

PATHOLOGY OF INFECTIOUS AND INFLAMMATORY DISEASES OF PROSTHETIC HEART VALVES

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Prosthetic heart valves are one of numerous cardiovascular prosthetic devices used for the management of valvular heart disease. Prosthetic heart valves, as well as most prosthetic cardiovascular devices, serve their "owner", well and for long periods of time. In the process, treating the serious underlying condition, as well as making the quality of life for the individual, much better. Prosthetic heart valves have been in use since the mid 1960's and came into their own, a few years later. Today, well over 2 million individuals receive a cardiovascular prosthetic device in the United States. Worldwide, the numbers are considerably larger.

Of these, prosthetic heart valves (PHV) account for over 250,000). Prosthetic heart valves may be mechanical heart valve prosthesis, when they are made totally of synthetic materials or they may be bioprosthetic valves when they are made, at least in part of biological materials (1,2). Clearly, the name bioprosthetic valves, is misleading, since they are only partly made of biological materials, which are in the majority of instances, porcine tissues. It is only in the autograft that the graft valve is a living tissue.

Prosthetic heart valves, as any other cardiovascular prosthesis can show post-implantation changes. These can be broadly categorized as:

1. Thrombi and thromboembolism
2. Anticoagulation related hemorrhage
3. Infection.
4. Pannus or an exaggerated response to the prosthetic heart valve
5. Tissue degeneration or other forms of biomaterials failure
6. Pannus or host tissue reaction including inflammation and / or toxicity
7. Adverse systemic effects: such as migration of entire device, of biomaterials or a hypersensitivity reaction to the materials.

Underlying Basis of Reactions:

Most of the reactions that are reported are

- A) the result of interaction of the device with the host's tissues or
- B) the effect of the host on the device and the results of this.

Device failure is usually a complex process with many potential and real causes some that are easily understood, while others that are still not clearly defined or understood. One must keep in mind that these PHV are constantly bathed in a rapidly flowing blood stream, in a living and often growing heart.

Prosthetic heart valves may be mechanical or biological

Mechanical heart valve prosthesis needs the individual to be on life-long anticoagulant therapy and that the patient's anticoagulant status (listed as the INR) be regularly measured (or checked), at least once every two weeks. Depending on the PHV, the INR is maintained at different recommended levels, ranging from 1.4 to over 2.2 international units.

Bioprosthetic heart valves, on the other hand, do not need anticoagulant therapy.

Contemporary prosthetic heart valves include:

A Mechanical Valves:

- 1a. Starr-Edwards, Ball in cage, mechanical prosthesis (Edwards Life Sciences)
- 1b. Bileaflet valves
2. Tilting disc valves

B. Bioprosthetic valves:

1. Stented porcine valves
 - a) Unstented - St. Jude Medical T-SPV; Medtronic - Freestyle
2. Pericardial valves:
 - a) Carpentier-Edwards bovine pericardial
3. Homograft valves:
 - a) Cryopreserved
4. Autografts (Ross procedure)

As already listed, inflammation of some degree at least, occurs at every heart valve implantation site. The act of removing the native valve, either partially or completely, damages tissues, leads to the formation of a small amount of thrombus, and the migration of a variable number of inflammatory cells. Implantation of a PHV, leads to further trauma and the presence of a new "foreign material", leads to further inflammatory cell exudation. Immediately after the patient comes off the Heart-Lung bypass machine, a variable film of thrombus is deposited on the fabric of the prosthesis stent and to an even more variable degree, the surface of the prosthetic tissues (especially bioprosthesis). Depending on the site at which the prosthesis is implanted, the reaction may be more or somewhat less aggressive.

A florid acute inflammatory reaction or Infective endocarditis is rare but may be seen through the lifetime of the device implant duration. While usually seen in about 2% of cases, it can range from 1 - 6% of prosthetic valve replacements and is associated with a 50% mortality. The effects of this infection include embolization of vegetations to different sites including coronary arteries, resulting in microemboli into the myocardium with resultant acute myocarditis (bacterial), congestive heart failure secondary to the obstruction of the orifice and resultant stenosis and / or regurgitation due to the presence of large vegetations and possibly destruction of the valvular tissues by virulent microorganisms (3,4,5).

In the case of mechanical heart valve prosthesis, tissue destruction surrounding the annulus or the sewing cuff of the prosthesis, generally results in a "ring" abscess, since micro-organisms cannot grow on the synthetic surfaces (6)

Mechanical and bioprosthetic heart valves have a more or less similar infection rate. The incidence of infective of endocarditis is higher in patients who have been operated for infective endocarditis and in intravenous drug abusers (4,5).

Incidence:

Prosthetic valve endocarditis (early), is generally highest in the first few months after surgery. In fact, it used to be even higher in the early post-operative period. In this instance, the endocarditis was likely related to microorganisms present on the device. Today, this is seldom seen, except in patients who undergo valve replacement for infective endocarditis. While common in the first few months, it can occur, through the life of the implant.

Microorganisms:

The large majority of cases of infective endocarditis are due to the common microorganisms seen in hospitals and on the patient's skin. Early infections are from the patient's own cutaneous flora suggesting possible contamination and bacteremia with resultant infective endocarditis.

Later infections are almost always due to an infection located at some other site and are generally associated with Staphylococcal bacteria, especially Staph. aureus and epidermidis. Less common microorganisms are gram-negative bacilli and fungi (5-9).

