Stents: Hisham Sherif, MD, PhD

Intro

My name is Hisham Sherif, and I'm a retired surgeon who has spent a little over 30 years in cardiovascular surgery. And during that time, I have been, I still am involved, actively involved in a wide range of research, including device design and development. I have two U.S. patents for implantable cardiovascular devices. And through that research, I decided to get a degree for all the research work that I've been doing. So I decided to get a PhD in Biomedical Engineering. And being in Newark, I decided to go have it where the UD. And I graduated a couple of years ago, finally.

Why are stents used?

I think it would be useful to set the definitions. There is a difference between a stent and a stented device. So a stent is a mesh that supports a vessel- keep it open. A stented device is something that incorporates a stent in its design, and it helps its function or it helps secure it in place. So there is vascular stents, which is the area where we have been exposed to. And there are other stents for other structures like in the biliary tree or the bronchi or the esophagus- and these have their own applications. So as a cardiac surgeon, we haven't been using stents like the interventional cardiologist. It started in the early 90s when they developed a percutaneous transluminal coronary angiography, PTCA, which is essentially a balloon dilation of the coronary artery lesion. During the early parts, early years in my training, we used to have an operating room ready for the cache because after dilating the artery, the coronary artery, there's a high risk of immediate hyper acute collapse, and that generates an acute MI. And we have to revascularize surgically on the spot. So around 1998 or so, people started adapting the Palmaz stent for coronary vessels. And the idea is, after you dilate the coronary artery with a balloon, you deploy a stent, which is mounted on the balloon to save time to keep the artery open. So that has led to a wider application of stents in the coronary circulation. And then, our friends, the vascular surgeons, started using stents for the abdominal aorta instead of doing an open resection and reconstruction of abdominal aortic aneurysms. They started doing a tube graft that has a stent on the outside, which is the definition of a coated stent, in this segment of the abdominal aorta that is aneurysmal, to maintain flow. So stents are designed to maintain patency of the vessel. They don't cure the disease. And they are not a long-term modality, a treatment modality for it. And the concept of stents in the aorta has been borrowed and used for the thoracic aorta, descending thoracic aorta. And the idea is stents offer a very good chance of resuming or rescuing the flow in the vessel.

What are stented devices?

There are percutaneous valves that are designed to be deployed in the mitral position and the aortic position. And in the aorta position, they have been called- the procedure has been called transcatheter aortic valve replacement. Although I prefer transcatheter aortic valve implantation because you're not really replacing the aortic valve. What is done is- there is a short stent that has valve leaflets mounted on it. And it's collapsed and mounted on the delivery catheter. And it's positioned in the aortic root inside the native diseased aorta. And when it's deployed, the leaflets are positioned like any other bioprosthetic valve, but they are- the stent part locks it in place. And these days they are in clinical trials for a similar concept for the mitral valve and even the tricuspid valve. So that's what I mean with a stented device. So in this application, the stent serves as anchoring. It doesn't have anything- or has little to do with the actual flow because the flow contacts the valve leaflets.

What is the difference between vascular stents and other types?

The major difference between these environments is that in the esophagus or the bronchi, the flow is of air and the hepatobiliary system- it's bile. So it's not a living tissue. In the cardiovascular tree, you have the blood, which is a living tissue, interacting with the vascular wall, which is another living tissue, and both of them regulate each other. So that's one of the major considerations when we're deploying a stent in a vascular environment. Because it has all sorts of impacts on the vascular wall, the flow dynamics, and stuff like that.

What impact does a vascular stent have on the native tissue?

