Carotid Stents and Embolic Protection Devices

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Mechanisms of failure and current requirements for preclinical analyses.

BY ALAN R. PELTON, PHD, AND ROY K. GREENBERG, MD

The Cleveland Clinic hosted the fourth Stent Summit from August 30 through September 1, 2007. The purposes of this meeting were to discuss recent research and development involving carotid artery stenting (CAS) with embolic protection and thoracic aortic aneurysm (TAA) endovascular grafting and to identify potential pathways to improving the design and evaluation of these devices. This interdisciplinary meeting included keynote presentations and open discussions involving representatives from the entire endovascular community, including clinicians, engineers, and regulatory officials.

In the April 2008 issue of *Endovascular Today*,[1] Dr. Robert G. Whirley et al provided a summary of the discussions involving TAA endovascular graft issues. In this article, we summarize the CAS and embolic protection device (EPD) discussions. Each of the keynote presentations on these topics is summarized in this article, followed by the conclusions and future directions identified by the summit participants.

KEYNOTE SPEAKERS

Anatomy/Physiology Overview

By Sunita Srivastava, MD, Department of Vascular Surgery, The Cleveland Clinic, Cleveland, Ohio

Dr. Srivastava summarized the unique anatomy and physiology of the carotid bifurcation in the vasculature. Most atherosclerotic lesions are located in the bifurcation area due to the combination of abnormal flow patterns and high pressure-induced wall stresses. Flow separation at the bifurcation creates areas of stasis leading to atherosclerotic lesions. The flow of the blood and its interaction with the arterial wall create fluid shear, with both high- and low-shear flow contributing to lesion formation. Low shear facilitates particle formation on the arterial wall, whereas high shear results in endothelial damage.

Arterial stress is concentrated at the apex of the bifurcation and at the carotid sinus where the arterial wall is thinner. There is a correlation between high-stress areas and the location of atherosclerotic lesions. The internal carotid artery (ICA) and external carotid artery (ECA) both contribute to stress formation in this region by pulling on the common carotid artery (CCA). In addition, cervical mobility produces unique forces on the carotid arteries. These forces can result from common motions, such as neck flexion/extension, chewing, and sudden movements. Dr. Srivastava explained that stented carotid arteries are subjected to increased torsional shear forces that may cause vessel injury. Because stented segments are inflexible, the strains resulting from head movements can increase the mechanical forces acting on the vessel and lead to restenosis. Furthermore, strain at the edges of the stented segments may lead to endothelial overgrowth and intimal hyperplasia. The more flexible, nonstented vessel segments can accommodate these movements through increased flexion or torsion, leading to friction at the margins of the stented segments, altered vessel compliance and flow-shear rates, and increased intimal response.

Dr. Srivastava also stated that differences in physiology between men and women lead to differences in outcome in treating carotid artery disease. For example, men tend to have a greater plaque burden from the ICA to the CCA, and women are more likely to have focal lesions and lesions in the ECA.

Clinical Carotid Stent Failure

By Barry T. Katzen, MD, Baptist Cardiac and Vascular Institute, Miami, Florida

Dr. Katzen addressed the important question of whether all carotid stents are equivalent when used clini-

cally. He stated that there have been many approaches to carotid stent design and use, but that there is a body of evidence evolving on important characteristics. Balloon-expandable stents are simple to deploy and are able to treat a lesion more precisely without unintentionally stenting the carotid bulb compared with similar procedures with self-expanding stents. However, balloon-expandable stents are rarely used to treat lesions in the carotid arteries due to their rigidity, which when combined with the superficial location of many carotid lesions, can often lead to irreversible crushing of the stent when external loads are applied. Dr. Katzen commented that stents are subjected to multiple stresses from delivery through the tortuous access anatomy and from deployment in calcified lesions that may affect the long-term performance of the stent.

Carotid stents change the carotid anatomy in a manner dependent on their rigidity and flexibility. According to Dr. Katzen, larger-diameter devices create more severe changes to the artery, including arterial straightening or dislocation. Interestingly, most restenosis is observed within the stent, not at the ends of the stented segment. In addition, conformability is a challenge when determining the most appropriate stent size for a given lesion because healing will be retarded in the absence of sufficient wall apposition.

Dr. Katzen also presented stent-by-stent clinical results demonstrating that the cell size of the stent also has a profound effect on the overall event rates. Dr. Katzen believes that there is a trend demonstrating that stents with closed-cell designs have a lower associated event rate, but that this correlation is weak and needs further validation. Dr. Katzen also noted in this comparison that two thirds of all complications occurred in the subacute phase (23 hours to 30 days after the procedure). Finally, Dr. Katzen stated that even though carotid stent fractures can occur, the true incidence rate is unknown. Although he does not believe there is any evidence indicating that stent fracture is a significant clinical problem, this situation should continue to be investigated.

