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Biology 582

And The Beat Goes On…

In this paper, I will be discussing the condition of aortic valve stenosis, a heart defect in which the aortic valve does not fully close during heart contractions. Furthermore, this paper will be focused on the treatment transcatheter aortic valve replacement surgery, which is a new development in the past few years that offers a much less invasive procedure to treat this condition in comparison to the conventional method of open heart surgery to replace the aortic valve.

The Problem: Aortic Valve Stenosis

Imagine this – your doctor informs you that there's something wrong with your heart, something mechanical. Occasionally, you feel slight chest tightness, experience frequent shortness of breath, and often times feel tired. After some consultation, you learn that you have a condition called aortic valve stenosis, a defect of your aortic valve in which it does not fully open and close. The first thing your doctor recommends is open heart surgery; it's invasive, painful, and slightly terrifying to imagine. But what if there was another way to treat this? What if there was a way that didn't involve cutting open your entire chest? Would you do it? It's called transcatheter aortic valve replacement, also known as TAVR, and it is used to replace the aortic valve. As instinct may dictate, you would likely say yes. Who wouldn't choose a less invasive and easier procedure? Open heart surgery has been the go-to method for aortic valve stenosis for multiple years, but with the rise of new technologies designed to ensure patient safety, comfort, and convenience, there is now a better way: TAVR.

More specifically, aortic valve stenosis is a progressive disease that effects primarily subjects in the range of age 80-89 due to obstruction of blood flow through the aortic valve and out of the left ventricle, therefore hindering adequate blood flow out to the rest of the body (Otto, 2014). Not only can this lack of blood flow be life threatening, but the death rate is over 50% for patients with the disease for at least two years (Otto, 2014). Aortic valve stenosis particularly affects the aortic valve of the heart, a trileaflet structure connected to the aorta by the ring-like, fibrous, cardiac skeleton of the valve (Leopold, 2012). The outer layer of the aortic valve is comprised of endothelial cells, which facilitate as a barrier to limit inflammation of the artery by blocking entry of inflammatory cells and rejecting the entry of lipids to avoid their accumulation in the valve; in other words, the endothelial cells aid in maintaining homeostasis within the valve (Leopold, 2012). The valve also contains three internal layers of cells: the fibrosa, the spongiosa, and the ventricularis (Leopold, 2012). These cell layers provide the aorta with elasticity and strength since a matrix is secreted by them containing collagen, elastin, and glycosaminoglycan, therefore aiding in proper mobility of the aorta to pump blood (Leopold, 2012). Disruption of this blood flow can be caused by calcification of the aorta, which will also be discussed in upcoming sections, since this process involves thickening of the leaflets and the aortic walls because of the buildup of calcium deposits, the entry of inflammatory cells, or the formation of lamellar bone (Leopold, 2012). With this buildup on the outermost layer of the aorta, blood flow would be impeded and cause stenotic behavior of the artery, therefore causing a need for treatment (Leopold, 2012). Even though there are currently no medical procedures for suppressing the disease itself, surgical options, such as open heart surgery and TAVR, provide solutions to maintain normal function of the aortic valve (Otto, 2014). Figure I, the aortic valve, ("Aortic Valve with Stenosis", 2015) is pictured below to illustrate the trileaflet structure, its crucial positioning within the heart, and its hindered ability to close fully when aortic valve stenosis is present.

