Biocompatibility of Stent Materials

Issel Anne L. Lim

Cardiovascular disease is the leading cause of death in the United States of America. A significant portion of these deaths are caused by coronary artery disease, the clogging of the arteries due to cholesterol buildup. A method for combating this vessel blockage is balloon angioplasty coupled with stenting. Using a catheter guidewire, surgeons insert a balloon into a blocked vessel. This balloon is attached to a stent. The balloon expands, pushing away cholesterol, while leaving the stent in place. This expandable mesh cylinder then supports the damaged blood vessel after the balloon and guidewire are withdrawn.

In order to provide effective treatment for coronary artery disease, the material creating the stent must be flexible, supportive, capable of expansion, and biocompatible. Biocompatibility is the property of not incurring a toxic or detrimental immunological response.

The normal host response to an implant includes trauma, inflammation, the immune system's reaction, and eventual healing or scarring. Biomaterials exhibiting a lack of biocompatibility could induce many complications, which might include long-lasting chronic inflammation or cytotoxic chemical buildup. To avoid these potential difficulties, scientists must test for the biocompatibility of substances, first *in vitro* and then *in vivo*.

A few of the medical complications arising from coronary stents today include thrombosis, cholesterol accumulation, restenosis, inflammation, and hyperplasia. Thrombosis is the formation of a clot, or the presence of a blood clot within a blood vessel. Cholesterol, which accumulates from saturated fat buildup within the blood vessels, can reform its original plaques atop the inserted stents. Restenosis is the re-closing or the collapsing of an artery. Inflammation might be caused by the body's immune response, warding off the invasive material. Hyperplasia is an abnormal increase in the number of cells in the surrounding tissue.

Presently, most stents consist of a stainless steel framework. However, this 316L steel is not fully biocompatible, and has induced high occurrences of restenosis and thrombosis. Scientists are therefore researching more biocompatible options, which include gold, titanium, cobalt-chromium alloys, tantalum alloys, nitinol, and various polymers. This article discusses the possibilities of tantalum and nitinol stents, as well as biodegradable and shape-memory polymers, along with the process of polymeric endoluminal paving.

Biocompatibility

According to Buddy Ratner in *Biomaterials Science: An Introduction to Materials in Medicine*, biocompatibility is "the ability of a material to perform with an appropriate host response in a specific application."[1]

Medical researchers perform i*n vitro* tests to examine the cytotoxicity of the material, judging the extent to which the material kills cells in culture. Usually, the material is placed in direct contact with a layer of cells from a cell line. This sample is incubated for at least 24 hours at 37°C along with positive and negative controls. Because there is no barrier between the material and the cell layer, this is the closest test for examining cytotoxicity in the body. Other *in vitro* assays include the agar diffusion test, in which a layer of gel-like agar is placed between the cells and the material, and the elution test, in which the material is soaked in a fluid that is later applied to the cells. However, the agar diffusion test detects only toxins that can pass through the agar, and the elution test does not determine the cells' reaction to structural or surface properties of the material. The major shortcoming of *in vitro* assays is their inability to disclose the interaction of the material with other cells in the body.

For *in vivo* tests, the medical device is implanted in animals with systems comparable to the device's targeted use in the human body. For example, dogs and sheep provide ideal models for testing devices to be used in bones, whereas guinea pigs are similar to humans in their subcutaneous structures. Porcine models are generally used for modeling cardiovascular disease.

The final phase of testing is implanting the device into human beings. Upon surgically inserting the medical device, trauma occurs around the implant region due to tissue injury. The "normal" response is then inflammation, healing of the wound, and a foreign body reaction due to recognition of the new material.[2]

Inflammation includes reddening, swelling, heating, and pain. The reddening and swelling are due to exudation, the escape of fluid and blood cells into the injured tissue. This allows the white blood cells that fight invasion and infection to access the tissue at the wound site. Chemical signals called cytokines are released by the damaged tissue cells. These cytokines trigger acute inflammation, attracting neutrophils, also known as polymorphonuclear [PMN] lymphocytes, which attach to microorganisms and foreign objects to kill or degrade them. These cells usually disappear from the site in 24-28 hours, making way for monocytes. In chronic inflammation, these white blood cells move to the region, differentiating into macrophages. They engulf debris through phagocytosis and also release growth factors that induce the rebuilding of the damaged tissue.

The healing process usually results in the formation of granulation tissue. Neovascularization also occurs as networks of small blood vessels form.