Carotid Artery Stent Fractures: An Engineer's Perspective

By Kenneth Perry, PhD, Echobio LLC, Bainbridge Island, Washington

Dr. Perry provided a literature survey of carotid artery stent fractures and observed that every reference indicated that fractures occur in the 6- to 7-month time frame. Fractures that occur this quickly are considered low-cycle fatigue fractures due to excessively high strains. He echoed Dr. Srivastava's position that there are significant mechanical challenges for carotid stents, including vascular tortuosity, bifurcation geometry, calcification-induced stiffness gradients, head movements, and deployment-related deformations. Dr. Perry stated that nickel-titanium alloy (nitinol) is an attractive material choice for carotid stents because of its superelastic material behavior allowing large recoverable deformations.

However, due to nonlinear elastic behavior and small device dimensions, traditional linear elastic fracture mechanics are not applicable to these devices. Consequently, crack growth mechanics do not apply to nitinol-based structures with such small features. For these cases, total lifetime testing programs are more predictive. According to Dr. Perry, uniform pulsatile fatigue strains are composed of both mean strains (from oversizing) and alternating strains (from cardiac cycles), and it is more effective to predict fatigue life from the maximum alternating strain as a limit line. Coupling of pulsatile and nonpulsatile deformation modes is required to understand the complex deformation modes experienced in the carotid environment. Dr. Perry explained that more accurate lifetime predictions for nitinol-based stents can be realized through the combination of medical imaging, benchtop testing to failure, and the development of more sophisticated computer simulations.

Nonpulsatile Carotid Artery Biomechanics

By Christopher Cheng, PhD, Department of Surgery, Stanford University, Stanford, California

Dr. Cheng described a study to look at specific motions and quantify the deformations of stents implanted in carotid arteries. The study included seven patients (four men and three women) with a mean age of 76.9 years. Each patient was imaged during swallowing, and six patients were also imaged during neck rotation. The previously implanted carotid stents, including two Precise (Cordis Corporation, Warren, NJ) and five Acculink (Abbott Vascular, Santa Clara, CA) stents, were 6 to 10 mm diameter and 30 to 40 mm in length. The investigators collected x-ray data from lateral and anteroposterior views using multiple body positions. The acquired images were digitized and analyzed to calculate bending, axial, crushing, and radial deformations.

The imaging data showed that swallowing caused a small amount of carotid artery bending between the CCA and ICA. In addition, swallowing decreased radial strain and increased axial strain in the stented carotid segment. Furthermore, the bending strain alternates with axial strain, such that locations of maximum axial strain had the minimum bending strain. Mean axial strains of 8% were calculated across the stent, but certain locations exhibited axial strains of approximately 20%. Crushing deformation

was also observed in swallowing, but Dr. Cheng did not think that this deformation mode was a significant contributor to stent fracture due to swallowing.

Ipsilateral rotation of the neck may compress the stent, whereas contralateral rotation will cause the greatest amount of stent stretch. In general, the results of these imaging data indicate that for total stent lengthening, contralateral motion is more significant than ipsilateral motion, although both motions are more significant than swallowing. For radial strain, neck twisting produces more significant deformations than swallowing. For bending and crushing, there was no significant difference between motions. Also, the external carotid is tethered to muscle branches in the jaw, which may protect the ECA from motions that might be harmful. The ICA is more free-floating and therefore is more likely to be affected.

Do We Need an Embolic Protection Device?
By Michel Makaroun, MD, Division of Vascular Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Dr. Makaroun noted that there is already a strong opinion within the clinical community that the use of EPDs should be routine during carotid intervention. Although some nonclinical and clinical data suggest better results with embolic protection, we lack clinical data from randomized, controlled trials that definitively show the incremental benefit of EPD use in the absence of potentially confounding factors.

