Tiny Solutions to Big Problems: How Nanopatterned Stents are Changing the Future of Cardiovascular Medicine

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Scientists are taking the fight against atherosclerosis to the next level—the nano-level, that is. Multidisciplinary teams of medical researchers and bioengineers are transforming medical devices with features as tiny as one nanometer across—that's 1/80,000th the width of the average human hair—to create technologies that can direct cellular activity without drugs or surgery. It sounds a bit like science fiction, and if you can't help but picture the Magic School Bus, you're not alone. However, these nanotechnologies are on the verge of revolutionizing clinical cardiovascular medicine. In a review article published in the *Methodist DeBakey Cardiovascular Journal*, researchers from Northeastern University and the Houston Methodist Research Institute describe the innovative ways nanotechnology is being used to improve stents.

A VICIOUS CYCLE

For years, the go-to treatment for atherosclerosis, a fibrous buildup of fatty plaque and inflammation that blocks blood flow through the arteries, has been balloon angioplasty. In this procedure, a tiny balloon on the tip of a catheter is threaded through arteries and inflated at the blockage, squashing the plaque against the arterial wall to restore blood flow. In 70 to 90 percent of angioplasties, the physician will simultaneously insert a stent, a metal mesh tube that expands to hold the artery open even after the balloon is removed.[1] For millions of Americans, stents can be lifesavers; uncontrolled atherosclerosis is the leading cause of most cardiovascular events, from heart attack to stroke.[2]

Unfortunately, up to one-fifth of implanted stents will cause the vessel to re-narrow, thus recreating the very problem they were intended to fix.3 Essentially, endothelial cells fail to cover the stent surface fast enough, exposing the bare metal to inflammatory cells. These cells attach to the stent and initiate an inflammatory response, causing monocytes, vascular smooth muscle cells, and mesenchymal cells to quickly build up a layer of scar tissue in the gaps between the metal mesh, once again blocking blood flow. This is called restenosis, and the main treatment is to remove the original stent and start all over again.

To thwart restenosis, many physicians use drug-eluting stents as an alternative to the bare metal devices. Drug-eluting stents slowly release compounds meant to suppress vascular smooth muscle cell growth and formation of extracellular matrix proteins. Although these stents reduce—or at least delay[4]—restenosis, they fail to solve the fundamental problem.

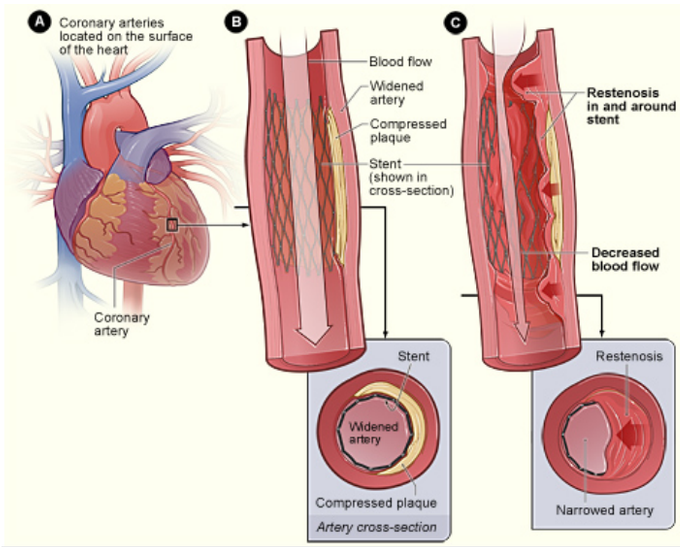


Figure A shows the coronary arteries located on the surface of the heart. Figure B shows a stent-widened artery with normal blood flow. The inset image shows a cross-section of the stent-widened artery. In figure C, tissue grows through and around the stent over time. This causes a partial blockage of the artery and abnormal blood flow. The inset image shows a cross-section of the tissue growth around the stent. (Image and caption courtesy of National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services)

NANOSOLUTIONS

That's where nanotechnology comes into play. As review authors Nicole Bassous, B.S.; John Cooke, M.D., Ph.D.; and Thomas Webster, Ph.D., report, advancements in nanotechnology offer a variety of opportunities to fine-tune existing stent designs. Researchers are examining methods of altering the topography of stents on the nano-level to encourage rapid endothelial cell growth and avoid restenosis.