Once the device is implanted, macrophages and foreign body giant cells rush to cover it. This coating usually gives way to granulation tissue formation that leads to a fibrous encapsulation. The properties of the material affect the capability of the surrounding cells to form scar tissue or to regenerate new tissue. Usually, an implant is termed "biocompatible" if the body undergoes the normal healing process after surgery.

Materials that are not biocompatible induce many complications in the body. Chemical or physical properties can cause prolonged chronic inflammation, resulting in local cell damage. Movement between the implant and the tissue would disrupt cells at any point of contact. As the body wears down plastics, small particles can cause irritation and also clog macrophage lysosomes; if the white blood cells cannot break down these particles, the particles will remain within the cells. Corrosion of metals can create toxic metal ions in solution. Finally, chemicals in the material itself could also be cytotoxic, inducing cell death.

The ideal biocompatible stent material is inert and does not chemically react with human cells. A stent must not evoke an overly prolonged inflammatory reaction, yet must still provide sufficient initial support to oppose the retracting force exerted by the diseased vessel.[3]

Stent Materials: Current Metal Options

Most stents are crafted from 316L stainless steel. Current examples include the Cordis Palmaz-Schatz stent, the Cordis Crossflex stent, the Guidant MultiLink stent, and the Medtronic Bestent. Disadvantages of steel stents include the high occurrence of subacute thrombosis and restenosis, bleeding complications, corrosion, and re-dilation of the stented vessel segment. According to the Medtronic website, the "adverse effects" of stents are "death, myocardial infarction, CABG, stent thrombosis, bleeding complications, stroke, vascular complications, stent failures; potential adverse events, e.g., acute myocardial infarction, myocardial ischemia, arrhythmias, dissection, distal emboli, hemorrhage, perforation, restenosis of stented segment, stent embolization, [and] total occlusion of coronary artery."[4] The radiopacity, or viewing capacity of stainless steel stents could also be improved.

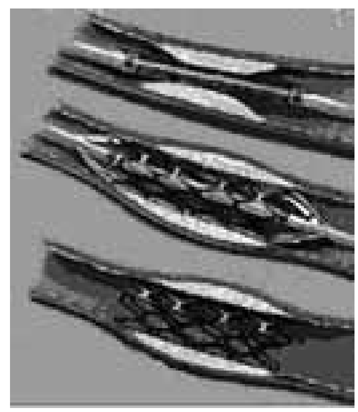

Figure 1. Palmaz-Schatz stainless steel stents in stages of deployment. Insertion of balloon and stent on guidewire, expansion of balloon, structural support of stent.
Source: http://biomed.brown.edu/courses/bi108/BI108_1999_Groups/Stents_Team/balloon.htm

Gold has long been known as a highly visible, biocompatible, and usually inert metal. Gold-plated hybrid stents exhibit good visibility and flexibility, but are also quite expensive. Medtronic's Bestent is a serpentine mesh of stainless steel with no welding point and two radio-opaque distal gold markers that allow precise positioning of the stent.[5]

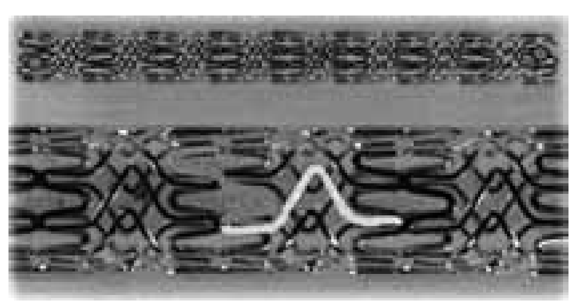

Figure 2. Medtronic's Bestent.
Source: http://www.medtronic.com

Currently, Conichrome®, Phynox™ and Elgiloy® are trademark names for the cobalt-chromium-nickel-molybdenum-iron alloy, which is specified by ASTM F1058 and ISO 5832-7. First invented to make watch springs by Batelle Laboratories in 1950, new variations of this "cobalt chromium" alloy can be used for manufacturing stents like the Schneider Wallstent.[6]

Tantalum, element #73, is a shiny, flexible, and highly radio-opaque metal. Though more brittle than stainless steel, tantalum exhibits high ductility and resistance to corrosion. Current examples of tantalum stents include the Wiktor Stent by Medtronic and the Tantalum Cordis Stent.[7]

However, newer models like the drug-eluting stents have yielded lower restenosis and revascularization rates. Tantalum is ideal for viewing and supporting, but more biocompatible options exist.

