Renu Virmani, MD

The recipient of the 2012 TCT Career Achievement Award shares her thoughts on several aspects of cardiac care from a pathologist's perspective and advice for overcoming obstacles she has faced in the field.

What is the most instructive specimen you have been able to share at the TCT Hands on Hearts exhibit?

It amazes clinicians, as well as device engineers, to see aortic stenosis and mitral valve incompetence. It helps to be able to look at these complex valve structures so they can understand how to overcome these anatomic challenges. I remember when the Cribier valve (now called the Edwards Sapien valve [Edwards Lifesciences, Irvine CA]) was being developed, we showed that in fixed hearts with aortic stenosis, a percutaneous heart valve can be placed and have a good, large-orifice aortic valve. It was amazing that you could open a fixed aortic valve specimen with a "stented valve." I was totally blown away.

I think that people learn a lot by looking at heart specimens and seeing what the disease actually looks like. There is three-dimensional reconstruction technology now, but it is different when you can feel it in your hands as compared to just seeing an image. You don't have to imagine, you can actually feel it, and that makes a difference.

What is the most important finding you have discovered from pathological examination of transaortic valves? What should operators know about percutaneous or surgical implantation going forward?

It's helpful to learn why surgical valves fail, because then we can easily recognize when a transcatheter aortic valve replacement (TAVR) device fails and make a connection regarding what the shared causative factor(s) may be. I would like to have a registry with surgically placed bioprosthetic valves and be able to compare them to TAVR valves so that we can make these comparisons regarding valve failure. Are the modes of failure similar or different? If calcification occurs, does it occur in the same anatomical location and after a similar duration? I think this would be a great place to start in our understanding so that we may eventually improve the next generation of transaortic percutaneous bioprosthetic valves.

Do device companies generally welcome your assessment of how their devices might have failed, or are these findings met with contention?

They have been very open and willing for us to assess cases of device failure, which I think is commendable. They want to know where and why the failure occurred, how the device interacts with bodily tissues, and when there is calcification, does it distort the valve? Through these assessments, they learn a lot, and we learn a lot. It's a shared benefit for patients, clinicians, and companies, because in the next generation of devices, they will be able to address specific, known problems.

For example, in the first generation of drug-eluting stents (DES), I insisted that these devices were not optimal and needed improvements. Sure enough, based on this feedback, the second-generation DES are better than the first. I think this will also be true for future generations of TAVR devices.

What is the next step in attempting to determine the genesis of sudden cardiac death? What tool might be the key to reaching this step?

To prevent sudden cardiac death, we've got to find a way to recognize the presence of coronary disease, aside from the Framingham risk index. We don't yet know why some patients in the intermediate-risk group slip through the cracks and later have serious problems. Maybe a better way to recognize which patients are at risk would be through detection of vulnerable plaque. We can identify the presence of vulnerable plaque by noninvasive means (eg, multislice computed tomography [CT]). It has been theorized that it might be possible to identify these patients based on the presence of carotid intimal medial thickening; however, I am doubtful about this because it doesn't tell us if there is coronary disease—only that there may be. We have to have better tools than the Framingham risk index, carotid assessment, or ankle-brachial index because none of these indicate whether there is coronary disease.

I think multislice CT is the best method we currently have for detecting coronary disease—or at least, severe

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narrowing. In the future, fractional flow reserve (FFR) derived from CT might prove useful, but as of now, we are not 100% sure that FFR is going to be the most accurate predictor; although it may be a useful tool in some ways.

I look forward to seeing further prospective study data. There was one study in which multislice CT was used in emergency settings. When patients presented with chest pain, multislice CT was performed, and this proved useful in making the decision of which patients to send home and which patients to take to the cath lab. Similar studies and long-term follow-up need to be performed in patients who are at intermediate or high risk based on the Framingham risk index, as well as those who have calcification as seen on multislice CT, to determine which patients are likely to have coronary disease.

Where is the medical community right now in terms of identifying certain types of vulnerable plaque, as well as treating them? What can physicians do to better recognize plaque progression in order to optimize treatment?