Dr. Thomas Webster is a biomedical engineer specializing in nanomedicine and the department chair of chemical engineering at Northeastern University. Webster is especially optimistic about nanopatterning the surfaces of existing metal stents. "We're altering the stent's nano-roughness to mimic the natural roughness inside our arteries and blood vessels. The idea is to trick the endothelial cells into covering the surface faster so that inflammatory cells won't recognize the metal as something foreign," Webster explained. Data support that theory. For instance, endothelial cells attach much faster to titanium surfaces imprinted with fissures less than 100 nm wide. A similar effect can be achieved by coating the metal with a nanopatterned collagen matrix.

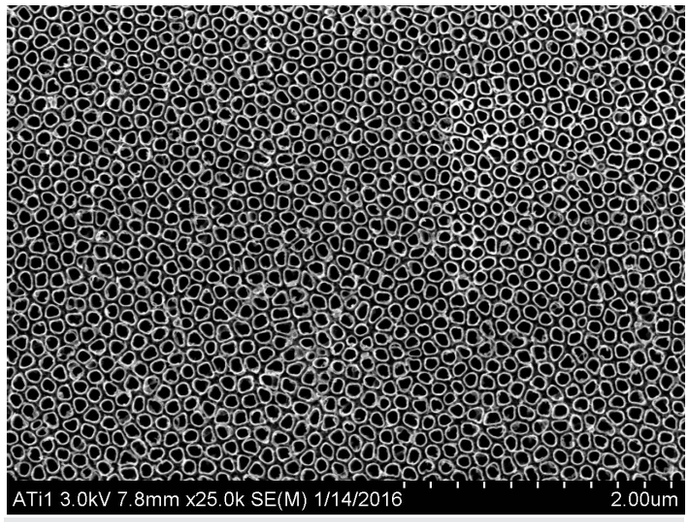
Interestingly, nanopatterning doesn't just hide the stent from inflammatory cells; it can actually affect the endothelium's biology. It all comes down to cellular alignment. Cells on nanopatterned surfaces grow longitudinally, as opposed to a cobbled pattern that sometimes occurs on traditional stents placed in areas of impaired blood flow (that is, areas more prone to atherosclerosis). Webster explains that longitudinal alignment allows cell receptors to bind together. This triggers an intercellular anti-inflammatory mechanism. Compared to the cobbled cells, longitudinally aligned endothelial cells release more protective nitric oxide and produce fewer adhesion molecules (the molecules that cause monocytes and smooth muscle cells to stick to the stent and cause restenosis).

However, improving endothelial coverage isn't a perfect solution, Webster cautions. The body still has to deal with foreign material for the rest of the patient's life. "Although the stent does a great deal of good by propping open the blood vessel, you almost always have to be concerned about restenosis because there's always that metal stent in there," he says. One potential alternative is absorbable, or biodegradable, stents. Rather than just being covered by endothelium, these stents would ideally completely integrate into the vascular wall, then gradually dissolve, creating what Webster calls "a completely natural interface." These absorbable stents could be made of biocompatible polymers or dissolvable metals such as iron and magnesium.

Absorbable stents are an exciting idea with profound implications for both atherosclerosis patients and children with congenital heart disease, who would benefit hugely from devices that would correct malformations but still allow vessels to grow. However, these stents still have one big downside: "The big issue with biodegradable stents right now is that the chemicals they degrade into are not always friendly," Webster explains.

Once again, nanopatterning could come to the rescue. Just as with bare metal stents, scientists could apply nanopatterns to absorbable stents to encourage rapid cell coverage. In this case, the cells have an extra duty: "If we can get more endothelial cells to cover the stent and metabolize the degradation products, then we have a more promising approach. The cells can act as a buffer," Webster says. "That's why a lot of researchers are putting nanopatterning on these magnesium stents. The cells can metabolize the degradation products faster so that they don't become a problem in the bloodstream."

