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Manufacture of Artificial Heart Valves

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Annotation: The heart is one of the most important organs in the human body. Improper functioning of the heart mainly affects the lifespan of the human being. There are several diseases that affect the heart, and in some conditions, these can result in failures. Diseases that affect the heart include valvular disease, obstructions in the blood vessels, heart muscle diseases, and heart failure. In all these cases, healthy valves will not be able to function properly. There are four valves present in the heart (two atrioventricular valves and two semilunar valves). Valvular disease mainly occurs in aged persons. In valvular disease, the valve will not function properly, causing the backward flow of blood. In all these conditions, it can be replaced by artificial valves.

Quality valves can be manufactured using materials like metals and ceramics, where study is difficult to perform. As polymers are more flexible than metals and ceramics, they are suitable for designing numerous types of artificial valves. There are two types of artificial valves: mechanical valves and bio-prosthetic valves. More research has been carried out to make artificial valves using biocompatible polymer materials and to add features like antithrombogenic properties and cell compatibility. Measures should be taken to ensure that, before using artificial valves in

clinical treatments, mechanical testing should be performed to check the valve function and wearability. There is no manual work to produce regular artificial heart valves; instead, the valves can be adapted to CAD, CAM, or rapid prototyping techniques. In recent years, the use of 3D printing in heart valves has yielded better results. Biocompatibility criteria should be analyzed based on the fabrication methods. Cartilage formation in existing artificial valves is known to decrease with the number of hinge paddles, larger valves, and small computational pressure

1. Introduction

Artificial heart valves (AHVs) are crucial tools in modern cardiovascular surgery. Due to the increased incidence of heart diseases, the global AHV market is expected to witness substantial growth during the forecast period. Moreover, the effectiveness of these devices in combating heart diseases will drive the demand in the future. Several types of AHVs are available in the market, including mechanical AHVs, tissue or biological AHVs, transcatheter heart valves, and a few other implants like monoleaflet and bileaflet tissue valves. As these artificial implants are to be used in extreme physical conditions, they are required to be very sturdy and durable and should provide efficient blood flow and minimal recoil. Depending on the health concern of the patient and the ability of aorta replacement, the implantation of the AHV is decided. However, these medical innovations possess certain challenges, which result in complex surgical operations. For instance, the removal of the diseased valves requires scraping and cutting out the calcium present around the healthy tissue. The broken small portions of calcium usually move along with the blood flow and may block small vessels at various locations in the body. In this context, interview-based surveys reveal that the major concerns of customers are the quality and durability of these implants. Moreover, an artificial heart valve must provide good hemocompatibility with optimal performance, such as having the maximum diameter/minimum profile, to facilitate less invasive surgery. Thus, at first, it is necessary to understand the critical aspects of natural human heart valves. This information will further help in understanding the suitable biomaterial for the manufacture of the valve. The second major challenge is the artificial heart valve's manufacturing processes because these processes are required to provide a thin compacted natural heart valve and have to follow the same functions and advantages of the human body heart valve. [1][2][3]

2. Anatomy and Function of Heart Valves

The human heart consists of four chambers, each of which is delimited by one or more one-way valve(s). There are four heart valves: mitral valve, tricuspid valve, aortic valve, and pulmonary valve. The mitral valve is located between the left atrium and the left ventricle. The tricuspid valve, the right counterpart of the mitral valve, is located in the right atrium and the right ventricle. The aortic valve, formed by three leaflets, is positioned between the left ventricle and the ascending aorta. The pulmonary valve is located between the right ventricle and pulmonary artery. The mitral and tricuspid function, collectively known as the atrioventricular function, occurs during the ventricular contraction. For diastole to occur, i.e., the ventricular relaxation, the free ends of the cusps come together, similar to the closing of a partly opened door, which prevents blood from flowing back to the atria. The semilunar valves, on the other hand, work intermittently; opening

when the ventricles contract and closing for diastole.

Defective function of heart valves causes chamber overloading, thereby increasing cardiac workload, ultimately leading to heart failure. A possible strategy to manage valvular heart diseases without surgery is the repair or replacement of the affected valves with artificial heart valves, which mimic the function of the natural heart valves without alteration in the systemic intra-cardiological pressure differences. Thus, the new artificial valve should be designed to withstand physiological conditions of the heart. [4][5]

3. Historical Development of Artificial Heart Valves

Early attempts at heart valve replacements and artificial valves can be traced back to the 1950s but have roots reaching to a century earlier. A pioneer in the development of heart-lung machines implemented one of the first intracardiac graft-leaflet heart valves, though it was only used experimentally. Subsequent development led to various models. One heart valve used a self-made ball coupling mechanism for the ball inside the valve housing made of a specific material. Another valve was soon improved to reduce the obstructing seams. The heart valve models made in the next twenty years were the outcome of the unsuccessful fusion of both known models: caged-ball valve and disc valve.

