1 Introduction

1.1 Prosthetic heart valves

Heart valves have an important function in the human and animal body as they take part in the process of pumping blood. The heart has four heart valves, which are called tricuspid, mitral, pulmonic and aortic valves [1]. Healthy heart valves provide a one-way gate that allows blood to flow only in the desired direction. The valves open and close with every heart beat. In the course of the life of a body they can become diseased or suffer malfunction from mechanical damage, and then have to be replaced by prosthetic heart valves. Since heart valve implants were introduced around 40 years ago for the treatment of heart valve disease, a tremendous growth of technology has been achieved [2-11]. 182,000 valves are estimated to be implanted annually for developed world markets and 78,000 are implanted annually in the emerging world. Currently, there are two general categories for heart valve substitutes, which are mechanical and tissue-based valves [2,3].

1.1.1 Mechanical heart valve

Mechanical valves have evolved through several geometries starting with the first caged ball devices, followed by the caged disk, tilting disk, and bileaflet configurations as shown in Figure 1-1 [3, 7]. The caged ball design is one of the early mechanical heart valves that uses a small ball which is held in place by a welded metal cage. The ball in cage design limits the flow of fluids to a single direction. Natural heart valves allow blood to flow straight through the center of the valve, which keeps the amount of work done by the heart to a minimum. Caged-ball valves, however, block central flow and, therefore the heart needs to pump harder as the blood needs to flow around the central ball.

In the mid-1960s, a new class of prosthetic valves was designed that used a tilting disc (Figure 1-1 B) to better mimic the natural patterns of blood flow [2, 5, 8]. The tilting-

disc valves have a polymer disc held in place by two welded struts. The disc floats between the two struts in such a way, as to close when the blood begins to travel backward and then reopens when blood begins to travel forward again. This tilting pattern provides improved central flow while still preventing backflow. The tilting-disc valves reduce mechanical damage to blood cells. The improved flow pattern reduced blood clotting and infection. However, the problem with this design is its tendency for the outlet struts to fracture as a result of fatigue from the repeated ramming of the struts by the disc [2, 3, 5].

In 1979, a new mechanical heart valve was introduced. These valves are so-called bileaflet valves (Figure 1-1 C), and consist of two semicircular leaflets that pivot on hinges. The carbon leaflets exhibit high strength and excellent biocompatibility. The leaflets swing open completely, parallel to the direction of the blood flow. They do not close completely, which allows some backflow. Since backflow is one of the properties of defective valves, the bileaflet valves are still not ideal valves. The bileaflet valve constitutes the majority of modern valve designs. These valves are distinguished mainly for providing the closest approximation to central flow achieved in a natural heart valve [3, 5].

As for materials, initially metals were used for the primary structural components and polymers were used for the balls and disks. Most commonly used materials include stainless steel alloys, molybdenum alloys, pyrolitic carbon for the valve housings and leaflets, silicone, Teflon, and polyester for sewing rings [3, 5].

The main advantage of mechanical valves is their high durability. Mechanical heart valves are placed in young patients because they typically last for the lifetime of the patient. Meanwhile, they are not a natural part of the body, and there is a danger that blood clots can form on it. Due to the rigidity of them, the blood cells can be damaged and stuck to their surfaces to result in blood clotting and subsequent thrombosis. As a result, mechanical valve recipients must take anti-coagulant drugs chronically [2-11]. As a consequence, these valves are associated with significant hemorrhagic complications. In fact, 75% of all mechanical valve-related complications have been reported to occur from thromboembolism and hemorrhage [5]. Even the incidence of

thromboembolism is 2-5 % per patient and year with adequate anticoagulant treatment. Anti-coagulants can also cause birth defects, rendering mechanical valves unsuitable for women of child-bearing age [7,8].

Current estimates for developed world markets are 55 % for mechanical heart valves and 45 % for tissue valves. On the other hand, 80 % of prosthetic heart valves are mechanical in the emerging markets, which is not expected to change in the near future [3]. Therefore the side effects from the constant medication are more serious in those countries.

