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Making Sense of Stents

By Dana Mackenzie

If someone gave you a stent without telling you what it was, you might think it was a toy. A braided wire contraption about the size of a pen cap, a stent can stretch and bend and then spring back to its original shape. A cat could have fun with it for hours—if you felt like giving your cat a $3000 toy, that is.

Unremarkable as they may appear, these devices save or prolong the lives of hundreds of thousands of people every year, by propping open arteries that have been narrowed by atherosclerosis. A surgeon slides a stent into a constricted artery through a catheter, lets go—and presto, the stent pops open (either on its own or with a balloon inside it), forcing the walls of the blood vessel outward (Figure 1). So far, they have been used mostly to treat coronary artery disease, although they can be used elsewhere, such as the carotid or femoral (hip) arteries.

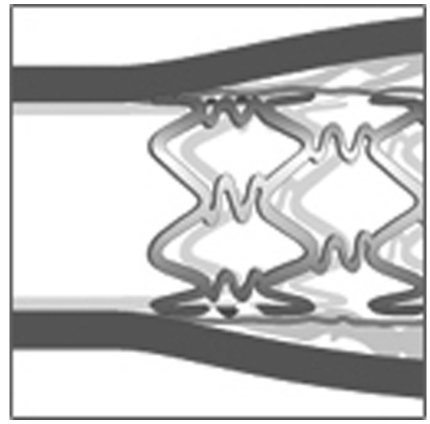

Figure 1. *Inserted through a catheter into a blood vessel narrowed by atherosclerosis, a stent pops open, forcing the walls of the vessel outward. To date, stents have been used mainly in patients with coronary artery disease.*

Recently, some surgeons have also begun to use stents in patients with other kinds of cardiovascular disease, such as aortic aneurysms (where the aorta bulges dangerously outward) and dissections (where the aorta springs a leak). Though the physical device is often the same, the purpose is different, and a device used in this setting is called a "stent graft." The surgeon attaches a stent graft to the aorta above and below the trouble spot. It channels the flow of blood into the center of the artery and relieves the pressure on the walls, making them less likely to burst. (Some companies, such as Medtronic, have started to make specially designed stent grafts, with polyester linings and optional bifurcations.)

But stents are not a perfect solution for patients with any of these diseases. About 20–30% of the patients who receive them for atherosclerosis enjoy only short-term relief. The arterial walls in these patients regrow, over and through the wire mesh. (Cardiologists call this "restenosis.") Stent grafts face even more difficult problems. Subjected to fluid forces as powerful as those in a garden hose, they sometimes fail to stay anchored, and migrate downstream from the aneurysm or get twisted into a useless tangle.

To understand why stents fail, some doctors are turning to mathematics, and specifically to computational fluid dynamics. "What we're finding is that flow patterns and stress in the artery wall—the changes induced by stent implantation—relate to the way the artery reacts," says James Moore, a biomedical engineer at Texas A&M University. Computer simulations based on the Navier–Stokes equations can predict whether a stent will create eddies or pools of stagnant blood near the walls of an artery, which can be a precursor to restenosis. Though such simulations are now too time-consuming to run for individual patients, eventually surgeons may be able to tailor a stent to the particular geometry of a patient's arteries.

Restraining Restenosis

Given the choice of having their chests sawed open for bypass surgery or having catheters snaked through small incisions in their legs, most patients opt for the latter. The popularity of this minimally invasive treatment has made stents into a booming, $2 billion per year industry. It has also provided cardiologists and manufacturers with a tremendous incentive to solve the problem of restenosis (see Figure 2).

So far, most of the headlines and money have gone toward "drug-eluting" stents, in which the wires are coated with a substance that gradually releases an inflammation-suppressing drug over a period of months. Johnson & Johnson, whose Cypher stent was the first drug-eluting stent on the market, reports that the restenosis rate for the device is only 5% and that no "late catch-up phenomenon" appears to occur once the drug has been used up.

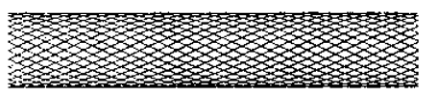
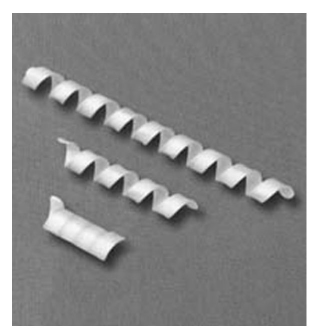
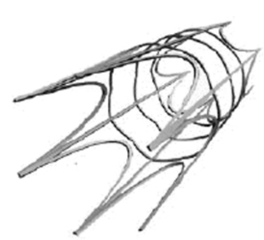


Figure 2. *Motivated by the problem of restenosis, designers have produced variations on the basic mesh design seen in stents like the Wallstent from Boston Scientific (upper left). Alternatives include (clockwise from upper right) the helical aSpire from Vascular Architects; Cypher, the first drug-eluting stent on the market, from Johnson & Johnson; and a compliance matching stent, whose parabolic end struts are designed for greater flexibility, from James Moore and Joel Berry.*