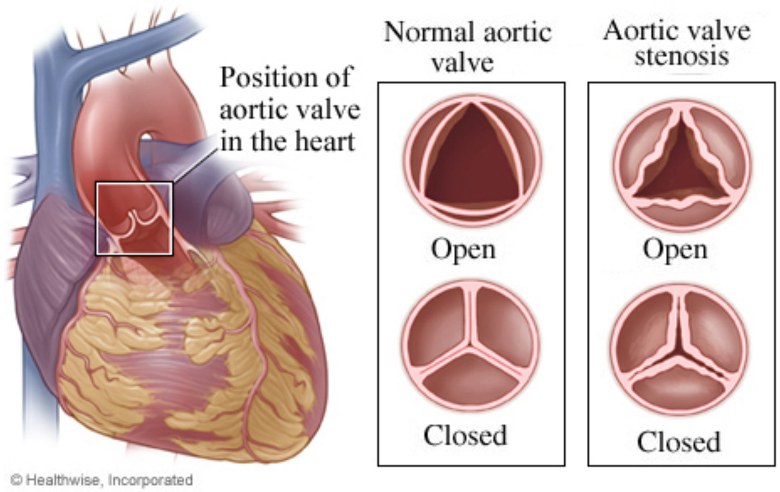

Fig. I: the aortic valve with and without aortic valve stenosis present

Treatment 1: Open Heart Surgery

Until recent technological advancements, the most widely performed method of treatment for aortic valve stenosis was open heart surgery (Coeytaux, 2010). However, certain drawbacks cause consideration for the newer, more beneficial method mentioned above. Open heart surgery is primarily used to treat the same condition as TAVR: improper valve function. At a more specific level, open heart surgery involves creating a somewhat large incision down the chest, folding back the ribs, and working in the chest cavity with the heart exposed and regulated by a heart-lung bypass machine ("Open Heart Surgery", 2016). This machine controls the heart's pumping of blood at a constant rate and serves to propel blood away from the heart; although, while working on the defective valve, the machine stops the heart's beating and allows a surgeon to operate on a still organ ("Open Heart Surgery", 2016). However, this is not the only method. This surgery can be performed while the heart is still beating, but this requires temporary rerouting of the coronary artery during the procedure ("Off-Pump Bypass Surgery", 2017). Both methods consist of the same procedure to fix the valve, in this place it would be the aortic valve, and replace it with a new one. Not only could the new valve be mechanical (made out of metal or carbon), but it could also be made of harvested animal tissues (often times pig valves can be used based on its similarity to human tissue since the body and cells won't react to the replacement as a foreign body) ("Valve Replacement Surgery", 2017).

Not only is this method incredibly invasive and painful, but the recovery period is quite substantial as well. It can take up to a week in the hospital before discharge, multiple weeks for the bone to heal, and if the replaced valve is mechanical, it is mandatory that a patient take a blood thinner for the majority of their remaining life ("Types of Replacement Heart Valves", 2016). This is necessary because blood flowing through and the mechanical valve could become stuck or clotted onto the sides since the makeup of a mechanical is far different from the human tissue and smooth muscle found on the inner layer; the mechanical valves often times contain hinges or cusps that blood can lodge into (“Types of Replacement Heart Valves”, 2016). By taking a blood thinner, the blood is less dense and able to flow through the new mechanical valve easier, and it also aids in preventing clotting on and around the valve or within other valves of the heart and body. However, the risks of this surgery are immeasurable. Not only is it quite possible that someone may experience a heart attack or stroke during the procedure, but it is also plausible that the heart experiences irregular beating. Blood clots forming during the procedure would contribute to a possible heart attack or stroke because of inadequate blood flow and supply to heart regulated by the machine (Dourdoufis, 2017). Another severe risk is the infection of the replacement valve; prosthetic valves are more prone to infection since they are able to easily house bacteria and form vegetations which can leak into the blood stream and up to the brain (Torpy, 2007).

Calcification of the Aortic Valve: The Main Cause of Aortic Stenosis

To refer back to the main cause of this treatment, aortic valve stenosis is the narrowing of the aortic valve, which hinders oxygenated blood flow out of the left ventricle and out to the rest of the body (Butany, 2015). The most common cause of this condition is senile degenerative calcification of the valve leaflets (Karwowoski, 2012). Some of the first signs of calcification at a molecular level is an influx of inflammatory cells, lipid accumulation, and deconstruction of the elastic lamina, or elastic tissue layer, of the valve (Leopold, 2012). Calcium found in the bloodstream also has the ability to infiltrate the leaflets, and, in the case of aortic valve stenosis, restricting their mobility and obstructing the continual flow of blood, its steady velocity, and arterial limberness (Karwowski, 2012). In addition, another factor involved in calcification is the misregulation of BMPs, bone morphogenetic proteins that increase formation of bone and cartilage (Leopold, 2012). Another contributor of calcification is the formation of a collagen sheet, or lamellar bone, on the valve which contains osteoblasts and bone marrow (Leopold, 2012). The Matrix Gla protein, a protein dependent on vitamin-K, aids in preventing calcification by inhibiting the production of these BMPs and therefore lowering the ability for lamellar bone to form (Leopold, 2012). However, with aortic valve stenosis, it has been observed that the levels of the Matrix Gla protein are significantly lower than normal, and, as a result, the inhibition of lamellar bone formation in the valve is not prevented (Leopold, 2012).

Calcification of the aortic valve is a relatively common condition affecting approximately “2-3% of the North American population aged 65 years and older” (Butany, 2015). The condition is slowly progressive. As the aortic valve becomes severely stenotic it can lead to left ventricular failure with resultant congestive heart failure and death (Dourdoufis, 2017). In addition, the fact that this condition seems to be more prevalent in elderly patients (Butany, 2015) signifies that the prevalence of this disease process is likely to rise as a result of increased longevity. As the longevity of our population increases, newer technologies and strategies are welcomed to treat this problem less invasively and with less morbidity.

