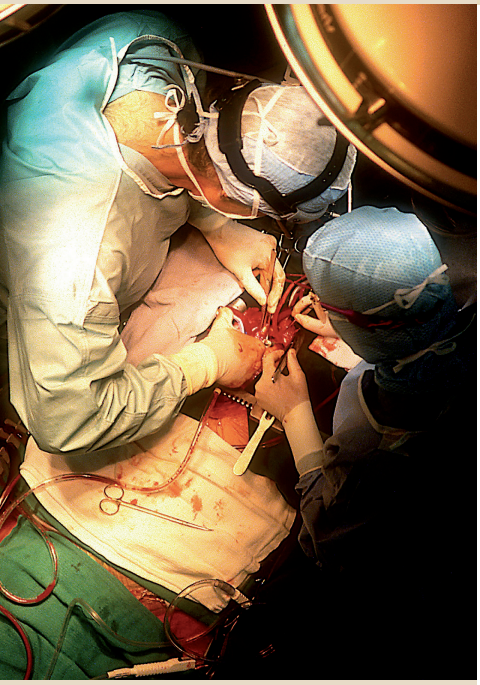
Tissue engineered human heart valves



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Abstract

The is no ideal heart valve substitute, both mechanical and biologic heart valve have significant limitation in term of durability, growth potential (for infant and children), compatibility, resistance to infection(1).

Tissue-engineered heart valve have been proposed by physicians and scientists alike to be the ultimate solution for treating valvular heart disease rather than replacing a diseased or defective native valve with a mechanical or bioprosthesis, a tissue engineered valve would be a living organ with the capability for growth, repair and remodeling in the same way that the native heart valve does.

Over the last decade attempts to create tissue engineered heart valve have been made with varying degrees of success, constructing these valve from a Varity of cell types and scaffolding materials. Early results in animals and limited clinical application are promising although it will take many years to demonstrate that long-term performance of this valve is comparable or better than conventional prosthetic heart valve.

Key words: tissue engineering- heart valve- technique- future

Introduction:

Excluding atherosclerotic coronary disease congenital and aquired heart valve disease are Second most common cardiovascular disease, account for approximately 60/000/ valve replacement yearly in USA and more than 300/000/ world wild, faced with such tremendous market opportunities (one billion $)[2].

Many companies and scientists alike have taken serious interests in developing a new type of heart valve that can potentially revolutionize the industry and the practice of medicine.

Both mechanical and biologic heart valve have significant limitation in term of durability, growth potential, compatibility, resistance to infection.

Neither mechanical nor biologic valve have any growth potential (except pulmonary autograft) and this limitation represents a major cause of morbidity and mortality for pediatric patients who must undergo multiple reoperation to replace valve or valve conduits as the patients grow.

Tissue engineered heart valve have been proposed to overcome these short coming, offers the possibility rather than replacing a diseased or defective native valve with a mechanical or animal tissue derived artificial valve, a tissue engineered valve would be a living organ with the capability for growth, repair and remodeling similar to native heart valve does.

For cardiac valve, the biomechanical demands are particularly high, heart valves open and close 40 million times a year and 3 billion times over an average life time[1-2].

Much of the strength and flexibility in normal tissue is due to the arrangement of the extracellular matrix which uniquely designed to provide a high degree of flexibility during systole but a high degree of strength to resist the diastolic pressure (aortic valve)[3].

Semilunar valve function, developmental biology and post development changes:

Normal heart valves ensure unidirectional blood flow through out cardiac cycle with minimal obstruction and without regurgitation. The ability of the valves to permit unobstructed forward flow depends on the mobility, pliability and structural integrity of their leaflets (in the tricuspid and mitral) and cusps (in the aortic and pulmonary).

Diastolic cooptation of the AV cusps is maintained by a mechanism that depends on a complex highly differentiated, dynamic tissue macrostructure and microstructure. The function of the semilunar valve also depends on the integrity and coordinated movements of the cuspal attachment and the dynamics of the aortic and pulmonary root structure. Thus, stiffening or dilation of the aortic root can hinder movement and/or proper cooptation of the AV cusps during closure and there by promote regurgitation.

