Renal Intervention Roundtable

Experts discuss the current issues surrounding renal artery therapy.

FEATURING RAJESH DAVE, MD; MATTHEW EDWARDS, MD; AND THOMAS A. SOS, MD

PANEL

Rajesh Dave, MD, FACC, FSCAI, is Chairman, Endovascular Medicine, Pinnacle Heart and Vascular Institute, Harrisburg, Pennsylvania. He has disclosed that he receives grant/research funding from Kensey Nash, ev3, and Boston Scientific. Dr. Dave may be reached at rdintervention@yahoo.com.

Matthew Edwards, MD, is Assistant Professor of Surgery and Public Health Sciences at Wake Forest University School of Medicine, Winston-Salem, North Carolina. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Edwards may be reached at medwards@wfubmc.edu.

Thomas A. Sos, MD, is Professor and Vice Chair of Radiology, New York Presbyterian Hospital, Weill Medical College of Cornell University, and Director, Peripheral Arterial Disease, Cornell Vascular, New York, New York. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Sos may be reached at tas2003@med.cornell.edu.

How does the issue of distal embolization affect renal interventions?

Dr. Dave: Renal artery stenting with embolic protection is an important and very attractive issue for the next decade. The question that comes to mind is: Should renal artery embolic protection be used universally in all renal arteries, or should it be used selectively in certain patients? There has been no randomized control trial that clearly demonstrates renal artery embolic protection to be better than renal artery intervention without embolic protection. However, as we all know, there are multiple studies demonstrating that at least 20% of patients who undergo renal artery intervention may have potential deterioration in their renal function. There are many causes for this deterioration. One of the important causes is atheroembolization, especially in those patients with baseline renal insufficiency or poor functional reserve. These patients may have greater clinical expression of these phenomena and are most likely at highest risk.

However, the currently available embolic protection devices are not specifically designed for renal arteries, and not all renal arteries are suitable for placement of these devices. Although we frequently use renal artery embolic protection off label in select groups of patients, a consensus or general recommendation for renal artery stenting and embolic protection cannot be made at this time. We should really support studies such as the CORAL trial, which is an NIH-sponsored study that allows randomization within medical therapy and renal artery interventional procedures with embolic protection.

The potential for deterioration in the renal function is greatest when the patient has heavy atheromatous disease

in the distal abdominal aorta, in a patient with baseline renal insufficiency, or in a patient who has only one functional kidney, or in a patient with severe bilateral disease.

Dr. Edwards: I would certainly agree that embolic protection is an area of particular promise in renal intervention. I think that there is an ever-mounting volume of *ex vivo* and *in vivo* evidence that embolization does occur during percutaneous procedures. The patients who have the most to gain are those with pre-existing renal insufficiency because it is a very different vascular bed than elsewhere. Those patients cannot tolerate any additional loss of function because they are already operating without any functional reserve. If you perform a meta-analysis of the available data, somewhere between 12% and 30% of patients would be expected to have functional deterioration after the procedure, and that is very likely, at least in some part, due to the atheroembolization.

With that being said, I agree that there is no level-one evidence supporting the utility of these devices. We are hopefully in the last 30 to 60 days of finalizing preparations to begin randomization into a clinical trial at our center investigating the utility of distal embolic protection using the PercuSurge GuardWire (Medtronic, Inc., Santa Rosa, CA), which we hope will provide some important data to answer these questions.

In terms of ease of use, I think that the use of embolic protection is not very difficult in the renal arteries and, in some ways, I think it facilitates the performance of renal intervention. For those of us who have residents and fellows, it almost acts as a tether to help secure the guidewire for device passage. However, until there are level-one data, there is certainly no way to make a consensus argument that it should be used in all patients because it is a large added expense. The second thing that I would offer is that we do not know whether recurrent stenosis, fibromuscular dysplasia lesions, or other nonatherosclerotic lesions have a similar embolic potential. Those are issues that also need to be addressed before any blanket guidelines for embolic protection in renal intervention are issued.

What are the devices that are currently being used off-label for embolic protection in the renal arteries?

