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Tissue Engineering of Aortic Heart Valve: New Directions

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Abstract

In this talk Professor Morsi will summarize the experience gained in the last 15 years at Swinburne University of Technology to develop a tissue engineered aortic heart valve. In doing so a complete analysis of principle and fundamental of heart valves are presented and discussed. Initially an introduction and discussion on the research questions related to current heart valve problems and the issues related to development of tissue engineering aortic heart valve are given, followed by background information on the clinical aspects of heart valve diseases treatments and diagnostics. The types of heart valves replacements and their limitations are then discussed followed by a full account of the design and manufacturing of the scaffolds from natural and synthetics materials. In vitro conditioning and Swinburne's experience is then given and the presentation is concluded with a full discussion on the research questions related to tissue engineering aortic heart valves to date and recommendations for future research to create a functional tissue-engineered aortic heart valve.

Keywords:

1. Introduction

Natural heart valves are remarkably adapted to allow unidirectional flow without regurgitation or trauma to the blood and do not permit any excessive development of local stress in the valve leaflets and supporting surrounding tissues. Moreover, healthy valves are biologically dynamic structures that are capable of repairing injury that could result from any excessive cyclic pressure loading (70 beats per minute, more than 100,000 beats per day, and more than 36 million beats per year) [1].

Valvular heart disease is a major health problem causing significant indisposition and death worldwide [2]. The incidence of valvular disease increases with age, ranging from 0.7% in the 18-44 year old group to 13.3% in the 75 years and older group [3,4], and this percentage is expected to increase due to an older and larger population in near future. Dysfunctional heart valve could result from inherited heart pathology, leading to stenosis or inefficiency of the valve or could part of diseases such as calcification, regurgitation, degeneration and stenosis or endocarditis. Endocarditis is a disease allied with the inflammation of endocardium, due to bacteria or an infection with rheumatic fever and has a significant adverse effect on the functionality and long-term life of the patient. Aortic valveis the most affected by these diseases as it carries the maximum load of the heart. In general, however, the treatment of a dysfunctional heart valve is either repair of or replacement with artificial ones.

Prosthetic heart valves are instigated regularly to replace damaged natural ones, and they are widely instigated in ventricular assist devices (VAD) and in total artificial hearts (TAH). These valves are of two types, mechanical ones with components manufactured of non-biologic materials (e.g., carbon, metal, polymeric materials) or tissue valves, which are constructed of either animal or human tissue, at least in part. Literature suggests that over 285,000 substitute valves are employed per year, and approximately 40% of these are tissue valves [5]. Subsequently, due to

a recent increase in the aging population, there has been a shift toward the increased use of tissue valves. However, in general, these artificial valves suffer from a number of drawbacks that are different for mechanical and tissue valves. Nevertheless, the composite rate of valve-related complications is similar for both types.

The principal disadvantages of mechanical valves are associated with a substantial risk of systemic thromboembolism and thrombosis (largely due to abnormal flow past the rigid occluder and the use of non-physiologic surfaces) and serious complications from hemorrhage associated with the necessary use of chronic anti-coagulation therapy.

Oppositely, tissue valves maintain a low rate of thromboembolism without anti-coagulation therapy. However, these bio-prostheseswhich are partly biologic tissue and partly synthetic, are normally subject to progressive tissue deterioration leading to structural dysfunction. Nevertheless, tissue valves demonstrate, in general, a beneficial potential of acclimatization to the patient's cardiovascular environment [6]. Nonetheless, the key factors limiting the development of tissue valve replacements include changes induced by preservation, fabrication, and methods of implantations. For example, it is known that the functional/structural characteristics of tissues used in bio-prostheses are modified by glutaraldehyde cross-linking. Moreover, the choice of fixation technique is vital, as using the wrong technique could adversely affect the microstructural of the valve, particularly leaflets, and subsequently the degree of compliance compared to the biological tissue [7, 8, 9]. Generally, the degree to which the tissues are affected depends upon the fixation technique adopted and the method of fabrication. Moreover, the major cause of bio-prosthetic valve dysfunction is deterioration of cuspal tissue,which is primarily due to the inability of artificial materials to mimic the natural tissue. Calcification contributes to failure of tissue valves leading to regurgitation through tears in calcified cusps. This deterioration originates from mineralisation, often deep within the tissue (intrinsic) or at the surface (extrinsic) that are influenced by the host, the design of the implant and/or by the induced mechanical stresses. Non-calcified damage to the valvular structure that could accrue through constrained abnormal valve motion is also a major mechanism of degradation in porcine and pericardial prosthetic valves. Clearly, the maintenance of tissue structural integrity is critical to extending durability of tissue heart valves [10].