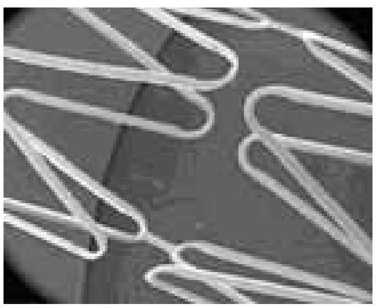

Figure 3. A Nitinol Stent.
Source: http://www.imagesco.com/catalog/nitinol/nitinol.html

Nitinol (from the "Nickel Titanium Naval Ordinance Laboratory") is an example of a biocompatible, super-elastic shape-memory alloy. As a shape-memory alloy consisting of 55% nickel and 45% titanium, nitinol has the ability to return to a specific shape upon heating to a certain temperature after its phase transition. Shape-memory alloys undergo a phase transition in their crystal structure when cooled from their stronger, higher temperature form in the Austenitic phase to their weaker, lower temperature form in the Martensitic phase. Nitinol also has a springy, "rubber-like" behavior that allows it to be super-elastic and contorted at its austenitic temperature.

The strong intermetallic bond between nickel and titanium has a very low reaction rate, even in patients with increased sensitivity to nickel. This prevents a strong immunological response and decreases corrosion.[8,9] According to Alan Pelton, PhD and research fellow at Nitinol Devices and Components, a subsidiary of Johnson & Johnson in Fremont, CA, "...having shape-memory properties and being biocompatible, nickel-titanium probably has the market tied up for quite a while."[10]

However, nitinol is also difficult to manufacture. A mere tenth of one percent change in its composition can drastically alter the transformation temperature. Also, the titanium component in the alloy is highly reactive with oxygen and nitrogen particles in the air, so all alloy formation must occur in a vacuum. Only about 5% of stents today are made of nitinol. Present examples include Boston Scientific's Nitinol-self-expanding Radius stent. Boston Scientific's Symbiot stent, available in Europe, is comprised of nitinol covered on both sides by 16-micron thick layers of ePTFE.

Polymeric Possibilities

Materials for polymer stents include biodegradable stents coupled with polymeric endoluminal paving, and shape-memory polymers.[11]

Silicone was the first organic material chosen for stenting. Silicone is a condensation polymer derived from alternating silicone and oxygen atoms which induces low rates of tissue trauma. However, silicone has poor biodurability, tensile and coil strength, and inner to outer diameter ratio.

Pure plastic biliary stents using polyethylene or polyurethane have also been used in patients. However, polyethylene induces sludge in 20-30% of patients, encourages protein adherence and biofilm formation, and entraps bile crystals and food particles. In contrast, polyurethane has good tensile and coil strength, and good biodurability, but it is also one of the most reactive materials available.[12]

Biodegradable and Bioabsorbable Polymers

Biodegradable and bioabsorbable stents are also viable materials for stenting. Though biodegradation, bioabsorption, and bioerosion are often used incorrectly as synonyms, they have different definitions. In biodegradation, a biological agent like an enzyme or a microbe is the dominant component in the degradation process. Biodegradable implants are usually useful for short-term or temporary applications. Bioresorption and bioabsorption imply that the degradation products are removed by cellular activity, such as phagocytosis, in a biological environment. By contrast, a bioerodible polymer is a water-insoluble polymer that has been converted under physiological conditions into water-soluble materials. This occurs regardless of the physical mechanism involved in the erosion process. The prefix "bio" in this case refers to erosion occurring in physiological conditions, as opposed to erosion via high temperature, strong acids or bases, or weather.[13]

Because of a stent's temporary structural support to damaged blood vessels, biodegradable polymers can be viewed as a biocompatible, yet easily disposable material, perfect for drug delivery systems. Some biodegradable polymers, such as polyesters, polyorthoesters, and polyanhydrides, may be able to modulate the local delivery of drugs and also degrade "safely" via hydrolytic and other mechanisms. Biodegradable drug delivery systems require steady degradation, permeability, and moderate tensile strength. In a stent, structural support must be accompanied by biocompatibility, hemocompatibility, and good hemodynamics. Currently, biodegradable stents usually induce thrombosis and vascular injury.