The New Treatment: TAVR

Luckily TAVR offers these advantages. In regards to the procedure itself, it only consists of a small incision in the upper region of the leg, only about two to three inches long, in which the catheter is inserted, advanced through the femoral artery, and through the heart's aorta (Transfemoral Procedure, 2015). By doing this, easy access to the aorta is created without disrupting surrounding arteries and organs and provides a clear path for the catheter to follow. The catheter is moved up the artery guided by X-ray imaging and an echocardiography machine to ensure correct positioning and routing (Dourdoufis, 2017). This treatment also does not require the use of a heart-lung machine to regulate or stop the hearts beating; the heart can continue to pump blood throughout the body during the procedure, which decreases the risk of sudden cardiac arrest or even death during the operation (Mueller, 2015). In relation to the new valve itself, it is spring loaded. This indicates that a small balloon is expanded once the catheter reaches the appropriate region of the aortic valve where the replacement must be discharged (Dourdoufis, 2017). The purpose of the inflation of the balloon is to push any hardened calcium deposits or excess buildup of debris to the outermost edges of the valve's interior (Bianchi, 2016). This fully allows the valve to return to its original, unobstructed condition to allow sufficient blood flow through the artificial valve.

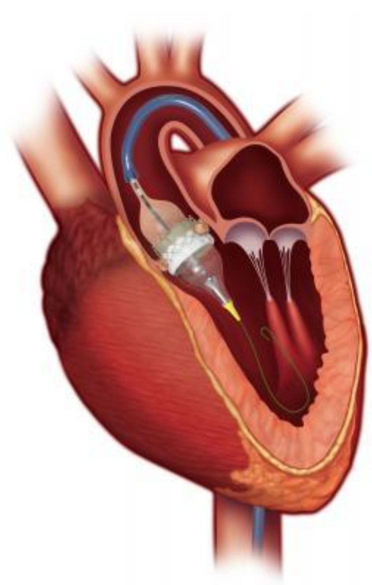

Fig. II: the transcatheter aortic valve placed in the heart

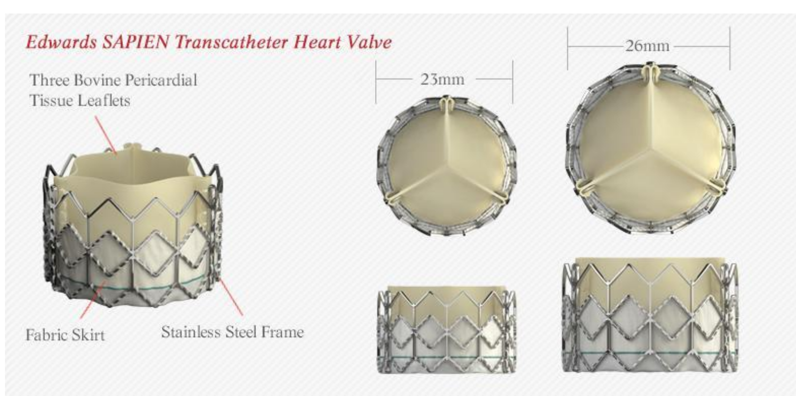

Fig. III: a more detailed image of the specificities of the transcatheter heart valve indicating the fabric skirt, steel frame, and tissue leaflets

Figure II (Sapien 3, 2016) pictures the catheter strung up through the aorta with the new biological heart valve and balloon attached to the end. It shows the inflated balloon, demonstrating where the new valve is placed by the mechanism that performs the action. Figure III (Edwards SAPIEN Transcatheter Heart Valve, 2017) pictures the new heart valve; the birds-eye view shows the biological tissue leaflets that mimic the former, defective aortic valve. It also exhibits the steel frame and fabric skirt that holds the new tissue in place by pushing up against the walls of the existing aorta and reduces the risk of blood leakage around the valve (Htun, 2016; Sapien 3, 2016). All these aspects of the Sapien 3 valve promote the device's technological improvements over the years to facilitate the acceptance of the device by the existing valve and the ability for prolonged sustainment as a working part of the heart.

Setbacks of TAVR

Since TAVR is a newer technology, there are still some reservations taken in regards to the procedure, and it cannot be fully implemented into the realm of cardiology for all patients, according to Dr. Peter Dourdoufis, the Chief of Cardiology at Portsmouth Regional Hospital. Currently, TAVR is only being studied in patients with mostly high and high-moderate risk for open heart surgery as the treatment for aortic valve stenosis. Patients at the highest risk for open heart surgery were offered TAVR as an option instead of open heart surgery, and these cases became part of a trial called PARTNER (The Placement of Aortic Transcatheter Valves) conducted in 2010 (Leon, 2010).

