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Review

A review of: Application of synthetic scaffold in tissue engineering heart valves

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ABSTRACT

The four heart valves represented in the mammalian hearts are responsible for maintaining unidirectional, non-hinder blood flow. The heart valve leaflets synchronically open and close approximately 4 million times a year and more than 3 billion times during the life. Valvular heart dysfunction is a significant cause of morbidity and mortality around the world. When one of the valves malfunctions, the medical choice is may be to replace the original valves with an artificial one. Currently, the mechanical and biological artificial valves are clinically used with some drawbacks. Tissue engineering heart valve concept represents a new technique to enhance the current model. In tissue engineering method, a three-dimensional scaffold is fabricated as the template for neo-tissue development. Appropriate cells are seeded to the matrix in vitro. Various approaches have been investigated either in scaffold biomaterials and fabrication techniques or cell source and cultivation methods. The available results of ongoing experiments indicate a promising future in this area (particularly in combination of bone marrow stem cells with synthetic scaffold), which can eliminate the need for lifelong anti-coagulation medication, durability and reoperation problems.

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1. Introduction

The prevalence of heart disease in adult U.S. population in the early of 21st century has been estimated at more than 5 million [1–3]. In the meantime, heart valve (especially aortic and pulmonary) dysfunction is a significant part of heart disease, which leads to death of approximately 20,000 people around the world annually [4,5]. The heart valves' physiological purpose is to maintain unidirectional, non-obstacle flow of blood [6–8]. Heart valve dysfunction is may be the result of development regulation and mechanical properties. Heart valve malfunction can be congenital (approximately 1% of the newborns have valvular defects), or due to the deposition of mineralized calcium, which causes calcification and genetic defects in matrix protein structure [9–11]. The

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four valves usually represented in a mammalian heart determine the direction of blood flow through the heart: (i) Aortic, (ii) pulmonary, (iii) mitral (bicuspid) and (iv) tricuspid [12]. The aortic and pulmonary valves are in the arteries leaving the heart and known as semilunar valves (SL) and the mitral and tricuspid are between the atria and ventricles and known as atrioventricular valves (AV) [13–15]. The aortic valve dysfunction is the third most common cardiovascular disease [16–18]. The valve leaflets (cusps) comprise of the extracellular matrix (ECM) of three distinct layers: fibrosa, spongiosa and the ventricularis [17,19–21]. The fibrosa, the away surface, is composed of parallel, dense collagen which associates the mechanical properties such as stiffness and strength of the cusps. The spongiosa, the middle surface, is composed of proteoglycans and lower abundance of collagen which facilitates the movement, and finally, the ventricularis, the adjacent surface, is composed of aligned fiber of elastin interspersed and short collagen fiber, which is responsible for the elasticity properties of leaflets [21–23]. The aortic valve leaflets comprise of 50% collagen (types I (74%), III (24%) and V (2%)), 13% elastin in dry weight and 37% of glycosamino acid [18,21,22].

Generally, the cardiac surgeries to replace the heart valves are common around the world and improve the life expectancy. Currently, the mechanical valves and the biological (glutaraldehyde xeno-grafts or cryopreserved homo-grafts) are used clinically as the state-of-the-art of artificial valves [13,24–26]. Fig. 1(a) and (b) depicts the biological and mechanical valves. The major drawback of mechanical heart valves is that these prostheses are foreign materials which may cause inflammation, infection and thromboembolic complication due to high sheer stresses of blood flow. To cope with the thromboembolism, an anti-coagulation medication such as a vitamin K antagonist (e.g. warfarin) is required along the life [10,26]. Although the warfarin could be efficacious to alleviate the coagulation, it shows the risk of hemorrhagic and also the embryo toxicity in fertile women [27,28].

On the other hand, there is no need for anti-coagulation treatment for the biological valves. Although, the thrombotic risk of biological valves is lower than the mechanical one (0.87% to 1.4% per annum respectively), but these prostheses' durability (10–15 years) due to the progressive tissue deterioration is almost half of the mechanical valves (20–30 years) [26,29–31]. Currently, all the clinically artificial prostheses basically represent non-viable structure and no capacity to grow, to remodel or to repair, particularly in infants' patients [13,31]. Almost 50–60% patients will experience the problem with artificial valves which required to reoperation. These limitations coerce the scholars to introduce the concept of tissue engineering heart valves (TEHV) [32,33] (Fig. 1(c)).

