increased affinity of fibrinogen and fibronectin for artificial surfaces, compared with albumin is evident, despite markedly lower physiological concentrations of the former two. The dynamic deposition study of fibrinogen on stainless steel supports the contention that the rate of deposition is limited to the availability of binding sites until saturation takes place. This time-dependent relationship corresponds to the exponential Langmuir adsorption model.[5] The higher retained protein fraction on metals as compared with polymers may be related to the higher total energy level of the former. However total surface energy was not predictive of protein uptake when polymers were compared with metals. Similar amounts of protein were adsorbed on PTFE, PU, and PDMS compared with metals, while PET adsorbed many times more protein than metals. However, no direct comparison can be made between metals and polymers because the latter were used in textured form, while the former were evaluated as flat solid surfaces. The textured polymeric total surface area was therefore likely to be much larger than the metal surface area evaluated.

The correlation of surface energy measurements and the amount of protein bound on artificial surfaces indicates a relationship with the magnitude of hydrophobic forces, which are ubiquitous in most prosthetic materials. A relationship between the amount of protein binding and hydrophobicity defined by the contact angle of water was observed by Prime and Whitesides,[6] but no such relationship was experienced by Rapoza and Horbett.[7] The retained fraction of the individual proteins to the surfaces we evaluated seems to be related to both the protein itself and the surface characteristics. A larger fraction of albumin seems to elute from most artificial surfaces, but the higher surface energy values for metals seem to cause a greater protein retention fraction. This supports the concept that hydrophobic interactions cause a more permanent attachment of proteins at surfaces. The low protein attachment to nonpolar PTFE contradicts this notion, suggesting that a polar component is also necessary for attachment. An attractive hypothesis postulates polar forces bringing proteins close enough to the surface to allow hydrophobic interactions by short-range forces. In contrast, plasma oxidation of hydrophobic polymers such as polystyrene seems to increase polar attachment of fibronectin to its surface compared with the nonoxidized counterpart.[8] The lack of protein attachment to predominantly hydrophilic surfaces such as polyhydroxyethylmethylmethacrylate (polyHEMA) and polyacrylamide[9] indicates that the opposite extreme, a totally polar surface, is inadequate for protein attachment. These observations support the concept that mixed surfaces are necessary for the attachment mechanism to occur.

Our evaluation of the effect of time on protein elutability was limited to fibrinogen on stainless steel. This single observation did not support the concept of increased protein attachment with time. Rather, a relatively fixed fraction of fibrinogen was removed at all time periods between 2 and 120 minutes. The uncertainty regarding mechanisms of interaction of proteins and artificial surfaces is made more perplexing if surface heterogeneity is taken into consideration.

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HEALING RESPONSE TO VASCULAR STENT-GRAFTS

Bart L. Dolmatch, MD
Cleveland Clinic Foundation
Cleveland, Ohio

A series of complex molecular and cellular processes contribute to healing of endovascular stent-grafts. These healing processes reflect the programmed response to foreign-body implantation in the vascular system and result in four tissue types: thrombus, neointima, endothelium, and inflammatory cell infiltrates. Both the extent and location of each of the four tissue types are influenced by a number of factors that include mechanical factors related to placement of the stent-graft, location of the metal stent struts, the type of polymeric graft, and the

microstructure and porosity of the graft material.

Trauma to the vessel wall occurs during placement of virtually all stent-grafts. Self-expanding stent-grafts are often balloon dilated when implanted in the peripheral arterial circulation. Some aortic stent-grafts require balloon dilation, as well. Beyond the implantation trauma that may be caused by balloon dilation, self-expanding implants impart a constant radial expansion pressure on the vascular wall. Balloon-expandable stent-grafts require forceful balloon-within-stent forces that reliably injure the arterial wall predominately at the ends of the implant often with disruption of the internal elastic lamina and media. A recent report by Farb et al[1] confirmed the importance of avoiding stent-related arterial wall trauma. In this report, stent-induced trauma to the media of human coronary arteries was associated with an increase of inflammation and in-stent restenosis. The recommendation from that study, as well as our conclusion from the laboratory, is that any dilation of a stent or stent-graft should be performed gently to limit neointimal stenosis adjacent to the ends of the implant.

