

Will heart valve tissue engineering change the world?

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In the same way as genetic engineering, nanotechnology and more recently artificial biology,¹ tissue engineering has captured the imagination of clinicians, scientists, investors and most importantly those who stand to be affected most, patients. This advance has heightened expectations, but the prospect of tissue engineering is coupled with legitimate concerns, fear of the unknown and ethical issues for consideration, particularly in relation to the expected use of stem cells and growth factors. Currently, tissue engineering is being actively pursued in neural tissue, skin, bone, cartilage and liver, to mention a few.² In the heart, the main three targets for tissue engineering are valves, coronary grafts and myocardium. In this viewpoint, we focus on tissue engineering of heart valves and try to establish whether we really need it and, if so, what impact will it have?

The incidence and prevalence of valve disease is increasing worldwide due to the world population's increasing age³ and the fact that we have failed to address the problem of rheumatic cardiac disease in developing countries and in indigenous populations in the developed world.⁴ Between 2005 and 2050 the world population will increase from 6.4 to 8.9 billion inhabitants, and the proportion of people aged over 60 years will increase from 10% to 21%.⁴ Concomitantly, the annual number of patients requiring heart valve replacement is estimated to triple from approximately 290,000 in 2003, to over 850,000 by 2050. Notably, the largest increase in the world population will be seen in third-world countries and, therefore, due to limited resources not all patients requiring heart valve replacement will even have access to this treatment. Strategies to address this global problem⁵ could have an important impact.

Although valve repair is currently the preferred method of treating patients with severe heart disease,⁶ a large number of valves are not suitable for repair and therefore require replacement. Valve replacement has significantly improved the life expectancy of patients with severe valve disease receiving optimum medical therapy. For

example, without surgical treatment a 60-year-old man with severe aortic stenosis has approximately 4 years to live; after aortic valve replacement his life expectancy increases to 13 years. This improvement, however, falls short of restoring the normal life expectancy seen in an age-matched, healthy individual living in the same environment. A 60-year-old man in the general population has a life expectancy of 18 years, 5 years longer than a patient who has undergone aortic valve replacement. The younger the patient, the greater the reduction in life expectancy compared with the general population. There is increasing evidence that most, if not all, of this difference is related to the use of suboptimum types of valve substitutes. Although there have been continual and significant improvements in the design and performance of both mechanical and tissue valves, they do not match that of normal valves. The most obvious complications of mechanical valves are thromboembolism, need for anticoagulation therapy, hemorrhage, imperfect hemodynamic performance and prosthetic endocarditis. Tissue valves solve some of these problems, but have a durability problem and lack the capacity to grow (except for the living pulmonary autograft). Moreover, they have an increased risk of endocarditis which, although slightly less than that for mechanical valves, is still significant. Given the need to reduce the occurrence of these complications further and, more importantly, the realization that normal heart valves perform extremely complicated functions (dependent on their biological characteristics and specific cellular and molecular profile),⁶ tissue engineering of heart valves appears to be the next logical step.

The structure and function relationship of heart valves has evolved over several million years to guarantee optimum hemodynamic function, durability and, importantly, a direct effect on myocardial function and coronary blood flow. In addition, the design and the mode of function enable smooth dynamic-flow characteristics that are coupled to cardiac contraction in morphodynamic behaviour.⁷ Valve movement has

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Received 23 November 2004
Accepted 21 December 2004
www.nature.com/clinicalpractice
doi:10.1038/npcardio0112

been shown to precede the movement of blood in anticipation of hemodynamic events.⁸ The different valve components change both their size and shape during different phases of the cardiac cycle. Additionally, valve tissue is innervated by sympathetic, parasympathetic and sensory fibres, including peptidergic nerve endings. Different parts of the valve respond to a variety of vasoactive substances normally present in the circulation in a dose-dependent manner.⁹ These functions are possible because of the specific pattern of gene expression in the different cellular components of the valve.¹⁰ The valve cells secrete different components of the extracellular matrix, unique in composition (which influences the physical properties of the valve) and effect on the cells. There is a constant cross-talk between the valve cells and extracellular matrix that can influence tension generation, polarity, proliferation and response to mechanical and chemical stimuli, among other factors. If they can be duplicated, we believe that these attributes should provide clinical benefit, in terms of longevity and patients' quality of life. So the question is, can tissue engineering reproduce all or most of these functions?

Several strategies for heart valve tissue engineering are evolving. They include the use of decellularized allogenic or xenogenic valve matrices followed by attempts to repopulate the valves with appropriate cell types *in vitro*, or relying on the natural remodeling powers of the body to repopulate the valves after insertion. A potential and possibly major limitation of the latter approach is that the processes involved in healing could fall short of, resist, or even reverse remodeling. A more ambitious, and in our view better, approach is to assemble biodegradable valve matrices populated by appropriate cell types that are conditioned to express optimum cellular, biological and physical properties, and then insert them. The use of various types of autologous or allogenic cells, including stem and progenitor cells, is being investigated and holds promise. The production of an 'off-the-shelf' product would require the use of allogenic or even xenogenic tissues coupled with the use of cellular or genetic modifications to ensure a patient-specific immune tolerance to the living-tissue engineered valve. So far, the matrices developed have been made from synthetic materials such as polyglycolic acid or biologic materials such as collagen and alginate. A particularly exciting possibility is the generation and design of matrices through nanotechnology, using atoms and chemical methods to imitate

biological material, (bionanotechnology) first envisaged by alchemists 300 years ago and so far best articulated by Richard Feynman.

The clinical application of tissue engineered valves requires a thoughtful and measured approach. When manufactured, tissue engineered valves need to replicate most, if not all, of the biological functions of a normal valve, and should be meticulously validated both *in vitro* and *in vivo* by the appropriate methods. This approach should be coupled with definition and minimization of the risks inherent to using stem cells, growth factors and artificial material. Pilot trials in defined populations of patients who stand to benefit most from the use of living tissue should follow, and should be ultimately followed by an expansion of the indications to include broader populations in an attempt to further enhance longevity and quality of life. Tissue engineered valves could also be a logical addition to percutaneous valve replacement.¹¹ Surrogate endpoints, such as hemodynamic performance, calcification and capacity to grow, coupled with the use of appropriate statistical methods, such as microsimulation and prospective randomized trials, are needed to validate or refute the speculation that replicating normal valve function by tissue engineering will enhance survival and quality of life in a large number of patients, and thus change the world.

Competing interests

The authors declared they have no competing interests.

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