The Duke Bioabsorbable Stent, designed by Stack and Clark, was the first biodegradable stent. Bier et al. have also tried incorporating natural polymers by forming Type I collagen from purified bovine Achilles' tendons

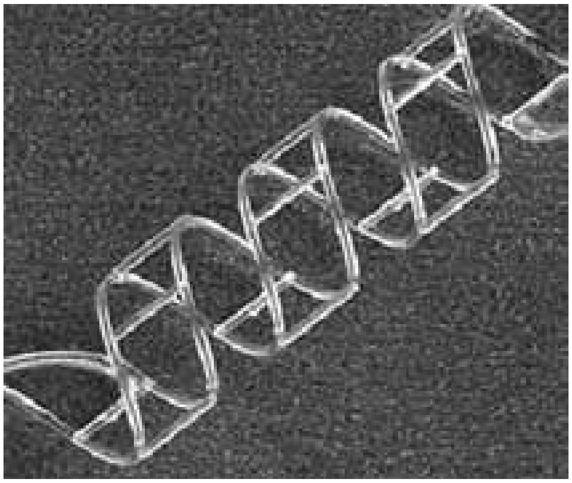

Figure 4. Cordis Corporation's prototype, molded by Tesco Associates, Inc.
Source: http://www.devicelink.com/mddi/archive/98/03/005.html

into a tube without slotted sides which was chemically cross-linked for structural stability. Collagen is quite hemocompatible because it carries an inherently negative charge. Collagen products are biocompatible throughout their lifecycle, and have shown a decrease in thrombobosis. Also, anticoagulants and fibrinolytic agents can be bound directly to collagen, which aids in its capacity for drug delivery.[14] Cordis Corporation has also developed a biodegradable stent prototype crafted from a blend of polylactide and trimethylene carbonate.

Some factors that accelerate polymer degradation include providing the product with a more hydrophilic backbone, more hydrophilic endgroups, less crystallinity, more porosity, and a smaller overall size. The most common chemical functional groups used are esters, anhydrides, orthoesters, and amides.

The ideal polymer would remain sufficiently strong until the tissue heals, does not invoke a detrimental inflammatory or toxic response, leaves no trace after being metabolized by the body, is easily processed into its final form, has an acceptable shelf life, and is easily sterilized.

One concern in using biodegradable stents is the unevenness of the material remaining after the degradation process. Various cells in the body are more likely to bind to uneven surfaces and induce complications. One solution to this dilemma is to provide a smooth surface using polymeric endoluminal paving. In this process, biocompatible polymers are applied to the surface of the organ or vessel. These polymers are simultaneously contoured *in situ* to yield a smooth layer of polymer in contact with the tissue surface, effectively eradicating irregularities in the tissue surface.[15]

In "solid" or "structural paving," tin tubes or sheets of biodegradable polymers are transported intraluminally or intravascularly using a catheter, positioned at the deployment site, and locally remolded with catheter-based thermoforming. This is an alternative to stenting: instead of relying on the expanding characteristics of a constrained stent or the mechanical deployment of balloon expansion, solid paving relies on catheter-based mechanical deformation as well as controlled phase changes of the polymer with a heating and cooling process. "Gel paving" uses hydrogels which swell in the presence of water, but eventually form adherent soft structural walls that develop effective drug delivery reservoirs. In liquid paving, flowable polymeric, macromeric, or pre-polymeric solutions are applied to the underlying tissue surface.

Shape Memory Polymers

A final polymeric possibility is the shape-memory polymers, newly developed by Dr. Andreas Lendlein and Dr. Robert Langer. They co-founded nmemoScience in Aachen, Germany to commercialize this new polymer and produce medical devices. Once the polymer is synthesized, it may be heated or cooled into myriad shapes. Upon introducing a suitable stimulus, the polymer will transition from its temporary state to a memorized, permanent shape. Lendlein and Langer have already demonstrated the ability of a polymer fiber to form a corkscrew shape similar to that of a stent.[16]

Most of these polymers are created from suitable segments, primarily determined by screening the qualities of existing aliphatic polyesters, especially poly(etherester)s, as well as L,L-dilactide, diglycolid, and p-dioxanone. Macrodiols can be synthesized based on these already-approved monomers.[17]

The toxicity of the shape-memory polymer system was measured using the chorioallaptoic membrane test (CAM test): In this procedure, a sterilized polymer film was incubated for two days in direct contact with the chorioallantoic membrane of a fertilized chicken egg. Then the blood vessels on and around the film were examined. In the first tests performed, the biodegradable multiblock polymers showed no influence on blood vessel growth, and had no damaged any of the underlying tissue. Further tests will follow.

