News from the SIS 2006 Emerging Technologies Symposium

Highlights from the Science, Innovation, Synergy (SIS) 2006 Emerging Technologies Symposium, July 18-22, 2006, Seattle, WA

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From the latest developments in structural heart disease to evolving imaging techniques and therapies for atherosclerotic vascular disease, the *Emerging Technologies Symposium* at the 2006 Science, Innovation, Synergy (SIS) course offered a wealth of information on the latest diagnostic and treatment approaches for patients with cardiovascular disease. This unique symposium provides a platform for physicians, scientists, and engineers from academia and the biotech industry to discuss investigational and evolving modalities, the majority of which are in the pre-clinical and early phases of development. Five of the most interesting and promising topics presented are reviewed here.

Reviewed by John J. Young, MD, Jill Jesurum, PhD, Mark Reisman, MD, William A. Gray, MD, from the Swedish Heart & Vascular Institute, Seattle, WA.

Radionuclide Imaging of Atherosclerotic Plaque

Lynne Johnson, MD, from Columbia University in New York, NY, presented a fascinating overview of evolving techniques for imaging atherosclerotic plaque that utilize radiotracers targeted to different components of the underlying biology. Techniques for imaging atherosclerotic lesions have traditionally been aimed at providing anatomic detail of plaque size and luminal narrowing. Few techniques are able to provide quantifiable information regarding the cellular, biochemical, and molecular composition of lesions that determine plaque stability. Radiolabeled tracer compounds capable of identifying important cellular or molecular processes may provide clinicians with a powerful imaging tool with which to identify vulnerable plaques and patients at high risk of atherosclerotic complications. In addition, due to its non-invasive nature, radionuclide imaging could be used to monitor the effects of therapeutic interventions.

Several components of the underlying atherosclerotic biology have been targeted with radiotracers. Macrophages play a central role in the destabilization of atherosclerotic lesions. Once recruited, these cells ingest oxidized lipoproteins, thereby generating foam cells. Foam cells secrete a host of pro-inflammatory cytokines, as well as enzymes such as

matrix metalloproteinases (MMP) that result in breakdown of the fibrous cap. Foam cells in atherosclerotic lesions also undergo apoptosis with extensive upregulation of caspases. Radionuclide tracers have been developed that can identify these important pathways associated with plaque instability (eg, Tc-99m Annexin V [apoptosis], Tc-99m MMP inhibitor [MMP activity], F-18 fluoro-2-deoxyglucose [FDG] [macrophage activity], I-125 monocyte chemoattractant protein-1 [MCP-1] [macrophage chemotaxis]). These radionuclide tracer compounds, as well as others, are currently being evaluated in animal models of atherosclerosis.[1]

The animal studies presented by Dr. Johnson provide proof of concept that radiotracers can be used to image atherosclerotic plaque inflammation and suggest that they can also quantify plaque inflammatory cell activity. This ability could potentially afford more sophisticated imaging, quantification, and functional assessment of atherosclerotic plaques. However, there are important limitations that need to be overcome. Radiotracers provide little or no anatomical resolution and so must be combined and co-registered with another imaging modality to ensure that the signal arises from atherosclerotic plaque and not an adjacent metabolically active structure. Combined positron emission tomography/computed tomography or positron emission tomography/magnetic resonance imaging scanners offer promise in overcoming this limitation. In addition, cardiac and respiratory motion, and the small plaque size of coronary arteries, represent unique challenges not seen in other vascular beds (carotid, peripheral). The future will, we hope, bring further advances in both tracer and detector technologies that will make non-invasive coronary plaque imaging a reality.

Cardiac Contractility Modulation for Congestive Heart Failure

Dan Burkhoff, MD, PhD, from The Jack H. Skirball Center for Cardiovascular Research in New York, NY, presented a new, experimental treatment approach for congestive heart failure (CHF). Cardiac resynchronization therapy (CRT) has been shown to be an effective treatment for patients with systolic ventricular dysfunction, prolonged (>120 ms) QRS duration, and New York Heart Association (NYHA) class III or IV symptoms despite optimal medical therapy. Because the majority of CHF patients have a QRS duration of less than 120 ms, CRT use is only applicable in 20% to 50% of the current CHF population. Dr. Burkhoff described the potential of cardiac contractility modulation (CCM) as a treatment option for CHF patients independent of the degree of ventricular dyssynchrony.