The essential components of the heart valves comprise cells, including the valvular endothelial at the blood contacting surfaces and the deep valvular interstitial cells (VICs), and extracellular matrix (ECM). The extracellular matrix of the semilunar heart valve is not homogeneous, and the arrangement of ECM seems uniquely designed. All cardiac valves have a similar layered architectural pattern, a dense collagenous layer close to the outflow surface and continuous with valvular supporting structures, and which provides the primary strength component, a central core of loose connective tissue, and a layer rich in elastin blow the inflow surface, for the AV valves, these are called the fibrosa, spongiosa and ventricularis respectively[3].

A recent publication by aikawa and colleagues demonstrates that the normal semi lunar valve undergoes significant in

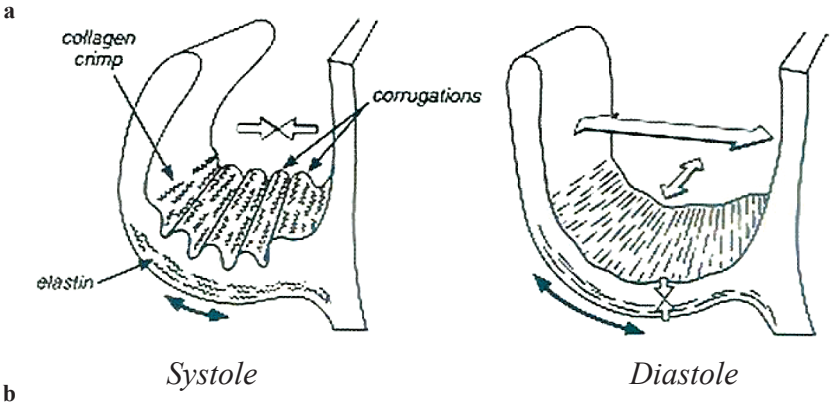

Figure 1:*AV caspal internal tissue dynamics across the cardiac cycle. A, schematic representation of architecture and configuration of collagen and elastin in systole and diastole*

vivo maturational change during development, which include change in ECM composition, collagen fiber alignment, and cellularity, and the development of a nonhomogeneous layered architecture[1].

Thus the semilunar valve undergo significant maturation in vivo under continuous biomechanical and other signaling conditions. (same changes have been observed in pulmonary autograft and tissue engineered heart valve implanted in animal).

VICs are the most abundant cell type in the heart valves and distributed throughout of its layers, strongly attached to and synthesize the ECM.

VICs mediate matrix remodeling and continually repair functional damage to collagen and the other ECM components, VICs comprise a diverse and dynamic population of resident cells that can modulate along a spectrum of phenotypes regulated by environmental conditions [3].

The insights gained from an understanding of normal semilunar valve development is of potential application to the development of tissue engineered heart valve.

Tissue engineering problems and progress:

over the last decade attempts to create tissue engineered heart valve have been made with varying degreases of success, constructing these valve from a verity of cell types and scaffolding materials.

Two main approaches have been attempted over the past 10-15 years, regeneration and repopulation. Regeneration involves the implantation of a resorbalbe matrix that is expected to remodel in vivo and yield a functional valve composed of the cells and connective tissue proteins of the patient. Repopulation involves implanting a scaffold of a naturally derived biomaterial or decellularized valve designed to attract circulating endothelial and other precursor cells and provide a fertile environment for their adherence, growth, and differentiation (also called guided tissue regeneration). Various modification of these two approaches have been examined.

If a tissue engineering approach to the creation of a heart valve substitute is to be successful, several basic question regarding, cell type, scaffolding, biochemical and mechanical signals necessary for the optimal tissue development, must be

addressed. Also should a tissue-Engineered valve construct be completely developed and mature prior to implantation, or can there be future maturation of these valve in vivo after implantation similar to the normal valve?[1-2]

Scaffold:

Any scaf fold for tissue engineering application must be biocompatible and have growth potential to allow cells to adhere and proliferate, ultimately the scaffold must either degrade or be able to remodeled.

A fundamental difference in the various tissue engineering strategies in different laboratories has centered on this choice of scaffold materials. One option is to use decellularized biologic tissue with the extracellular matrix remaining after the decellularization process serving as the scaffold for cellular attachment.

The disadvantage of these grafts include, agent used for cell extraction can be quite detrimental to matrix (in most cases, mechanical properties remain well preserved after cell extraction) and relative shortage of available homograft's and potential iminunogenicity problems with the xenograft and the density of residual extra cellular matrix may prevent penetration of seeded cells into the interstices of the matrix.

