11. Artificial Heart Valves: From Caged Ball to Bioprosthesis
11. Artificial Heart Valves: From Caged Ball to Bioprosthesis

The heart is a dual pump. The right side receives blood from the body into the right atrium. From this chamber it passes to the right ventricle, a muscular pump capable of driving the de-oxygenated blood through the lungs *via* the pulmonary artery.

Freshly-oxygenated blood returns to the left side of the pump *via* the pulmonary vein. From the left atrium blood passes into the left ventricle, an organ powerful enough to pump blood through all the organs of the body.

The heart therefore pumps by a reciprocal mechanism. Blood enters a chamber *via* one orifice, then is pumped out through another. This means that valves are necessary to ensure that flow continues in the desired direction. Thus when the ventricles are contracting to direct blood to the lungs or to the general circulation, valves between the atria and ventricles are closed by pressure. This ensures that flow is directed through the pulmonary artery or the aorta. When the ventricles stop contracting, regurgitation of the blood back into the heart is prevented by valves that close the openings of these vessels (Fig. 11.1).

Valvular Defects

The cardiac valves are amazingly effective. They are flexible, economical on space, delicate in design yet remarkably strong. They survive great fluctuations of pressure every second throughout life and ensure a unidirectional flow of blood through the heart. It is therefore not surprising that if heart valves are affected by disease quite severe pathology ensues.

Lack of adequate patency of a valve (stenosis) or valvular incompetence can be due to congenital malformation, infection or atheromatous changes.
The pathology produced is that expected when an abnormal load is imposed on a chamber of the heart, or a back pressure created through the lung circulation.

Thus if the aperture of the mitral valve is narrowed, the left atrium and right ventricle bear the brunt of the defect. Both become enlarged (hypertrophied) and dilated. If regurgitation occurs, due to valvular incompetence, then the left ventricle will be involved and it too will hypertrophy. The pulmonary circulation may become engorged, with dilatation of the vessels, thickening of the alveolar walls and reduced oxygen transfer.

With serious defect of the mitral valve, death could be due to a variety of causes; maybe congestive heart failure, or cerebral embolism from a thrombus arising in a fibrillating atrium.

Similarly, in aortic valve disease, regurgitation results in gross enlargement of the heart (even to a weight of 1kg) with left ventricular hypertrophy and compensatory dilatation. Stenosis will produce a slowly developing hypertrophy. A patient with aortic valve disease will be prone to dizziness and fainting and will most likely die from congestive heart failure.

Damage to the tricuspid will tend to oppose the return of the blood to the heart, whereas defects of the pulmonary aortic valve will cause hypertrophy of the right ventricle (Fig. 11.1).

Treatment for Valvular Disease

Before the 1950s there was little one could do for serious valvular disease once it was established. In 1832 Corrigan stated: “cure of inadequacy of the aortic valve is probably beyond the reach of medicine” (1).
Even much later, White in his 1951 treatise (2) suggested nothing further than to advise the patient “to protect himself against strenuous exertion or fatigue.”

The development of the cardiopulmonary bypass technique, together with cardioplegia (see Chapter 10) provided a completely new outlook for the patient with valvular disease. The ability to open the heart and operate within it for perhaps hours, raised the possibility that defective heart valves could be excised and replaced with artificial substitutes.

Artificial Heart Valves: Early Designs

Natural heart valves are exquisitely designed. The mitral, for example, consists of two flaps of tissue, the free margins of which are anchored to the floor of the ventricle by thin strands of connective tissue called chordae tendineae. It offers virtually no impedance to the flow of blood into the left ventricle, yet prevents completely blood being forced back into the left atrium during the powerful contraction of the ventricle that sends blood throughout the system. It is an extremely effective valve yet takes up little space, being thin, pliable but totally unyielding to the pressures it is designed to resist.

It is not surprising that the earliest attempts to design a prosthetic valve tried to mimic the anatomy of the mitral valve with artificial materials.

One of the most intensive investigations was carried out at the University of Minnesota Medical School (3). The remarkable strength of cardiac valves is due to their collagen content. The team at Minnesota digested the valves of cattle and human cadavers with a proteolytic ferment that removed all protein except collagen. This enabled them to study the distribution of collagen fibres and their orientation along lines of stress.

