Neurovascular Intervention Roundtable

Endovascular Today interviews Bernard R. Bendok, MD; Lee R. Guterman, MD, PhD; and Kieran P. Murphy, MD, regarding the latest developments in interventional neuroradiology.

MEET THE PANEL

Bernard R. Bendok, MD, is Codirector, Neuroendovascular Program at Northwestern Memorial Hospital, and Assistant Professor of Neurological Surgery and Radiology at the Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Bendok may be reached at (312) 695-0464; bbendok@nmff.org.

Lee R. Guterman, MD, PhD, is Associate Professor of Neurosurgery and Radiology, Director of Endovascular Fellowship, and Co-director of the Toshiba Stroke Research Center, School of Medicine & Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York. Dr. Guterman may be reached at (716) 887-4960.

Kieran P. Murphy, MD, is Director, Interventional Neuroradiology at Johns Hopkins, Department of Radiology, Baltimore, Maryland. Dr. Murphy may be reached at (410) 955-8525; kmurphy@jhmi.edu.

INTRACRANIAL STENTING: SYMPTOMATIC, ASYMPTOMATIC, AND ACUTE STROKE PATIENTS

Endovascular Today: The first topic we would like to discuss is intracranial stenting. What are your thoughts on when and if angioplasty and stenting should be used as opposed to medical management alone?

Dr. Bendok: Atherosclerosis throughout the body is increasingly being treated with angioplasty and stenting, and the brain is the final frontier because there are some unique aspects to the brain that make stenting lag behind other vascular beds. As technology has improved over the last couple of years, however, we have seen progressively better results in tackling particularly symptomatic intracranial atherosclerotic lesions with angioplasty and stenting. Dr. Guterman and his team are some of the leading pioneers of this area, and the results are improving on a yearly basis. It should be kept in mind that people with symptomatic intracranial atherosclerosis have a very poor prognosis even with the best medical management. Medical trials have shown that other than aspirin, nothing seems to offer a substantial benefit. The WASID trial showed that warfarin is not a suitable medicine for this indication because of hemorrhagic complications. There is a tremendous need for better solutions for these patients. The challenge now is to prove that angioplasty and/or stenting will improve the natural history with acceptable complication rates. The technology is rapidly evolving, which makes trials difficult.

Dr. Guterman: Intracranial stenting has two different applications—atherosclerotic disease and cerebral aneurysms. For treating intracranial aneurysms, the stent is used to cover the neck of an aneurysm, where you want to contain some embolic material. For intracranial atherosclerotic disease, there is a good body of literature beginning to form that demonstrates that stenting may provide improvement over the natural history of symptomatic disease, especially in the posterior circulation. The natural history of symptomatic intracranial atherosclerotic disease in the posterior circulation is grim, so we can consider stenting in this bed to be an acceptable application. As far as the rest of the circulation is concerned, however, we don't have level 1 evidence to prove that it's the best thing to do, but we certainly have numerous level 2 papers to support it. When it comes to asymptomatic intracranial disease, the benefit of intervention becomes even less well defined.

In patients with asymptomatic intracranial atherosclerotic disease, it's important that we be very judicious about who we send for revascularization using carotid angioplasty and stenting, because we don't have much data on the long-term natural history of the disease. The risk-benefit ratio in the asymptomatic population has not been worked out, and I look at these patients as a precious commodity with whom we should be very careful. I believe such patients should only be treated in the setting of a clinical trial.

For coronary applications, patients can be given a stress test. Even if the patients have no chest pain, a stress test can help determine which patients should go on to be revascularized. In asymptomatic intracranial atherosclerotic disease, we do not have an equivalent test. Nuclear images can demonstrate vascular reserve compromise and perfusion deficits. When we have nuclear or MR imaging evidence of this hypofusion of vascular reserve compromise, this evidence can help guide who should be considered for revascularization. So, it's a question of designing the trials and getting them underway so that we move ourselves down a path like the cardiology world did years ago.

Dr. Murphy: I believe there are two reasons to stent intracranially: a cranial aneurysm and atherosclerosis. Our policy in the anterior circulation is to perform angioplasty first to avoid stenting; we only consider intracranial stenting to occur if it takes place above the ophthalmic artery. We don't consider anything outside the dura to be intracranial stenting. Stent-assisted coiling is a sensible approach, and there are many good devices currently available in the US and other countries. The Cordis intracranial stent (Cordis Corporation, a Johnson & Johnson company, Miami, FL) also looks very promising.

