Evolution of prosthetic heart valves

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Charles Hufnagel developed and successfully implanted the first prosthetic cardiac valve in the descending thoracic aorta in a patient with aortic regurgitation on September 11, 1952. When the heart-lung machine was successfully introduced in 1954, dreams of replacing diseased heart valves with prosthetic devices initiated the great “valve rush” of the late 1950s and early 1960s. By 1967 the principal categories of valvular substitutes were introduced in patients and all major complications of valve replacement were realized. Since that time, progress has been substantial but evolutionary rather than revolutionary.

The first replacements were imaginative, crudely constructed devices of untested synthetic materials that prolonged lives of rare operative survivors a few months (Figure 1). In March 1960 Nina Braunwald successfully replaced a mitral valve in a 44-year-old woman, who lived about 3 months. Later that year Dwight Harken reported a small series with a caged-ball prosthesis in the aortic position. In 1961 Albert Starr and Lowell Edwards introduced state-of-the-art manufacture and reported a series of long-term survivals with their classic caged silicone rubber ball valve. Valvular homografts appeared the next year; the first xenografts were used 2 years later. By 1967 Donald Ross had transposed a native pulmonary valve to both the aortic and mitral locations.

During the late 1960s, the 1970s, and the early and mid 1980s, prosthetic valve development focused on mechanical and chemically preserved xenografts and tissue valves. Nearly all designs featured an annular sewing ring to facilitate insertion of the prosthesis in the native annulus. The sewing ring and opening impedance produced pressure differences between 5 and 25 mm Hg across the open valve, depending on velocity of flow across the valve, anatomic location, annular size, and valve design. This drawback was “accepted” because valve prostheses greatly improved symptoms and circulatory hemodynamics and because other complications peculiar to prosthetic heart valves were more severe and troublesome. However, as perioperative mortality and morbidity rates steadily decreased, surgeons and cardiologists realized that the patient had merely exchanged one diseased valve for another. Morbidity and mortality rates were low, but they were also cumulative and stubbornly persistent.

Time had to pass to appreciate the magnitude of the long-term complications and to assess the effect of each new prosthetic heart valve on longevity. In the interim, new mechanical valve designs and new stented bioprostheses were introduced; some were early failures, and others required more time to reveal structural problems or a comparatively high incidence of thromboembolism. Designers and manufacturers of each new valve “believed” that their improvements reduced late complications and would prove superior to the “competition.” There were little data available and new valves were installed in patients who needed them, although with minimal preliminary testing on the bench or in animals. The accumulated but chaotically acquired experience reflected the pioneering mentality of valve designers, manufacturers, surgeons, and cardiologists; it also reflected the absence of long-term data.

Presentations and published reports documented the major complications of each new mechanical or bioprosthetic valve, but the quality of follow-up information and the definitions used to describe complications precluded useful comparisons between different valves and different reports. A committee-generated document that attempted to rigorously define valve-related complications and to offer guidelines for collection of follow-up information and statistical analysis helped, but problems of different patient demographics, different standards of postdischarge care, and selected reporting continued to confound detailed comparisons between different prosthetic heart valves. As experience accumulated, physicians began to realize that incidences of various postdischarge complications differed between mechanical and bioprosthetic valves, but that within either group only small and poorly documented differences occurred. The type of valve (mechanical or bioprosthetic) made a difference, but the incidence rate of specific complications of different mechanical or bioprosthetic valves fell into narrow ranges without clear superiority of any particular prosthesis (Table I).

In a nutshell, mechanical valves are durable but require lifelong anticoagulation to control thromboembolism. Durability was achieved after a few well-publicized incidences of structural dysfunction and manufacturing imperfections led to government regulation and implementation of good manufacturing practices and protocols. Bioprosthetic valves are less durable than mechanical valves and begin to deteriorate

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after 5 to 6 years\textsuperscript{11}; they are not suitable for children, usually do not require long-term anticoagulation, result in far fewer bleeding events, and possibly produce slightly fewer thromboemboli. Endocarditis and nonstructural valve dysfunction occur with approximate equal frequency in both types of valves. Both types of valves are associated with reduced survival in patients who receive them compared with age-matched healthy individuals (Figures 2 and 3).\textsuperscript{12,13}

The persistent deficiencies of mechanical and bioprosthetic prostheses stimulated renewed attempts to repair diseased valves and to make greater use of tissue valves in selected patients. Incremental improvements in cardiopulmonary bypass, cardioplegia, intraoperative assessment of valve function, and patient selection made the longer operations that were needed for valve repair or the insertion of stentless xenografts, allografts, and autografts safe. Nevertheless, at the beginning of this new century, 99% of mitral valve replacements and 89% of aortic valve replacements are either mechanical or xenograft bioprosthetic valves with sewing rings and well-documented deficiencies.\textsuperscript{14} The newer valves and repairs, described below, address these deficiencies and early reports are encouraging, although without long-term follow-up.