Armed with this information, they manufactured valves from Silastic rubber-coated Teflon or Dacron felt. Imitation chordae tendineae were prepared by braiding strands of the felt prior to applying the rubber coating. It would of course be unthinkable to attempt to implant such a prosthesis into a patient without evidence that it could actually function. Therefore, as with all the various types of valve prostheses that were being made, they were put into dogs after excision of the mitral valve. The artificial flaps were sewn onto the mitral ring and the imitation chordae pulled through the wall of the heart and anchored outside at a suitable tension.

---

1 White did however refer to some palliative surgical interventions for some valve defects. For example, construction of an anastomosis between the aorta and pulmonary artery to ensure oxygenation of blood in severe stenosis of the pulmonary aortic valve.
This surgery was rather difficult. The prosthesis was emplaced successfully in only 7 out of 10 dogs. Only 2 of the 7 survived for a reasonable period (12 and 14 days). Small thrombi were observed on the atrial side of the prosthesis, particularly around the sutures.

It was soon realised that attempts to design a valve anchored by artificial *chordae* was going to be too difficult. If the *chordae* were made too long the valve flaps everted into the auricle, if too short, the valve was incompetent. Workers at the Mayo Clinic thus designed a “flexible cusp” valve (4). This, in essence, consisted of a firm plastic (*Mylar*) ring, to this was attached a thin, flexible sheet of plastic, strengthened by transverse “slats” of firm plastic. The flexible cusp was slightly larger than the ring, so that when forced against the ring by pressure it closed the orifice. The solid slats preventing the cusp being everted through the ring.

The comparatively simple design of the flexible cusp valve meant that the insertion of the prosthesis was relatively easy. Thus the dogs in whom it was tested were walking around within 5 hours of the operation and the valves appeared to function well initially. However the incessant movement and stress to which heart valves are subjected revealed the fragility of man-made materials compared to the archetype. Damage to the experimental valves occurred, in some cases as early as 5 days. Such poor durability precluded use in humans, where one would need to anticipate years of function.

Despite the disappointment of the lack of long-term success with these and the many other prostheses tested in the early 1960s, the experiments produced useful information. It was realised that for durability more robust materials were required. Thus the tendency for fatigue fracture was minimised by using woven material such as knitted *Teflon*. The increased durability resulted in increased post-operative survival, some dogs living for 72 days. The availability of even a few short-term survivors enabled the study of the anticipated problem of valve thrombosis.

Clot formation is bound to occur upon foreign surfaces, and within the heart or blood vessels where there is damage to the inner surfaces, for example where there are sutures. The workers at the Mayo Clinic noted that in their dogs clots tended to form at the suture lines then spread over the surface of the valve. The use of “non-irritant” suture, such as siliconised silk, or covering the sutures with *Ivalon* or natural valve tissue produced minimal benefit. Similarly, experiments with 9 different materials for the manufacture of the valve (including gold plated *Mylar*) had no significant effect on thrombosis formation. However it was established that valve design should ensure that there were no “nooks or crannies” where blood could stagnate and hence tend to clot (4).
There were many attempts to develop flexible, non-rigid artificial valves made of a wide variety of materials including, besides various compressed plastics and knitted Teflon, biological tissue such as pericardium and auricular wall. None was really reliable enough for human use.

There was undoubtedly a pressing clinical demand for an effective prosthetic valve. Eventually, it was realised that attempts to design a flexible prosthesis that would mimic faithfully the function of an endogenous valve would be abortive, at least without the advantages possessed by the original designer i.e. omniscience and unlimited time.

The Caged-Ball Valve

The cardiac surgeon Starr believed that one could not depend on the long-term flexibility of plastic materials emplaced in the heart, and opted for the development of a total replacement prosthesis that would not require extensive adjustment and manipulation in the theatre.

Starr developed a simple caged-ball valve (5). It consisted of a Teflon cloth ring to which is attached a lucite cage enclosing a Silastic ball. The ring was sewn into the mitral orifice of a dog, with the caged portion projecting into the ventricle. When the ventricle contracted the pressure increase forced the ball against the ring, effectively closing the orifice.

Compared to the other relatively delicate prototypes being tested at the time, Starr’s ball valve must have seemed cumbersome, yet it was haemodynamically very good. The presence of the cage in the ventricle appeared to cause no damage to the inner surface, and contact between the cage and the ventricle wall produced no disorders of rhythm.

In Starr’s first experiments, 80% of the dogs survived for at least 10 days, one was described as in “ferociously good health” 7 months after the operation (5) and later Starr reported survival continuing at 13 months (6).

The survival of these dogs enabled careful examination of the effectiveness of the valve by cardiac catheterisation (to measure left atrial pressure), angiocardiography and cine angiocardiography even 12 months after implantation. In some dogs steel pins were inserted into the Silastic balls so that valve function and ball spin could be observed with fluoroscopy.

