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The Role of Tissue Engineered Products in Cardiac Regeneration - Current Trends and Future Direction

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Abstract: *This paper aims to talk about current tissue engineered (TE)valves in clinical use. As TE valves are still considered unconventional, bioprosthetic and mechanical valves will also be discussed in this literature review. This will also be done to exemplify how TE valves overcome the faults of the pre-existing, more common valves. Tissue engineering has been acknowledged as a viable method for decades. Over the years, many in vitro experiments and clinical animal trials have been carried out, showing promising results. Although there are numerous TE products on the market which are successful upon implantation, it has been challenging to develop a TE heart valve that has longevity within a patient's body and does not deteriorate due to mechanical wear. Several clinical trials using TE heart valves, have ended in failure. However, the unique and desirable properties offered by these valves, namely the fact that they are highly biologically compatible with the physiological make-up of humans, combats the issues posed by the valves currently available, and makes their further exploration, vital.*

Keywords: *Tissue engineered valves, bioprosthetic, mechanical valves, in vitro, mechanical wear.*

1. INTRODUCTION

Heart valvular disease impacts one or more (multiple valvular disease) of the heart valves. Valve deterioration can occur due to stenosis where valves narrow, restricting the volume of blood flow. Valvular disease can also be caused by valvular prolapse where the valve flaps slip out of place, causing backflow or regurgitation of blood. Valve replacement is used if other proceduresare unsuccessful[1].

Heart valve surgery has evolved greatly from its introduction in1914, when the firstclosed heart procedure was used to repair a stenosed valve2. In 1952, the first valve replacement option- the "sutureless valve" was invented by Dr Charles Hufnagel. He used this in a heterotopic valve replacement in which the prosthetic was inserted into the descending aorta of a patient suffering from aortic regurgitation3. A surgeon and an engineer, Dr Albert Starr and Lowell Edwards joined forces in 1957 and developed the first mechanical valve replacement that was continuously met with success upon implantation4. Dr Starr was the first to perform a mitral valve replacement using his own mechanical prosthesis (the Starr-Edwards ball-valve). A written record of how this surgery went, shows that some of the challenges faced, are stillrelevantnow5. One of these, is the dilemma of whether treatment of valve disease should be executed via physical means or via replacement procedures. Other relevant challenges are that of durability and anticoagulation. One problem that has improved since Dr Starr's surgery in 1960, is the mortality levels during surgery6. The properties of mechanical valves that cause them to increase antigenicity within the body, are still present and are now overcome by the use of anticoagulation. As this review will reveal, tissue engineered (TE) valves are the most hemodynamically suitable and biocompatible for the use of human valve replacements.

Now, valve replacements are typically mechanical, bioprosthetic, or donor. Mechanical and bioprosthetic valves are more common because donor options such as homografts/autografts and allografts are more burdensome during reoperations and arehard to find[7]. TE valves are fresh, tissue-derived valves that can grow in response to stimuli produced by the body, like native valves do. Neither mechanical nor bioprosthetic valves can do this, making them inappropriate for the pediatric population[8]. As foreign components (carbon, metal, polymer) constitute mechanical valves, they need ongoing anticoagulation[9], due to them causing risk of bleeding. Despite the use of anticoagulants, thromboembolisms

can occur[7]. Due to allogenous and xenogenous bioprosthetic valves potentially causing immune responses, thrombosis, and undergoing deterioration (due to their lack of strength), reoperation rates are high. Although autologous bioprosthetic valves (like the pulmonary autograft from the Ross procedure), would not trigger immune reactions due to them possessing an identical genomic compositionas the patient, the procedure is complex, demanding inevitable reoperations[9]. A study found that the Ross' procedure resulted in repeated aortic valve replacement[10]**.** What makes theprocedure complex, is that a replacement valve needs to be surgically inserted into the location the pulmonary autograft was.

Using tissue engineering, synthetic scaffolds (derived from polymers or hydrogels), can be seeded with autologous cells. Assuring outcomes were seenwhen these scaffolds were cultivated in bioreactors before the TE valves were put into animals[9]**.** This method combines the strength and durability of the mechanical valve, the non-immunogenicity of the autologous valves, and the lack of anticoagulation in bioprosthetic valves.