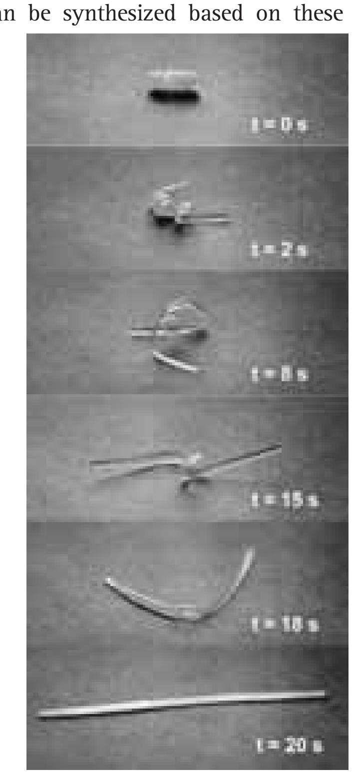

Figure 5. Series of photographs showing the macroscopic shape-memory effect of AB-polymer networks. Permanent shape is a rod, temporary shape is a spiral. The pictures show the transition from temporary to permanent shape at 70°C.
Source: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=14671

Conclusions

Biocompatibility, the ability of a material to induce a "normal" response within a host, is a key factor in determining the material from which to craft stents. Stainless steel, the most common inexpensive and relatively biocompatible stenting material in use today has much room for improvement. The current metal options available seem to incur high restenosis and thrombosis rates, and a need for repeat revascularization. Gold provides a radio-opaque but highly expensive material. Tantalum wire stents provide excellent radiopacity, flexibility, and structural support, but tend to promote high restenosis levels. Nitinol, a shape memory nickel-titanium alloy, has excellent biocompatibility and structural capabilities, but is very expensive to manufacture.

The next step in the stenting market is polymer materials. Though existing plastic stents are highly non-biocompatible, biodegradable stents, polymeric endoluminal paving, and shape-memory polymers provide very promising options for the future. Biodegradable stents will hopefully become viable drug delivery options that can provide support then degrade without further complications. Polymeric endoluminal paving can provide a smooth tissue surface through which fluids can flow without obstruction. Shape-memory polymers also show promise, due to their structural flexibility and shape variability. According to Dr. Robert Langer, these polymers should be "very cheap" in relation to the current materials today.[18]

Stenting is one of the most common procedures used in combating cardiovascular disease. The ideal stent is inexpensive to manufacture, easy to deploy, sufficiently rigid to provide support, able to deliver therapeutic agents, and disappears after treatment without leaving harmful materials in the body. With these new, biocompatible options, we can hopefully create the "perfect" stent.

References

1. Ratner, Buddy D., et al. *Biomaterials Science: An Introduction to Materials in Medicine.* Academic Press: San Diego, 1996.
2. Ibid., p. 216 – 221
3. http://www.mse.cornell.edu/courses/engri119/Class_Notes/E119_9p.PDF
4. http://www.medtronicave.com/noflash/physicians/coronary_indepth/s7otw_warnings.shtml
5. Tan, HC, and YT Lim. "What you need to know – Coronary Stenting – What's New in the Horizon?" Singapore Medical Journal. *Singapore Med J* 1999; Vol 40(06): http://www.sma.org.sg/smj/4006/articles/4006me2.html
6. http://www.fwmetals.com/spec_sheets/conichrome.htm
7. http://biomed.brown.edu/courses/bi108/BI108_1999_Groups/Stents_Team/balloon.htm
8. http://www.sma-inc.com/biocomp.html
9. Ryhänen, Jorma. "Biocompatibility evaluation of nickel-titanium shape memory metal alloy." University of Oulu. 1999. http://herkules.oulu.fi/isbn9514252217/
10. Freiherr, Greg. "Untapped Potential." *Device Link.* http://www.devicelink.com/mddi/archive/98/03/005.html
11. Ibid.
12. http://www.bostonscientific.com/common_templates/articleDisplayTemplate.jhtml?task=tskMedArticleOverview.jhtml&sectionId=4&relId=8,386,387,388,389,390&deviceId=134&uniqueId=MPA0541
13. Ratner, p. 66.
14. Middleton, John C. and Arthur J. Tipton. "Synthetic Biodegradable Polymers as Medical Devices." http://www.devicelink.com/mpb/archive/98/03/002.html
15. http://www.jhu.edu/~matsci/teaching/510.420/Selpian3.pdf
16. http://www.azom.com/details.asp?ArticleID=1542
17. http://www.mnemoScience.com
18. Langer, Robert, Ph.D. Personal Interview. March 2003