Dr. Bendok: There are two developments in the stenting arena that we need to watch closely. One is the fact that industry is working on self-expanding stents that will be easier to deliver intracranially than coronary balloon-expandable stents. The second is the potential applications of drug-coated stents intracranially to reduce in-stent stenosis.

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Dr. Murphy: The use of drug-coated stents in the cerebral vasculature is something about which we need to be very wary. In Europe, 20% of coronary stenting procedures involve the use of drug-eluting stents, whereas in the US, this number approaches 80%. There are reports from the AFIP indicating that there are issues related to chemotherapy/drug-elution causing a polyarteritis nodosa-type syndrome, and causing sarcomas in vessels. We can't have that kind of issue in the neurovasculature, so we must be very prudent when drug-coated stents are used. When you coil an aneurysm and partially cover the neck with a stent, you're ultimately getting intimal hyperplasia. I am interested to see how many people over the next 20 years develop symptomatic stenosis across the stents that have been placed across their aneurysms. Regarding atherosclerosis of stents, the smaller the diameter is, the greater the restenosis rate will be. We know that in the coronary and the vertebral arteries, restenosis rates are approximately 33%, and that's significant. If you look at the rates of sudden death from drug-coated stents in small vessels, it's the same kind of vessel size that we're dealing with intracranially. There is reason to be wary of using stents, especially drug-coated stents, in this anatomy.

Dr. Guterman: I agree that we should be very careful in our approach to adopting these new platforms. I do, however, believe drug-coated stents may hold some promise in the neurovasculature. There has been a great deal of activity in the research lab to look at *in vivo* models of drug-coated stents and their effect in the central nervous system, but there has not been a large number of drug-coated intracranial stents placed in humans, mainly because the platform of drug-coated stents is not as flexible as some of the other stents manufacturers are making, therefore, placing them intracranially may be difficult. The majority of the vessels we treat intracranially are 3 mm or less, and if you're in the mid-

dle cerebral artery territory, it could even be 2 mm or 2.5 mm. The coronary data indicate that especially in diabetics, these small vessels are problematic and have high degrees of restenosis. In time, it may prove sensible to use drug-coated stents in intracranial circulation, if it can be done safely, especially in diabetics. To that end, we need to see some self-expanding nitinol platforms drug-coated so that the neurostents that Dr. Bendok mentioned earlier—the Wingspan and the Neuroform, which can be placed easily—are also drug coated. We have to wait for the manufacturers to invest the time and energy necessary to accomplish that task.

Endovascular Today: What role does stenting have in the setting of acute stroke?

Dr. Guterman: I think that the use of intracranial stents for acute stroke should be reserved for bailout situations. In other words, if you have a patient with acute stroke, you've tried lytic therapy and clot-grabbing devices, or mechanical thrombolytic techniques have not worked after two or three passes and there's still an occluded vessel, I think stenting is warranted in those situations. Initially, that may seem like a heroic event, but in fact, all trials indicate that revascularization is achieved in less than 70% of the patients, regardless of technique. That seems to be the benchmark that we've hit for the maximum revascularization intracranially. In the past, I've said that intracranial vessels are unlike coronary vessels in that an embolus produces the occlusion rather than primary atherosclerotic disease at the site of occlusion. But, because we can't get 30% of them open, maybe that 30% occludes due to intracranial atherosclerotic disease and is more analogous to the coronary setting for acute vessel occlusions because of a primary atherosclerotic source. I'm beginning to feel that the ideal application of this technique should be in patients who have native intracranial atherosclerotic disease and go on to occlude. And, it would be great if industry developed some imaging modalities that could help us realize who those patients are. In fact, with better imaging, we might even perform primary stenting in these cases. At present, we're confined to using techniques we know to have a relatively proven track record, and we are using stent technology only as a bailout or as an investigational device.

COIL TREATMENTS FOR INTRACRANIAL ANEURYSMS

Endovascular Today: How has the role of coil treatments for intracranial aneurysms evolved in the recent past, and what does the future hold for this technology?

Dr. Bendok: In the 1990s, there was only one company making coils, and that was Boston Scientific (Natick, MA) making the Guglielmi Detachable Coil. In the last 5 years, however, many more systems have become available. Although animal data on bioactive coils are certainly interesting and there is a great interest in using them, there have been limited human data on their superiority over bare platinum coils. Another interesting development has been the development of new three-dimensional coils that result in better packing of aneurysms and better neck coverage.