2. NATURAL VS SYNTHETIC BIOMATERIALS

The term 'biomaterials' encompasses all the devices that will be mentioned in this article. According to the National Institute of Biomedical Imaging and Bioengineering, biomaterials "may be natural or synthetic and are used in medical applications to support, enhance, or replace damaged tissue or a biological function."[11]Synthetic materials include metals, polymers and ceramics, while natural materials include tissues that originate either from the same individual (autologous), same species (allogenous), or a different animal species (xenogenous). Biocompatibility refers to the ability of an implanted device which is derived from biomaterials, to settle into its new environment without instigating harmful immune responses. The gold standard for a biomaterial to be inserted into a patient is that, it should be durable, powerful, and pliable enough to endure 2 billion cardiac cycles in a standard person's lifetime. Another crucial factor of biomaterials in deciding whether they are ideal for implantation, is their biological properties. These ideal properties would be "anti-thrombogenicity, noncalcification, hemostasis, nonimmunogenicity, and endothelialization capability." Unfortunately, due to synthetic biomaterials such as mechanical valves possessing components that are foreign to the body, non-immunogenicity and anti-thrombogencity are not an option, leading to, in this case, patients requiring constant anticoagulation medication due to increased risk of blood clot emergence. Another danger posed by synthetic biomaterials is their possibility of biodegrading within the body if they are capable of doing so. This problem is not seen in autologous tissue, as it is nonimmunogenic, due to its genome being identical to the recipient. However, the process of obtaining the quantity of tissues required, as well as the question of whether the patient is well enough to endure the extraction of a large amount of their tissues, poses an issue. A way to maximize on the individual strength of each biomaterial so that it is formed into a useful product, is to combine several biomaterials into a "composite".

3. MECHANICAL VALVES

Mechanical valves are renowned for being physically hardwearing, making them good candidates for mitral valve replacements, as the mitral valve has to be particularly strong to endure the high blood pressure in the left heart. However, as aforementioned, they need ongoing anticoagulation to prevent blood clot formation, which would otherwise result in thromboembolism.They also need hemorrhage control due to the excess anticoagulants in the bloodstream[12]. The collective danger of thromboembolisms is has been shown to be higher than surgical mortality during reoperations in patients receiving mechanical valves. Surgeons are hence leaning towards using bioprosthetic valves for their patients, even though this insinuates a higher reoperation rate[8]**.** One recent study however, showed that the variation in occurrence of post-operative embolisms in patients with bioprosthetic valve implants compared to those with mechanical valves, was not statistically significant. This study also revealed that mechanical valve implants in fact allowed patients with infective endocarditis to have a better trajectory[13]**.** Another comparative study suggested that the superior hemodynamic capabilities of the mechanical valve as well as the anticoagulant's ability to prevent thromboembolism formation, amounted to better results in patients than if they were to have bioprosthetic valves[14]**.** Although lifelong anticoagulation may be an added burden to

some patients, for patients who are already compelled to consume anticoagulants for other health issues, mechanical valve implants are a sensible choice[1]. Nevertheless, the dosage of anticoagulants required to prevent blood clot formation (in the presence of a mechanical valve), can often lead to severe internal and external blood loss, resulting in "death, stroke, reoperation, and hospitalization." Further to the adverse health impacts lifelong anticoagulation yields, are the adverse lifestyle impacts, which can harm some people-those from a lower socioeconomic background-more than others. For example, patients have to constantly get their blood drawn, and have their anticoagulant levels recorded. Their eating habits and exertion levels are altered. Individuals from poorer areas, may have to deal with high prices of medication, as well as commuting to the nearest hospital which may be far away[7]. Another category of patients who would be disabled by mechanical valves, are pregnant women. Due to the dangerous side effects of anticoagulants, miscarriage rates can vary between 20-70%, depending on the type of anticoagulation treatment being administered. Furthermore, the rate of severe heart issues that arise in pregnant women due to mechanical valve implants is 20%, around double that of bioprosthetic valves. The collection of disadvantageous complications mechanical valvular prostheses have had on patients, may be what caused the drastic decline of their implantation in the ten years leading up to 2008, from 70% to 30%[1]. Ultimately, the longevity of mechanical valves is downplayed by the fact that they necessitate lifelong anticoagulation, which brings with it unfavorable repercussions to the quality of one's health and overall lifestyle[15].

