive imaging techniques. The development of transcatheter heart valves showcases the power of a multidisciplinary approach which merges technologies from numerous devices, including coronary stents and balloon angioplasty, and disciplines, interventional cardiology and cardiac surgery, to create a paradigm shifting advance. While there are many advantages to a transcatheter approach, added complexity arises because the valve must now work with the patient's diseased anatomy. In the past the diseased valve was typically removed and for this very reason, the designs and their ability to succeed rely heavily on the patient's anatomy. For example, in the case of a transcatheter aortic valve, it is secured in place by applying an outward force on the surrounding calcium deposits on the native leaflets. An additional obstacle which transcatheter technologies have had to overcome is the loss of direct visualization which open-heart surgery provided. This is especially important when deciding where to place the valve to ensure it is secured while avoiding the coronary ostia, which is crucial to supplying blood to the heart (See figure 4). As a result advancements in non-invasive imaging have followed which allow for real time imaging utilizing multiple modalities, such as echocardiography, to visualize the native anatomy and flouroscopy to visualize the device.

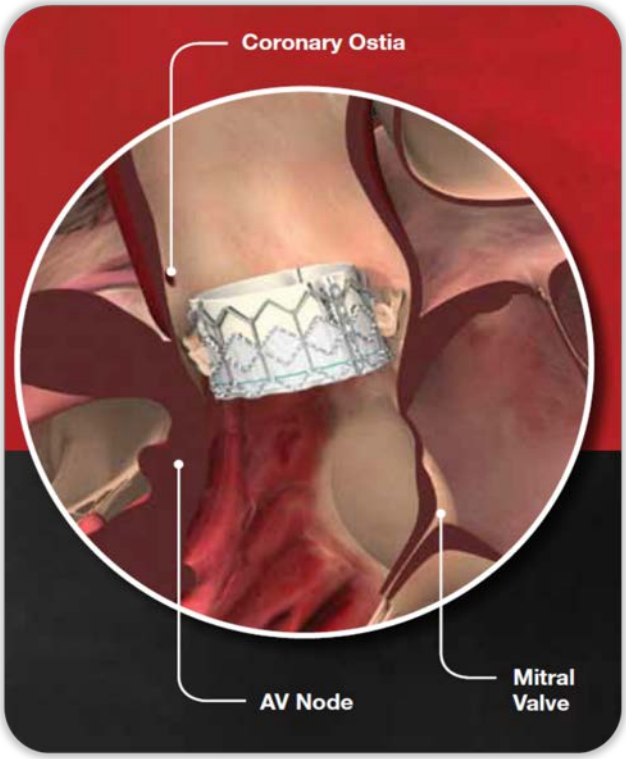

Figure 4: Transcatheter heart valve using the surrounding calcium in the native aortic valve to anchor.

Future Technologies

The valve replacement industry is just now beginning to focus on the other valves in the heart. Additionally, efforts are ongoing to develop devices which aim to work in concert with the native

anatomy for purposes of repairing instead of replacing native valve function. The number of repair procedures is on the rise as compared to replacement procedures which have remained similar from year to year. Recent trends favor repairing the native valve as opposed to replacing it with approximately 32,000 mitral repairs as compared to 21,000 replacement procedures conducted in the US in 2013 (Millennium Research Group 2013).Now is an exciting time for heart valve development whereby companies are pushing the limits, expanding into new areas and succeeding in helping even more patients than ever before.

The introduction of transcatheter heart valves has recently brought new excitement to tissue valves. With the major hindrance in tissue valves being its durability, transcatheter valves are providing a way around this by placing a transcatheter valve inside a defective tissue valve. Thus a physician may choose to place a tissue valve in a younger patient with the idea that they can place another valve in side of needed at a later date.

Valve manufactures are expanding the diseases which they aim to treat through transcatheter technologies. Recent trends have companies aiming to treat mitral valve regurgitation, as this is a much larger market compared to aortic valve pathology. As mentioned before, there are many hurdles in transfer of technology and techniques to the mitral valve as the valve itself is more complex and the patients themselves tend to be in worse overall health with multiple co-morbidities. Technology has advanced to the point where you can begin to attack more subtle pathologies and not just people whose valve is completely failing. Mitral valve repair technologies today aim at correcting the specific pathology. The devices target all aspects of the valve, from replacing the chords, which attach the leaflets to the ventricle, to reducing the size of the annulus, as well as approximating the leaflets. In attempts to replace the native valve, the designs must find an anchoring location as they cannot be sewn in as with traditional surgical replacements. Thus, engineers take advantage of holding on to the native leaflets or the annulus. Due to the direct interaction and reliance of functionality of the native valve, engineers must expand their horizons and become experts on tissue mechanics as well. The frontier of heart valve engineering is less about engineering and more about applying engineering principles in a way that requires understanding of anatomy and physiology instead of dominating. This results in traditional engineers working side-by-side clinicians, biomedical engineers and biologists. It is these collaborations which result in the best heart valve designs.

The future of heart valves is also reliant on new engineering materials. While strides have been made in the past with regards to synthetic materials, especially with the mechanical valve, new biological and polymeric materials are being developed. With the advent of transcatheter valves, the limits of current materials are being challenged. Tissue, polymeric and cloth designs are being pushed beyond what previously thought possible; aiming to increase strength, durability and reduce profile. To reduce the profile of the devices, thinner leaflets are needed, which requires ingenuity to develop a strong but thin material. Additionally, new treatment processes of tissue are being developed and tested. A recent advancement allows valves to be shipped dry no longer requiring the leaflets to be stored in solution. This development once again is driven to support transcatheter valves, allowing the valve to be shipped on the delivery catheter and thus eliminating the need for an engineer to be present at the procedure.

