Expert Insights

Pioneers and thought leaders provide perspectives on some of the hottest topics for

Our cover story for this issue deviates from our customary format. The following presentations were made at the Masters & Legends Symposium at the New Cardiovascular Horizons in New Orleans, October 2003. The articles printed herein are intended to represent each author's original lecture.

Stents from the Past, Present, and Future

To appreciate the potential of stenting, we must first understand the biological processes required for them to function properly.

BY JULIO C. PALMAZ, MD

In view of the incredibly favorable biological response of diseased vessels to stents, the success of these devices should not be surprising. During the past 10 years, there have been some evolutionary changes in stents. However, the drug-eluting stent (DES) is undeniably the most fundamental change in stent technology since its inception.

The first human pathological specimens of an implanted stent that we retrieved were from a patient who died of cancer 2 years after receiving one of the early coronary stents. Examination of the stent confirmed many of the fundamental findings we had observed in animal models in the early 1980s. This first specimen was of the right coronary artery, and the offending lesion was displaced outwardly by the stent. The device itself was completely encapsulated in tissue, maintaining a patent lumen and forcing this artery to an external diameter of 9 mm.

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The changes produced by the stent were so remarkable that I was forever committed to the idea that the healing of stents was to be promoted, and that whatever technological development we did in the future had to follow this principle.

A major question in the early days was: If this technology is going to be fundamental, would it have the same beneficial results in other applications within the cardiovascular system? Fundamental technology should work through a range of sizes and circumstances in the vascular environment. Stents had such a broad impact in cardiovascular disease that they deserve to be considered fundamental technology.

As DESs come to play a major role, the challenge that they must face is whether they are universally effective. There is no question that DESs have had incredible success based on their huge impact in the coronary circulation. But as they prove to

be less successful in other vascular territories, it becomes necessary to question why. DESs have not been very successful in the femoral popliteal area and dialysis access fistulas, and it is not likely that the performance of large stents will be improved upon. The failure mode of stent healing in the small vessels is inflammation and proliferation. Inhibitory technology, such as the DESs, addresses that problem in a direct fashion. In large vessels, the failure mode of stents is inadequate healing marked by thrombus formation and delayed tissue colonization. Inhibitory techniques do not address the problem; they actually may make it worse.

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The largest implantable vascular device is the mechanical heart. Modern mechanical hearts, such as the Abiocor (ABIOMED, Inc., Danvers, MA) are a marvel of electronics and engineering. Nonetheless, it still suffers from the same problem that affected the early mechanical hearts—microembolization.[1] This is evidence of a lack of healing of the implant. The materials that mechanical hearts are made of do not prevent thromboembolization and are not incorporated by the tissues, resulting in an expected failure mode. A variety of devices, all large in size, share similar problems. Each of the failure modes of these devices, in whatever proportions they are reported to exist, are related to lack of tissue response. The AAA bypass grafts, the ASD and PFO occlusion devices, the left atrial appendage occlusion devices, and the early results on implantable transcatheter valves all show that leaks and dislodgment are going to be a problem. DES technology will not address the limitations that affect all large vascular implantable devices.

PROMOTING HEALING

Leon et al pointed in this direction as early as 1989, when they foresaw the need to enhance the healing response to stents.[2] Their approach was to apply genetically modified endothelial cells to stents prior to implantation to accelerate healing and improve patency.

Currently, there are a few approaches to promote healing in endovascular devices. One example is a stent covered with an antibody against CD34, intended to promote the adhesion of circulating progenitor endothelial cells.[3] Another similar approach is a stent graft covered with ePTFE impregnated with an adhesive peptide (P15) aimed at enhancing the endothelialization process.[4]

The way that a lesion in a vessel heals after it has been treated with an invasive technique that does not involve the placement of a material, such as atherectomy or balloon angioplasty, is a highly organized cascade of reactions by agents that exist in micromolar concentrations but have a very high specificity. By contrast, vascular materials interact with blood and tissues in a different way. At the material-blood interface there is no organized sequence of events. Rather, interaction is a chaotic phenomenon, actually dominated by acute phase reactants, which are present in large concentration. The relevance of the factors involved in the early phases of the healing of materials is based on the concentration in the blood and the relative surface affinity for the material. Fibrinogen plays a very important role in the early interaction of materials with blood because of its abundance and its highly adaptive surface adhesive mechanisms.