Problems with tissue valves had already originated in earlier times. The mechanical valves are relatively durable and have remained in the field even in the 20th century. The focus was usually placed on meeting the functionality needed for life-saving procedures, and thus little attention was given to the blood-material contact. The use of a specific lining in one valve is an early adventure into the problematic field of biocompatibility. Only after a presented test bed in 1970, the focus was completely shifted from the convenience of design and function to the biocompatibility of heart valves. The test bed presented was based on the idea of some twenty years earlier - a disc in his caged-ball size valve was made from a specific material, and the valve can be experimentally placed into the aortic positions of dogs for a set duration.

4. Materials Used in Artificial Heart Valves

Like every other human body part, an artificial heart valve is also made up of different materials. The use of materials to make an artificial heart valve is very important to make it durable and biocompatible. Depending on the use of materials, artificial heart valves can be classified as biological, metal, polymeric, and composite. Out of the four materials, biocompatible materials are more preferable in artificial heart valves to avoid rejection and an immunological response from the body. The implantation of an artificial heart valve requires anticoagulation therapy to avoid the load of blood coagulation, and for this, the thin slice of artificial valve materials is essential to avoid mechanical stress and to achieve natural valve movement. Similar to this, there are the other two materials such as metal and composite. The very common types of metals are nickel, titanium, and its alloy. However, the use of composite materials is very rare in the preparation of an artificial heart valve. There are some biocompatible polymers and metals that are used in the construction of an artificial heart valve. Biocompatible alpha-grade titanium is used for superior blood compatibility compared to commercially pure titanium.

The mechanical properties of materials determine the durability of the artificial heart valve under normal function at physiological conditions. Therefore, the application of low mechanical strength can be achieved by coronary leaflets, artificial root tissues, and blood-contacting surface materials. Currently, there is a paradigm shift towards the development of polymeric and metal artificial heart valves, mainly due to advancements in the fields of biochemistry and materials science. Many researchers are working tremendously to improve the performance of artificial heart valves by adopting different polymeric matrices and reinforcing them with synthetic and natural materials that possess biomechanical and biocompatible properties. The wastage of artificial heart valves normally occurs and leads to breathing problems, which become more dangerous than the metallic valve. Hence, an effort has been made to analyze the different materials of an artificial heart valve

to improve the life of the tissue. Artificial heart valves have the potential to eliminate the need for scarce human donor hearts, longevity, and growth potential, can decrease the use of anticoagulants for patients, and can come in various styles. [6][7][4]

4.1. Biocompatible Materials

4.1. SECTIONING 125 Biocompatible materials An important feature of any valve replacement is ensuring that the implant, which is not made from human biological materials, is still accepted by the patients and does not cause an adverse immune response or rejection. This is known as biocompatibility, and it is linked to the materials used to construct a biological implant. Among the important characteristics of biocompatible materials are their non-toxicity and an ability to interact with and grow with or be integrated into the surrounding tissues. There are two main classes of biocompatible materials mainly used in the construction of a biological implant: (i) biomaterials and (ii) biological materials. The biomaterials used to fabricate a synthetic biological implant are usually polymers, ceramics, and in a few cases, metals. There are also some metallic biological implants that are covered with a biological material or a polymer. The most common biomaterials used in current tissue-engineered heart valves include collagen protein-based scaffolds, synthetic blend/composite polymers, and biologically derived polymers. The contemporary research on the application of biomaterials in tissue-engineered heart valves is focused on improving the lifespan and function of the engineered valves by ensuring that the materials used to fabricate the valve are biocompatible and that the cells that are to be used in seeding the scaffold have the ability to fully and automatically repopulate the scaffold post-implant. Although biomaterials are designed to be biocompatible, thorough testing is carried out on them by the manufacturing company as per the guidelines provided for these investigations. These testing guidelines apply the same amount of testing to a drug, device, or biological material that is to be used in humans. All patients implanted with a tissue-engineered heart valve are part of an ongoing research study until approval is provided for the valve to be implanted as a registered valve. All tissue-engineered heart valve medical devices to date are only semi-registered medical devices and can only be used within the bounds of a research study under the ethical approval of the hospital where the operation is to be carried out. [8][9][10]

4.2. Mechanical Properties

This subsection discusses the importance of the mechanical properties of biological tissues, biomaterials, and tissue-engineered valves, as these properties impact the design, fabrication, testing, and performance optimization of artificial heart valves. Firstly, the material property "tensile strength" determines the force required to permanently stretch the material or to cause the material to rupture. Next, the apparent Young's modulus indicates the capability of regaining shape following the removal of a deforming force and can be used for design criteria categories such as tissue compliance. "Fatigue resistance" is also a mechanical criterion that shows how materials fare following repeated loading at a sub-fracture level. This property is important in heart valve applications, as the worth of an artificial valve is quantified by the period for which the replacement valve can offer reliable service.