Absorbable nanopatterned stents may be the stent of the future. Despite the byproduct dangers, Webster believes that "the promise of having a biodegradable stent is so powerful that it still drives the field forward."



This scanning electron microscope image shows a titanium sample anodized with 1% hydrofluoric acid for 10 minutes at 20 V. After anodization, the titanium surface showed nanotubular-like structures with an inner diameter of ~80 nm. (Image courtesy of Luting Liu, Webster Nanomedicine Lab at Northeastern University)

UNTAPPED POTENTIAL

Nanopatterning stents is merely the tip of the iceberg when it comes to using nanotechnology in cardiovascular medicine. The really thrilling technologies—those that are making science fiction a reality—involve using nanoparticles to mimic or deliver drugs to target specific cells. Such advances could revolutionize the way we treat cardiovascular diseases. However, nanostructured stents are a critical jumping-off point to reach the much broader future of nanomedicine.

The FDA divides nanotechnology into two areas: nanostructured surfaces (those discussed in Webster's article) and nanoparticles. Webster serves on an FDA nanotechnology task force that advises the agency on how to regulate nanomedicine. He explains, "There are two different pathways to commercializing cardiovascular nanomedicine. Nanostructuring current devices is a much faster pathway to FDA approval because we're not changing the chemistry of stents; we're just altering the surface texture. In the nanoparticle area, we're much farther away from approval because we'll have to demonstrate toxicity and biodistribution of where those particles go over time. There are a lot more questions with nanoparticles."

Webster is part of a project that already has a nanopatterned stent under FDA review. Clinicians may not have to wait long for nanopatterned stents to hit the market. In fact, Webster estimates that such stents could be available within a year, although nanoparticle technologies are probably five to ten years away from approval.

In the short-term, Webster hopes that the immediate success of nanopatterned stents will not only help current patients, but also bring nanomedicine into the mainstream. Nanotechnology is already used in oncology and orthopedics, but it is far from reaching its full potential in cardiovascular medicine.

So what kind of future might nanomedicine bring? Webster imagines a time when we move away from stents altogether, or instead use stents as vehicles to deliver nanoparticles to the site of vascular injury. Nanoparticles are so small that the immune system doesn't recognize them. Therefore, it's possible to put drugs into nanoparticles so that the compounds last longer in the circulatory system and target specific tumors or plaques. Theoretically, physicians could use much smaller concentrations of pharmaceuticals to achieve the desired result.

Drug-mimicking nanoparticles are being developed to treat a disease or injury without the drugs' negative side effects. Similarly, nanoparticles could replace certain risky procedures. For instance, researchers are developing nanoparticles that target atherosclerotic plaque and break it up using heat. "Then you don't have to put a catheter inside a patient or do anything invasive. You just send the nanoparticle into that plaque, heat it up via infrared excitation, and then the particle will destroy the plaque and return blood flow," explains Webster.

Other nanoparticles are being used to target cells, even specific organelles within cells. "It's like an arcade game," Webster says. "You can turn off or on certain parts of a cell with those nanoparticles. You can deliver drugs to the nucleus or the mitochondria. We could have the ability to use nanoparticles to get an exact response from a cell, which is incredibly powerful."

Powerful, indeed. These unimaginably tiny particles and structures may be the future of cardiovascular medicine, a future that's much closer than many of us may have imagined. Nanopatterning stents could soon transform the way we manage atherosclerosis and restenosis. Even more importantly, these stents could usher in a nanotechnology revolution.

At least, that's how Webster sees it: "Stents can provide the success story to encourage more people to look at nanomedicine in the cardiology. Right now, nanotechnology is an untapped resource in the cardiovascular sector, so there's incredible promise for using this new size scale in treating cardiovascular disease."

Conflict of Interest Disclosure:
Laura Gerik is assistant managing editor at the *Methodist DeBakey Cardiovascular Journal*.

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