The metallic portion of stent-grafts influences healing as well. In their current form, all stent-grafts are composed of a metallic skeleton (stent) that supports a polymeric barrier (graft). The metallic supporting structure is an important determinant in thrombus formation, and thrombus ultimately undergoes organization into neointima. Within the first few seconds after implantation, fibrin and other plasma proteins are deposited on metallic stent struts exposed to flowing blood.[2] This, in effect, passivates the electronegative stent surface and prepares it for cellular colonization. It has been shown that within the first 15 minutes after "bare" stent implantation, platelets and leukocytes adhere to the fibrin-covered stent surface and contribute to early thrombus formation. The degree of thrombus that forms on the stent struts influences the proliferation of subsequent neointimal growth.[3] After several days, the earliest myointimal cells and some inflammatory cells (polymorphonuclear leukocytes and macrophages) are seen within the thrombus. This cellular response proceeds with deposition of a collagenous matrix, proliferation of myointimal cells, and development of a monocellular endothelial layer.

While these responses are related to "bare" stent placement, there is no reason to believe that this process is any different for stent-grafts that are designed with portions of the metallic skeleton of stent-grafts exposed to blood flow. We have seen initiation of neointima within stent-grafts arising on metallic stent struts at 1 month that progresses to a complete luminal neointima by 3 months[4] in a canine model. Therefore, the "stent" portion of a stent-graft cannot be ignored when considering healing of these endoluminal implants.

Finally, the type and construction of graft have a profound effect on the incorporation and healing of a stent-graft. Three synthetic polymeric materials have been used in stent-grafts: expanded polytetrafluoroethylene (ePTFE), polyethylene terephthalate (PET), and polyurethanes (PUs).

Expanded polytetrafluoroethylene (ePTFE)

ePTFE has a complex microstructure consisting of parallel "nodes" and cross-bridging "fibrils." This design has been optimized to yield a synthetic conduit that has acceptable handling and healing characteristics for surgical bypass grafting.

Endoluminal ePTFE stent-grafts heal differently than surgically created interposition ePTFE bypass grafts. Most clinical experience has been obtained using ePTFE stent-grafts made by suturing this graft material to a Palmaz stent. These homemade ePTFE stent-grafts, therefore, have a composite luminal surface of ePTFE graft and metallic stent. We looked at healing of this type of device as well as an ePTFE stent-graft with the stent not exposed on the luminal surface in a canine model. We found that both types of implants developed a mature neointima that was completely covered with an endothelial monolayer by 6 months.[4]

Many other investigators have confirmed that endoluminal ePTFE stent-grafts develop a more complete endothelial lining than surgically placed interposition grafts.[5-7] However, Ohki et al[5] also found a greater degree of neointimal hyperplasia on the luminal surface of ePTFE stent-grafts compared with conventional bypass grafts in a canine model, while Ombrellaro et al[6] and Weatherford et al[7] noted an attenuated neointimal response for the stent-grafts. Despite these disparities, which may be explained by difference in the experimental method or stent-graft design, the finding of enhanced endothelialization for ePTFE stent-grafts compared with surgically placed ePTFE in a canine model is probably predictive of a similar response in humans.

The time for an endothelial lining to form is also considerably shorter for ePTFE stent-grafts than surgically placed ePTFE grafts. Others have confirmed this finding in dogs, pigs, and humans.[8-10] ePTFE stent-grafts of varying designs develop neointimal healing with a complete endothelial monolayer at 4 to 6 weeks. This is different than results for surgically placed interposition ePTFE bypass grafts, where

endothelial covering is usually incomplete after many months.[11,12] The reason(s) for this is not known.