This is a testament to the benefits of new technologies; it forces development beyond what was previously thought possible.

Designing for the Future

Next generation heart valves have brought excitement to the field, but it is also important to understand how we as engineers go from a concept to a life-saving device. Many of the steps and hurdles still exist from the original days of valve development. There are many lessons we do not need to learn again, and new challenges we must address. We must first survey the patient population and identify a need, then develop a concept which can solve the problem. Bench studies as well as animal studies are used in conjunction to test the design functionality and durability. Then the materials are tested to ensure there are no adverse effects which arise as a result of interactions with the body. Along with device development, new imaging protocols are developed to ensure the device can be visualized and delivered to the correct location. Currently a combination of imaging techniques are used including echocardiography, angiography, MRI and CT. This allows the implantation team to visualize both the device and anatomy without opening the chest to provide direct access. These imaging techniques are also used to determine the success of the procedure both at the time of implantation as well as provide useful follow-up to ensure the device's continued functionality.

Initial device development moves much faster these days as existing materials and technologies can be leveraged together. Where development is slowed is the transition from a developmental stage, to implantation in humans. When heart valves were first implanted, regulatory requirements were minimal if nonexistent to review the process for implantation, resulting in much more freedom for innovators. Now extensive testing must be conducted to ensure short- and long-term success prior to implantation. The data is then submitted to a regulatory body and reviewed before implantation can be cleared. Often times, a first-in-human study is conducted in compassionate cases, in which the patients have no other options. These trials are usually limited to about 10 patients. Once these show success a much larger clinical study is initiated, which can include hundreds of patients. From there the data is submitted to the regulatory body to get approval to commercialize the device and make it accessible to the approved patient population. It is when the device is made available for the masses that the device can now fulfill its original goal and save many lives. While this process may slow the time to market it ensures that the patient's safety is the priority.

As with many engineering creations the design process is never complete. Once the device is implanted in humans, improvements are constantly being made to the device based on learning's from implantation in humans. This can be seen with the many design iterations of both mechanical and tissue valves, and now with transcatheter valves. We do our best effort to recreate and simulate the human environment on the bench and in animals, but there are always lessons to be learned and from there improvements. Additionally, as new technologies and innovations are introduced to the market place, even in different industries these are applied to existing devices for optimization as necessary. A great example of this is with biomaterials, as new materials are being developed for orthopedic and other cardiovascular applications, just to name a few, their findings and testing history can be leveraged for the valve area. Our job as engineers is never complete.

Conclusions

The past history of heart valve development has shaped where we are today and paves a road for the future. Advancement of materials will continue to move development forward. While we may have optimized the current designs we are now pushing the borders and expanding into other disease states with next generation designs and approaches. With increased confidence in current device durability, for both mechanical and tissue valves, focus is changing from surgical to transcatheter implants, as well as from replacement to repair devices. As we move to repair devices which are implanted with transcatheter methods we must work even harder to understand the disease state of the valve. Our greatest successes will come when we learn to work in concert with the human body.

References

Anderson, R. H. and M. Kanani (2007). "Mitral valve repair: critical analysis of the anatomy discussed." Multimed Man Cardiothorac Surg **2007**(102): mmcts 2006 002147.

Gulbins, H., I. Anderson, E. Kilian, S. Schrepfer, A. Uhlig, E. Kreuzer and B. Reichart (2002). "Five years of experience with mitral valve homografts." Thorac Cardiovasc Surg **50**(4): 223-229.

Gulbins, H., E. Kreuzer, A. Uhlig and B. Reichart (2000). "Mitral valve surgery utilizing homografts: early results." J Heart Valve Dis **9**(2): 222-229.

Kumar, A. S., S. K. Choudhary, A. Mathur, A. Saxena, R. Roy and P. Chopra (2000). "Homograft mitral valve replacement: five years' results." J Thorac Cardiovasc Surg **120**(3): 450-458.

Millennium Research Group, I. (2013). US Markets for Heart Valve Devices 2014.

O'Brien, M. F., E. G. Stafford, M. A. Gardner, P. G. Pohlner and D. C. McGiffin (1987). "A comparison of aortic valve replacement with viable cryopreserved and fresh allograft valves, with a note on chromosomal studies." J Thorac Cardiovasc Surg **94**(6): 812-823.

Ruel, M., V. Chan, P. Bedard, A. Kulik, L. Ressler, B. K. Lam, F. D. Rubens, W. Goldstein, P. J. Hendry, R. G. Masters and T. G. Mesana (2007). "Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age." Circulation **116**(11 Suppl): I294-300.

Schoen, F. J. and C. E. Hobson (1985). "Anatomic analysis of removed prosthetic heart valves: causes of failure of 33 mechanical valves and 58 bioprostheses, 1980 to 1983." Hum Pathol **16**(6): 549-559.

Schoen, F. J. and R. J. Levy (2005). "Calcification of tissue heart valve substitutes: progress toward understanding and prevention." Ann Thorac Surg **79**(3): 1072-1080.