4. BIOLOGICAL (TISSUE) VALVES

A study by Brown and colleagues released in 2009, revealed that between the years 1996 and 2006 there had been a significant shift from mechanical to bioprosthetic valve replacements. This was due to lower mortality associated with aortic valve surgeries[16], amongst other reasons. Another study showed that between 1997 and 2014, the use of bioprosthetic valve replacements, in the aortic position had increased from 14% to 47%[17]. Mitral valve replacement done with a bioprosthetic valve instead of a mechanical valve was shown to reduce in-hospital mortality[18].

Biological valves are composed of tissues extracted from porcine valves or bovine pericardium[19]. They can also be composed of tissues grafted from another human (autograft). The porcine and bovine tissues are usually cross linked in glutaraldehyde which is supposed to prevent deterioration by decreasing their immunogenicity. If the fixation of the porcine and bovine tissues did not occur, then upon the implantation of the bioprosthetic valve, antigenicity would rise, causing an immune reaction. Due to the "residual toxicity of glutaraldehyde" upon implantation, cells do not elicit any immune reaction with the glutaraldehyde-fixed valve. Additionally, these animal tissues are also exposed to other chemicals in order to help them avoid calcification, and to consequently enhance their durability[8]. Although cross linking the valvular animal tissue in low concentrations of glutaraldehyde is vital, this is what gives bioprosthetic valves arguably their most unfavorable characteristic: structural deterioration. This can only be undone by treating the scaffold with anti-mineralization treatment. Hence, although lifelong anticoagulation is not required for these valves, their major flaw does not allow for the same longevity provided by mechanical valvular prosthesis. Although there are a multitude of other valves in clinical use (including stented and stentless), upon viewing their benefits and disadvantages, it is justifiable to claim that human valves would be hemodynamically the best suited to serve as valve replacements. However, these are scarcely available, and although the anatomical structure of these are ideal for humans, immunogenicity, leading to valve deterioration, will still be a problem if the valve is obtained from another body (and hence contains a different genotype)[20].

Bioprosthetic valves are beneficial as they maximize on the strength of human valves, that is, they are hemodynamically similar to human valves, while they minimize on the immunogenic disadvantage of human valves due to their glutaraldehyde fixation which reduces their immunogenicity[12]. Nonetheless, the durability of bioprosthetic valves remains stunted due to the calcification and degeneration they undergo once implanted. Degeneration of bioprosthetic valvular implants is sped up in children as they demand a more vigorous hemodynamic output. This is also the reason why these tissue valves

degenerate at a faster rate in the mitral location compared to the aortic location[1]. As a result, bioprostheses are elected when their estimated longevity is greater than the patient's life expectancy[7]. For this reason, these valves are mostly recommended to those over the age of 60 (in a western population), whose hemodynamic demand is low. In patients under 40, at 10 years following implantation of a bioprosthetic valve, the rate of deterioration is 20%, which is quadruple the rate of patients over 60. Another group of people who should carefully consider choosing a bioprosthesis, are pregnant women. The hemodynamic stress placed onto a bioprosthesis during pregnancy, reduces its longevity, and it is thus recommended that the patient should get impregnated within five years of the valve replacement surgery[1]. Furthermore, in conditions which significantly increase a patient's mortality, such as end stage renal failure, the bioprosthetic valve is likely to outlive the patient, so it would be an appropriate option[21]. In developing countries where the average life expectancy is lower, a biological valve may be recommended at a younger age[7]. Finding a way to clinically reduce calcification in bioprosthetic valves, can be game changing when patients elect which type of valve replacement is most suitable for them[16].

As mentioned in the previous section, patients suffering from conditions which require them to take anticoagulation therapy permanently, may believe it is justifiable to get a mechanical valve as anticoagulant consumption would not be an added issue. However, it has been found that in patients with a persistent case of atrial fibrillation (a condition which requires constant anticoagulation), simultaneous biological valve implantation and ablative surgery can restore the patient to sinus rhythm[21]. Patients have a 75-90% chance of patients maintaining the sinus rhythm six months after surgery.