Thrombosis was a serious complication with all valves tested in the dog so that evaluation of the long-term efficacy of valves had been difficult. Nevertheless with the caged-ball valve it was “possible to obtain long-term dog survivors without anticoagulant treatment” (7). This meant it was possible to establish the adequate functioning of the valve.
Encouraged by the experimental results, Starr performed mitral replacement in patients with a ball valve prosthesis from September 1960 (Fig. 11.2). This clinical work was published in October 1961 (7). By that time 12 patients had had mitral replacements. There were 2 post-operative deaths (not related to prosthesis) and 3 deaths from staphylococcal endocarditis (unfortunately there had been an epidemic of staphylococcal infection which eventually necessitated the closure of the operating suite). The remaining patients were well. The first 2 patients operated on were back at work. The Starr-Edwards caged-ball valve is still in use (8).

Fig. 11.2 Surgery to replace a mitral valve. Heart valve replacement surgery would not be possible without animal experimentation. The development of cardiopulmonary bypass techniques and cardioplegic solutions, necessary to carry out surgery on the heart, were explored in Chapter 10. © Science Photo Library, all rights reserved.

Refrining Designs: Disc Valves

The relatively bulky construction of the caged-ball valve made it less suitable as a replacement for a defective aortic valve, particularly if the patient had narrow aortic roots. There was also the problem of the occlusion of the origins of the coronary vessels, which branch from the aorta just above the aortic valves.² So-called “low profile” valves were developed, such as a caged-disc

² Actually, Hufnagel (17) had used a ball valve to combat aortic valve failure in 1951. Since this was before the development of cardio-pulmonary bypass techniques he implanted the valve in the descending aorta. Although not the ideal position, the prosthesis prevented 75% of the insufficiency and reduced the work load of the heart.
valve, which took up less room and would thus fit into the position of the aortic valve. This was not really an improvement for mitral replacement however, since the ball valve, having a freely rotating occluder, suffered less wear (Fig. 11.3).

The relative success of the caged-ball valve provided a boost to research on prosthetic valves. Engineering principles were used to study aspects of design that would provide maximum flow and minimal clotting. Davila and his colleagues from Temple University implanted many variations of suspended occluder valves in over 100 calves (9). They found that blood coagulation round the valve could be minimised by using highly polished surfaces on the prosthesis, hydraulic streamlining to reduce areas of stagnation or “wake” and graphite-benzalkonium-heparin coatings.

The design most favoured at present stems from the experiments of Wada, who implanted a tilting disc valve in the dog in 1964 and in man in the following year. The disc opened by a hinge mechanism which occasionally failed, resulting in fixation of the disc in the open position. Shiley designed an experimental valve with a freely rotating disc in 1968. Björk used a slightly modified design and evaluated it clinically in 1969. The Björk-Shiley valve is arguably the manufactured prosthesis of choice today (Figs. 11.4 and 11.5). Its simple design consists of a free-floating disc occluder suspended in a Stellite cage covered with a Teflon ring. The disc opens to 60° and closes between two eccentrically situated legs (10). As with all other synthetic prostheses however, some

Fig. 11.3 Artificial heart valves were successfully developed in animals.
anticoagulant treatment is essential to prevent thrombosis. This is a distinct disadvantage of these devices, despite their proven efficacy over 30 years.

Fig. 11.4 The tilting disc aortic heart valve, with the tilting action shown in cross sectional profile. Picture courtesy of Medtronic, all rights reserved.

Fig. 11.5 Tilting disc aortic heart valve. © Science Photo Library, all rights reserved.
Allograft Valves

Carrel had shown that vascular tissue could be transplanted and arterial grafts had been used to counter various vascular defects. Until 1952 however, only cylindrical sections of blood vessels had been so transplanted. Stimulated by the success of the ball valve, implanted in the descending aorta, in the treatment of aortic valve insufficiency, Lam transplanted the aortic valve from a donor into the aorta of a recipient dog (11). The transplanted valves would function but only if the recipients own aortic valve was rendered incompetent by cutting one of the cusps. Of significance was the fact that there were no thrombotic complications. This allograft transplant technique was used in humans (12) in 1960 and later Duran and Gunning actually managed to place the donor valve in the natural, subcoronary position. Not surprisingly, the valves functioned well haemodynamically. The rejection complications that were experienced with these non-vascular, relatively inert pieces of tissue in many cases appeared to be minor. Therefore there were many experimental studies in dog to establish the optimal methods of preparation and storage of the valves before transplantation (13). With the limited techniques examined, the use of fresh tissue appeared best, although freeze drying or storage in betapropriolactone conferred some advantages.

