Cleveland Clinic Stent Summit 2006

Discussions on clinical testing of AAA endovascular grafts.

BY ROBERT G. WHIRLEY, PHD; MATTHEW S. WANINGER, PHD; AND ROY K. GREENBERG, MD

From August 24 to 26, the Cleveland Clinic hosted a summit to discuss past testing and clinical performance of endovascular devices with the intent of identifying measures to improve future testing and device design. The meeting brought together 130 representatives from the endovascular community, including engineers, physicians, FDA representatives, and others involved in the design, development, and testing of endovascular devices. The conference focused on superficial femoral artery stents and endovascular grafts used for the treatment of infrarenal abdominal aortic aneurysms (AAAs). The first 2 days of the meeting involved a small number of focused presentations by keynote speakers followed by extensive working roundtable discussions by the summit participants. The final day was intended to be a consensus meeting to identify areas of potential improvement in current testing of these devices. This article summarizes the AAA endovascular graft discussions.

KEYNOTE SPEAKERS

The AAA day focused on metallic fractures: the reasons why devices have fractured; the clinical implications of the fractures; and the imaging tools available to find fractures and to study *in vivo* conditions. The following is a brief review of the keynote presentations.

FUNDAMENTALS OF INFRARENAL AORTIC ANATOMY AND PHYSIOLOGY

Mark Fillinger, MD, Dartmouth-Hitchcock Medical Center

Dr. Fillinger gave a comprehensive overview of the aortoiliac anatomy as it relates to endografts. He presented a series of clinical images that clearly illustrated the need for multiple views to assess proximal neck angulation. He also presented data from more than 700 patients with 2-year follow-up indicating that the neck angulation becomes more stable over time after endograft placement. Dr. Fillinger then highlighted the influence of physician implantation technique on loads experienced by the endograft, including variables such as device orientation, accuracy of deployment, patient selection, use of accessory devices, and oversizing of the implant. He concluded that the anatomy is knowable to a degree, but device-anatomy interaction can change over time.

FLUID DYNAMICS AND COMPUTER MODELING

Ender Fenol, PhD, Carnegie Mellon University

Dr. Fenol summarized some of the previous work done on aortic computational fluid dynamics and finite element analysis and then presented the results of fluid-structure interaction computer modeling of AAAs. His data indicate that, for a given maximum diameter, asymmetric anterior bulging produces higher peak wall stresses than a symmetric aneurysm. Furthermore, his data show that including fluid-structure interaction in the simulations yields peak wall stress predictions that are slightly higher than those obtained with traditional finite element methods. Additional studies indicated that the effects of spatial variations in AAA wall thickness may be more significant. Ongoing work focuses on validation of these results with *in vivo* data.

PHYSICS OF LOADS AND DEVICES

Robert G. Whirley, PhD, TriVascular/Boston Scientific

Dr. Whirley provided an analysis of the AAA endograft environment from an engineering fundamentals perspective. He described how loads can arise from flow, pressure, and aortic motion interacting with anatomic angulation and device design—as well as the relative importance of each category. He reviewed the mechanisms that produce *in vivo* longitudinal loads on AAA endografts and showed that the difference between aortic blood pressure and aneurysm sac pressure is the dominant factor that creates longitudinal loads, and that viscous flow drag was a negligible contribution. Dr. Whirley concluded by showing that local structural effects due to the interaction of longitudinal loads with endograft angulation can be significant.

MECHANISMS OF AAA ENDOGRAFT FAILURES

Jim McKinsey, MD, Columbia Medical Center

Dr. McKinsey outlined the known and suspected causes of endograft failure. He highlighted the biological challenges facing an endograft, including aortic neck angulation and dilatation, sac conformational changes, and mural thrombus. He then discussed how these factors contribute to mechanical failures involving device migration and metal fatigue/stent fracture. Dr. McKinsey noted that even open repair, in which a graft is sutured in place, carries a significant complication rate due in part to the challenging environment in which the graft must function. He echoed the theme that preclinical testing should be improved to more effectively replicate the nonidealized aortic environment, and he showed a specific example of an off-axis fatigue test set-up that may improve detection of potential durability issues for some endograft designs.