Due to tissue valves being more susceptible to structural deterioration, their reoperation rate is higher than mechanical valves in both the mitral location (50% for tissue valves compared to 29% for mechanical valves) and the aortic position (30% for tissue valves compared to 10% for mechanical valves)[1]. Despite porcine valves being chemically reinforced (through glutaraldehyde fixation), they are still not as mechanically hardwearing as allograft valves, which last longer despite essentially being dead tissue and being void of chemical association[22]. Furthermore, at one time, it was believed that porcine valve implants were optimal in terms of longevity, however through clinical use of the Carpentier-Edwards pericardial valve, these were deemed to be better in that aspect[23]. Interestingly, the risk posed to middle-aged patients by reoperations of bioprosthetic valves, and in bleeding caused by mechanical prostheses, is the same[7]. Additionally, the risk of death associated with reoperations has decreased due to the development of new and improved bioprosthetic valves[21]. The "valve-in-valve transcatheter aortic/mitral valve replacement" has been carried out for the aortic position, but in this position, this method has been linked with a higher mortality[24]. Only one study attempted a mitral valve replacement using this procedure[19]. However, overall this procedure in the future, will supposedly be a way to further reduce the risk of mortality in reoperations, allowing patients to consider their options more carefully[7]. In addition to this advantage, stentless bioprosthetic valves are available which lack metal scaffolding, offering a wider diameter through which blood can flow. Due to the lack of metal, the antigenicity of these products are lower than their stented counterparts[1]. A vital feature absent in bioprosthetic valves, possessed by TE valves, is that due to them being stored and undergoing fixation, they are unable to grow and adapt[20] with the patient's physiology.

5. Biological and Mechanical Prosthetic Valves

There are some similarities which both biologic and mechanical valves share, which will make it simpler to understand why TE valves are required. To determine which of the two valves is better than the other, is a difficult task as the number of "large, multi-centered, randomized clinical trials" are few[7]. The most recent of these rare studies was carried out between1995-2003. It showed that bioprosthetic and mechanical valves in the aortic position yielded the same mortality levels[25]. One of the major causes for a faster onset of structural valve deterioration and calcification (in the case of bioprosthetic valve implants), in both prostheses, is younger age[26]. Pediatric patients being considered for valve replacement with a mechanical prostheses

have the risk factors of their younger age and smaller valve size, that can increase their mortality[10]. Furthermore, the inability of conventional biological and mechanical valves to expand in size with the patient, poses an obstacle for pediatric patients[27]. Thus, the necessity for a living valve implant is most crucial for these pediatric patients who require a valve replacement option that will grow with them[12]. Anticoagulation therapy, needed upon the implantation of mechanical valves, poses a thromboembolic risk, while bioprosthetic valves pose the risk of calcification both of which[28],demand a newer, improved valve that overcomes these obstacles.Although the process of constructing bioprosthetic valves involves the reconfiguration of animal tissues, this is not tissue engineering as no major changes are made to the "internal molecular structure for the purpose of enhancing their biological performance."[8]

6. Tissue-Engineered Heart Valves (TEHVs)

Tissue engineered heart valves (TEHVs) have been more widely explored recently to discover whether there is a way to make the ideal valve, free from the downfalls presented in tissue and mechanical valves. TEHVs are attractive due to them being non-immunogenic, biocompatible, able to expand and develop with the patient's age, having simple implantation, longevity and being hemodynamically suitable[15]. TEHVs have been predominantly implanted either by regeneration or repopulation. Regeneration is when a resorbable material is implanted and transforms in vivo to form a serviceable valve that constitutes human tissue[20]. This process involves a bioresorbable material being seeded with cells that have all differentiated in the same way, so that upon implantation, these cells will form the body structure they are naturally a part of. The creation of an organ by these cells is concomitant with the degradation of the scaffold. This method is generally used for patients who require a valve in the pulmonary position. This is due to the incompetence of a scaffold once it wears away, to cope with the high pressures at the aortic region[29]. Repopulation is a method where the cleaned xenogenic valve in its entirety is inserted into the patient and then human cells populate the acellular graft, thereby giving it the ability to behave as a regular valve[20]. This process of cleaning the xenogenic valve off its native cells, is called cell extraction. This process has said to be destructive to the matrix as it destroys the proteins in it. This damaging effect as well as others, reduces the competence of the valve to function properly and the immune response given off by the body[30]. Unfortunately the methods of regeneration and repopulation have been unsuccessful when used in human clinical trials[20]. Repopulation has commonly been unsuccessful demonstrated in studies where the expected reseeding of cells in vivo did not occur, and instead, the implanted scaffold was destroyed[31]. Although human donor tissues would be the most compatible material for TE valves, these are scarcely available[15], so the next best material, which is also highly available, is decellularized porcine, bovine, or other animal tissues[32].