Dr. Dave: There are two design concepts for embolic protection devices: filters and balloon occlusion. Our current experience comprises five different devices, including the PercuSurge GuardWire, SpideRX (ev3, Plymouth, MN), TriActiv FX embolic protection system (Kensey Nash, Exton, PA), FilterWire EZ (Boston Scientific Corporation, Natick, MA), and the AngioGuard XP (Cordis Corporation, a Johnson & Johnson company, Miami, FL). Specifically, the TriActiv FX embolic protection system is a balloon occlusion device that uses CO_2 as an inflation material. However, it is also associated with the flush and extraction system; perhaps using flush and extraction to remove all the debris from the renal artery may be more beneficial than just aspirating into the renal artery. There can be a potential distal embolization from flush extraction, but the debris that is likely to be present in the renal artery after intervention is usually not that large, and it would be unlikely to cause a major peripheral arterial atheroembolization from flush extraction alone.

Dr. Dave

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The second concept is the filter protection device. The advantage of filter protection devices is that the visualization is better. The most common filter that we use off-label is the SpideRX.

I want to mention that there is a need for industry to step up to design more devices that are renal specific. After talking to many operators in the field who perform renal artery interventions, one of the things that I hear a lot is that some operators like to perform renal intervention on stiffer wire, such as an .018-inch wire. There is no .018-inch wire in an embolic protection device, but I'm certain there will be one in future devices. Possis Medical, Inc. (Minneapolis, MN) has a device called GuardDog, which was just approved by the FDA. It is a balloon occlusion device on a .035-inch wire.

The last thing I wanted to mention is the design of the currently available filter. One of the problems in filter design in the renal artery is that the landing zone is shorter than a landing zone that is available in the vein graft or carotids. We like to have a shorter length filter system so that you can appropriately place it without having the bushing of the filter extending close to the ostium. A shorter filter and a shorter tip are going to be necessary so that you can sometimes put it in a deeper position in the renal artery. This does not solve the problem of a large bifurcating renal artery, and that is an issue that will likely require further investigation in the future.

Dr. Edwards: Our practice has been limited, for the most part, to the occlusion and aspiration systems. We

Dr. Edwards

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have used the FilterWire and the short AngioGuard in limited applications but favor the PercuSurge GuardWire temporary balloon occlusion and aspiration system. We have moved away from the filter type systems for two reasons: (1) we have published *ex vivo* data showing that the greatest number of liberated particles are very small debris (<100 µm) that can pass through the interstices of the filters; and (2) we have some concern with filters because they must be put in the terminal renal artery, and the floppy end of the filter guidewire will often be in one of the branches. I worry that this will tilt the filter and further reduce its ability to catch embolic debris. With all of this being said, I have been fairly enamored with the distal occlusion because you can confirm complete occlusion.

Dr. Sos: We all agree, that ideally, embolic protection is desirable in the renal artery; however, we also agree that the ideal device does not yet exist, and that the few, almost anecdotal, studies on protection are seriously flawed. Both types of devices (occlusion and filter) have advantages and disadvantages. The pore size of filters (~100 µm) is too large for most cholesterol crystal emboli, whereas occlusion devices result in warm ischemia and potential reflux distal emboli, and both can result in trauma to the treated artery.

One other little-discussed aspect of cholesterol embolization in the renal arteries is the fact that a lot of the embolization probably occurs during manipulation of diagnostic and interventional devices in the often very diseased abdominal aorta prior to placement of the protection device. This can be minimized by good technique, but not eliminated, and certainly not by any protection device.

What are the important points regarding utilization of renal artery stenting in clinical practice? When is renal artery intervention appropriate?

Dr. Edwards: I think that there is a fair volume of literature out there on this topic that has been widely misinterpreted to support prophylactic intervention. I think that an intervention, especially one that is clearly defined as having a 15% to 25% rate of damage in renal function, has absolutely no application in patients who have not demonstrated problems from their renal artery stenosis, such as severe difficult-to-control secondary hypertension or that same hypertension combined with excretory renal insufficiency. The most common argument put forth is that intervention needs to be performed to prevent future occlusion with the thought that you can't go back and do something for that kidney. I think those data have been extrapolated in a way that is a very big stretch. The data that are out there show progression to occlusion to be sure, but only in highly selected patients. All of the patients involved in the cohort studies cited to support this argument were identified because they had severe hypertension or ischemic nephropathy and were not intervened upon for some reason.