Conversely, the main drawbacks of artificial heart valves are the physical barriers and the restricted lifespan associated with them. The types and configurations of current artificial heart valves are well documented in literature, and a number of alternative designs have been suggested and examined structurally and hydrodynamically. Although the results from these studies revealed satisfactory correlation between *in vitro* measurements and *in vivo* clinical and pathological findings, they serve to highlight the continuing need for the development of long-term replacement valves [11]. In general, it is highly desirable that valve designs have durable membranes or leaflets and support structures that resist degradation due to *in vivo* environmental factors and mechanical stressing while retaining the functional characteristics and hemodynamics associated with the natural human heart valves. More importantly, no currently used valvular replacement devices provide growth potential, which is a major restriction for younger patients.

2. The Concept of Tissue Engineering

Full account of this concept is given by Morsi [12]. Recently, it has been recognized that an alternative to the fabrication of prosthetic valves is tissue engineering (TE) of an anatomically appropriate scaffold containing cells and controlling the development of normal functional valve architecture in vivo. This is indeed an exciting concept.

Figure 1 shows one concept of tissue engineering heart valves (TEHVs). This notion focuses on the development of a functional identical copy of a healthy heart valve to overcome all the disadvantages associated with the current clinical use of mechanical and bio-prosthetic heart-valves. However, existing results are still preliminary, and various issues remain to be addressed before the clinical application of a tissue-engineered heart valve will be possible for replacement [4, 13]. The three most important parts of tissue engineering are cells, biomaterialsand

conditioning techniques such as in vitro and in vivo. Out of these three components, cells are the only living part, and hence the other two parts need to be optimized to suite the cells used for tissue regeneration.

Overall, TE of heart valves can be divided in two general strategies. The first strategy uses decellular(not made up of or divided into cells) natural biomatrices.With this decellularization (remove cells or cellular material from an organ or tissue) approach, the Extra Cellular Matrix (ECM) of say porcine heart valve is used as a scaffold (after elimination of their cellular antigens to reduce their immunogenicity) to guide the repopulation of the new cells after implementation in the patient. With this repopulation technique, various methods for decellularization have been proposed to ensure that the mechanical properties of the biomatrices or the reconstitution of the tissue in vivo is not affected. In general, as will be discussed in Chapter 7, various concerns regarding the stability and resorption of the natural biomatrices have to be addressed. Nevertheless, it has been argued that in contrast to biodegradable polymer scaffold TEHVs (the second approach), decellularbiomatrices maintains natural ligands and Extra Cellular Matrix (ECM) constituents that could be more suitable for cell adhesion and proliferation [9, 14].

