Engineering Heart Valve Treatment Strategies for Tomorrow

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Heart Valves – Pure Mechanics

Heart valve disease is the 3rd leading cause of cardiovascular mortality and morbidity in the US and with current aging trends, will continue to increase in prevalence in the coming years. The historical approach to valve disease treatment is open-chest, surgical replacement. While this tried-and-true approach is very good at treating a large portion of the population, it is not ideal for very young or very old patients. Heart valves are in many ways like the simple check valves that are in your household plumbing system and automobile engines – they are controlled by inertial fluid forces and assure that flow is unidirectional. Unlike toilets or cars however, our hearts are never idle or stop pumping blood, meaning the valves must work to near perfection for ~3.5 million cycles per year or ~3 billion cycles over a 75 year lifetime.

Heart valve biomechanics has been an active research field for over 50 years (Sacks, Merryman et al. 2009) and more recently, heart valve mechanobiology has become a topic of great interest (Merryman 2010). The distinction between biomechanics and mechanobiology is subtle (Merryman and Engler 2010), but essentially, biomechanics is the application of the principles of mechanics to study living organisms and their components, while mechanobiology is the application or analysis of the role of mechanical forces in eliciting a molecular response, leading to a change in form and/or function that can be quantified. In the past decade, it has become quite apparent that heart valve disease is not simply a wearing out of the valve but is more accurately an active biological process that can possibly be understood and exploited in various ways.

Congenital and Degenerative Heart Valve Disease

Heart valve disease comes in two forms – congenital and degenerative. Congenital valve disease is a malformation that occurs *in utero* that can be detected days after birth or not until decades later when the patient become symptomatic. Degenerative valve disease is a collective term describing age-related valve disease and occurs later in life, typically beginning around 65 years of age and increasing in prevalence with each passing year. For these two patient populations, different engineering strategies are needed.

For those with congenital valve disease, they often need intervention as infants or during adolescence. The ideal solution would be a living tissue engineered heart valve that could be grown in a laboratory and implanted surgically, which would grow with the patient. Currently, infants receive size-matched biosprosthetic valves (porcine valves or bovine pericardium) that are chemically fixed and are thus not alive. This approach is very limited because as the patient grows (quite rapidly), their implanted valve does not grow and they require reoperation; some patients need up to four open-chest procedures to get to adulthood and the mortality rate for the 4^{th} open chest procedure is ~50%.

Degenerative valve disease has been treated with improved effectiveness over the past 50 years with either bioprosthetic or mechanical valves through open-chest procedures. While this is an effective solution for many cases of valve disease, it is not a desirable option because the morbidity associated with an open-chest procedure is significant – it is estimated that it takes up to a full year for a patient to return to their previous level of activity. As such, there has been concerted efforts in recent years to develop non-surgical approaches for adult patients.

Tissue Engineering

The realization of a tissue engineered heart valve that is capable of growing with pediatric patients and would prevent reoperations has been pursued for the past 20 years (Shinoka, Breuer et al.

1995, Breuer, Shin'oka et al. 1996). In 2000, a trileaflet valve was grown in the laboratory (by combining autologous cells and a non-woven felt scaffold) and implanted into a large animal model, which survived for 20 weeks and afterwards looked very similar to the native valve from the sheep (Hoerstrup, Sodian et al. 2000). It was expected that this was the breakthrough needed to translate engineered valves to the clinic, but that has not been the case and no other studies have been able to replicate the success seen in this seminal report. Since this time, there has been a concerted focus on off-the-shelf scaffolds that are easy to use/mold and closely match some of the mechanical properties of native heart valves (Engelmayr, Hildebrand et al. 2003, Engelmayr, Rabkin et al. 2005, Engelmayr, Sales et al. 2006, Merryman, Engelmayr Jr et al. 2006) and also of novel hydrogels that are much better at controlling the behavior of the valve cells (Kloxin, Kasko et al. 2009, Wang, Haeger et al. 2012, Sewell-Loftin, DeLaughter et al. 2014). In addition to the material source used, it is quite unclear what cell type should be used to populate a tissue engineered heart valve; valve interstitial cells are unlike most fibroblasts and are very specialized (Filip, Radu et al. 1986, Roy, Brand et al. 2000, Taylor, Allen et al. 2000, Taylor, Batten et al. 2003, Rabkin-Aikawa, Farber et al. 2004, Yperman, De Visscher et al. 2004, Merryman 2008), while valve endothelial cells are distinct from vascular endothelial cells (Butcher, Penrod et al. 2004, Simmons, Grant et al. 2005, Butcher, Tressel et al. 2006, Young, Wheeler et al. 2007). Unfortunately, tissue engineered heart valve work started off fast with early success, but today, it is still quite a long way from being implemented clinically.

Percutaneous Strategies

While a tissue engineered heart valve does require an invasive, open-chest procedure, there has been considerable work recently at developing shorter-term solutions for adult patients, namely transcatheter aortic valve replacement. This strategy was initially created for patients that were deemed non-operable candidates for open-chest surgery, but the early success has been encouraging and the procedure will likely expand to patients that are able to undergo open-chest surgery.

The mitral valve, unlike the aortic valve, undergoes a unique pathology called mitral valve prolapse in which the leaflets lose their ability to close properly and billow back into the atrium, causing regurgitant blood flow. Mitral valve prolapse is often treated with a percutaneous strategy called the Alfieri technique or 'edge-to-edge' repair (Alfieri and Maisano 1999, Alfieri, Maisano et al. 2001, Alfieri, De Bonis et al. 2004, George, Varghese et al. 2011), but many more are currently being developed. Among these are the use of radiofrequency energy to shrink the leaflets and implantation of a 'purse string' mechanism around the valve to reduce orifice area (Boronyak and Merryman 2012, Tommaso, Fullerton et al. 2014).

Pharmacological Intervention

Historically, aortic valve disease, particularly calcification, was thought of as an idiopathic phenomenon and likely associate with atherosclerosis; however, it is now believed that calcific aortic valve disease is an active mechanobiological disease process and can therefore be potentially targeted with drugs. The contractile machinery of the valve interstitial cells that leads to calcification is of particular interest (Walker, Masters et al. 2004, Merryman, Huang et al. 2006, Merryman, Youn et al. 2006, Merryman, Lukoff et al. 2007, Merryman, Bieniek et al. 2009, Yip, Chen et al. 2009, Yip, Blaser et al. 2011, Fisher, Chen et al. 2013, Hutcheson, Chen et al. 2013), and there are multiple potential targets that may slow or reverse the progression of aortic valve disease (Hutcheson, Aikawa et al. 2014), including the serotonergic pathway that was involved in some drugs *causing* heart valve disease in late 1990s and mid 2000s (Hutcheson, Setola et al. 2011, Hutcheson, Ryzhova et al. 2012).

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