2. Concept of tissue engineering heart valves

Tissue engineering (TE) is a multidisciplinary science between the engineering principle and life science to overcome the limitation of artificial heart valves. The concept of heart valve tissue engineering was introduced by Shinoka et al. in 1995 [34]. The concept of TE is to provide a 3D scaffold as a template for a specific tissue to develop the neotissue from their cellular components. The scaffold provides an environment for cell attachment and tissue growth [35–37]. The cell can be either seeded onto the scaffold matrix in vitro (pre-implementation) or in vivo (post-implementation) to develop a neotissue for replacement or repair the damaged tissue [36,38–40]. The ultimate goal of tissue engineering is to fabricate a neotissue from cellular combination which depicts most of the characteristics of original tissue such as non-inflammation and non-immunogenic reaction, adequate mechanical properties and durability [41,42]. The concept of tissue can be summarized in three major parts: (I) the 3-D biomaterial scaffold fabrication, (II) the cell source and cell cultivation, and the (III) development conditions of the TE before implantation [43–47]. Fig. 2 illustrates the concept of TEHV.

2.1. Synthetic "3D" heart valve scaffold

The scaffold determines the shape of a native particular tissue and a space for meiosis [40,48,49]. In the scaffold role, two major cases of material selection and scaffold fabrication techniques are debatable [50–52]. The scaffold architecture (matrix) is very important as the basic of TE concept. The original heart valve cusps consist of an extracellular matrix [40,42]. The following characteristics ensure the success of the scaffold: (I) The structure should provide extensive network of interconnecting pore; a channel should be designed throughout the scaffold matrix to provide the oxygen and nutrients to those cells which are far away from the surface (usually more than 1 mm) [53,54], (II) the materials which are used should be biocompatible and biodegradable, and (III) the shape and the size of the scaffold should associate the native tissue with appropriate mechanical properties [48,55–59]. The heart valve leaflets synchronically open and close approximately 4 million times a year and more than 3 billion times during the life (75 years of average life expectancy) [60–62]. One of the hurdles that must be surmounted for TEHV is the possibility of leakage [61]. The low mechanical properties of the scaffold may lead to failure of TE concept [60–62]. The mechanical tests that have been done previously represent that the heart valve cusps have a non-homogeneous anisotropic structure with non-linear mechanical properties [63,64]. Ragaert et al. [65], in an experiment between a decellularized porcine aortic heart valve leaflets and a recellularized one, indicated that the reseeded leaflets retained the mechanical properties while the unseeded diminish. Generally, three types of mechanical test are accustomed: Biaxial stretching which represents the appropriate tensile strength for leaflets, local indentation which is used to evaluate the elasticity properties and flexural test (which are related to the opening and closing of loops) which is used to define the requirements of leaflets to retain the basic form [66–69].

Whereas, the biaxial stretching test is limited to a small central area of leaflets due to boundary effects [68,70], and local indentation test is limited to hardness and stiffness the results cannot immediately be translated to comparison between native tissue and synthetic scaffold.

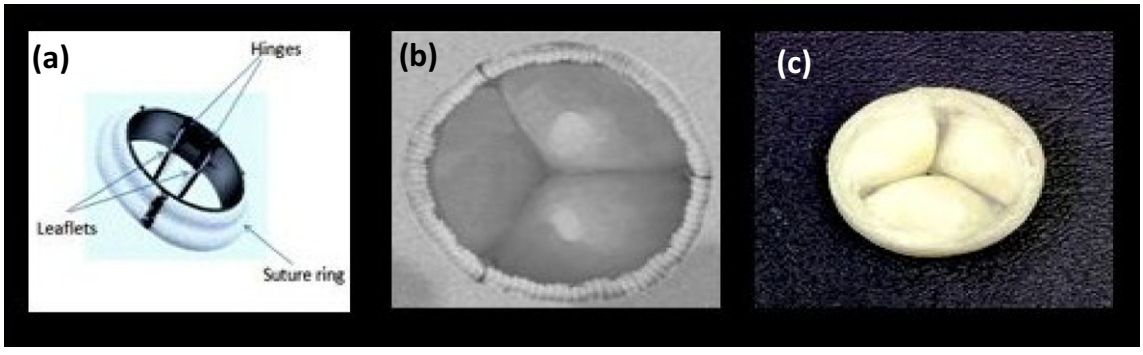

Fig. 1. (a) Mechanical, (b) biological and (c) living tissue engineering heart valves (from Syndaver's & Medtronic open pivot™ Lab) [174,175].