Decellularization makes tissue less antigenic, reduces inflammatory responses, and decreases the rate of tissue degeneration. The ultimate goal of organ decellularization is to remove all cellular material from the scaffold without adversely affecting the composition, biological activity, or mechanical integrity of the three dimensional matrix[33].The creation of an acellular scaffold is required to remove any traces of foreign cells from the scaffold so that the valvular implant has a low immune-ogenicity[34]. Whether or not a decellularized graft shows immunogenic tendencies, depends on the process that was used to decellularize it (e.g. immersion, perfusion, etc), as well as the post-processing procedures.The process of decellularizing xenogenic tissue visibly causes the deterioration of the collagen matrix and decreases its elastic strength[27]. Da Costa et al, however, showed decellularized allograft valves to be more hemodynamically ideal, in comparison to allograft valves that had not undergone decellularization[35].

Following decellularization, some extracellular matrix materials (ECM) and proteins remain, forming a scaffold which enables impaired tissue to mend the surrounding area. TE implants consist of various chemicals and drugs that amplify the differentiation of seeded cells and encourage them to grow in a way that will make them useful for cardiovascular-related transplants (eg: valve replacements)[36]. Upon decell-ularizing xenogenic tissue, it is recellularized to allow the function and life of the tissue to return. (Crapo, Gilbert, & Badylak, 2011)[27].

Something important to consider at the time of decellularization, is the age of the patient's heart. Stephens et al found that depending on the maturity of the patient's heart, different amounts and types of materials are present in the matrix. Older patients' heart valves typically have a higher amount of collagen. Thus, TEHVs should be constructed while bearing in mind the composition of valves depending on the respective patient's age[37].

The process of recellularization involves tissue cells from the patient's own body (usually harvested from a vein), being seeded onto the acellular, valve-shaped scaffold[38]. Recellularization of acellular allograft scaffolds has been proven viable through successful clinical and animal trials. The ability of decellularized tissues to regain life, and to be reseeded with cells, is absent in bioprosthetic implants. This is due to the glutaraldehyde fixation which they undergo, disabling cells from settling on their surface, and altering the tissue structure[12].However, some studies have revealed that homograft scaffolds once implanted, may fail to be reseeded with host cells.These reports have also claimed that these scaffolds can become completely acellular after months of implantation[39].These alarming reports have prodded researchers to reseed acellular scaffolds in vitro, prior to implantation[29]. Despite the reports antagonizing the efficacy of homograft valves, their implantation into the tricuspid position in children has shown to be an attractive option. The reasons for this include their ability to avoid anticoagulation, as well as the fact that these valves do not undergo degeneration in the long run[40]. However, the mechanical strength of a processed xenograft is equivalent to or higher than the homograft. The anti-calcification treatment the graft is put through, reduces its calcifying potential in comparison to homografts. A variety of detoxification protocols neutralize the toxic residues that remain after this chemical treatment, making it safe for human use[41].Another situation in which xenografts have been opted for over homografts, is in heart surgeries involving RVOT and TOF corrections. These surgeries previously employed homografts as the repair materials. However, their limited availability, high cost, and restriction laws made these surgeries challenging. Subsequently, decellularized xenografts were employed. One study demonstrating the nine year follow up of RVOT/TOF patients who received these bioprosthetics, showed promising results[42].