Type of vegetation:

The types of vegetations associated with Staphylococci infection are generally small, and highly tissue destructive, reflecting the virulence of the microorganism. Streptococcal infections tend to lead to larger vegetations with slower milder destruction of tissue.

Fungi: Fungi, being generally of low virulence, are associated with large bulky vegetations.

Due to the location of the infection to an avascular or virtually avascular milieu, host defense mechanisms, as well as antibiotics cannot really lead to a cure. Bioprosthetic materials allow the growth of thrombotic vegetations with the microorganisms in them and can result in the gradual destruction of the cuspal tissue.

Mechanical prosthesis, on the other hand, not having any biological components, do not support either bacterial or fungal growth. Infections, in these instances, are almost always located in the periprosthetic tissues that are at the interface of the sewing cuff and the native tissues. They often are associated with a ring abscess and the prosthesis itself may be nearly, totally dislodged, at least from its "anchorage" to the native vascular or myocardial tissues.

This tissue destruction leads to "valve dehiscence" giving rise to a fairly typical echocardiographic appearance of a "dancing" prosthesis. It also leads to a paravalvular leak, which gradually increases in size and significance, with resultant deterioration of cardiac function.

Biological reaction to heart valve prosthesis:

Inflammatory reactions (other than infective endocarditis) to biological heart valves are rare. A mild mononuclear cell reaction, invariably macrophages, is at times seen in biological materials. This is particularly common in pericardial valves where a single layer (or a multilayer) rim of macrophage-like cells is seen on the surface of the "cusps".

This reaction is more pronounced on the sinus or non-flow surface. In time, this appears to increase and can be seen on both the flow and non-flow surfaces. The significance of these macrophages is uncertain, since they are seen in areas where there is relatively mild, or even no destruction of cuspal tissue, as well as in areas where there is significant damage to cuspal tissue. Whether this is the same mass of mononuclear cells, that was present soon after implantation or appeared later, is uncertain.

Macrophages contain lytic enzymes and it is difficult to imagine that these lytic enzymes do not release the enzymes with resultant destruction of the cuspal tissues. Whether the process is slower and longer in aldehyde fixed (cross linked collagen) tissue or not, is difficult to assess.

Mechanical heart valves:

Most of these prosthesis have "naked" synthetic fabric as the material of the sewing cuff. Some have sponge-like material forming the body of the sewing cuff. A reaction to this fabric material is usual and has been listed above.

St. Jude Medical leaflet, Silzone® Coated:

A few years ago, the St. Jude Medical bileaflet valve-sewing cuff was coated with elemental silver. This was an effort to eliminate infective endocarditis. In the early post implant period, there was clinical evidence of infective endocarditis / annular abscesses from some centers. At the time of surgery, these abscesses were huge, associated with a marked degree of native tissue destruction and at the time of surgery, some of these devices were found to be held in place by just one or two sutures and were found in a deep abscess-like cavity filled with grey necrotic material. This material was invariably culture negative. Examination of the tissues showed necrotic debris and again no morphologic evidence of microorganisms was seen. However, the tissues surrounding the "abscess" or "annular abscess" showed abundant tissue necrosis. No good explanation has been available for this. The tissue necrosis was possibly related to the effect of the elemental silver, which may have leached out of the fabric into the surrounding tissues and resulted in myocytolysis, as well as the destruction of the interstitium.

These early explants showed several other features, different from those seen with the old model of SJM valves.

Biological valves have seldom, if ever, been reported to induce a significant cellular reaction, in the absence of infective endocarditis. Whether this is due to the fact that this is dead tissue, aldehyde fixed tissue on a stented frame or some other reason, is not yet certain. There have been virtually no reports of cellular or humoral rejection of these xenografts or even of homografts.

The stentless valves, not having a prosthetic stent or sewing cuff, could be more likely to have a cellular reaction against them (10-14). However, in most instances, including homografts and the Toronto-Stentless Porcine Valve®, this has not been reported. The tissues have never shown a reaction, either the porcine aortic tissue, nor the porcine cuspal tissue. In the instance of the other stentless valve, the Freestyle valves, there is only a minimal cuff of fabric covering the proximal edge of the porcine aortic tissue. We have recently seen a mononuclear cell reaction to the tissue with resultant damage to the porcine aortic tissues. Clinically, this has resulted in prosthesis dysfunction, with resultant incompetence. This reaction is suggestive of graft cellular rejection

Infective endocarditis has also been reported with the stentless porcine valves, just as it has with the stented porcine valves. The role of biofilms in the infections seen with mechanical heart valves is still to be determined (15).

Conclusion:

Prosthetic heart valves, Mechanical or biological (Xenograft valves, stented or unstented, have been reported to show an inflammatory reaction (infective endocarditis). This is predominantly associated with bacterial / fungal infection. Somewhat surprisingly, no immune reaction has been reported thus far. This may, amongst other reasons, be related to the fact that the tissues "sit", virtually in a cocoon of synthetic material (the valve ring and the fabric covering it). The stentless valves, however, have no such "cocoon". While the T-SPV has such a "cocoon", albeit significantly thinner and narrower, the Freestyle valve has no such "cocoon". It is perhaps not so surprising therefore that at intermediate term (five to six years), we are beginning to see some occasional cases in which such a reaction is noted.

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