First, we use stents because they are what everybody else is doing. I guess you can call it peer pressure. But stents are not benign by any means. They are temporizing. And the latest guidelines from the American Heart Association and American College of Cardiology, European Society of Cardiology, are all recommending stents or percutaneous coronary intervention, as it is more accurately known, to be restricted to acute ischemic episodes. If somebody has an angina or myocardial infarction in progress, which means that there is a sizable chunk of the myocardium at-risk, that's the indication for stenting. The same with the aortic malperfusion syndrome that we've discussed. So that's its role. Unfortunately, the interventional cardiologists since 1998 started running around with the stents, deploying it left and right. So we ended up having people with stable coronary artery disease that is recommended for maximum medical therapy, as per the guidelines- the latest guidelines- having stents. And then when you put the stents, you're disrupting the endothelium of the blood vessel- of the artery. And the endothelium is fundamental for the health of the vascular wall. It is through the mechanotransduction- the force of the pulsation against the epithelium that is transmitted through the wall- that all the extracellular matrix regulations start and is maintained. If the artery loses its pulsatility, all of these mechanisms get disrupted and you have a pro-thrombotic, pro-fibrotic response. And that's one thing. The other thing is that the stent triggers a foreign body reaction. And what you're hoping will happen is that the artery will regenerate its endothelium. The whole reason there is a plaque which ruptures or get progressive so that it will create a critical stenosis, is that there is an endothelial dysfunction and/or an endothelial disruption. So this is the basic step towards forming an atherothrombotic- because I don't like the term atherosclerotic- atherothrombotic plaque formation. And that feeds into the regulatory loops in the arterial wall. So it makes things worse. What you're hoping is to find a really smooth, intact functional endothelium that will give you endothelial nitric oxide and will transmit the change in pressure and will also help with the thrombogenicity of the blood because the blood when it's moving against the endothelium is happy. It doesn't meet anything that irritates it. Once there is a dysfunction or disruption of the endothelium, there is the intrinsic pathway that gets activated. And you have platelets, platelet aggregation, and you have microthrombi and that begins the plug. And because- this all happens because you have an interaction between two living tissues. And if you disrupt this balance by putting a foreign body in it, the body acts aggressively against any foreign body. So there is a fibrotic layer that happens inside the stent. And that can progress to what's called an in-stent stenosis, which over time recreates the malperfusion syndrome on a chronic time scale. And because it's not healthy endothelium, that can trigger thrombosis. So you can have in-stent thrombosis, which is the exaggerated version of coronary artery disease. So we recreated the same clinical problem again.

What are drug-eluting stents?

Somebody along the line thought, hey, we use immunosuppressive agents in exaggerated inflammatory response, like in lupus and that sort of thing, that group of autoimmune diseases we use those. So why not impregnate tiny little particles and place them inside the mesh of the stent so that it will reduce the inflammatory response? Well, sounded like a great idea at the time. We started seeing acute thrombosis of

these stents, these are the drug-eluting stents. The stents we've been talking about are called bare metal stents, which sounds like a great rock band name. So the drug-eluting stents are supposed to limit the fibrotic reaction in the vessel. Well, newsflash-- once the stent is deployed, it actually stretches the native vessel to a diameter larger than its native diameter. So you already have a disrupted endothelium, and you have made it a little bit worse by the dilation. Remember this is within the context of a percutaneous transluminal coronary angioplasty. Angioplasty, by definition, means enlarging the diameter of the blood vessel. The late Dr. DeBakey is the one who invented this procedure, basically. It started in the carotids, and then he took it to the other vessels. So you have an unhealthy endothelium that is supposed to react in a fibrotic way. You have a stent in there, the drug-eluting stents, it's preventing this reaction. So two things happen. The stent doesn't get secured well enough. And the metal elements of the stent trigger the thrombotic reaction because the blood is flowing through it. And that's why drug-eluting stents require the patient to have dual and sometimes triple antiplatelet therapy for life.

What is the impact of stent length?