Mechanical properties can be determined through tests such as tension tests or strip-biaxial tests for uniaxial or biaxial tensile and tear properties. Dynamic mechanical properties can also be assessed, giving important insights into material behavior in dynamic, pulsating environments. Mechanical failure occurs in cases of rupture, tearing, or safety factor breach. To minimize valve failure, the interactions between the specific failure mechanisms and the mechanical properties must be well-explored and optimized. Materials should have the highest possible fatigue resistance, among other desirable mechanical properties. Thus, fabric materials treated in vitro and in vivo are employed in biological valve designs, as they favorably mimic the mechanical properties of the natural trilayered aortic heart valve. Furthermore, mechanical testing is a valuable tool in characterizing these properties, procedure materials, and testing new treatments and technology.

5. Manufacturing Processes of Artificial Heart Valves

Manufacturing of artificial heart valves (AHVs) is an extremely vital process, essential for developing a type of biomedical device that is implanted in the human body and is expected to function for the rest of the patient's life. Though all three types of heart valves—caged-ball, tilting-disc, and bileaflet principle-based mechanical valves—differ in design, research on cast parts manufactured using various materials like titanium, cobalt-based alloys, or sternal connectors, rather than PMMA, composite, or stent materials, is found everywhere. The majority of the valves and these manufactured products share common fabrication techniques like casting, machining, and, recently, 3D printing. Casting is among the widely used fabrication techniques, employing lost wax in ceramics. Machining or subtractive manufacturing removes excess material based on computer designs from blank materials with mass.

Along with manual machinery or CNC technology, many firms are turning towards automation in die casting and removal of burrs in SM processes. Conversely, additive manufacturing or 3D printing is being particularly employed to fabricate miniature artificial organs or heart valves. In AM, photon polymerization or fusion techniques, along with inkjet 3D printing, barrel printing, or valve jetting stamping, are now in great focus to fabricate large-sized devices. Regardless of the employed method, at present, automated and customizable engineering techniques focus on creating the surfaces of the heart valves. Concentrating on heart valves, titania and hydroxyapatite coatings are compatible with human tissue. Since 3D printing has become popular for engineering structures, it is also a promising tool for rapid prototyping and investing time in the production of full titanium–carbon AHVs. As a result, the manufacturing process has been improved to match the shape and configuration of such an endovascular spread pattern that can be combined with, for example, bioprosthetic or bioabsorbable heart valves. [11][12][13]

5.1. Casting

In the context of artificial heart valve manufacturing, two main methods of casting can be employed as the first stage of production. Firstly, investment casting is a precise casting process intended to allow the production of items with complex shapes, fine detail, and a smooth surface finish. Most metal valves are produced using the investment casting process. Several sub-processes are involved, in sequence, beginning with the production of a quality wax replica of the final valve shape, around which a mold is made. After the wax is melted and the template removed, the mold, filled with molten metal, is allowed to cool and solidify. Once broken from the investment cast and any defects corrected, each valve must undergo extensive post-casting processes to ensure that it is of a high enough quality for commercial use. Alternatively, in sand casting, further chosen for its potential for replica valve production, molten metal is poured over a sand mold, which has been made using a pattern of the valve to be cast.

The major advantages of the various casting techniques include little or no waste of the raw materials and the potential for the production of materials with excellent mechanical properties. The processes enable a high level of complexity in shapes and the creation of detailed features such as hollow parts. These processes are discussed separately in this subsection. The complexity of the desired overall shape of the valve is one key factor to consider for casting choices and their subsequent effects on the ability of production to achieve optimal quality. This, in turn, affects the durability and functionality of the valve. [14][15]

5.2. Machining

Although the fabrication of polymeric materials is considered to be the domain of molding, machining in most cases is the vital finishing process. Artificial heart valves made from metallic and/or ceramic materials will not be subjected to as hostile an abrasive environment as those implanted in the circulatory system, but appropriate corrosion must be assured, and products must be free from defects. Because positive closure of the valve discs is essential, especially in the mitral valve design, operating surfaces must be designed to be smooth, bearing around the joint edge and

providing a leak-proof seal when closed. Furthermore, the detail on the ventricle flanges to provide outlet grooves and prevent blood from collecting in the body pockets becomes an essential part of the design geometry. Such configurations are difficult and, in the patient-specific case, generally impossible to cast reproducibly, but are relatively simple to machine.