This trial specifically tested the usage of TAVR surgery compared to the standard therapy, open heart surgery, in high-risk patients only with severe aortic valve stenosis and cardiac symptoms (Leon, 2010). To be considered high risk, the diameter of the aortic valve was taken into account, the aortic valve gradient, as well as the velocity of blood flow per second (Leon, 2010). In addition, health factors and cardiac symptoms of the patient, such as diabetes, old age, or failure of other organs such as the kidneys, were taken into account when labeling the high-risk candidates (Dourdoufis, 2017). The study proved that mortality rates were significantly less with the use of TAVR than with open heart surgery; the rate of death after a 1-year follow up for TAVR was 30.7% compared to 50.7% for the standard group (Leon, 2010). To add, the risk of major stroke or death from any cause was proven lower in the TAVR group at 33.0% versus 51.3% in the standard (Leon, 2010). Overall, the PARTNER trial was extremely favored and prompted studies on TAVR procedure to extend into moderate risk patients since it proved successful with high risk (Dourdoufis, 2017; Fornell, 2016). The Sapien 3 transcatheter replacement valve (pictured above) implemented in TAVR was just approved by the Food and Drug Administration last year for moderate risk patients, providing a huge step in the progress of this procedure, since it allows expansion into a larger group of individuals for treatment (Fornell, 2016). It is expected that as more TAVR procedures are conducted, more experience will be gained in relation to the actual surgery and will lead to more technologically advanced methods of implantation of the catheter and replacement valve, therefore increasing the likeliness of this procedure becoming standard (Dourdoufis, 2017).

Risks of TAVR: Vascular Harm, Blood Leakage, and Precision Errors

However, as with open heart surgery, there are still major risks present for TAVR that still must be addressed as advancements continue. One of the largest risks of this procedure is the vascular aspect of it and the possibility of blood vessels or arteries being punctured with the catheter or wires (Dourdoufis, 2017). It is a sizable device, which means that it could cause perforation of the leg or chest artery as it travels up to the aorta, and could lead to interior bleeding of the vessels, especially in weaker, older patients (Dourdoufis, 2017). Another risk could be presented after the replacement valve is actually placed; possible leaking of blood around the valve itself could occur due to the increased pressure around the valve if there was a great deal of calcification to start, and the valve may not be able to form in its entirety, causing a deformation leading to increased blood leakage (Dourdoufis, 2017). This demonstrates that even the advanced construction of the Sapien 3 replacement valve does not guarantee enactment of the valve itself with even the slightest bit of error in formation after placement. It is still extremely necessary to take into account the previous stenotic condition of the aortic valve and its intensity in order to ensure consideration of possible malfunctions and deformations that may occur and alter the outcome of this procedure. The risk of stroke, which occurs if any calcium or cholesterol plaque becomes dislodged due to the positioning of the valve and showers up into the brain, is about 7% risk, but this factor still remains more prevalent in open heart surgery (Dourdoufis, 2017).

Lastly, and most rare, the exact placement of the valve raises the need for extreme accuracy throughout the process, and even the slightest error in mapping techniques could lead to misplacement, therefore effecting how much it extends into the aorta or the correct area for the balloon to expand (Dourdoufis, 2017). Throughout the procedure, a CT scan is performed to ensure proper positioning and mapping of the catheter, but errors are still plausible (Dourdoufis, 2017). The CT scan also determines whether someone is a good candidate for the procedure by identifying the diameter of their arteries, since they need to be of enough width to properly accept the device and facilitate easy threading up the artery to the aorta (Dourdoufis, 2017). It has been shown that the deployment of the Sapien 3 replacement valve minimized risk of dislocation of the device due to the increased strength of the anchorage using the TAVR procedure (Bianchi, 2016); this signifies not only that there is a higher rate of acceptance of the valve but also that the biological valve used for TAVR provides a more permanent and beneficial long term outcome and dislodging of the device is less likely to occur.

TAVR as the Future of Aortic Valve Stenosis Treatment

In time, TAVR should continue to push the envelope on new valve replacement technology, but questions still arise in relation to the device's longevity and value of the procedure, as expressed by Dourdoufis (2017) based on the advancements made thus far. As with the rise of angioplasty, it was an evolution of the procedure, not simply an emergence that then became standard (Dourdoufis, 2017). As with most surgeries, however, it all comes down to experience with the techniques to really hone in on the specifics of the operation that make it so beneficial and useful. However, even with these reservations, TAVR is a more preferable option to treat aortic valve stenosis. The advantage of the entirety of the chest cavity staying closed, the benefit of a biological catheter, and the decreased recovery time and death rate encompass some of the main reasons why TAVR should be more widely utilized. It's extremely innovative and cutting edge, and as the conduction of studies and familiarity with the procedure augments (Sokalskis, 2017), the usage and exposure of it is likely to exceed expectations (Dourdoufis, 2017).

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Sapien 3 valve used in TAVR procedure pictured in the aortic valve. *DAIC*, daic.s3.amazonaws.com/s3fs-public/styles/content_feed_large_new/public/field/image/X0000_Edwards_SAPIEN%203%20Commander_Anatomical_2.jpg?itok=QcdwbJFS. Accessed 7 Feb. 2017.

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