Mitrail valve repair is the preferred method for nearly all diseases of the mitral valve because postdischarge complications of thromboembolism and bleeding are roughly half those associated with mitral valve replacement (Table I). The incidence of endocarditis is similar to that of mechanical and bioprosthetic valves; the incidence of structural deterioration and reoperation falls in between. Mitrail valve repair is particularly well suited for degenerative valve disease, ruptured chordae, mitral valve prolapse, myxomatous valves, and some cases of rheumatic valve disease. Chronic ischemic mitral regurgitation is usually treated with an undersized annuloplasty, but long-term results are disappointing.\textsuperscript{15,16} Aor-
tic valve repair is used for very selected patients; cusp replacement operations are uncommon.17 The only “prosthetic” heart valve that grows as a child grows is the pulmonary autograft used to replace a diseased aortic valve.18 Available data indicate that these valves enlarge and endure; they are also free of...

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**Figure 2**


**Figure 3**


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thromboembolism without anticoagulation and produce a very low incidence of endocarditis.\textsuperscript{19} When the valve is inserted by skilled surgeons, the operative mortality rate is low (<5%). The major drawback is reoperation for early or late aortic valve insufficiency, which is often due to dilatation of the annulus (~6% to 8% at 8 years). In approximately half these patients the annulus can be narrowed and the valve saved. Another major cause for reoperation is stenosis of the pulmonary or aortic allograft used to replace the pulmonary valve. Cryopreserved pulmonary allografts are preferred over aortic allografts, particularly in children. At 8 years freedom from failure for pulmonary allografts is 80%, for aortic allografts 56%.\textsuperscript{20} Freedom from all causes of reoperation at 8 years ranges from 82% to 90%.\textsuperscript{21}

Aortic valve allografts are inserted in a variety of ways and offer improved durability, freedom from anticoagulation, excellent early hemodynamic function, rare thromboembolism, and a low incidence of endocarditis.\textsuperscript{22} Only a few “homovital” or freshly harvested aortic valves are used for logistic reasons. The majority are frozen cryopreserved allografts of the in situ valve and ascending aorta (Figure 4); this method of preservation produces a more durable valve than other methods do.\textsuperscript{23} Although controversial,\textsuperscript{23} cryopreserved allografts do not contain living cells.\textsuperscript{24} Allograft aortic valves are inserted as freehand grafts of the trimmed valve in the subcoronary position, as replacements of the aortic valve and adjacent ascending aorta as an intact unit (total root replacement), or as an intra-aortic inclusion cylinder containing the allograft valve (miniroot). Both the miniroot and total root replacement operations require reimplantation of the coronary arterial ostia. Increasing experience suggests that total root replacement (valve and proximal aorta) may be superior to freehand grafts or inclusion cylinders. The major complication is reoperation for valve deterioration; thromboembolism and endocarditis are uncommon.\textsuperscript{23} Freedom from reoperation ranges from 88% to 94% at 8 years for cryopreserved allografts inserted in the 1990s\textsuperscript{21}; O’Brien’s actuarial survival results for cryopreserved and cold stored aortic allografts appear in Figure 5.

Cryopreserved and fresh mitral allografts are more recent clinical additions (Figure 6). These grafts can be used to replace either a part or the entire valve. The operative mortality rate is low in selected patients, and early follow-up indicates that only 12% to 15% of patients have mild (2+) regurgitation at 1 year.\textsuperscript{25} The tricuspid valve has also been replaced with a mitral homograft.\textsuperscript{26} Other substitutes for the diseased mitral valve include a tricuspid valve autograft and a pulmonary valve autograft. In a small series, pulmonary autografts were inserted into short dacron conduits; the distal end was sutured to the mitral annulus and the proximal end to the atrial wall with a pericardial collar. One-year follow-up reports excellent function in 20 of 22 patients.\textsuperscript{27} A single patient followed up for 6 years remains well.\textsuperscript{28}