Such studies began to subside when it became clear that there were severe logistic problems in the reliance upon the availability of sterile, allograft valves of the ideal size. By the mid-1960s it was realised that valves from other species would “solve all procurement and size problems if combined with a suitable sterilisation method” (13).

Transplantation of Animal Heart Valves: Xenografts

Freeze-dried pig aortic valves were placed into the aortae of dogs (14), some of which survived 8 months. Following this experiment there were many other studies where valves from pig, sheep, calf or goat were transplanted into other species, usually dog (15). Rejection phenomena were variable and were inhibited by azathioprine, although the use of long-term immunosuppressant therapy in patients was not considered a viable prospect. Significantly, there were no problems of clotting around the valve.

Research became focused on methods of treating the valves before transplantation to ensure durability and, by reducing antigenicity, prevent rejection. One of the most comprehensive studies was that of Carpentier...
and his colleagues (16). These workers made various extracts of xenograft valves and tested their antigenicity by agglutination tests in appropriately inoculated rabbits, intradermal tests in guinea pigs and immunofluorescent studies of differently treated valves implanted subcutaneously in rat. It was found that extensive washing or electrodialysis could remove much antigenic material, the remainder (mainly glycoprotein) was denatured by metaperiodate oxidation. The remaining free reactive groups on the valve were bonded together by a tanning agent, glutaraldehyde (this also prevents the subsequent denaturing of the collagen in the implanted valve, which would result in loss of shape and flexibility).

By this treatment Carpentier and his colleagues produced a biologically inert, functional and durable valve. After such treatment it could not accurately be termed a xenograft. Carpentier described it as a “bioprosthesis” – something between a graft and a synthetic prosthesis. Clinical experience with the bioprosthesis (usually porcine) has been good, with a negligible rate of thromboembolism.

Corrigan’s quote: “cure of inadequacy of the aortic valve is probably beyond the reach of medicine” has been confuted. Today patients that develop serious valvular defects need no longer simply be advised to avoid “strenuous exertion or fatigue.” With a prosthetic or bioprosthetic valve they can anticipate a decade symptom-free, possibly without the disadvantage of anticoagulant therapy. It is difficult to imagine that this could have been achieved without the animal experiments that began in 1933 with Gibbon’s first attempt at cardiopulmonary bypass in cat.

Anticoagulants for Prevention of Clotting Around Heart Valve Prosthesis

The foreign surfaces of artificial valves will inevitably initiate clotting. Anticoagulant therapy is thus essential for patients with valve prostheses. Although heparin (which is extracted from animal tissues) is a valuable anticoagulant that can be used temporarily after the immediate post-operative risk of haemorrhage, it is not orally active, and thus of no use for long-term anticoagulant therapy.

The standard anticoagulants used for prophylaxis with heart valves are all chemically similar to the prototype drug, Warfarin.

Warfarin was developed as a consequence of the study of a strange bleeding disorder that suddenly occurred in cattle on the northern prairies of the USA
in the early years of the last century. Surgical procedures such as dehorning could result in fatal haemorrhage. In severe cases animals developed large haematomas and would bleed from the nose.

An astute veterinarian noted that the condition invariably followed the ingestion of hay or silage of sweet clover which had become spoiled during storage. Sweet clover had been planted on the comparatively poor soil of North Dakota at the end of the nineteenth century since it could be used as a substitute for corn for use as silage.

The isolation of the active anticoagulant from the “biochemical rag-bag” of the spoiled clover/hay was no easy task (18). An assay method had to be developed to track the effects of the “haemorrhagic agent” during the various extraction procedures. A measurement of the activity of the extracts on the prothrombin time, performed on diluted plasma from a particular strain of rabbit was ultimately chosen as the most suitable assay. After four years the active substance was identified as dicoumarol (3,3’-methylenebis(4-hydroxycoumarin)).

Many derivatives were synthesised, including Warfarin. These are used today to treat deep vein thrombosis as well as to limit the danger of thromboembolism in patients with synthetic valve replacements.

An earlier version of this chapter was published as: Artificial heart valves: from caged ball to bioprosthesis. RDS News October 1995 6-11.
References


4) Frater R & Ellis L (1961) Problems in the development of a mitral-valve prosthesis, in Merendino, Ref. 3.