If the process of recellularization, which allows vitality to be restored to the xenogenic graft, is done incompletely, or if for some other reason the xenogenic valve instigates an immune reaction after implantation, this could lead to speedy graft deterioration. This was the main challenge observed from in vivo trials[43].The process of quick recellularization by cells seeding on the graft, is vital especially in pediatric patients who have rapid growth spurts and hence require the valvular implant to grow and develop with them. Post recellularization, the seeded scaffolds are cultured in a sterilized tube or dish prior to implantation[12].Scaffolds with different properties (such as varying degradation rates) and fluctuating polymer levels are combined in order to produce valves with desirable physical propertiessuch as flexibility[44].

Another challenge for the creation of tissue engineered heart valves (TEHVs), is that human donor tissue is scarce, and while decellularizing xenogenic tissue improves immunogenicity, there is still always a risk of rejection by the immune system[12]. In particular, finding allograft tissue for pediatric patients is harder as a deceased person in the same size range is needed[45]. If human tissue, whether allograft or autografts became the only scaffold material option, the next inquiry would be whether the decellularizing or the cross linking process is more beneficial for valvular implants in older patients[12]. Furthermore, another stipulation of TEHVs in the pediatric population is that the implants should not be oversized as Rüffer et al found that this can result in premature graft failure[46].

Two viable scaffolds for the construction of TEHVs have been identified, which both adhere to a suitable criteria. The two options are decellularized, and synthetic scaffolds. The criteria is as follows, the scaffolds should have "mechanical and biological integrity, providing dynamic and biochemical signals, allowing cell attachment and migration, securing diffusion of vital cell nutrients and expression factor and allowing dynamic changes of the scaffold architecture"[47].Popular material choices for TEHVs are the natural components of extracellular matrixes (ECMs) such as collagen and proteins. As collagen is found in actual human valves, this material is ideal to use in TEHVs such as for their leaflets

and other elements[48].The insoluble protein fibrin can be converted to soluble fibrinogen in the presence of thrombin, and this end product is useful in TEHVs as it encourages collagen proliferation of middle-aged to older patient's periodontal ligament cells and intensifies the glycosaminoglycans held back in the ECM[49].However, leaflets composed of proteins like fibrin tend to be weaker under pressure, so these would not be able to adapt to the high pressure environment in the cardiovascular region and hence be incompetent[50]. Solely using collagen to construct TEHVs has been found to be problematic owing to the entrapment of cells in collagen gels leading to cell death[51].Hence, substances like chitosan are used in conjunction with collagen to produce viable biomaterials[52].Another biological substance that has been explored to construct TEHVs, is hyaluronan. Its chemical and physical properties, including the fact that it aids in the formation of the cardiovascular system in embryos, and that it is biocompatible across all species, makes it a viable option as a material for use in TEHVs[53].Although biological components are beneficial for the construction of TEHVs, synthetic materials offer advantages that the former cannot. These include the ability to manipulate the mechanical and chemical aspects of the valve[54]. However, in vivo studies showed that these valves could not cope with the pressure resulting from the hemodynamic environment surrounding the valve[55].Decellularized scaffolds offer four variations, following two principles. The first involves the recellularization process happening in in vitro conditions, requiring a bioreactor[20]. This process of which endothelial seeding could serve as an example, minimizes the thrombogenicity of the scaffold, thereby reducing immune responses against it[56].The second involves inserting the decellularized valve into the patient for recellularization to occur in vivo. Here, a bioreactor is not required as the patient's body serves as one. A study by Booth et al revealed that decellularization, while leaving the scaffold unharmed was only completely able to occur in procedures involving deoxycholic acid (DOA), and sodium dodecyl sulfate (SDS). However, Rider et al, Bodnar et al, and Caamano et al all contradicted these findings, agreeing on SDS being toxic to the tissue on the scaffold[20].