We have the myocardial blood supply completely dependent on the epicardial vessels, which are the coronaries and their branches going inside the myocardium. And that's why oftentimes you hear that term sub-endocardial infarction. Sub-endocardial myocardial infarction, which is the area in- this happens especially in thick myocardium, like concentric left ventricular hypertrophy, or hypertrophic cardiomyopathy. So these branches are crucial for the supply of the entire myocardium at-risk. And, in many patient populations, especially diabetics and to a certain degree- especially diabetics for this discussion- they have small vessel vasculopathy. So these are small vessels are already badly diseased, and they are less than a millimeter or less than half a millimeter, sometimes, in diameter. So we have the coated stent, which is supposed to be kinder to the vessel, than the bare metal stent. And by definition, it has a fabric coating whether PTFE or Dacron or just for discussion sake. So the problem is, most of the time, in coronary artery disease, you have a discreet, well localized lesion, a short distance. You're putting a stent behind it- I mean, across it. So you're stenting the vessel for a longer distance. In the process, oftentimes, a couple of branches get obstructed, and we call that a jailed branch. And sometimes it's a big branch like the diagonal, which supplies a significant part of the anterolateral surface of the left ventricle. And there's no way of perfusing that, of restoring blood supply to that. And when this happens in somebody with small vessel disease, you don't get the benefit that you're expecting because a good part of that myocardium at-risk has already been eliminated from the game. And that's why it's not advisable. It's frustrating to see a long stent that doesn't need to be that long. But manufacturers, I guess they have certain set dimensions for stents.

Can you remove a stent?

In my opinion, the biggest disadvantage and frustration with coronary stent use is that it's completely irreversible. It cannot be removed. And when you have-- I'll just call it stent malfunction, which includes in-stent stenosis and in-stent thrombosis-- the only solution to address that is to put another stent inside the stent and dilate it to even a larger diameter, which I think it doesn't make sense to me. But that's just me. You have a diseased vessel and you already have disrupted its mechanics- both wall mechanics and flow dynamic mechanics inside- and you're repeating the same thing in the stent.

So this is the major aggravating factor with stent use- is that it's something that is uncontrollable. You cannot retrieve it; you cannot remove it. There were attempts, short clinical or limited clinical series, when we went in and surgically took out the stent, dissecting it from the artery. It was a big bloody mess. Literally a big bloody mess. Because you have the vessel- you've lost all the endothelium. And the subendothelial layer is just raw and it's even more thrombogenic than the diseased artery. So outcomes were not promising. People who were doing that stopped doing that because you're adding risk to the

patient. The principle in medicine generally, in health care generally, and specifically in surgery or interventions, is "*primum non nocere*": First do no harm. So if you have something that will benefit the patient, you always have to weigh that against the risk that you are subjecting the patient to. If somebody is willing to accept the risk of a repeat operation to change their bioprosthetic valve, that's their decision, that's something that they have to balance on their own.

Can you use multiple stents?

When there is an in-stent stenosis, it affects the distal runoff. So the distal part of the vessel which we are hoping will thrive because we've restored the blood flow to it, it gets reduced pulsatile flow, and it starts getting stenotic in its own right. So the solution is to put another stent distal to the first stent. I remember a few years ago- we've seen that quite often. We call it the Full Metal Jacket. In one patient, we counted 11 stents in their coronary circulation. Another patient had nine stents. And at that point, if they are still having angina, there is absolutely nothing that you can do for them.

For a number of years, especially in the ten years between 2000 and 2010, so many hospitals and institutions developed standalone cath labs, catheterization laboratories, so that they can put more stents in people. And they bill for them. It became a money-making machine for the hospital. And at that time, no one was concerned enough about the long-term effects. What will happen when the patient lives for 10-15 years? What will happen to the stent? What will happen to the artery? What will happen to the ventricular function? Because like we said, stents are not curative. They are palliative, temporizing measures, but they have been treated as the end all, the definitive treatment for stents.

One of the basic principles in surgery or interventions is that you're aiming for something that will end the disease process, completely reverse it or eliminate it, or stop its progression for life. So if you have a device that you're expecting to function for the rest of the patient's life, you should closely watch it.

But putting stents in stable coronary artery disease, just because it's financially favorable, should not be done.