Stentless aortic xenograft valves are similar to cryopreserved allografts except that the tissue is usually fixed in gluteraldehyde. Porcine xenografts are most commonly used. The frame or stent is omitted, and a textile sewing ring is either absent or much reduced in width; thus, for a given annulus, stentless aortic xenografts are usually 1 or 2 sizes larger than stented xenografts. These valves generally require 10 to 15 minutes more time to insert than do stented xenografts,\textsuperscript{29} and in most reports postoperative pressure gradients across the valve are reduced to a mean of 5 to 6 mm Hg under resting conditions. Left ventricular mass is reduced at 6 months\textsuperscript{30} and is greater for stentless compared with stented valves but similar to mechanical prostheses.\textsuperscript{30} Stentless aortic valves can be inserted as freehand grafts in the subcoronary position with proximal and distal suture lines, as inclusion cylinders, or as total replacements of the valve and proximal aorta. The latter two procedures require reimplantation of the coronary arterial ostia. In a retrospective matched-case series, David et al\textsuperscript{31} found that freedom from any valve-related complication was 81% for stentless aortic valves and 50% for Hancock II stented prostheses. In a collected series, actuarial survival for patients with stentless aortic prostheses was 82.6% at 6 years.\textsuperscript{32}

Stentless mitral and tricuspid porcine xenografts have also been developed. The xenograft consists of valve leaflets and rim of annulus, chordae, and tips of both papillary muscles. The chordae are sewn to the native
papillary muscles with multiple interrupted, pledgetted sutures. Sizing and orientation of the valve are critical; early results in 74 patients followed up a mean of 14 months are encouraging. Since the introduction of prosthetic heart valves, many deficiencies of early models have been overcome or greatly reduced. The return to autographs, allografts, and stentless xenografts in the 1990s has reduced transvalvular pressure gradients to near-normal levels under resting conditions and may be associated with reduced left ventricular hypertrophy and improved long-term survival. This trend is also associated with a marked reduction in thromboembolic events and, because anticoagulation is usually not required, bleeding events and the nuisance of maintaining patients on warfarin have nearly vanished. The incidence of endocarditis is reduced but still remains greater than occurs with undiseased native valves. Although not documented, the incidence of perioperative valve leak in the absence of infection is uncommon. Thus substantial progress has been made, and more and more patients can be offered these newer biologic valves because of advances in cardiopulmonary bypass, cardioplegia, and intraoperative and postoperative care.

The success of the newer biologic valves has diminished the appeal of mechanical valves. The designs of natural valves still appear better in rheologic terms than do those of our most brilliant scientists, clinicians, and engineers. Yet mechanical valves are durable and biologic valves are not. Moreover, well-designed mechanical valves rarely require reoperation for valve dysfunction that is not due to thrombosis or infection. Last, mechanical valves are still the most commonly implanted valves. These observations underlie efforts to design hemodynamically improved mechanical valves and to find better methods to control thromboembolism and endocarditis. New designs address issues of rheology—turbulence, cavitation, stenosis, stagnation, and backflow—in and around the valve. Various surface coatings and modification processes address the issues of thromboembolism and infection. Although the obstacles are great, the advantages of an “ideal” mechanical heart valve prosthesis justify efforts to find the right design and the right materials and surfaces.
Simultaneously the encouraging experiences with the new “biologic valves” spur efforts to improve durability and to reduce reoperation rates for valve dysfunction. Xenograft valve prostheses are usually preserved in glutaraldehyde at rigorously controlled concentrations and conditions. Glutaraldehyde cross-links collagen and preserves flexibility of the slightly stiffened leaflets. The preservative prevents antigenicity; in adults approximately 90% are durable for 10 years. On the other hand, glutaraldehyde-fixed valves are cytotoxic, are not resistant to infection, and tend to become mineralized in inverse proportion to the patient’s age.

Several strategies have been developed to retard or prevent mineralization of xenograft valves and some have been applied to commercially available valves. Non-aldehyde fixation includes the use of Denacol, an epoxy compound, Acylazide, Carbodiimide, or dye-mediated photooxidation.33 Premix treatments of glutaraldehyde-fixed valves include the detergents, polysorbate 80 (Tween 80), or sodium dodecyl sulfate.34 Chemicals used to modify glutaraldehyde-fixed valves after fixation include 80% ethanol,35 chitosan,36 2-amino oleic acid,37 bisphosphonates, and metallic ions (Hirsch 92), and a proprietary product, the “No React” detoxifying process. Time must pass before the results of these antimineralization strategies are known.

As we enter the new millennium, surgeons have embraced nature’s design as the superior prosthetic heart valve. Safe cardiopulmonary bypass and cardioplegia and improved preoperative, intraoperative, and postoperative care have facilitated longer, more precise operations; the sew-and-run era has ended. For adults, cryopreserved allografts and xenografts are attractive choices, but lingering durability and infection issues need resolution. For children, the need for growth and exceptionally long duration focuses attention on bioengineered valves. Indeed, bioengineered prosthetic heart valves represent a new and promising strategy that is just now beginning to unfold.

References