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Dr. Guterman: Coil treatment is intended to cause scarring such that the aneurysm neck heals and the opening to the parent vessel becomes smooth and endothelialized, resulting in complete permanent occlusion. There have been some 510(k)-cleared products that have relied on some form of suture material to be intermingled with the platinum to induce a healing response. There are also the bioactive coils that have a hydrogel coating on a platinum frame. This design is intended to induce fibroblasts and other cell-wall elements to adhere to the hydrogel coating on the coil after it swells, which occurs 20 minutes after implementation, and ideally produce neck healing. Radioactive coils seem to induce a delayed fibrous reaction, leading to complete obliteration of the aneurysm. I agree that human data have not yet been collected in an organized fashion to prove level 1 evidence of their superiority over bare platinum. Part of the reason is the density of coil packing would affect the results using either platform; there is great variability in the way interventionists pack aneurysms such that it is difficult to achieve a consensus result. It is being studied, and the jury is still out whether biologically active coils will clinically demonstrate reduced recanalization rates in the long-term.

Dr. Bendok: One of the advantages of having many coil products available is that it has given us many options to choose from. On the other hand, it has made data analysis more ambiguous. In the 1990s, there were data that you could analyze because everyone was using the same coil, but now, not only are practitioners using different coils, they are also mixing coils, so it is increasingly difficult to analyze angiographic results. Is it the mixture of coils that's resulting in better aneurysm treatment? Or, is it the

bioactive component? Or, is it the better engineering of the coils? Certainly, a learning curve also plays into this. Because aneurysms are so heterogeneous, it's difficult to obtain good data unless practitioners are using similar techniques.

Dr. Murphy: I agree, we need more follow-up regarding the long-term benefit of these devices, and there are so many on the market now that it's getting very difficult to identify which is the safest and most effective. I think that in this increasingly crowded market, it's important that interventionists keep using the devices with which they are most comfortable in order to reduce the incidence of issues related to unfamiliarity. Dense packing is still necessary. If you get loose packing and think that a coated coil will fix the problem, when the coating on that coil reabsorbs, you will have even less dense packing than you anticipated because so much of the coil volume was taken up by the coil's coating.

ACUTE STROKE: THE ROLE OF MECHANICAL DEVICES AND LYTICS

Endovascular Today: We've discussed the role of stenting in acute stroke patients, but when are patients best treated using mechanical devices and lytic agents, both alone and in conjunction with one another?

Dr. Bendok: Acute stroke is a tremendous opportunity for the neurointerventional field because this population of patients really has no good alternatives, particularly in cases involving intracranial large-vessel occlusions. In general, these patients have a poor natural history without treatment. There is currently no other treatment for patients who are outside the 3-hour window for intravenous thrombolysis. Recently, the Merci device has been approved by the FDA, and that has made history because it is the first time the FDA has approved a device for stroke intervention. It is my impression that what works best for interventional stroke thrombolysis is a combination of low-dose lytic plus a form of mechanical thrombolysis. Although the results of the trials are encouraging, this treatment remains very challenging. Outcomes are not fantastic with intervention, but we are seeing a glimmer of hope with developments such as the Merci trial and others that will shed more light on this treatment modality. Mechanical thrombolysis is a tremendous area for research because we still don't have a perfect way to open up a cerebral vessel when it becomes occluded. Even when we sufficiently open intracranial vessels, we don't always achieve a good outcome because there are other issues at play such as ischemic injury, delayed occlusions, and hemorrhagic conversion, etc.

Dr. Murphy: We have been using antiplatelets as well as antithrombolytics in combination and finding doses that are safe for a wide range of people to deliver. I believe there should be different levels of catheter-based intervention depending on the skill set of the physician on the spot. If you were in a community-level hospital, you may do a nonselective internal carotid artery injection but not intracranial injection of a combination of lytic and an antiplatelet agent. If you're in a tertiary-level institution with more experienced fellows, nurses, and ICU support, then you might use an intracranial clot removal device. Appropriate technology for each individual hospital setting is important. Different standards and expectations must be acceptable in medical/legal terms and politics internally within individual hospitals, within individual societies, and between societies.