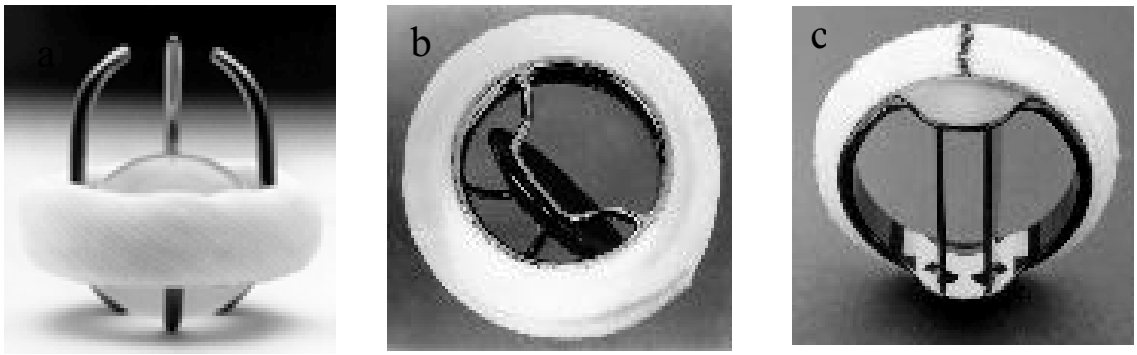

Fig. 1-1. Mechanical heart valves; (a) caged ball design, (b) tilting design, (c) bileaflet valve [7].

1.1.2 Prosthetic tissue valve

The use of tissue as part of bioprosthetic vascular devices such as heart valves and vascular grafts has long been the focus of research [8-18]. Prosthetic tissue valves are made entirely or partly of materials of biologic origin and can be classified into two groups. One is human tissue valve (homografts) and the other is tissue valve from another species (xenografts or heterografts). Both types are often referred to as bioprosthetic valves.

The animal tissue valves are typically fabricated from porcine aortic valves (Figure 1-2) and bovine pericardial tissue. In porcine valves, the valve tissue is sewed to a metal wire stent, often made from a cobalt-nickel alloy. The wire is bent to form three U-shaped prongs. A Dacron® cloth sewing skirt is attached to the base of the wire stent, and then

the stents themselves are also covered with cloth. Porcine valves have good durability and usually last for ten to fifteen years. Bovine pericardial valves are similar to porcine valves in design. The major difference is the location of the small metal cylinder which molds the ends of the wire stents together. In the case of pericardial valves, the metal cylinder is located in the middle of one of the stent post loops. Pericardial valves have excellent hemodynamics and exhibit a durability equal to that of standard porcine valves [8].

Both the porcine and bovine pericardial valves are stented valves. The metal stent in these valves takes up room which could be available for blood flow. Stentless valves are made by removing the entire aortic root and adjacent aorta as a block, usually from a pig. The coronary arteries are tied off, and the entire section is trimmed and then implanted into the patient.

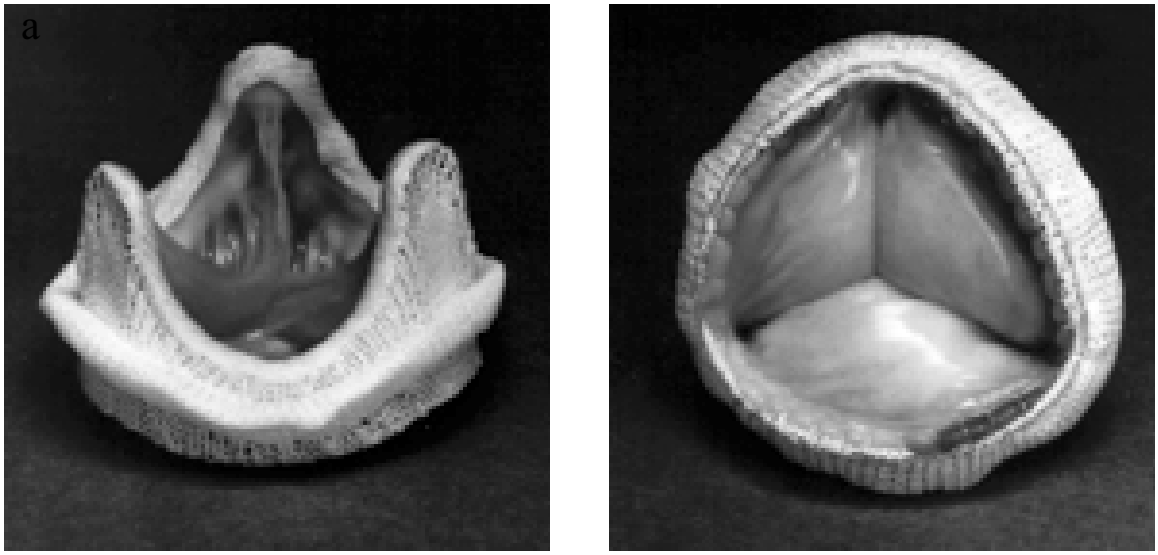

Fig. 1-2. Porcine tissue heart valves; (a) a view from side, (b) a view from bottom [7].