"Pore area" is an important determinant of ePTFE stent-graft healing. It is derived from the product of internodal distance times interfibril distance, with a correction for the area occupied by the polymer itself (IND × IFD × correction for solid polymer = Pore area). For ePTFE with little pore area the luminal neointima consists of a poorly adherent rind of organized thrombus that easily separated from the graft surface. Seromas and flow channels within the neointima may form. ePTFEs with larger pores develop a neointima with better attachment.[13] We therefore believe that there is a lower limit of pore area that allows the development of a durable and limited neointima. It will probably be important to determine this lower limit, if ePTFE endografts are going to successfully limit transgraft tissue proliferation yet develop a stable neointima.

The degree of inflammation associated with polymeric vascular implants correlates with neointimal proliferation, and the fact that ePTFE is less inflammatory than a number of other polymers, in particular polyethylene terephthalate (PET), is an important attribute of this polymer.[8] In animal models of noncoronary vascular implants, macrophage infiltrates may be seen, but giant cells are rare. Overall, ePTFE stent-grafts in peripheral arteries are relatively inert. There are data, however, that show this is not true in the coronary arteries. Virtually all polymeric implants in the coronary arteries incite inflammation,[14] and the development of coronary artery stent-grafts may be limited by these findings.

In summary, ePTFE is noninflammatory and has a microstructure that can probably be tailored for different stent-graft applications. It may be the most acceptable material for use in small- and medium-sized arteries with diameters between 5 and 10 mm.

Polyethylene terephthalate (PET)

PET is a medical grade textile that has been used historically as an aortic and iliac artery bypass conduit and has proved to be durable and reliable. Although the success of PET can be attributed to the development of this polymeric material through years of research, Wesolowski et al[15] demonstrated the relatively high tolerance to a number of materials when surgically implanted as an aortic replacement in dogs and pigs. Both woven glass and perforated metallic lead pipe remained patent for many months in the aorta, a high-flow vessel of large caliber that rarely develops occlusive thrombus or neointimal stenosis. Yet while many materials may serve as an aortic substitute, PET has been adopted as a first line synthetic aortic graft material because it is easily handled by the surgeon and well tolerated by the patient.

PET aortic stent-grafts in animal and humans are similarly well tolerated from a healing and hemodynamic perspective. Stenosis of the aortic cuff has not been reported, and occlusion of the bifurcating iliac limbs of these stent-grafts is an uncommon event. PET implants, however, are not free of clinical problems. Following PET stent-graft implantation for treatment of abdominal aortic aneurysms, there may be an associated "postimplantation" syndrome in up to 25% to 35% of patients.[16-18] This syndrome, characterized by fever, pain, and leukocytosis, is believed to be related to either the PET polymer itself, or adsorbed contaminants from the manufacturing process. While no long-term adverse effects have been reported in association with this clinical syndrome, it is nevertheless uncomfortable for the patient and a cause for concern regarding the possibility that the stent-graft has become infected. There are no doubt many additional tests performed to "rule out" infection, including repeated complete blood counts, blood cultures, chest radiographs, and even CT scans. Hospitalization may be prolonged, thereby increasing the cost of aortic endografting.

Despite the "postimplantation" syndrome, PET will probably continue to be a widely used polymeric graft material for aortic stent-grafting. The real challenge for this material, however, remains in designing stent-grafts for use in vessels 5 to 10 mm in diameter. We have characterized PET-covered Wallstents, called Wallgrafts, in a canine arterial model.[8] Inflammation related to PET Wallgrafts at 1 month was seen in gross specimens as mild to moderate adventitial swelling with enlargement of adjacent lymph nodes. Histologic evaluation revealed macrophages and foreign body giant cells around the individual fibers and fiber bundles. Within 3 to 6 months, this inflammatory response had become quiescent, adventitial swelling was not seen, and there were only small infiltrates of macrophages and giant cells around the graft fibers. In place of the inflammatory response seen at 1 month was a diffuse fibrotic neointima at the luminal surface of the graft, sometimes producing a diffuse in-stent stenosis. Similar reports of inflammation and neointimal proliferation have been described in sheep iliac arteries; rabbit aortae; and the human aorta, iliac, and femoral arteries.[17-22]