The only data that exist in patients more indicative of an asymptomatic population-based cohort, with true incidentally found disease, were published last year by Jeff Pearce, MD. These data looked at an elderly cohort that was followed over time, and there were a small number of patients with incidentally discovered renal artery stenosis. A small but significant number of those patients were restudied, and essentially none of them had progression to occlusion. I think these data, although very limited, are probably much more indicative of what truly happens in the patient with a nonclinically significant stenosis. I am very opposed to prophylactic intervention. I think the data that most strongly support this come from renal intervention and from other areas, indicating that renal function is a strong predictor of subsequent adverse cardiovascular events.

Patients with impaired or deteriorating renal function after intervention have a much higher rate of subsequent adverse cardiovascular events, dialysis dependence, and mortality. These increases are probably due to a multitude of reasons that are beyond the scope of this discussion. But, if we are employing therapy that can damage renal function in patients who do not have a clinically apparent problem, we may be creating a situation in which the course of treated disease is worse than the natural history of the disease left untreated.

Dr. Dave: Currently, we would not treat clinically asymptomatic (ie, normotensive) renal artery stenosis, except in those patients who have severe bilateral renal artery stenosis, or in a patient who has a unilateral kidney. Those are the two patient groups who we believe may benefit from renal intervention, despite being normotensive. I agree with Dr. Edwards that prophylactic renal intervention should not be performed at the current time. However, besides hypertension, other indications, such as flash pulmonary edema and ischemic progressive nephropathy, should not be forgotten. If we are to use embolic protec-

tion with an appropriate device and if we can take deterioration of renal function secondary to atheroembolization out of the equation, perhaps the indications for renal interventions can be widely expanded.

To summarize the debate on whether to treat, there are some patients who I believe we should be treating, including patients with uncontrolled hypertension, patients with bilateral renal artery stenosis, patients with severe renal artery stenosis and deteriorating renal function, and of course, the unfortunate patient who has a single kidney and renal artery stenosis or renal artery stenosis causing acute pulmonary edema. Certainly, fly-by renal arteriography should be discouraged without appropriate indication.

One other subset that pertains more to our cardiology community is the patient with bilateral renal artery stenosis and severe left ventricular dysfunction. Use of ACE inhibitors has demonstrated improvement in mortality in these patients and there can potentially be a significant deterioration in renal function due to ACE inhibitor use in patients with bilateral renal artery stenosis. We will treat these patients even if they are not hypertensive so that we can introduce ACE inhibitors or angiotensin receptor blockers.

Dr. Sos: I agree wholeheartedly that there is no place for intervention in clinically asymptomatic renal artery stenoses that are approximately 50% and have no gradient. You cannot benefit these patients, but you can make them worse by causing cholesterol embolization, even if the damage may not become apparent until much later, when renal function declines. Most importantly, most of the natural history studies on the progression of renal artery stenosis predate modern lipid-controlling medications, such as statins, and lifestyle modifications, such as smoking cessation. In fact, there is now solid evidence in the carotid and coronary arteries that aggressive lowering of lipids results in arrest of progression and, in some cases, even regression of plaque. These results completely shift the paradigm in the renal artery from "prophylactic" intervention to aggressive medical therapy, albeit while continuing to follow the status of the artery and the kidney. Although this seems intuitively obvious, it may form the subject of a prospective randomized study.

Intervention should be reserved primarily for those with bilateral severe disease or severe disease in a solitary kidney—these patients will usually have some renal impairment; patients with hypertension only and unilateral disease can be considered for intervention but only after careful and individual assessment of their medical and technical risk benefit profile.

Dr. Edwards: I agree with the indications for intervention being severe difficult-to-control hypertension, severe difficult-to-control hypertension combined with renal insufficiency, and cardiac disturbance syndromes that are worsened by hypertension. I would also include those hypertensive individuals that we cannot adequately ACE inhibit for either diabetic treatment or congestive heart failure treatment. I think that in these patients, the onset of renal failure with application of ACE inhibitors proves the physiologic significance of their lesion. Before considering prophylactic intervention, I believe that we need better natural history studies to define whether patients with high-grade bilateral disease truly have long-term problems. In patients who are clinically insignificant, we do not know this answer. The second piece of information we need is randomized data to determine whether embolic protection removes that risk, which can alter the natural history of the disease treated. If we can remove that risk of procedure-related renal function harm, there would be a potential rationale for more liberal application of renal stenting. Until we have that data, I think the risk/benefit ratio is just too high.