The use of these natural biomaterials has typically required chemical pretreatment aimed at preserving the tissue by enhancing the resistance of the material to enzymatic or chemical degradation, improving mechanical properties, and sterilizing the tissue. The most commonly accepted pretreatment reagent is glutaraldehyde, whose use has dominated since its introduction into biomedicine in the late 1960s [19]. Its success as a crosslinking and sterilizing reagent is in part due to its amphiphilicity, that is,

hydrophobicity from the alkyl group and hydrophilicity from the aldehyde group, which allows the molecule to rapidly penetrate both aqueous media and cell membranes.

As shown in Figure 1-3, glutaraldehyde (II) reacts with the Ů-amino group of lysine residues in collagen (I), which results in the formation of a Schiff base intermediate (III). Cheung et al. [20-24] suggested that crosslinking involves the formation of glutaraldehyde polymers (IV) due to aldol condensation reactions. In addition, the formation of an Ŭ-ƀ unsaturated Schiff base intermediate (V) followed by Michael addition of a collagen amino group with the unsaturated group of V to give VI results in the formation of a crosslink. Furthermore, formation of a crosslink is possible by the reaction of amino groups with the free aldehyde groups of V to give VII (n = 0), or a free aldehyde group remaining after aldol polymerization of V to give VII (n > 0).

Others claim that Schiff base are unstable intermediates that react further during the crosslinking reaction. A reaction between a protonated Schiff base and a glutaraldehyde-related enol, resulting in the formation of a secondary amine (VIII), has been suggested [25-27]. After aldol condensation and subsequent reaction with collagen amino groups the formation of aliphatic crosslinks (IX) is possible.

Host endothelial cells which normally cover the inside of all blood vessels do not typically grow on bioprosthetic tissues when implanted into patients, and the cytotoxic effects of glutaraldehyde presumably contribute to this lack of endothelialization. The crosslinking chemicals have been shown to leach slowly from tissue-derived bioprostheses fixed in glutaraldehyde, producing cytotoxic effects [28, 29].

The most common cause of bioprosthesis failure is stiffening of the tissue due to the build up calcium salts. Calcification can cause a restriction of blood flow through the valve (stenosis) or cause tears in the valve leaflets as shown in Figure 1-4. In the valve shown there, cusps of the valves are totally distorted and degenerated due to dense calcification. The exact mechanism for calcification is not known, but the process has been attributed to several factors: the presence of unreacted glutaraldehyde, the attraction of calcium ions to glutaraldehyde or the disruption of cellular calcium regulatory mechanisms by glutaraldehyde. This detrimental side effect of

glutaraldehyde processing severely limits the lifetime of treated tissues [30, 31]. Even though this problem is not solved yet, many approaches have been under investigation to neutralize the toxic effects of glutaraldehyde. For example, L-glutamic acid was used to extract and neutralize aldehyde groups from treated tissues [32, 33]. Other approaches include the use of chondroitin sulfate [26], protanmine [34], diphosphonates [35] and homocysteic acid [36].