In our experience, both the inflammatory response to PET stent-grafts and the degree of luminal narrowing seem related and cannot be ignored in small and medium sized vessels 5 to 10 mm in diame-

ter. In the dog, these findings are most pronounced in the femoral artery, less apparent in the iliac artery, and relatively minor in the aorta. In an intriguing clinical series of PET stentgrafts, Sapoval and colleagues[23] treated stenoses at the venous anastomosis and outflow veins of arteriovenous dialysis shunts with the Cragg PET-covered stent-grafts. Clinical signs of inflammation were seen in all three cases where the stent-graft was placed in forearm shunts. In fact, one of these stent-grafts was removed at 15 days because of severe inflammation and adjacent hematoma leading to skin necrosis. Patency was poor, as well, with 28.5% primary patency at 6 months.

Because of inflammation and neointimal stenosis, we doubt that PET will be useful in a human vessel much smaller than 8 to 10 mm. While the relationship between vessel size and PET stent-graft performance is unclear, it is likely that PET use will be limited to the aorta and iliac arteries, and that clinical manifestations of the "postimplantation syndrome" will be unavoidable for some patients in whom PET stent-grafts are placed.

Polyurethanes (PUs)

This broad class of elastomers has been under evaluation as a surgical bypass graft material for nearly 40 years,[24] but only recently incorporated into stent-grafts. Most of the early polyurethanes proved to be "biounstable," developing brittleness[25] and even degradation. Recent modifications have led to polycarbonate PUs such as Corethane that are believed to be resistant to degradation in vivo. Corethane serves at the polymeric graft material for the Corvita endoluminal vascular prosthesis. In dogs, the Corvita Endoluminal Graft develops a fibrous collagenized neointima with little inflammation or myointimal cell proliferation similar to earlier reports of healing related to microporous polyester PUs implanted as bypass conduits.[26] Excellent patency rates for these surgically placed 4-mm composite Corethane/PET bypass conduits in dogs have been reported.[27,28] This success, however, has not been reproducible. Working on prior data that showed microporous PU had a more rapid healing response and better neointimal incorporation than PET in large caliber prostheses,[26] Geeraert and Callaghan[29] looked at PU as a small vessel replacement. They implanted 3-mm internal diameter PU conduits in various locations in the dog and noted an exceedingly high rate of early thrombosis. Similarly, van der Lei et al[30] implanted short interposition PU grafts in the rabbit carotid artery. They prepared half of the grafts with heparin bonding and half without, hoping that bonded heparin would reduce early thrombosis. None of their grafts, however, remained patent at 14 days. It therefore seems that the theoretical advantages of PUs, such as compliance, lack of an associated inflammatory response, and versatility of fabrication, do not confer any benefit regarding patency when PUs are used as a small artery substitute.

The above data suggest that PU may be a useful bypass material for use in medium and large diameter vessels. Regarding possible use of PU stent-grafts in humans, there are virtually no data. The Corvita endoluminal stent-graft trial in human iliac and femoral arteries in the United States was halted in part because of early implant occlusion. The reason(s) for these occlusions is not clear, and it is possible that there were early technical problems associated with device implantation. Nevertheless, at this time there are no plans to restart this clinical trial. The Corvita abdominal aortic aneurysm trial has similarly been halted, but for nonmedical reasons. While biostable PUs are conceptually attractive for use in medium and large endovascular stent-grafts, there are no clinical studies planned in the foreseeable future. The role of PUs for endovascular treatment of aneurysms and occlusive vascular disease may not be known for many years.

Materials in development

Extensive testing of a number of polymers that are poor vascular bypass substitutes, such as Nylon, Vinyon-N, Orlon, Ivalon, and Silicone, has been described.[31,32] There are no data available for use of these materials incorporated in vascular stent-grafts. Biodegradable materials have been studied, as well,[33-35] but again, the concept of endovascular use was not considered. Finally, collagen has been considered as a biologic polymeric covering for stent-grafts. Different properties can be obtained by selecting specific types of collagen and cross-linking them to various degrees. This affords a final material that may have different rates of biodegradation. A preliminary report[36] demonstrated the feasibility of a collagen-covered stent-graft placement in a pig model, but there are no clinical trials planned at this time.