Intricate occluder designs, including a heart embossment, are possible. A negative joint clearance of 30 μm is achievable. The prototype artificial heart valve occluder embossment, geometry bounded by coinciding lines across the axis of the occluder, when manufactured using NC milling or CNC turning machines, is shown to have an area of 63.6 mm^2. The milled occluder tip is shown to be generally acceptable to a surface waviness of 244 nm angularly over 360 degrees. Polymeric materials are relatively easy to shape and generally have the added safety of reducing edge negative joint clearances in the occluder interface as an advantage. Simple polycarbonate of the required size is readily available, but more bio-stable materials offer more balanced properties of transparency, mechanical characteristics, and blood compatibility. It is manufacturable, scalable up to the size of the original prototype, and manipulatable into the carryable generic for non-destructive testing and development of the artificial heart valve. Quantitative Scanning Electron Microscopy analysis of debris produced by the machining of either brass or polycarbonate is provided, and no standard scopic inclusions or phase separation is apparent. [16][17][18]

5.3. 3D Printing

3D printing, also known as additive manufacturing, is a cutting-edge technology that is only beginning to be applied to the area of tissue-engineered heart valve fabrication. A variety of 3D printing techniques are available, which can be suitable for producing in vitro, in vivo, and ex vivo models on a range of length scales for medical device model generation. Two-photon polymerization allows for the production of 3D structures on the micron level. Direct ink writing provides the opportunity to produce bespoke structures intended for defect-specific implants or for model development. Fused deposition modeling is being investigated to develop alginate scaffolds for potential use in heart valve tissue engineering studies. Stereolithography uses pre-crosslinked gelatin methacrylate as the main photopolymerizable component for cell-laden hydrogel valve leaflet production at the millimeter scale. The appeal of 3D printing is the rapid prototyping and hence customization, from the CT or MR images of a patient's valve leaflet or from the cellular component of the developing valve.

From the perspective of manufacturing heart valves, advanced manufacturing strategies such as 3D printing present an opportunity to develop new, patient-specific valve designs. A number of studies and strategies have been presented for the 3D printing of formulated biodegradable PVAL/TEC and PHBV molded heart valves, but to date, the short-term results for these valves in vivo have not been reported. From a manufacturing perspective and in consideration of the need to achieve regulatory approval, there is a wide range of experiments and analyses that remain to be conducted, such as determining shelf life and fatigue life, and undertaking in vivo evaluations in original animal studies up to and including preclinical proof of concept. Furthermore, there are limited data in relation to the rheological profile of the material from manufacture to implant, which becomes extremely pertinent due to the rheology of the gelatin. This latter research is ongoing and is the subject of a separate national study. Only after these issues have been successfully navigated and the design and manufacturing steps discussed herein have been followed will the regulatory hurdles be addressed. The technology, which began development in 2001, is intended to bring to industrial production the next generation of specialized aortic and pulmonary tissue-engineered heart valves, replacement heart valves, and onlay heart valve repair devices.

3D printing techniques can be used to produce a part with specific properties and geometric requirements using a range of materials, including ceramics, polymers, and metals. The range of materials available for 3D printing has expanded significantly in recent years; however, not all materials are suitable for use in fabricating heart valves. This is due to the need to ensure

biocompatibility, as valve fabrication materials will be in direct contact with blood. When developing replacement heart valves from 3D printing, it is essential that the materials and processes are carefully selected to ensure the safe and effective performance of the valve. In addition, using 3D printing will enable the production of devices that match the exact anatomic requirements of a specific individual, ultimately allowing the development of patient-specific devices. Decellularized heart valves have also been generated using a multimodal 3D printer, which combines extrusion and lithographic approaches. Furthermore, a customized, computer-designed, and 3D-printed controlled porosity aortic heart valve was shown to exhibit low trans-valvular flow and pressure losses, while also remaining immune to valve-in-valve calcification and inflammatory response, as evidenced by results of a patient implantation. Histological analysis of this valve also revealed regenerated tissue formation on both the inflow and outflow surfaces.

6. Quality Control and Testing of Artificial Heart Valves

Quality control and testing are of great importance to guarantee the safety and functional capacity of an artificial heart valve before clinical use. For this purpose, two types of tests are commonly performed according to existing standards and regimes: mechanical tests and biological tests. The results of these regulatory in vitro and ex vivo assays are compulsory for the certification and market entry of a device. In the field of mechanical studies, such tests can be, e.g., fatigue or durability tests. Fatigue tests are subjected to regulatory statements in the standard series. This set of documents describes the testing scenario, such as the expected number of cycles ordered to specific regimens, the type of fixtures used for the test, the necessary conditioning and aging procedures, and the minimum sample size. The standardized fatigue experiments are used in the prediction of valve correctness concerning the end of life.