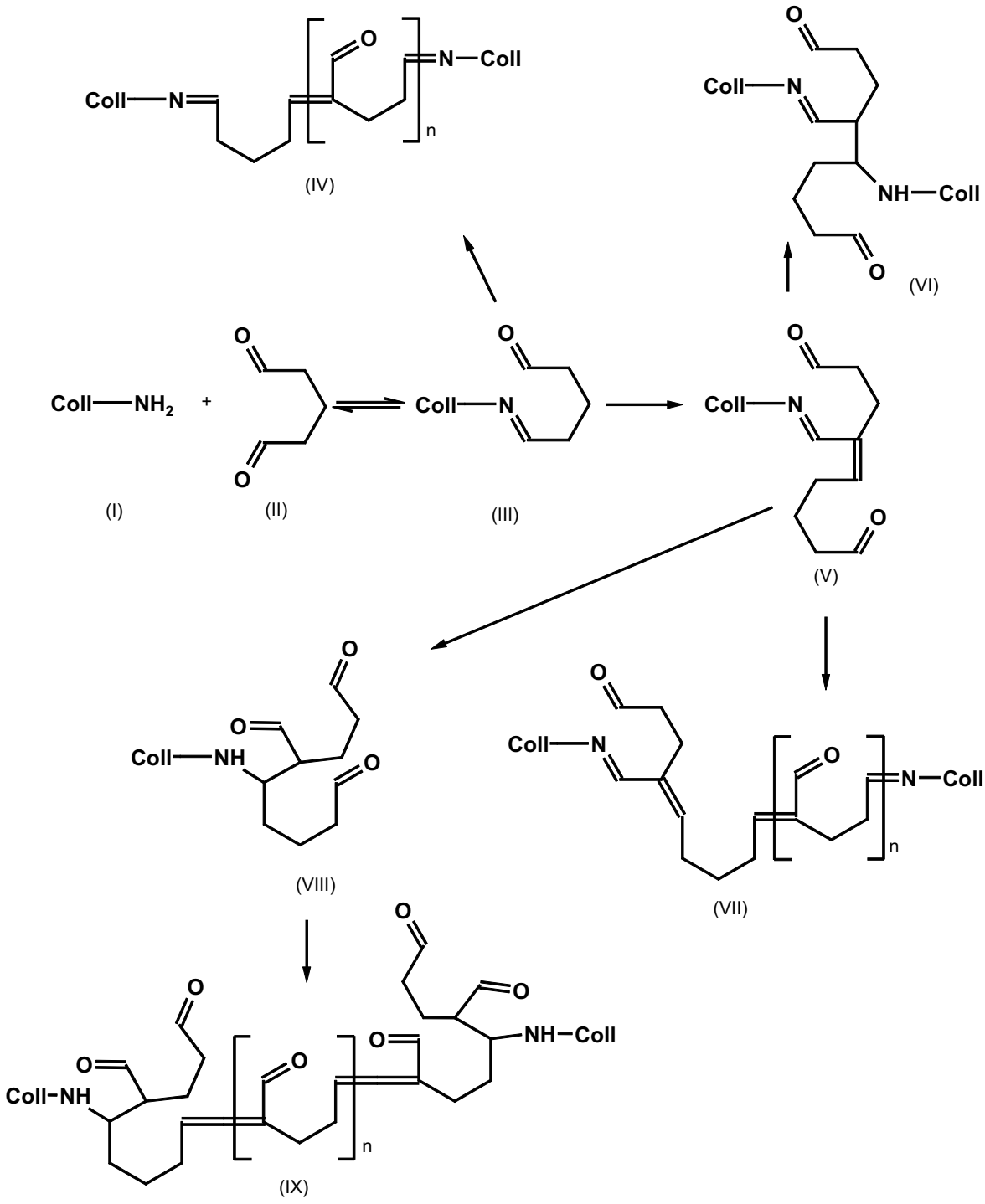

Fig. 1-3. Crosslinking of collagen through Glutaraldehyde treatment.

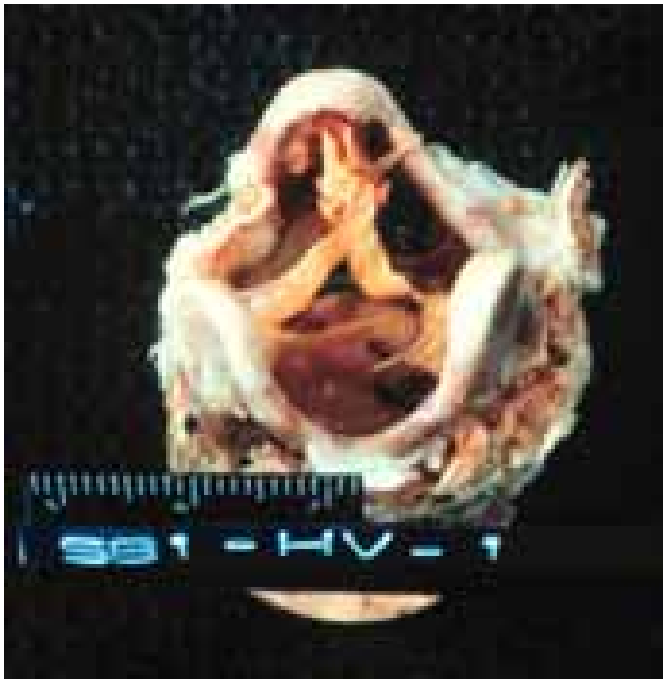

Fig.1-4. Calcified and degenerated porcine aortic heart valves after being implanted in the human body. This clinical porcine bioprosthetic valve was removed because of extensive calcification, which can result in cuspal tears and stenosis or narrowing of the valve opening.

Bioprosthetic valves hold many advantages over mechanical valves. The design of bioprosthetic valves is closer to that of natural valves. Bioprosthetic valves do not require long-term anticoagulants, have better hemodynamics, do not cause damage to blood cells, and do not suffer from many of the structural problems experienced by the mechanical heart valves. On the other hand, the disadvantage of bioprosthetic valves over mechanical valves is indurability due to calcification as described above. Since the calcification is caused by the absence of endothelial cells on valve surfaces, re-endothelialization is very attractive subject to this area. If the endothelial cell adhesion on the bioprosthetic valves is improved, they will have a significant advantage over mechanical valves.