Even so, some people feel that drug-eluting stents treat only the symptom, not the cause. "The drug-coated stents sledgehammer the artery walls and then handcuff them so

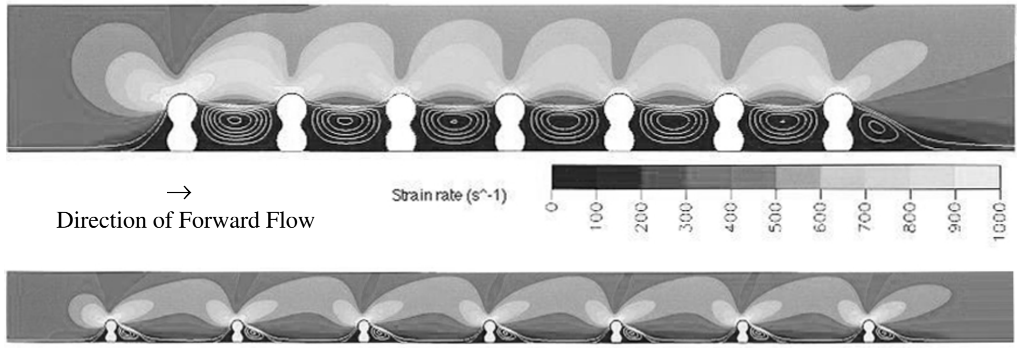

Figure 3. *Strut spacing has been implicated in the stagnation or eddies in blood flow seen in many patients with stents. Simulations by James Moore and colleagues show grayscale-encoded strain rates for two strut spacings in a Wallstent; the eddies and pooling seen with closely spaced struts (above) are replaced by flow reattachment with wider spacing (below). From* Annals of Biomedical Engineering*, Vol. 30, 2002, reprinted with the permission of the Biomedical Engineering Society.*

they can't react," Moore says. "What we're working on is a different strategy that can be done in parallel with drug coating."

According to the simulations of Moore and others, most existing stent designs create zones of stagnation or eddies in the blood flow. "The spacing of struts is the main cause," Moore says. When the struts are spaced too closely, pools of recirculating blood form in the spaces between them (Figure 3). For unknown reasons, slow or stagnant blood flow promotes an inflammatory response in the wall of the blood vessel. It is this inflammation—not the original arterial disease—that leads to restenosis.

Inflammation frequently occurs at the ends of a stent, and mathematical simulations explain this, too. The abrupt change from a compliant artery wall to a stiff stent places unnatural stress on the blood vessel and disrupts the smooth blood flow. Moore and Joel Berry of Wake Forest University have patented a new "compliance matching" stent; the relatively flexible ends of their device create a more gradual transition zone be-tween the natural and manmade linings.

Abdul Barakat, a biomedical engineer at the University of California at Davis, has yet another idea for improving the blood flow through a stented artery: Make the stent helical. Most stents made today have mesh-like designs, and blood is frequently trapped in the meshes. A helical design lets the blood flow in a continuous path. This common-sense idea is borne out by Barakat's simulations, which are the first fully three-dimensional models of a stented artery.

It may seem surprising that progress in simulating blood flow through arteries has been this slow, but there are good reasons. First, an artery is a living, flexible tube—not a fixed pipe. As the blood pressure changes, the artery adjusts its width and curvature. Mathematically, this means that the Navier–Stokes equations have to be coupled to another set of equations modeling the pressures on the artery wall, and possibly even a third set describing the behavior of the stent. Second, blood flow is pulsatile, not steady. From a practical point of view, the pulsatile flow means that researchers can't simply plug a few parameters into commercial software. Instead, they have to go to some trouble to input realistic pulses of blood flow into their models, and they may need to wait several cycles for unrealistic initial effects to die out. With each heartbeat taking up to a week of computer time, it is easy to see why most researchers have opted for simpler two-dimensional or even one-dimensional models.

For all these reasons, no one advocates trusting the models on their own. "It is true that you can get a tremendous amount of detail from a simulation," says Barakat. "However, your model is only as good as the assumptions that you make. I think it is absolutely crucial to validate the computations," by following up with laboratory and clinical tests.

Until clinical results are in, some physicians remain skeptical of new stent designs. Julio Palmaz of the University of Texas at San Antonio, the inventor of the first FDA-approved stent, says that helical designs have actually had worse rates of restenosis than mesh designs. And, he adds, "I am not convinced that stent–artery compliance match is all that relevant in the ultimate outcome of stenting." He believes that the inflammation may be provoked by the materials used in the stent or by chemical contaminants on its surface.

Perhaps the skepticism toward computer modeling also has something to do with the sheer number of stent designs that have been tried already. In a 2002 paper, Dieter Stoeckel, executive vice president of Nitinol Devices and Components (a subsidiary of Johnson & Johnson), listed more than a hundred different stents currently or formerly on the market. But, Stoeckel wrote, "The development [of stent designs] has mainly been driven by patent and marketing issues rather than actual scientific considerations."