The alternative approach is to use synthetic biodegradable polymer matrixes to provide these scaffold function with anticipation that the cells in the tissue-engineered construct will produce their own extracellular matrix and the synthetic scaffold will be degraded and eliminated [1-2-3-4].

Various biodegradable materials have been used ploy-glycolic acid (PGA), ploy.L.lactic acid (PLLA) with different modification. Despite promising early results using PGA, P4HB (poly.L.hydroxybutyrate copolymer), there is some problems with these material with loose of structural integrity with longer periods of time in an aqueous tissue culture environment, with suture retention and actual tearing of the wall of the conduits and they are significantly stiffer than a normal valve leaflet. In addition of the influence of the chemical, degradation, and mechanical properties of the scaffold material, the fabrication techniques (dimensions of the pores within the scaffold, scaffold fiber orientation) can affect the mechanical behavior of the scaffold [5].

Cell type:

There are two main questions regarding the cells used for tissue engineered valve. First to seed or not to seed cells before implantation and which type of cells are preferred.

Although early experience with acellular xenograft (cryolife synergraft) showed disastrous result, different cells (fibroblast, stem cell, endothelial progenitor cells) have been used (1-2-3).

Interesting observation on mesenchymal stem cells is that the phenotype of these cells seems to be dependent on the local environment in which they come to reside.

For EPCs there is evidence that these cell have the ability to transdifferentiate in response to various signals in a tissue-Engineering environment.

Acumulating evidence suggests that circulating endogenous cells can be recruited in vivo to adhere to intravascular sites of injury or prosthetic material via a pathway that likely mimic the adherence of inflammatory cells to the endothelium during physiological inflammation[3].

For example, endothelial progenitor cells (EPCs) are bone marrow-derived cells that circulate in the blood have the ability to differentiate into endothelial cells, express a numbers of endothelial and stem cell-Specific surface makers (eg, CD34, CD133, and vascular endothelial growth factor R2) and exhibit numerous endothelial properties. Various cytokines, growth factors, and hormones cause them to be mobileized from the bone marrow and into the peripheral circulation, where they ultimately are recruited to regions of angiogenesis, EPCs are thought to participation in phathological angiogenesis such as that found in retinopathy and tumor growth, and they may play a role in the physiological repeir of damaged blood vessels, such as after myocardial infarction.

Thus, a potential strategy may be to coat a degradable polymer scaffold (in the configuration of a valve) or biological matrix with appropriate cell-signaling molecules in an effort to encourage and direct EPCs and other cell adhesion and differentiation.

Experimental and clinical application:

Most of the in vivo studies have been carried out in the lower pressure pulmonary circulation, which is more forgiving of an imperfectly functioning valve construct. (failure cause less tragic consequences).

J-E Mayer and colleagues at the children's hospital, Boston report their intial experience, with autologous EPCs that were isolated from the circulating blood of lambs and then seeded onto decellurized arterial segments. These seeded arterial grafts were them implanted as an interposition graft in the carotid artery of the donor lamb. These graft remained patent and functional for up 130 days. In their subsequent studies, Sutherland and associates used ovine bone marrow mesenchymal cells to seed a biodegradable scaffold formed into a three leaflet valve within a conduit, these valve conduits were implanted to replace the pulmonary valve for periods up to 8 months and functioned well hemodynamically [6].

Figure 2: *The tissue-engineered substitute pulmonary valve viewed from below prior to implantation.*

Hoerstrup, SP and colleagues reported the same result and the functional growth potential of this valve up to 100 weeks.
S, cebortari and A, haverich and colleagues have recently reported an initial experience, in two Childs using decellularized pulmonary allografts reseeded with autologous endothelial progenitor cells isolated from human blood, with 3/5 years of follow up with good hemodynamic results (7).
P.M. Dohmen and W. Konertz report mid term follow up with decellularized xeno grafts with acceptable results (8).

Conclusion:

There has been considerable and ongoing progress in understanding the dynamic pathophysiological basis of heart valve function. Although currently available mechanical and bioprosthesis have good hemodynamic and acceptable long term result (up to 20 years).
A tissue engineered heart valve would be a living organ with the capability for growth, repair and remodeling.
The more realistic option for the use of tissue engineered valve in the near future is in the pediatric population with congenital heart disease.
Although occasional experimental and clinical use of tissue engineered heart valves are promising, it may take anther 20 years before the many complex challenges are finally solved.

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