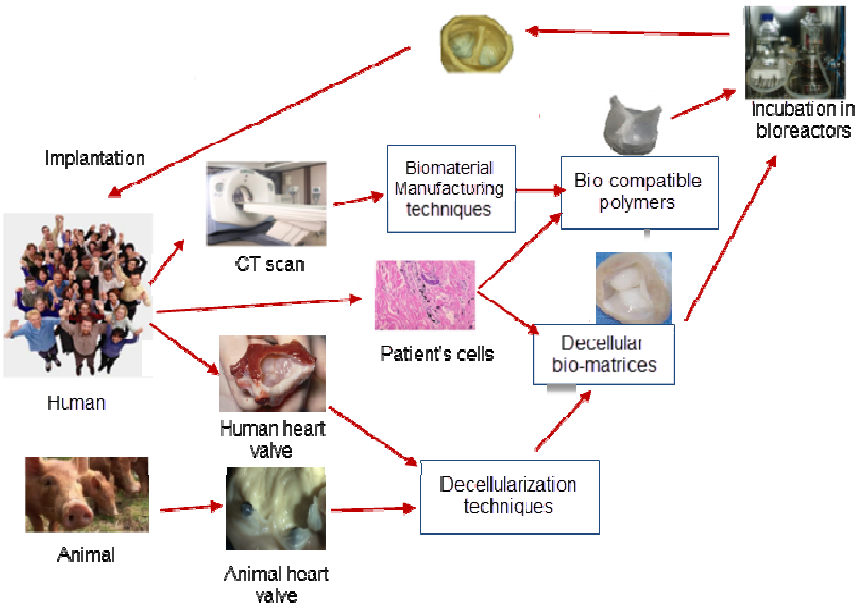

Figure.1. Illustration of the general concept of tissue engineeringheart valve.With permission (Yosry S Morsi, Tissue Engineering of the Aortic Herat Valve: Fundamentals and Developments, Book, Nova Science Publishers, 2011. http://www.amazon.com/Tissue-Engineering-Aortic-Heart Valve/dp/161942939X:

The second strategy is to use biocompatible degradable nature or polymeric scaffoldsmoulded into heart valve geometry. Generally, cells isolated from donor tissue are cultured and then seeded onto these scaffolds, resulting in constructs that can be implanted in vivo after a specific cultivation period in vitro. The cells grow, develop, and produce Extra Cellular Matrix (ECM) as the polymer degrades, ultimately leaving a natural tissue heart valve without any synthetic or natural component. Ideally, eliminating immunological responses to the TE-construct and facilitating the growth and remodeling processes, autologous cells should be used. However, other types of cells such as stem cells have been proposed [15, 16].With this approach, the cell-polymer interaction is also critical because the quality and extent of ECM formation will determine the overall structure and mechanical properties of

the newly developed tissue. Moreover, with this approach, biological materials have been also used as scaffolds for TEHV alone or with various types of polymers.

Still, degradable nature or polymeric scaffolds approach became very popular recently and currently is the most favorable one by most researchers. Morsi et al. [8, 17] accentuated the urgent need to develop new materials for heart valves scaffolds, particularly leaflets that are capable of mimicking the deformation and coaptation of natural heart valves and called for hybrid approach, i.e., using artificial and natural materials, which will be discussed in Chapter 7. Moreover, further development is required in the areas of scaffold design, fabricationtechnology and biomaterials with suitable mechanical properties. However, while improvements are progressing, the manufacturing processes available to date still need to be optimized so that the scaffolds produced are suitable for tissue engineering of aortic heart valve. The use of harsh organic solventsfor dissolving polymers and other chemicals required by the conventional fabrication process may produce toxic by-products. This in turn affects the biocompatibility of the scaffold and raises concern about safety of patients [18]. Rapid prototyping technology, on the other hand, may offer an attractive and cost-effective approach. Nevertheless, it can be expected that continual research into the fabrication process will lead to advancements and breakthroughs in addressing the complex requirements of manufacturing scaffolds for tissue engineering of heart valve. Moreover, the developed scaffold must continually withstand the physiological conditions that natural valves are subjected to (engineering simulation and in vitro conditioning play important roles in this). Other issues that need to be addressed include understanding the factors that control cell adhesion, differentiation and proliferation, the optimal period of culture and its environment (static or dynamic) and methods of cell seeding (selective cell or mixed cell population seeding), which are vital for the development of a complex, tri-layered, flexible structure of the aortic valve that can function as a viable and efficient one. All these issues are fully discussed in this presentation.

3. Conclusion

In a nutshell, tissue-engineered heart valves clearly have the potential to improve our ability to treat valvular heart disease and to abolish many of the undesirable physical properties observed in the present heart valve substitutes. In addition, research and improvements are called for TEHVs scaffold from both polymeric and decellularized biometrics. Clinical use of TEHVs within the next decade is believed to be perceptible. In essence, tissue engineering can utilize the existing and future information and data in the field of biology, biochemistry and molecular biology to formulate the correct concept of generating new tissue. Likewise, progress in the science of bioengineeringsimulation and numerical modelling as well as advancement in biomaterials would, in principle, provide the right platform to engineer tissues of the required chracteristics, which will compliment the realistic application of engineering principles to human implementations. Equally, developments of genetic engineering, cloning and stem cell biology, which are dependent on each other,can further enhance our understaing of various tissue human diseases and greatly assist the development of correct treatments.

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