Various propagation methods for valve fracture are studied, with newly developed technology aiming for heightened sensitivity to critical valve structure-related stresses in vitro. These include a full valve lifetime bench-top testing technology which can be used to hasten the wear and fatigue predictions, as well as the reapplication of non-contact in vitro assessment tools. It is greatly acknowledged that a rigorous assessment protocol is essential before a new paradigm for valve assessment can enter broad epistemic acceptance. The element of risk directly translates to the risk experienced by the patient and clinical outcome. Lack of proper quality control is inadmissible. Regulators use in their scrutiny results of in vivo real-world tests; hence, exposition to controlled ex vivo conditions, including fluid-structure interaction and multi-axial movements, is positively valued. [19][20]

7. Conclusion

In this essay, the main focus is directed to the manufacturing of artificial heart valves. Critical manufacturing aspects regarding polymer, tissue, and mechanical heart valve prostheses were presented and discussed. The medical need for mechanical and biological heart valves and the worldwide interest in the expanding market were first investigated. One of the main points presented discussed the proper formulations used for manufacturing heart valve leaflets. An important chapter was dedicated to manufacturing methods and techniques that can be used to guarantee heart valve device compliance with quality and affordability requirements. Different manufacturing methods were discussed. For example, origami manufacturing was described in detail, explaining the different steps of the manufacturing route and some devices that can be recapitulated with this approach. The importance of quality control was further discussed, and some quality assessment strategies were proposed and revisited. The main chapter of this essay discussed the manufacturing arena per se. Considered manufacturing methods, possible problematic aspects, and some material formulation aspects were critically discussed. A dedicated effort has been made to explain and propose innovative materials, geometric design, and manufacturing method candidates. In closing, future perspectives and trends were discussed; they included organ-on-chip representations and some mechanical and biological heart valves manufacturing options and deepening. Today, approximately 1 million heart valve replacement

procedures are performed worldwide. Research and development will further investigate the above-mentioned trends and continue within in silico analysis and in vitro and in vivo performances. For this, teamwork among researchers, clinicians, and engineers is crucial.

Keywords: artificial heart valves; tissue engineering; regulatory aspects; natural valve anatomy; valvular disease displaced patients; heart valves replacements

Research, advances, and active investment continually improve new strategies and solutions to artificial heart valves. Dedicated and continuous research is needed to direct and guide surgeons to unique and reliable patient-specific solutions. Natural valve anatomy favors the development of simplified solutions. In the posttraumatic car accident case presented, at short term important infection complications motivated the explant of both artificial heart valves. For the above-mentioned drawbacks of artificial heart valve prostheses, we are continuously investigating tissue engineering for the development of entirely biological and living heart valve scaffolds. We believe that the re-colonization of decellularized porcine scaffolds with autologous cells will favor the development of a perfect heart valve anti-rejection solution. In in vitro and in vivo preclinical settings, these anti-inflammatory issue coatings demonstrated unaffected and still stable endothelial cell maturation.

In summary, this essay gives a detailed overview of how artificial heart valves are manufactured, focusing on products and problems, and proposes unique strategies and solutions for the improvement of tissue-engineering candidates.

Executive Summary

Natural vein graft and homograft and artificial stentless and stented heart valves are applied to enhance life quality and increase the life span of patients suffering from ischemic and functional cardiomyopathy and multisubclinical organopathy. This protective patient value increases day by day even in terms of the early start-up of the application of artificial heart valves in diseased children and very young infants at maximum risk of post-traumatic challenge. Surgeons supported by industry have investigated and clinically introduced innovative strategy solutions, for example, the reverse implantation of biological stented heart valves that could alter the ventricle-to-aortic roots relationship and the diastolic and systolic ventricular function in diastolic heart valve disease. In selected left ventricular remodeling and base dislocation, we have introduced the world's first reverse drawn pig heart valve interposition graft in the left anterior oblique position of the heart. Managing the perfect size of a pusher heart seal with a large drawn proportional pig leaflet allows for the repair of functional and ischemic cardiomyopathy valvular regurgitation. Our unique reverse implantation chapter deals in particular with percutaneous reverse Ross' and reverse coronary implantations. The big medical problem is the difference between the quality control and the quality systems guidelines control of the cardiologic and neuroradiologic devices.

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