The manufacturing of the TEHV are most commonly done either by suturing or molding[54]. The other ways in current use are decellularization (mentioned above), electrospinning, and 3D bioprinting[12].Forming TEHVs via in vitro procedures (such as by molding biomaterials into valves), is usually more problematic than in vivo procedures which involve human tissue settling and growing around the implanted valve[57].A study by Kishimoto et al[58]revealed that in vivo implantation of TEHVs is advantageous due to the fact that it results in lower dangers associated with cells and tissue cultures. However, bodily responses to the foreign scaffold pose some challenges. Usually, these immune responses to valvular implants is what precedes calcification[59].Suturing is time consuming and often leads to erroneous situations, with a consequence being calcification.

Although these techniques have been successful in some clinical trials, they have their downfalls. The varying dimensions and sizes needed to create an entirely anatomically accurate valve for differing age groups, poses its challenges. Furthermore, since most TEHVs only utilize one material, theyare dissimilar to a human valve, and will thus not carry out its function in the same way or be as competent. The common polyester utilized for TEHVs often leads to stenosis. To overcome this issue, a variety of fabrication techniques must be employed. 3D bioprinting can construct the entire human valve without compromising its anatomical integrity. However, even this technique, as well as the others, present the obstacles of calcification, overload of stress placed on valve leaflets, amongst other problems that occur after implantation[54].It has been found that in order to prevent calcification, TEHVs need to be examined under simulated, controlled conditions.

A commercial TE heart valve released by CryolifeInc, incorporated the two following principles in attempts to construct the ideal TEHV. The first principle was that the valves possessed low antigenicity despite the xenogenic tissue comprising them possibly expressing proteins that human tissue do not. This was explained by the high pressure environment experienced by the valves, in which blood flows at a fast rate, disabling

white blood cells from attaching to the implant. The second principle was that the implanted scaffold would be immediately repopulated by host cells post-implant, reducing antigenicity of the foreign object[60]. However, clinical use of this valve resulted in catastrophic results[61].

Upon the creation and subsequent implantation of TEHVs, issues such as degradation of the valve may arise. This is when the scaffold deteriorates at a quicker rate than the production of ECM[62]. The converse of this, can cause other issues such as inflammation which ultimately leads to the demise of the TEHV. The ideal scaffold should last the lifetime of the patient and should be able to undergo growth itself. At a large scale, it should have anatomical integrity including correct dimensions so it can carry out the valve's function well. This means that the scaffold should ultimately be able to withstand pressures experienced by the mitral valves. At a microscopic scale, TEHVs need to have the capacity to control (a) the entry of foreign cells, (b) cell differentiation, and (c) phenotypes[12].More broadly, they should have the mechanical capacity to open and close without hesitation, they should have low antigenicity, and integrate into the body's biological environment[63].

Currently, the prosthetic valve industry is dominated by mechanical and tissue valves. As these have proven to be relatively suitable for older patients, and as the inhibiting qualities of the aforementioned conventional valves mainly impact pediatric patients, the TE valvular industry is mainly directed towards younger age groups[64]. This is due to their ability to grow with the patient[12].Unfortunately the demand for valves designed for children is minimal, and thus the production of these is economically unfavorable[8].

Looking forward, there are some measures that can be taken to obtain favorable cells that would ease the implantation of TEHVs and improve their effectiveness. For example, autologous cells which have an identical makeup to the patient's cells, can be extracted from excised pericardial tissue which is usually discarded during cardiovascular surgeries. Ultimately, for TEHVs to be effective upon implantation, they should be hardwearing and be biocompatible with the tissues in the body[65].

As demonstrated in the Cryolife study described above, an issue arose upon implantation, which could have potentially been avoided had the scaffold been composed of better biological materials, that were functionally superior. As the aortic valve is the gold standard in terms of its mechanical integrity, and its remarkable ability to cope with high ventricular pressures, it has been heavily studied in order to determine the properties that give it its longevity. However, the intrinsic structural features the aortic valve possesses that gives it its durability, has not yet been found[8]. This should be something for further exploration in the future.

Furthermore, as adolescents and children in poorer countries are more prone to having valvular heart diseases[12], they are the market for TEHVs. The cost of TE heart valves therefore, needs to be made more affordable for these populations. Oddly, although developing countries do require TEHVs the most, due to their large number of pediatric patients with severe cases of valvular heart disease, there is a scarcity of valve replacement studies that have been done in them[7]. This is therefore, something that would also need some future investigation.

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