Vulnerable plaque is a reality, especially thin-cap fibroatheroma, as we suspect that those with the largest necrotic core and excessive macrophage infiltration are likely to rupture. However, we cannot currently recognize the eroded plaque because the underlying plaque is quite different in individual patients. Sometimes, there is pathologic intimal thickening or fibroatheroma, which may be present without luminal thrombus and have no specific morphological feature that separates these plaques from those with thrombi. The one we can easily distinguish is thin-cap fibroatheroma, which resembles plaque rupture; therefore, we have tried to recognize it in living patients in order to predict which ones are likely to rupture.

I believe that the use of FFR is very useful in many ways (eg, in patients who have severe disease), but I don't necessarily believe that only patients who are FFR positive should be treated. I think that if it were possible to identify vulnerable plaque when the vessel is 50% to 70% narrowed and treat it by invasive or noninvasive means, then perhaps we can prevent future myocardial infarcts. However, unless we perform a trial, we will never know for sure whether we should place a stent or not.

There are some plaques that thrombose and cause an acute myocardial infarction (AMI), for example, but FFR is not typically performed in AMI patients. Such patients benefit from opening these arteries, even if they are not severely narrowed. We should not have closed minds in thinking that FFR is the be all and end all for assessing vulnerable plaque. We must keep AMI patients in mind and identify vulnerable plaques before they rupture and cause damage to the distal myocardium. If we take this into consideration, perhaps it will help us to reduce sudden death by recognizing vulnerable plaque lesions before patients have an AMI or sudden death.

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We don't have all of the tools we need to identify when there is definitely a necrotic core. With optical coherence tomography, for example, we aren't able to tell when there are macrophages on the luminal surface because high-intensity signals prevent the deeper tissue from being easily identified. Even with multislice CT, we can't recognize macrophages or a necrotic core in all cases, especially if there's high calcification. We still do not have a perfect imaging tool, but I think we're coming close to it. Maybe a combination of optical coherence tomography and intravenous ultrasound will help because then we can also measure the vessel size and assess for positive remodelling.

Does your examination of vascular tissue lead you to believe that the use of drug-coated balloons (DCBs) will eventually outpace stent implantation? How much of a factor is it that foreign bodies are left behind in the vasculature?

To me, DES in the coronary tree are certainly effective. But the use of DES in the periphery, especially the femoral and popliteal arteries where there is a lot of flexion, rotation, and elongation during walking and running, is difficult for any stent to withstand. So that's where I believe DCBs might be a more effective tool than DES. Also, we can always go back with another DCB if the artery undergoes restenosis.

In the coronary vasculature, I don't think DCBs will be on par with DES because there is already a very low rate of restenosis with DES (approximately < 10%). But we are not even close to this in peripheral artery disease. I think we can improve DCBs by applying a more even distribution of the drug, which would increase efficacy in the long run. The biggest benefit of not leaving a foreign body behind is that you can go back and treat the area again whenever you want (via surgery, stenting, or repeat DCB use).

What seems to be the best way to prevent neoatherosclerosis and, therefore, late stent failure with DES and bare-metal stents? Do the devices themselves need to be modified in future generations?

I think we either have to learn when endothelial cells regenerate within an underlying stent and form competent interendothelial junctions, or we should use drugs that target only smooth muscle cells and don't affect endothelial cells. But even with bare-metal stents, in 7 to 10 years, we see neoatherosclerosis. It could be that we need to make better bioabsorbable stents to enhance the endothelium, which disappear early and therefore do not have an underlying rigid stent. The problem right now is that most of the drug-coated bioabsorbable scaffolds last for 2 to 3 years, so they are still stiff, and the endothelium is incompetent. I think we have to be more innovative in thinking about how to make the endothelium more competent. Maybe the answer is in new types of drug coatings; there are companies that are currently working on this technology.

What has been the greatest obstacle to overcome in your career in the cardiology arena?

I remember when DES first arrived, I pointed out problems with the first generation of this technology, because of delayed healing as well as the presence of a large number of uncovered stent struts. Nobody wanted to listen and told me I was just being negative. Eventually, I was proven correct that the first generation of stents had problems (eg, late stent thrombosis). In recognizing the problems, we have been able to improve the devices.

You have to stand by your convictions and do not let people pull you down just because you have a different idea. If you believe strongly in your idea, then you must stick with it and try to convince the world that you're right however you can. You shouldn't always sit back and say, "Okay, if somebody says I have a bad idea, then I must be wrong."

So stick by your convictions and then have your work published, and present your ideas at scientific meetings. Don't give up! ■

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