Dr. Makaroun argued that EPD use might not always be appropriate for several reasons. First, the use of EPDs prolongs the cost and duration of the procedure. Second, clinical studies demonstrate that EPDs do not reduce the risk of "silent" ischemia, as assessed via magnetic resonance imaging (MRI) of the brain. Third, the use of an extra device during the procedure carries its own risk of complications, such as filter basket dislodgement, unintentional vessel occlusion, and vasospasm. Fourth, the results of the ARCHeR premarket studies indicate that the absence of EPD usage resulted in fewer cerebrovascular adverse events than when such devices were used, although this difference was not statistically significant. Finally, Dr. Makaroun reported the results of a clinical trial of which he was the principal investigator, in which high-surgical-risk subjects were randomized to receive CAS with or without EPD use. The subjects who did not receive an EPD experienced greater technical success and fewer incidences of MRI diffusion defects indicating cerebral ischemia. However, the small sample size for this study (36 subjects) prevents the formation of any significant conclusions. Dr. Makaroun concluded that there are still open questions surrounding routine EPD use during carotid intervention.

Embolic Protection Device Failure
By Daniel Clair, MD, Department of Vascular Surgery, The Cleveland Clinic, Cleveland, Ohio

Dr. Clair stated that there are currently three main clinical approaches to embolic protection: distal occlusion, distal protection, and proximal occlusion. Although each approach has its associated advantages and limitations, all EPDs are subject to some common failure modes due to the presence of connections and bonds between EPD segments. When EPD failure does occur clinically, it may take place during device insertion or during deployment and may result in inability to track the device through or beyond the lesion, embolization of EPD components, damage to the surrounding anatomy, insufficient apposition of the EPD to the vessel wall, inability to deploy or retrieve the device, and vasospasm. Specific anatomic factors that can lead to EPD failure are a severely angulated ICA, diffuse atherosclerosis, the presence of thrombus or heavy calcification, and a "string sign" or near-total ICA occlusion.

Dr. Clair noted that all currently marketed carotid EPDs are associated with stroke rates that are not insignificant. In addition, Dr. Clair reported the results of a search of the FDA's Manufacturer and User Facility Device Experience (MAUDE) database for medical device adverse event reporting. The results indicate that of the 200 to 250 EPD-related adverse events reported in 2006, approximately 45% involved stroke. In addition, approximately 35% involve problems with device retrieval, with 20% involving some interaction between an EPD filter and the carotid stent. Other reported event types include the inability to cross the lesion, entanglement of the stent and guidewire, separation of the distal wire or filter, deployment problems, and filter breakage. In contrast, publications on CAS with embolic protection rarely report EPD-related complications >2%, with most of these events involving vessel dissection and retrieval problems. Dr. Clair believes that the ideal EPD should provide early embolic protection, timely deployment, and easy retrieval.

An Overview of Clinical and Engineering Issues
By Paul Adler, Medtronic Vascular, Santa Rosa, California

Mr. Adler reviewed the current statistics demonstrating the cost of stroke in both public health and monetary measures and outlined the goals of CAS with respect to stabilization of both carotid blood flow and plaque. Mr. Adler then reported that delivery complications could occur in up to 5% of patients due to excessive atheroscle-

rosis, anatomic variations, and vascular tortuosity. Specific types of potential delivery complications are listed in Table 1. Mr. Adler identified the crossing profile and the effects of stent postdilatation on fatigue life as specific ways that engineering can have an impact on the incidence and severity of delivery and deployment complications.

Mr. Adler pointed out that the carotid anatomy presents unique stent loading conditions because these stents are frequently used to treat two distinct lumen diameters, those of the ICA and the CCA, often with little support at the carotid sinus. As a result, carotid stents are subject to complex loading conditions, for which we should develop more sophisticated quantification methods both in vivo and in vitro. Mr. Adler also identified several design characteristics of carotid stents and EPDs that could affect their clinical performance. He then explained how mean and alternating strains and stent overlapping could affect stent durability and thus affect the potential for stent fracture. He concluded that carotid intervention would improve as the tools used during the procedure evolve.

TABLE 1. POTENTIAL DELIVERY COMPLICATIONS INVOLVING CAROTID STENTS

- Crush recovery and resistance
- Excessive device-crossing profile
- Inadequate delivery system flexibility
- Inaccurate deployment
- Delivery and deployment aspects potentially affecting restenosis
- Reduction in fatigue life due to stent postdilatation
- Air entrainment and embolization
- Plaque embolization due to excessive scraping of the vessel wall ("snowplow effect")
- Delivery-induced stent fracture

Current Testing Methods and Standards

By Kenneth Cavanaugh, PhD, Division of Cardiovascular Devices, US FDA

Dr. Cavanaugh began by stating his position that the clinical focus of CAS is mainly on embolization instead of other failure modes, such as fracture and restenosis, which are more frequently associated with stenting in other vascular beds. This approach may be due to the emphasis on plaque stabilization rather than luminal gain and possibly by the belief that carotid arteries are inherently more resistant to restenosis and injury. However, the engineering of carotid stents is an important determinant of their clinical performance, and preclinical testing may predict clinical failures, provided that the testing appropriately simulates anticipated clinical conditions.