CLINICAL IMPLICATIONS OF FAILURES

Roy K. Greenberg, MD, Cleveland Clinic

Dr. Greenberg focused on the clinical significance of endograft failures. He first categorized failures as a lack of device integrity, stent fracture, fixation system disconnect, or migration of an intact device. He then described the challenging process of deciding who should be treated and how, and how failures might be interpreted. He followed with a memorable illustration of proximal fixation by inviting Dorothy Abel on stage to play the role of a migrating endograft. Dr. Greenberg emphasized the importance of high-resolution image acquisition and interpretation of results using 3D techniques to assess and determine proper treatment options for patients with failed endografts. He concluded by noting that current knowledge regarding migration is immature: "We are still in an information-gathering mode."

IMAGING: CT ADVANCES AND LIMITATIONS

Geoff Rubin, MD, Stanford University

Dr. Rubin summarized the three main methods for imaging endografts *in vivo*: MRI, projectional radiography, and CT. The greatest disadvantage of an MRI is that there is less resolution compared to CT; MRIs are also susceptible to image artifacts produced by differences in magnetic susceptibility between tissue and metallic stents. Projectional radiography has terrific spatial resolution and is used extensively for assessment of endograft integrity. Unfortunately, there is substantial acquisition variability that reduces the utility of the images. Modern multidetector CT has resolution approximately 10 times

TABLE 1. DISCUSSION SUMMARY ON KEYNOTE PRESENTATIONS AND LESSONS LEARNED FROM INDUSTRY

Faulty Assumptions About Preclinical Testing

- It can fully simulate the aortic environment
- Barb penetration in synthetic tube mimics that in the aorta
- Longitudinal load distribution is circumferentially symmetric
- Lack of local compression
- Boundary conditions are static over time
  - Persistent versus dropping sac pressure
- Angulation is not 3D
  - Centerline algorithms give a complete picture of *in vivo* device configuration
- Not accounting for transient hypertension effects on loads
- Type II endoleaks do not affect device loads and/or configuration
- Amount of oversizing in testing represents clinical use
  - Adequate imaging and training
  - Appropriate range selected for testing
- Optimal for device to follow shortest path in all cases

New or Modified Test Methods

- Better anatomic models for fixation testing
- Standardized 3D models for delivery/deployment testing
- Improved computational models
- Longitudinal fatigue testing of proximal fixation
  - Off-axis fatigue to incorporate angulation effects
- Testing to failure
- Testing at tolerance limits for some variables

Outstanding Questions

- Definition of angulation (radius of curvature?)
- Expected ranges of anatomical parameters (diameters, lengths, angulation, tortuosity)
- Expected physical loads and influence of:
  - Vessel properties
  - Longitudinal range of motion
  - Renal artery flexure
  - Longitudinal forces for different proximal diameters
- How to address variability in clinical measurements of diameter and length
- How to address anatomic changes over time
- Appropriate tubing mechanical properties for various endograft tests
- Durability of open repair
- Appropriate controls for trials

that of MRI and allows volumetric assessment that cannot be done with projectional radiography. Therefore, CT is the standard modality for assessing endoleaks. Technical aspects of the imaging protocol greatly influence the quality of the resulting data and merit careful attention. New techniques and equipment are enabling CT to be used for endograft integrity (stent fracture) assessment and are also providing time-varying images of endograft behavior *in vivo*.

LESSONS LEARNED FROM INDUSTRY

Robert G. Whirley, PhD, TriVascular/Boston Scientific; Matthew S. Waninger, PhD, Cook; David Stevenson, Vascutek; Trevor Greenan, Medtronic

Representatives from the industry were invited to share their experiences, with a focus on issues uncovered rather than on how they were addressed in a particular design. Presenter recommendations included the following: carefully review follow-up imaging to assess device performance; consider making anatomical models from real anatomy and use these as a development target; and incorporate active fixation in device designs because it appears beneficial in preventing endograft migration.

