

PATHOLOGY OF VENTRICULAR ASSIST DEVICES AND THE ROLE OF BIOFILMS

Robert Padera, M.D., Ph.D.
rpadera@partners.org
Department of Pathology
Brigham and Women's Hospital
Harvard Medical School

Introduction

Ventricular assist devices (VADs) have been used for more than a decade to improve hemodynamics and end-organ function as a bridge-to-transplant in patients with end-stage heart failure. Treatment with VADs as destination therapy has also been shown to increase survival over optimal medical management in patients with end-stage heart failure who are not transplant candidates. Infection in patients with VADs is common, difficult to treat and one of the most common causes of death in patients with VADs.

Infection in Ventricular Assist Devices

Infection is unfortunately a common complication of mechanical circulatory support. The presence of infection may delay transplantation in bridge-to-transplant patients, and is a major cause of both pre-transplant mortality in bridge-to-transplant patients and overall mortality in patients with destination therapy VADs. In contrast to most permanent implantable cardiovascular medical devices such as coronary artery stents, heart valves, pacemakers and automated implanted cardioverter defibrillators, most currently available VADs maintain percutaneous connection with the epidermal surface and external environment via a driveline, which is required to provide power and controller functions.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated the superiority of mechanical circulatory support to optimal medical management in sustaining the lives of patients with severe symptoms of congestive heart failure that were not heart transplant candidates. However, infection was a common complication in the VAD arm of this trial. Freedom from sepsis was only 58% at 1 year and 48% at 2 years in the VAD arm, with the hazard for initial diagnosis of sepsis peaking within the first 30-60 days after implantation. The most common cause of death in the VAD arm was sepsis (20/52 patients). A total of 28 patients suffered a sepsis syndrome, 19 patients had a driveline infection and 11 patients had a pump infection. Many other studies have yielded similar rates of infection in bridge-to-transplant VAD patients.

The most common organisms responsible for VAD infection are biofilm-forming bacteria such as *Staphylococcus sp.*, *Pseudomonas sp.*, and *Enterococcus sp.*, as well as fungal infections such as *Candida sp.* Not surprisingly, the percutaneous driveline is the most common portal of entry for these organisms. Many VAD related infections occur early after implantation before the driveline site has fully healed and been integrated into the host tissue. Factors that retard healing, such as excessive movement or trauma at the exit site, poor nutritional or overall status of the patient at the time of

implantation, and diabetes mellitus, may also increase the likelihood of driveline infections in these patients.

Biofilms

It has long been known that a substantially smaller number (by several orders of magnitude) of organisms is required to form an infectious abscess in the presence of a foreign material than in the absence of one, largely due to the advantages afforded an organism by its development of a biofilm. A biofilm is a multicellular consortium of microbial cells that is irreversibly associated with a surface and enclosed in a self-produced extracellular matrix composed primarily of polysaccharides. Van Leeuwenhoek first described this phenomenon as he investigated organisms on tooth surfaces using his simple microscopes. Others later described that bacteria demonstrated enhanced growth and activity in the presence of a surface, and that the concentration of organisms on a submerged surface was significantly greater than that in the surrounding fluid. The advent of the electron microscope allowed detailed analysis of surface biofilms, first in environmental (e.g., rocks in a stream) and industrial (e.g., water pipes) arenas, and later on medical devices. Biofilms also grow on native tissue surfaces, examples being *Pseudomonas aeruginosa* biofilms forming in the airways of patients with cystic fibrosis and organisms forming biofilms on teeth resulting in dental plaque.

When a foreign material is placed into the body, a host of molecules interact with the surface, including fibronectin, vitronectin, fibrinogen and other proteins, glycoproteins, proteoglycans, polysaccharides, lipids, and ions, to form a conditioning film. The nature of this conditioning film depends on properties of the material, such as surface chemistry and charge, microarchitecture and degree of hydrophobicity or hydrophilicity, as well as the properties of the tissue/fluid, such as pH, protein concentration and hydrodynamic forces, to which it is exposed. These interactions occur over the time course of seconds to minutes upon exposure of a surface to biological fluid. Free-floating (or planktonic) organisms initially interact with the conditioned surface nonspecifically through electrostatic, Van der Waals and hydrophobic interactions to reversibly adsorb to the material. Properties of the organisms, such as their surface charge, the presence of fimbriae and flagella and the production of an extracellular polysaccharide coat, also influence the attachment of microbes to a surface. Some microorganisms such as *Staphylococcus epidermidis* have surface molecules through which they can directly attach to bare polymer surfaces (staphylococcal surface protein-1, autolysin E). These same molecules, as well as others such as the fibrinogen receptor ClfA (clumping factor) and the fibrinogen-binding protein FbpA in *Staphylococcus aureus*, allow organisms to attach to the components of the conditioning film. Once attached, the organisms begin to proliferate and accumulate in multicellular clusters, spread across the surface and secrete extracellular polysaccharides to further their adhesion to the surface. These activities require intercellular adhesion mediated by, in *Staphylococcal sp.* for example, polysaccharide intercellular adhesin (PIA – a glycosaminoglycan) and accumulation associated protein (AAP). The organisms also can communicate with each other through diffusible molecules in a process termed quorum sensing in order to coordinate their behavior. The biofilm develops into a three-dimensional structure with internal architecture including pillars and channels through which fluid can flow. The mature biofilm is composed of about 10-25% organisms and 75-90% extracellular material mostly in the form of polysaccharide matrix.