Dr. Cavanaugh discussed specific nonclinical test considerations that may be especially important for CAS. Specifically, stent durability assessment should ideally encompass all expected mechanical loading conditions. Dr. Cavanaugh remarked that a new paradigm to durability assessment, a "fatigue-to-fracture" approach using supraphysiological loads, might lead to improved characterization of stent fatigue life and development of more robust devices. Other bench tests, such as trackability and simulated use, should incorporate worst-case anatomic models to ensure that the stent is appropriately challenged. For each of these tests, Dr. Cavanaugh identified relevant FDA guidance documents, published standards, and initiatives in progress that may facilitate performance characterization. Dr. Cavanaugh concluded by stating that collaboration between clinicians and engineers is a critical step to improving the design and evaluation of carotid stent systems.

Embolic Protection Device Failure

By David Vale, Director of Carotid and Neurovascular Research & Development, Abbott Vascular, Santa Clara, California

Mr. Vale presented an overview of the medical device design process, with emphasis on the importance of identifying potential failure modes early in the development cycle. Mr. Vale explained that each type of test selected to evaluate a particular performance characteristic could possess particular advantages and disadvantages. Mr. Vale then focused on three particular performance characteristics that are critical to EPD performance: deliverability, capture efficiency, and retrieval. The key factors affecting these performance characteristics and the potential clinical consequences of failure are summarized in Table 2.

Mr. Vale emphasized the value of virtual models to assess the effects of small design changes that benchtop tests might not be sensitive enough to detect. This approach may assist with developing an optimal device design, rather than a design that is merely acceptable. Mr. Vale also emphasizes that the size of filter pores is a critical design decision for EPDs because small pores can produce shear stresses high enough to activate platelets and promote thrombosis. He also explained that hydrophilic coatings could decrease the potential for shear-induced platelet activation, potentially allowing the use of more small-diameter pores in the filter. Mr. Vale concluded by reiterating that extensive prototype testing should be encouraged and by stating that different tests may be most appropriate for different devices or at different stages of the development process.

TABLE 2. KEY EPD PERFORMANCE CHARACTERISTICS

Performance Characteristic	Potential Clinical Consequences of Failure	Key Device Factors
Deliverability	Increased procedural time	Device profile/geometry
		Flexibility
	Failure to cross the lesion	Trackability
		Pushability
	Lesion trauma/embolization	Torqueability
		Stiffness transitions
Capture efficiency	Embolic material release	Wall apposition
	Flow restriction	Pore size and quantity
	Thrombus formation	Material/coating
Retrieval	Increased procedural time	Device visibility
	Embolic material release	Filter stability
	Filter/stent entanglement	Retrieval catheter flexibility
		Stent design
		Stent delivery system flexibility

SUMMARY AND FUTURE DIRECTIONS

Based on the presentations and discussions on carotid stent and EPD failure, the summit participants concluded that development of improved carotid stent designs could be enhanced through greater understanding of the physical and mechanical environment in which the stents are deployed. Specifically, we should strive for better characterization of torsional, axial, and bending forces acting on the carotid vasculature, as well as the effects of vessel shape, compliance, and mean and alternating strains on vessel deformation.

Based on clinician input, the most clinically relevant failure mode for these devices is embolization. The participants believed that the use of simulators for CAS procedures and increased standardization of device trackability evaluation could reduce the rate of procedure-related embolization. The causes of postprocedure embolization are less clear, although collection and analysis of imaging data from patients who experienced late events may provide some insight regarding the patient characteristics that may predict such events.

Another important failure mode is restenosis, which the participants believed to be most closely associated with the radial force exerted by the stent against the vessel wall after deployment. The stiffness of the stent in nonradial orientations may also affect the frequency of restenosis.

Finally, evaluation of EPD performance could be improved through the increased standardization of particle capture efficiency testing. The value of standardized capture efficiency testing has since been communicated to the American Society for Testing and Materials International for consideration as a future work item. In addition, the value of capture efficiency assessment could be enhanced for filter-based devices by differentiating between particulate that passes through the filter pores and material that passes between the filter frame and vessel wall.

These efforts represent consensus pathways to enhance the public health contributions that carotid stents and EPDs can offer. As our clinical and design experience with these devices increases, we believe that the safety and effectiveness of CAS with embolic protection can be further increased. We expect that the endovascular community will continue to work together to optimize the design and evaluation of these devices. ■

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