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Editorial

The future of bioprosthetic heart valves

Two types of prosthetic valves are used for heart valve replacement surgery - mechanical or bioprosthetic. Mechanical valves have long-term durability, but require lifelong anticoagulation, with risks of thrombosis, thromboembolism, or spontaneous bleeding, and are therefore, less than ideal, particularly in young patients (injury-prone, menstruating, or pregnant) and in patients in the developing world, where close monitoring of anticoagulation may be difficult.

Bioprosthetic heart valves (BHVs) are constructed from porcine heart valves or bovine pericardium preserved with glutaraldehyde. Patients with BHVs do not require anticoagulation, but structural valve deterioration may occur, particularly in younger patients, necessitating replacement, with its associated higher risk of mortality.

The majority of the estimated 275,000 to 370,000 annual valve replacements are carried out in elderly patients in the developed world[1]. However, globally, there are an estimated 15 million patients with rheumatic heart disease, mostly young people in the developing world, with at least 280,000 new cases per year[2]. Only approximately 7-8 per cent of the Chinese and Indian populations have access to cardiac surgery[1,3], but demand is likely to increase markedly as the economies of these nations grow and technology continues to develop, making valve replacement more feasible. For example, percutaneous transcatheter valve replacement (in which BHVs are used) is currently performed in elderly patients too ill for standard open heart surgery[4], but should minimize the intensity of post-operative care required, potentially making it suitable for patients worldwide. Thus, there is a huge potential 'market' for BHV replacement.

Structural valve deterioration or failure occurring in BHVs is age-dependent, with <10 per cent occurring in patients >65 yr of age, but almost uniform failure within 5 years in patients <35 yr old[5]. BHV calcification is most likely a result of a combination of chemical processes related to glutaraldehyde-fixation and an immune response to the xenograft (both humoral and cellular)[6]. The likely reason that young patients demonstrate such aggressive destruction of a BHV is heightened immune competence and calcium metabolism.

The failed valves show evidence of inflammation (macrophage and mononuclear cell infiltration) and thrombosis (platelet and fibrin deposition)[7], histopathological features similar to those seen in experimental live tissue/organ xenotransplants. Thus, advances in the field of experimental organ xenotransplantation may be applicable to designing more durable BHVs, especially for young patients.

In the porcine-to-human xenograft combination, the galactose α1, 3 galactose (Gal) antigen (present on most pig tissues) is the major target for anti-pig human antibodies[8]. This antigen-antibody reaction has been implicated by several groups in the calcification and failure of BHVs[9,10]. This problem may be at least partially resolved if BHVs are constructed from the genetically engineered pigs that have been developed as sources of organs for xenotransplantation.

α1, 3-galactosyltransferase gene-knockout (GTKO) pigs (that do not express Gal antigens) have been cross-bred with pigs that are transgenic for human complement-regulatory proteins, (*e.g.*, CD46 CD55) and are known to provide resistance to human complement-mediated injury. GTKO pigs will soon be available expressing human 'anti-inflammatory' or 'anti-thrombotic' genes, both of which may provide further protection to a BHV from the human inflammatory and immune responses.

If BHVs could be fashioned to provide prolonged survival in young patients and in patients in whom long-term anticoagulation is contraindicated, there would likely be a paradigm shift to valve replacement worldwide. The raw materials required to fashion BHVs (*e.g*., valves or pericardial tissue from wild-type, unmodified pigs or cows) can be obtained at minimal cost from slaughterhouses. The costs of valves from genetically-modified pigs would undoubtedly be significantly greater (though would decrease significantly as breeding herds expand). Given the population of patients who might benefit most from improved BHVs, *i.e*., young people particularly in developing countries where the incidence of rheumatic heart disease remains high, the cost of the BHV is a major consideration. Perhaps because of this, to date, companies involved in this field have shown no enthusiasm for investigating genetically-engineered pigs as future sources of valves or pericardium. An innovative approach from entrepreneurs in countries such as China and India, coupled with increasing access to genetically-engineered pig herds, should resolve this dilemma.

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