Chain Reactions

Understanding how materials react in blood has been largely influenced by the theory proposed by Leo Vroman.[5] Vroman postulated that when a material is placed in contact with blood, there is a sequential deposition of blood proteins onto the surface of that material. Albumin, IgG, fibrinogen, fibronectin, and high-molecular-weight kininogen predominate on the surface transiently, giving way to the next protein. Protein-specific ligands are momentarily available on the surface, causing specific cellular adhesion, such as neutrophils, monocytes, and platelets. The eventual appearance of high-molecular-weight kininogen, which is a nonadhesive protein, hopefully will render the surface relatively passivated.

Unfortunately, this sequential protein deposition does not occur with the majority of the known vascular materials. In our laboratory, we observed that the interaction of materials with blood proteins is actually chaotic and simultaneous, and they that blood proteins occupy the surface sites in relationship to their relative affinity for the surface and their concentration in blood.

For this reason, fibrinogen is of primary importance in the biocompatibility of blood-contacting materials. Fibrinogen, an abundant protein measured in grams per liter, is an acute phase reactant, highly prepared to deal with foreign surfaces, whether they are hydrophilic or hydrophobic. It has the ligands for the cells most relevant to thrombus and inflammation—platelets and

monocytes. Also, it may provide adhesive sequences for endothelial cells. Although it is not clear, it seems that depending on the configuration of the molecule after it is immobilized on a surface, ligands for desirable or undesirable cell interactions may predominate on fibrinogen-coated surfaces. It appears that it is not the physicochemical properties of the surface that determine blood and tissue responses. Rather, it is the amount and conformation of fibrinogen on the surface and the resulting ligand exposure that determine the type and amount of cells populating the surface. Of course, other adhesive proteins such as vitronectin and fibronectin play a role, but given their miniscule concentration in blood compared to fibrinogen, they seem to be less relevant.

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We have found, using monoclonal antibodies designed to bind to sites of the fibrinogen molecule containing a specific ligand sequence, that certain materials, such as 316L stainless steel, induce a favorable conformation of fibrinogen with a relatively higher concentration of adhesive sites for endothelial cells than for platelets and monocytes. By contrast, gold exhibits as many sites for endothelial cells as it does for platelets and monocytes, explaining its poor performance when used as a material to coat vascular stents.

Nanotechnology

The surface of most of the materials currently used to fabricate stents and stent grafts is actually a mixture of polar and hydrophobic areas in a rather irregular mosaic distribution. Unfortunately, some of these areas are relatively large and/or irregularly distributed. In other words, these surfaces are not engineered. An engineered surface would have a homogeneous distribution of sites of regular size and shape across the surface's plane. With engineered surfaces, it might be possible to design strategies such as to provide polar centers to bring a protein molecule close to the surface and trap it by hydrophobic adhesion. The hydrophobic areas must be commensurate with the molecular size, and the polar areas need to be designed to provide enough attractive force to be effective.

Cells React to Surface Micropatterning

The fact that cells are sensitive to surface patterning was shown at Harvard University Hospital.[6] These investigators recognized that when endothelial cells are placed in a nonadhesive area dotted with adhesive sites, they undergo a change in growth and migration behavior. As cells try to reach out and find adhesion sites, they get larger and develop shapes that reflect the geometry of the adhesive pattern. Interestingly, the apoptotic rate decreases at the same time that DNA synthesis and growth rate increase. This may be good news from the point of view of what we are trying to do—endothelialize a surface quickly and improve the survival rate of the endothelial cells. This group identified the mechanism for this phenomenon as being caused by spreading the cytoskeleton and molecular signaling originated at the adhesive integrin-ligand complex through the cycling cascade to open up the G1-S gateway. Interestingly, this mechanism is rather the opposite of what sirolimus does. As such, micropatterning could be an intriguing possibility to antagonize the effect of sirolimus on endothelial cells. What it is most fascinating about surface micropatterning is the fact that a profound biological effect can be elicited without the use of powerful pharmacological agents by arranging and combining conventional materials.

THE FUTURE

From the perspective that we have today, there is no question that DESs are here to stay and they have achieved a profound impact on patient care. In the future, my prediction is that they will have a specific, rather than a wide application. Techniques that we have seen using CD34 antibodies or adhesive proteins will increasingly appear, marking a trend toward promoting healing. I would like to think the engineering of surfaces by using conventional materials and the application of microelectronics will be the next major step in the evolution of stents. ■

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