Dr. Sos

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As for the low-grade renal artery lesions, there is absolutely no way I could see a rationale for treating a 50% stenosis. I think it would have to be a 60% or 70% stenosis with some demonstration of hemodynamic significance either through Doppler velocities or pressure gradient measurement. I tend to shy away from pressure gradient measurement due to fears of atheroembolization from additional lesion crossing. Furthermore, I almost always have a duplex demonstrating hemodynamic significance with velocities in excess of 2 m/s and post-stenotic turbulence in patients for whom I'm planning an intervention. I do measure pressure gradients on the way out after I have placed a stent and aspirated to make certain that I've resolved any hemodynamic disturbance across the lesion.

Dr. Dave: We don't necessarily use a pressure gradient as an identifier for the patient who needs renal intervention. It usually is pretty obvious that the patient with severe stenosis will have dampening of blood pressure by catheter placement into the ostium, confirming findings of duplex ultrasound almost universally in our first investigation in these patients. It is a rare instance in which the Doppler findings and angiographic findings do not correlate. In such instances, we would use a pressure gradient to determine the therapeutic course, if the patient has an appropriate indication. Again, it would certainly not be a patient with a 50% stenosis, but it would be a patient who has a lesion with just a hard-to-delineate lesion. There are no standardized criteria available in what pressure gradients are important, although generally we use a 20-mm Hg pressure gradient that is usually an accepted indication to treat.

Dr. Sos: I am not confident enough in duplex or visual assessment of the angiogram for severity and physiological significance of stenoses (both underestimates and overestimates have been documented in the literature). Therefore, I really believe in getting a gradient on all patients; after all, you already have a catheter across, although the much more expensive pressure wires are more accurate. Similarly, I would not deny intervention to a patient solely on the basis of an abnormally high noninvasive resistive index.

What is the significance of in-stent restenosis, and what is the role of drug-eluting stents in renal interventions?

Dr. Edwards: I do not use covered stents for in-stent stenosis. I tend to treat those patients preferentially with routine balloon angioplasty and occasional application of cutting balloons followed by repeat dilatation with standard balloon angioplasty. I think that our approach leads to suboptimal results, but so does everything else we have tried with restenosis of the renal artery. Our group has not tried covered stents for that application yet.

Dr. Dave: We have not used covered stents universally for in-stent restenosis, but our recent limited experience since the availability of the iCast balloon-expandable covered stents (5 mm and 6 mm; Atrium Medical Corporation, Hudson, NH) has produced some very encouraging results in a very small group of patients who had repeat restenosis.

If a restenosis exists in a small-sized renal artery, we would potentially utilize a coronary drug-eluting stent for a repeat restenosis after a first round of treatment by balloon angioplasty only. I have a small number of patients in whom a bifurcated renal artery is treated using a drug-eluting stent with a very nice result. Of course, there are some very important considerations that have to be taken into account to use a coronary drug-eluting stent, as well as a covered stent. First, it is very important to determine if the patient can be continued on long-term antiplatelet therapy because there is a potential for thrombosis in both of these devices. We have not had to use warfarin therapy for any patient who had received covered stents in our lab for repeat in-stent restenosis, but we would absolutely make certain that a patient can remain on prolonged dual antiplatelet therapy to prevent an unfortunate event of stent thrombosis.

Dr. Sos: I now use cutting balloons for in-stent restenoses. Based only on anecdotal observation, the immediate results "look" better and recurrence is less.

Dr. Edwards: I am glad to hear that here are some promising results with covered stents; I look forward to seeing that in print. I am also glad to hear that someone may be making some progress on in-stent restenosis. The majority of in-stent restenosis we see is almost like a rind within the stent and throughout the stent. We suspect that this represents some sort of cellular in-growth throughout the stent. I think there is some theoretical appeal to drug-eluting stents in this circumstance if you assume the lesion is the myointimal hyperplasia-type lesion that is a cellular restenosis. In such a case, a cytotoxic agent may be very helpful.

One area in which I think the covered stents may hold promise is in future application as a primary tool. If we indeed find that atheroembolization is the big culprit in limiting renal function response, I think covered stents may have a role. We have talked about distal embolic protection in limiting procedure-related atheroembolization, but it may very well be that atheroembolization goes on afterward. There is no reason to believe that once you place the stent, there may not be fragments of plaque hanging out through the interstices of the stent, continually embolizing the kidney for some period until that lesion reorganizes and heals with a fibrous cap. I think that if we find that embolic protection does help limit renal function damage, but does not completely take it out of the equation, there may be some rationale to study covered stents for primary applications in the renal artery.