A lively discussion period followed the presentations. Audience response indicated that most in attendance felt the industry was moving toward active fixation (hooks/barbs) to prevent migration. On the issue of columnar strength, the audience was split between less support and the same support as that of current devices; no one thought more columnar support was needed. It was generally agreed that most endograft clinical failures are from conditions not anticipated and have been subsequently replicated in bench testing. This observation highlights the importance of improving the understanding of the aortic environment to improve the reliability of preclinical testing in predicting clinical performance.

Based on these presentations and subsequent discussion, the attendees summarized some of the faulty assumptions in designing preclinical testing, identified new test methods or necessary modifications to existing test methods, and listed outstanding concerns requiring additional research or consideration (Table 1).

Dr. Waninger then continued the review and critique of preclinical testing of endovascular grafts by outlining the history of this testing.[1] Discussion after this presentation focused on the following questions: What are the limitations of required (FDA/ISO) testing? Why didn't these tests find the problems that have led to clinical failures?

Group discussion noted that preclinical tests are limited by their ability to represent accurately the aortic environment and its effect on a device. The true anatomy and the loads or deformations it imposes on an endograft are not well understood, may be design specific, and may change over time. There was a general agreement on the value of incorporating some angulation effects into a longitudinal "off-axis" fatigue test.

Another question was: In view of lessons learned, do we need to place more emphasis on understanding the aortic environment or do we know enough and just need to test differently to better understand device vulnerabilities?

The group indicated that a combination of the two is needed. Although there are improvements in testing that can be made based on what is currently known (as discussed previously), there are substantial gaps in our understanding of the aortic environment. Aortic motion and its effect on devices were cited as particularly

TABLE 2. CHALLENGES IN PRECLINICAL TESTING OF AAA ENDOVASCULAR GRAFTS

Problem: Past and Current Preclinical Testing Did Not Predict Some Clinical Failures Due to These Testing Limitations

- Inappropriate boundary conditions/test parameters
- Testing does not address stent/aorta interface (eg, neck angulation and dilatation)
- May need sequence of tests using different diameters and angles
- Problems with pulsatile fatigue test
  - Not subjecting devices to adequate loads/deformation; fixtures do not represent true anatomy
    - May know native anatomy, but not over time
    - Do not know physiology
  - Simulated flow has not been incorporated but may or may not be needed
  - Additional testing needed to address other types of loading (beyond radial dilatation)
  - Abrasion and wear data from radial dilatation testing are not reliable
- Problems with assessing overlapping components
  - Straight tube is not good simulation of reality
  - Need to be in model-simulating application
- Need evaluation of what can reasonably be expected with clinical use
  - Balloon-expandable stents are often used at the proximal attachment site to treat endoleaks, so testing incorporating these devices in an overlap condition should be conducted
  - Should the label suggest specific things to avoid based on this evaluation?
    - Conduct risk analysis to determine appropriate warnings and precautions

unclear. Although some clinical data do exist on aortic parameters such as neck diameter/length, aortic curvature, and iliac tortuosity, that information is not readily available to device engineers. Further, reverse engineering of devices having clinical failures was identified as a potential path to better understand the effect of the aortic environment on an endograft. There are numerous challenges to maximizing the benefit of lessons learned, including information dissemination and confidentiality.

IS THERE VALUE IN "TESTING TO FAILURE"?

Testing to failure was generally felt to have value in revealing device vulnerabilities. Testing at increased loads or at extreme angulation was felt to provide more useful information than just continuing with "test to pass" parameters beyond 400M cycles. It was agreed that these tests may not have *a priori* acceptance criteria and need not have statistically valid sample sizes. The objective was seen as gathering data on how test (and anatomic) parameters affect device performance. Some participants felt it is too early to place much emphasis on testing to failure given the current uncertainties in defining the aortic environment. Physicians commented that information on device performance in challenging anatomy (potentially beyond label indications) would be useful input in device selection for a particular patient if the data were presented in a context that could be meaningfully interpreted. This raised numerous questions from the industry participants on regulatory and legal considerations.

Tables 2 and 3 present a compendium of the challenges and opportunities identified by the group for preclinical testing of AAA endovascular grafts.