The only nonpreserved biologic covering that has been used for human stent-grafts has been autologous vein.[37-41] The potential benefits of autologous vein are related to its natural properties, such as compliance, tolerance to radial dilation, and resistance to infection. Its thin wall makes delivery into small blood vessels feasible. In addition, there are theoretical advantages regarding thromboresistance and long-term healing, since it is the patient's own tissue. Autologous vein,

however, is not problem free. It must be harvested from the patient at the time of stent-graft placement, therefore necessitating a surgical procedure. The quality of the vein may vary depending on the condition of the vein and the technique used to harvest it. Finally, unlike commercially prepared synthetic stent-grafts where the stent and graft are integrally related, preparation of a vein stent-graft requires suturing vein to the stent. Therefore, there is no way to ensure that the vein has not contracted on the stent or detached from the stent entirely, since the vein segment cannot be seen fluoroscopically.

In one report using a pig model, autologous vein stent-grafts placed in the iliac arteries were thromboresistant and healed with minimal hyperplasia.[42] In another porcine experiment[43] patency of vein-covered stent-grafts in the iliac and carotid arteries was poor, and a significant number of implants migrated. Dilatation of these implants is clearly an important component of the procedure that may limit migration and thrombosis. While all of this work is intriguing, the ultimate patency of vein stent-grafts in humans is not known. To date, most of the recent published literature consists of case reports without follow-up.

Summary

There are three polymeric vascular graft materials that have the potential for successful use in vascular stent-grafts. While ePTFE and PET are being incorporated into stent-grafts for treatment of aneurysmal and occlusive vascular disease, neither has been optimized for endovascular use. PET induces an inflammatory response that may be seen clinically as fever, leukocytosis, and pain. As the degree of inflammation increases, the tendency to develop a fibrotic neointimal stenosis within the stent-graft increases, as well. Regarding inflammation and neointimal proliferation, PET is best tolerated in the aorta and iliac arteries where it is predominately used to treat aneurysms. ePTFE is far less inflammatory than PET and may offer advantages in treating arteries from 4 to 10 mm in diameter. Because of its microstructure, there are a number of modifications that can be made to customize ePTFE for different applications such as for treatment of occlusive peripheral vascular disease. PUs are still in a developmental phase and may not progress further as a viable option for use in endovascular stent-grafts. A number of other synthetic polymers, evaluated decades earlier for surgical use, have not been assessed as stent-graft coverings.

Biologic barriers such as autologous vein and perhaps even collagen can be incorporated into stent-grafts. Stent-grafts covered with vein have been used successfully in humans. While they must be custom-made at the time of the procedure, vein-covered stent-grafts offer certain advantages that synthetic polymers cannot, such as resistance to infection, low profile, excellent compliance, and tissue compatibility during the healing phase. It is apparent that as the application of stent-grafts becomes more diverse, many of the materials that have been evaluated for surgical bypass conduit during the past decades will need to be revisited.

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STENT-BASED ADJUVANT THERAPIES—TECHNICAL ISSUES AND THERAPEUTIC APPLICATIONS

Douglas E. Drachman, MD
Elazer R. Edelman, MD, PhD
Campbell Rogers, MD
Brigham and Women's Hospital
Boston, Mass

The target

While restenosis has been ascribed to an orchestrated series of events including thrombosis, inflammation, smooth muscle cell migration and proliferation, matrix production, and vascular remodeling, debate exists regarding the relative importance of these pathophysiologic mechanisms.[1-14] In one camp are those who propose that extracellular matrix production and cellular migration and proliferation—or, neointimal hyperplasia—cause luminal narrowing after vascular injury; and, in the other are those who emphasize the importance of vascular remodeling, particularly after balloon angioplasty, as the chief determinant of late luminal