Once a microorganism has attached to a surface, there are changes in gene expression that allow the formation of the biofilm; the discovery of this phenomenon and the realization that surface-associated organisms are behaving in a fundamentally different manner than their planktonic counterparts is advancing the understanding of material-associated infections and providing insight into potential therapeutic targets. DNA microarray analysis and gene expression profiling, common research tools in the study of tumors and many other human diseases, are being used to study differences in gene expression between organisms in a biofilm and planktonic organisms under a variety of different environmental conditions and as a function of time over the development and growth of the biofilm. There is even evidence of differences in gene expression within the biofilm, depending on where the organism is in relation to landmarks (e.g., deep within the polysaccharide matrix vs. at the outer surface of the biofilm) and the environmental conditions (e.g., pH, pO₂) at that location.

Several mechanisms are employed by organisms in biofilm to evade the host defense system. The extracellular polysaccharide matrix impedes the penetration of opsonizing antibodies so they do not reach the underlying organisms, making uptake and killing by phagocytes less efficient. The presence of the matrix has been shown to reduce the phagocytic ability of macrophages and polymorphonuclear leukocytes both on material surfaces and even after organisms have been released from the biofilm, promoting sepsis. There is evidence that this may be at least partially due to a resistance to reactive oxygen species produced by the phagocytic cells.

The biofilm also hampers the efficacy of antibiotics in the treatment of material-associated infections. Organisms in a mature biofilm divide at a lesser rate, making them less susceptible to certain antibiotics. The organisms tend to be organized deep within the extracellular polysaccharide matrix, making them less accessible to therapeutic antibiotics. Antibiotic concentrations between 1,000 and 15,000 times greater are needed to kill biofilm-associated organisms than their planktonic counterparts as a result of the physicochemical properties of the matrix. The difficulty in eradicating organisms from a biofilm often necessitates prolonged periods of antibiotic use, furthering the development of resistant organisms within the biofilm. Bacteria within a biofilm can become resistant to certain antibiotics through the accelerated acquisition of resistance plasmids (extrachromosomal DNA) from other bacteria through the process of conjugation, which occurs with greater ease within the physically protective environment of the biofilm. Another change in biofilm-associated organisms is that of the proteins of the cell wall, often furthering resistance to antibiotics.

Organisms from the biofilm, or parts of the biofilm itself, routinely dislodge into the bloodstream. This dissemination of organisms can lead to sepsis and the metabolic alterations that arise therefrom, or embolic phenomenon resulting in ischemia and infarction in the affected organ. Gram-negative bacteria within biofilms may shed lipopolysaccharide into the bloodstream causing septic physiology. These mechanisms are common pathways resulting in mortality in patients with ventricular assist device related infections.

Implications for Patient Care

The risk of a patient with a VAD developing infection is greatest around the time of implantation, so careful attention to infection prevention and control guidelines in the perioperative period is essential. Considerations include patient selection and preparation, correction of malnutrition, appropriate prophylactic antibiotics, proper

maintenance of indwelling catheters and lines, and elimination of other sources of potential bacteremia (e.g., poor dentition) prior to implantation, meticulous attention to sterility and proper implantation technique in the operating room, and attention to immobilization, promotion of wound healing and sterility of the driveline in the postoperative setting.

It is extremely difficult to eradicate a device-related infection, especially in light of the protective properties of the biofilm. Identification of the offending organism and its susceptibility to antibiotics is an important first step in controlling the infection. Treatment with appropriate antibiotics is essential. In bridge-to-transplant VAD patients, infection tends to delay, but not preclude, eventual transplantation, and does not tend to negatively affect long-term survival. A likely explanation for this is that the device, and therefore source of the infection (biofilm), is removed at or around the time of transplantation. In destination VAD patients however, it is possible to control the infection over prolonged periods of time, but recurrences of the infection are common and cause significant morbidity and mortality in this population.

Future Directions

A decrease in the incidence of device-related infections would be expected to yield a further increase in survival and decrease in morbidity in VAD recipients. Several strategies are being employed to address the issue of infection, now with a better understanding of the mechanisms and physiology of biofilm and its role in VAD infections: 1) development of completely implantable systems with transcutaneous energy transmission to eliminate the need for a percutaneous driveline, 2) materials technology to promote tissue integration and prevent biofilm formation, to allow host tissue to win the "race to the surface", 3) controlled release technology to allow for prolonged antibiotic release from component of the VAD itself, 4) improvements in patient selection, operative technique and postoperative management, 5) development of novel therapeutics that may interfere with the mechanisms of biofilm formation such as intercellular adhesion or quorum sensing, 6) device design to smaller and more durable pumps, and 7) creative placement of driveline exit sites (e.g., postauricular) to allow for better tissue integration. It should be noted that substantial progress has already been made, as evidenced by lower infection rates in the post-REMATCH era, and lower infection rates for many of the newer devices in clinical trial and use currently.

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