TABLE 3. POTENTIAL IMPROVEMENTS IN PRECLINICAL TESTING WILL ARISE FROM IMPROVED UNDERSTANDING OF THE AORTIC ENVIRONMENT COMBINED WITH DEVICE TESTING TO FAILURE

What Is Needed to Understand the Aortic Environment

- Published data from existing databases to define basic anatomic and physiologic parameters
- Need to define aortic motion better
- Need to apply reverse engineering to gain understanding of why some designs fail and why some designs work in the clinical setting
- Need to improve dissemination of information

Considerations in Testing to Failure

How should testing to failure be conducted?

- Not continued testing within "test to pass" parameters until device breakage occurs (ie, >400M cycles)
- Testing outside of the specified limitations for the device may be beneficial (eg, extreme angulation, sizing)

What would be the purpose/benefit of testing to failure?

- Determining the probability of failure would not be the purpose
- Demonstration of the type of failure and the reaction of the device (eg, infolding, migration, fracture, inadequate seal) to conditions beyond the label (eg, oversizing, neck angulation) may be possible
- Could be useful to physicians in predicting how the device will function in difficult anatomy (ie, to avoid disaster situations)
- Evaluation of device manufacturing or clinical use tolerance limits
- For durability testing, use of exaggerated loads can
  - Identify potential failures quicker than other methodologies
  - Rapidly compare effects of different conditions (ie, wider variety of inputs)

What are some considerations in conducting this type of testing?

- Understanding the aortic environment is also necessary for this type of testing
- May not have acceptance criteria, just a sense for how conditions affect test outcomes
- Do not need statistically valid data

What steps can be taken to implement testing to failure?

- It may be possible to define some standardized test parameters specifying the conditions (eg, angles, oversizing)
  - Testing of various aggregated conditions may be of use
  - May be possible to use defined models from true patient anatomies
- There is much to be learned about the best way to conduct and interpret these tests

NEXT STEPS

The following two action items were formulated by the group to best address resolution of the preclinical testing deficiencies identified in the symposium: (1) Explore a standardized nonradial fatigue test under the umbrella of ASTM. (2) Investigate standardization of some test fixtures and anatomy models, including those used for simulated use testing, under the auspices of the Association for the Advancement of Medical Instrumentation Vascular Prosthesis Committee.

Interested readers are encouraged to participate in these activities.

Some of the topics identified in this Stent Summit have been discussed previously in other forums but have been difficult to address as a community. In some cases, basic research is needed, but investigators and funding sources have been slow to emerge. In other cases, the action items have proven difficult to address. The next steps identified in this Stent Summit are therefore best viewed as extensions to the recommended actions from prior workshops on endovascular grafts.[2,3]

THE FUTURE

Substantial progress is being made in understanding the preclinical testing of endovascular grafts. The anatomic and physiologic information needed for better testing is more clearly defined than in past meetings of similar scope. The types of testing needed to better predict clinical performance are also becoming more clear. Although today's devices are benefiting many AAA patients, this progress in preclinical testing should drive significant improvements in endovascular grafts within the next few years. ■

The authors would like to acknowledge the substantial contributions of Dorothy Abel, Terry Woods, and Angela Smith of the US Food and Drug Administration to Stent Summit 2006.

Robert G. Whirley, PhD, was formerly Vice President of Research and Development at TriVascular/Boston Scientific. Dr. Whirley may be reached at rwhirley@pacbell.net.

Matthew S. Waninger, PhD, is Vice President of Engineering at Cook Medical. Dr. Waninger may be reached at matt.waninger@cookmedical.com.

Roy K. Greenberg, MD, is the Director of Endovascular Research at the Cleveland Clinic. Dr. Greenberg may be reached at greenbr@ccf.org

1. Abel DB, Dehdashtian MM, Rodger ST, et al. Evolution and future of preclinical testing for endovascular grafts. J Endovasc Ther. 2006;13:649-659.
2. Abel DB, Beebe HG, Dedashtian MM, et al. Preclinical testing for aortic endovascular grafts: results of a Food and Drug Administration workshop. J Vasc Surg. 2002;35:1022-1028.
3. Abel DB, Smith AC. The preclinical testing of endovascular grafts. Endovasc Today. 2004;Nov/Dec:63-64.