It seems almost certain that this attitude will change. One place where innovative designs may emerge first is the femoral artery, whose blockage creates a condition called claudication, which makes it very painful for patients to walk. "Guidant, Johnson & Johnson, Medtronic—they're all working on it," says Matthew Salkeld, vice president for sales at Vascular Architects in San Jose, California. "Stents to date have not worked well there," Salkeld explains. "About half of them close down after six to nine months." The femoral artery undergoes a lot more bending and twisting than coronary arteries, so it requires a more flexible stent. Vascular Architects is betting that a helical design will work there, but the company has not yet conducted peer-reviewed clinical trials or received FDA approval.

The Taming of the Inchworm

Because stents for coronary occlusion are already a nearly mature technology, mathematically based designs may have trouble finding a niche there. Stent grafts for aneurysms, however, are still very much in the experimental stage—and the need for them is great. Ruptured aortic aneurysms are the 13th leading cause of death in the United States. One of them killed the well-known actor John Ritter last year. Another claimed the father of Suncica Canic, a mathematician at the University of Houston.

"Even though we knew he had an aneurysm, in Croatia no one had a nonsurgical treatment, and no one wanted to treat a 78-yearold man surgically," Canic says. Unfortunately, her father never got to meet Zvonimir Krajcer, a doctor at the Texas Heart Institute who treats patients exactly like him with stent grafts. When Canic learned about Krajcer's work, she realized that, with her background in compressible fluid flow, she might be able to help him improve the durability of stent grafts.

Unlike a stent, a stent graft contacts the vessel wall only at the anchor points at the ends, which means that the fit has to be very snug. To ensure that the device stays in place, the stent graft is designed to expand to occupy an opening wider than the aorta, so that it will press outward on the vessel wall. Even so, a stent graph sometimes fails to hold its ground and gradually, like an inchworm, makes its way down the artery. In a study at the Texas Heart Institute, 21 out of 191 stent grafts traveled downstream by more than half an inch over a three-year period. Until they can be relied on to stay in place, stent grafts are not really superior to open-heart surgery, but they are a good option for older patients like Canic's father, for whom surgery poses too high a risk.

Canic and Krajcer are just beginning a project to simulate the behavior of a migrating stent graft, using both computer and laboratory experiments. Canic has found already that conventional wire-mesh stents are too flexible to work well in the wide open spaces of an aneurysm; as these devices expand and contract, they tug on the aorta walls with as much as two pounds of force. Canic and Krajcer's simulations show that placing a second layer of two short stents within a longer stent dramatically reduces the strain—as surgeons at the institute had already discovered empirically. In general, Canic says, stent grafts need to be stiffer in the middle and more elastic at the ends.

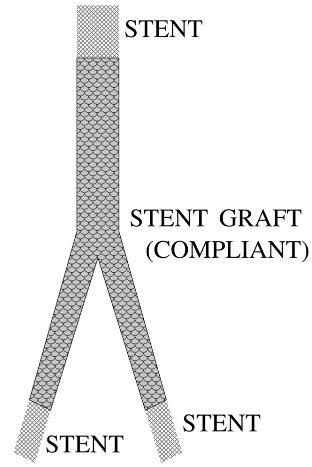

Figure 4. *Bifurcating grafts are useful for treating aneurysms that occur where the abdominal aorta divides into the two iliac arteries. The design sketched here, which features both compliant ends and an optimal geometry, would reduce shear stress on the ends of the graft. From Suncica Canic.*

Canic has also studied bifurcating grafts, because many aneurysms occur where the abdominal aorta splits off into the two iliac arteries. In commercial designs, the "daughter" channels are half as wide as the "parent." Because of conservation of mass, this forces the flow to speed up through the daughter arteries. None of the commercial grafts has the optimal ratio of diameters, in which the daughter channels are $\sqrt{2}/2$ times as wide as the parent. This would be less convenient for the stent makers—who would have to sew in an extra triangle of wire mesh and polyester lining—but probably better for the patients. Canic says that the two changes in tandem, compliant ends and an optimal geometry, would reduce the shear stress on the ends of the graft and possibly enable it to stay in place longer (see Figure 4).

According to mechanical engineer Harry Dwyer and mathematician Angela Cheer of UC Davis, who are also working on the migration of stent grafts, the proper treatment of aneurysms will soon become not only a medical problem, but also a societal issue. "As the price of a CT scan comes down under $1000, more and more people are going to get them and see the weaknesses in their arteries. We'll have pictures of all these aneurysms. And then what are we going to do?" Right now, if the aneurysms are relatively small, the best advice is to do nothing. But if stent grafts improve, the decision might become harder, and it might be different for each patient. Eventually, a model of the cardiovascular system that uses computational fluid dynamics could become a routine part of the decision.

"In the automotive industry, for every flow problem they do a computer simula-tion," say Dwyer and Cheer. "There is no reason that our bodies should be any different. The heart is the engine of our body, and the blood flow determines how well it works."

Dana Mackenzie writes from Santa Cruz, California.