Dr. Dave: We are in the process of starting the study for vascular approval for the iCast stent. Once we receive vascular approval for the iCast covered stent, I hope that industry will step up and have a study in which we can utilize the covered stent without embolic protection, or a stainless steel or a cobalt-chromium stent with embolic

protection. It will be very interesting to see the difference in the results between these two approaches. It certainly does make intuitive sense that the covered stent may have a potential role in preventing atheroembolization; however, the safety of this device needs to be established in the renal artery, and the anticoagulation regimen needs to be further defined because the question that remains unanswered is whether a patient with a covered stent in this location would require further anticoagulant therapy as opposed to dual antiplatelet treatment.

Dr. Edwards: I think we would be remiss if we did not mention that there is still the fundamental question of whether renal artery stenting has any utility, especially in this era of ACE inhibitors and angiotensin receptor blockers that really have just about eliminated the cases of refractory hypertension; CORAL is underway to try to determine the answer. I look forward to the results of CORAL. In my mind, I am confident that renal artery stenting has utility. I think, though, that the utility will likely be in selected populations of patients, and I hope that CORAL gets us a lot further toward identifying those patients who are most appropriate for any application of therapy.

What measures can be taken to prevent nephropathy?

Dr. Edwards: Because we work with a nonionic, iso-osmolar contrast agent as a routine, we have not seen much contrast nephropathy. I can think of maybe one or two temporary cases in the last several years. I use the iso-osmolar agents, and I am very conservative in patients with ischemic nephropathy, performing most of my planning and securing access to the renal artery with CO_2 and, occasionally, gadolinium. I use very small amounts of contrast to perform the intervention, and I can usually perform an intervention with 10 mL to 20 mL of contrast if someone has a very high creatinine level, but I have not found that to be much of a limiting factor.

Dr. Dave: I do not use the CO_2 or gadolinium in my own practice, but an experienced renal artery stent operator can usually complete the procedure in using less than 50 mL of contrast, sometimes even less. We would use a diluted contrast. We routinely use nonionic iso-osmolar agents for almost all of our vascular interventions.

I do want to discuss the utilization of intrarenal fenoldopam in patients with severely reduced creatinine clearance and who are in need of renal intervention. The Benephit catheter (FlowMedica Inc., Fremont, CA), which is the currently available device, is a two-pronged catheter device used to deliver fenoldopam intrarenally. This is a potential limitation, however, and new device development of a single-arm catheter will solve this issue in the near future, which will allow administration of intrarenal fenoldopam during the procedure and it has shown great promise in reducing the rate of contrast-induced nephropathy. In our routine practice, we are usually not faced with contrast-induced nephropathy in this intervention because the amount of contrast being utilized is so small.

Dr. Sos: I routinely perform renal artery interventions using 50% dilution of low-osmolar contrast and use only a total of 10 mL to 15 mL, including the pre and post angiograms. Careful technique will always trump the next wonder drug and the next additional mechanical device, which has its own added risks for dissection and embolization.

What are the issues surrounding reimbursement for renal artery intervention?

Dr. Dave: The current medical reimbursement for renal artery intervention is only for renal vascular hypertension and uncontrolled hypertension; however, for a patient who has progressive renal insufficiency (ie, a patient with bilateral renal artery stenosis and ischemic nephropathy) there is no way to get reimbursed because that's not an acceptable billing code for renal artery interventions. I think it also needs to be defined further, and CMS needs to readdress the issue of how some of these other subsets of patients can be billed. With the use of drug-eluting stents, covered stents, and embolic protection devices, the expense of this intervention is quite substantial, and hospitals cannot bear the burden of intervention, which is clearly justified. Adjustment needs to be made, especially for embolic protection devices.

Dr. Edwards: I do not think that reimbursement issue from a diagnosis standpoint is a problem. Every patient who needs renal artery stenting should have severe hypertension and qualify for the renovascular hypertension ICD code. We feel that severe hypertension is an absolute prerequisite for intervention. It has been shown to predict better functional outcomes following intervention, and this makes sense; the natural renin angiotensin response is to increase blood pressure in response to falling perfusion to prevent excretory failure. Thus, activation and hypertension should precede and coexist with any renal insufficiency that is secondary to renal artery stenosis. A problem may exist, however, if more expensive adjuncts such as embolic protection and covered stents are necessary to improve outcomes. This will need to be addressed as data accumulates supporting these adjuncts. ■