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Dr. Guterman: Lytic therapy has been looked at in two trials (ProAct I and II). It appears that there is an increase in modified ranking at 90 days (45%) in the patients who have recanalized with intra-arterial therapy compared with 25% recanalization in the intravenous heparin control patients. Therefore, there is a 15% improvement, which is statistically significant, but not overwhelming. There are some data to support use of intravenous tPA, especially in strokes with lower stroke scores. The Merci trial showed us that in about 114 patients, they were able to achieve a recanalization rate somewhere around 54%. The investigator showed that in the patients that were recanalized there was a shift to better outcomes. It's good evidence to suggest that mechanical thrombolysis plays a role in the care of acute stroke patients. The downside of lytic therapy is that you have to infuse it in a patient who has an ischemic vascular bed downstream. If you were unable to recanalize or if there were blood pressure fluctuation, the lytic would increase your potential for intracranial hemorrhage. Lytics should be used in lower doses so that risk starts to go away. The farther out you are on the time window (0-8 hours), the less lytic you want to use because the more likely they are to bleed. It's our practice to try mechanical lysis; if that doesn't work, we add some lytic, and if that doesn't work, we resort to angioplasty and potential stenting.

Dr. Bendok: One area of research that is extremely interesting is the better refinement of the brain's status when a patient presents with a stroke. We currently rely on time to judge eligibility for intravenous or intra-arterial thrombolysis, but the extent of brain injury may vary in different patients, and that distinction may have bearing on whether a patient is eligible to have a vessel opened. It is possible that a patient 6 hours out from a stroke may have minimal infarct compared to a patient who is only 1 hour out from symptom onset. The risk of hemorrhage after opening a vessel and outcomes after intervention may depend more on the status of the brain tissue than time from symptom onset.

Dr. Guterman: It will be possible to use imaging in the future to define who should undergo acute revascularization therapy and who shouldn't, based solely on perfusion/diffusion imaging. It will tell you who's more likely to bleed, who already has a completed stroke, and essentially who has viable brain tissue at risk that needs revascularization. This would obviate the need for a time window because you'll choose your patients based on their clinical condition and their perfusion/diffusion imaging or spectroscopy etc, and that will determine who will be treated, not how far they are from the onset of symptoms.

Dr. Bendok: There is also interest in interventional MR techniques. The advantage is you'll be able to look at the issues that Dr. Guterman mentioned in addition to treating the patient simultaneously.

THE FUTURE: INTERVENTIONAL ROLES REDEFINED?

Endovascular Today: In the coming years, what role will endovascular procedures have in the neurovasculature? How will this impact the interventional specialties involved?

Dr. Murphy: The patient population for acute stroke is expected to increase as baby boomers age. I think the question is, who applies for the job? Only 40 of 160 positions for personal interventional fellowships were filled this year. There is a similar issue with vascular surgery; people just do not want this lifestyle. We need to change the way we approach IR/INR training in general. There is no need to spend an internship and 4 years of radiology prior to doing 2 years of diagnostic neurology and 1 year of interventional neurology in order to perform interventional neuroradiology. We need to streamline this process to make it economically possible for people with large college loans to pursue such careers. We also need to streamline training and acknowledge that many different backgrounds are equally acceptable. We, as a group of image-guided therapists, are wise enough to accept physicians from specialties other than our own, train them, and then foster their careers and mentor them in the future.

Dr. Guterman: In order to offer a high level of care nationwide, I think we need 1,000 to 2,000 interventionists who have the ability to perform stroke procedures at cath labs throughout the country. We should follow the trauma center model and have stroke level of care designations based on ER, imaging, and interventional capabilities. A tertiary stroke center would need an interventionist available 24/7/365. To pull that off in the US given our demographics, it's going to require more physicians than we presently have performing neurointerventions; to my knowledge, there may only be 300 qualified neurointerventionists in the US. With that number in mind, consider from which specialties the other people might come. If we count on neurosurgery, neuroradiology, and neurology to train another 1,000 new people, it will take years and we still might not have enough practitioners. So, we must look to interventional radiology because they can develop the skills to work intracranially. Others with catheter skills who could be trained are vascular surgeons and cardiologists. At least a portion of enrollees into the neurointerventional training for stroke must come from the diversity of those groups to build the numbers of stroke interventionists where we need them to deliver adequate care to the population that needs to be served. The thought of training this diverse group, ensuring an adequate level of skill, and monitoring clinical outcomes is frightening. Yet, there appears to be a ground swell of support to organize this effort.

Dr. Murphy: Also, standardization and credentialing must be done by people who perform the procedures, not the archaic sects who govern those fields. These organizations are often irrelevant because they do not have the day-to-day knowledge of what actually happens. Rather, they are more concerned about the politics than they are about making sure the interventionists performing the procedures are properly trained.

Dr. Bendok: We must be careful to maintain high standards of training. To the greatest degree possible, qualifications for practice should be standardized with patient interests as the most important priority.

Dr. Guterman: I think any smart, competent physician who dedicates his or her life to the treatment of stroke patients has the opportunity to make a great contribution in this final frontier. ■