CCM signals are non-excitatory signals applied during the absolute refractory period utilizing a pacemaker-like device. Acute studies carried out in animals and humans with heart failure suggest that CCM signals can enhance the strength of left ventricular (LV) contraction, while decreasing LV end-diastolic volume. Interestingly, CCM treatment also normalized gene expression in CHF patients, which is demonstrated to be a unique indicator of reverse LV remodeling. Initial results from chronic treatment studies, designed mainly to demonstrate feasibility and provide preliminary safety information, appear promising and are providing the basis for 2 prospective, randomized trials currently underway.

BVS Bioabsorbable Drug-Eluting Stent

John M. Capek, PhD, president of Cardiac Therapies at Abbott Vascular, reviewed the Bioabsorbable Vascular Solutions (BVS) program at Abbott Vascular in Santa Clara, CA. Dr. Capek reviewed the evolution of intravascular technology from the initial balloon angioplasty through metallic stents and the current era of drug-eluting stents (DES). As these iterative technologies have resulted in better clinical outcomes, DES are being used in increasingly complex anatomical locations. In addition, as our understanding of the underlying vascular biology associated with these devices improves, there may be benefit in not leaving a permanent implant behind in the vessel. The goals for a bioabsorbable DES are complete and natural absorption, deliverability and conformability similar to a metallic stent, and good long-term clinical results similar to, or better than, current DES technology.

The history of bioabsorbable stents dates back to 1983, with the development of the first poly-lactic acid (PLA) self-expanding stent developed at Duke University Medical Center (Durham, NC).[2] The first balloon-expandable PLA stent was developed in 1988, but it lacked scaffolding strength and deliverability as compared with evolving bare-metal stents. Advances in technology, as well as interest in a bioabsorbable delivery system for drugs, led to resurgence in interest in bioabsorbable DES platforms.

The Abbott BVS stent consists of the bioabsorbable PLA polymer and stent platform, the immunosuppressant drug everolimus, and the VISION® balloon stent delivery system (Guidant Corporation, St. Paul, MN). The BVS stent has a tailored bioabsorption rate, is fully bioabsorbed with no drug left behind, and breaks down to lactic acid, a natural metabolite. Porcine models have demonstrated safety and efficacy with minimal inflammatory response (less than that seen with a

current DES at 6 and 9 months). Dr. Capek described the ongoing ABSORB clinical trial, in which the safety and efficacy of the BVS stent will be evaluated in up to 60 patients with follow-up out to 5 years. Six-month follow-up data are expected in the first quarter of 2007. If clinical trial results are positive, this bioabsorbable technology holds great promise in the treatment of atherosclerotic vascular disease, not only in the coronary arteries, but in other vascular beds as well.

Magnesium Absorbable Metal Stent

John J. Young, MD, from the Swedish Heart & Vascular Institute, Seattle, WA, presented current information on the magnesium absorbable stent from Biotronik, Inc. (Lake Oswego, OR). With the clinical success of the 2 Food and Drug Administration (FDA)-approved DES platforms in the United States, as well as that of several other platforms outside the United States, the cadre of DES products in development has escalated. Multiple companies with different approaches have entered this arena to try to improve on current technology and improve outcomes. Differential coatings on stents (adluminal vs abluminal), multiple drugs, bioerodable polymers, and, certainly, bioabsorbable technology are all being evaluated. Negative consequences of a permanent metallic implant in an artery include continued mechanical stress on the tissue, continued biological interaction, inability of the tissue to heal or behave in a normal physiologic way, possible stent fracture issues, potential limitation of future treatments in the same area, and inability to perform non-invasive diagnostic testing due to the composition of the permanent implant.

The ideal vascular absorbable device would need to demonstrate biocompatibility, appropriate mechanics for the time required, and complete absorption without an adverse tissue response. Biotronik has developed a unique magnesium absorbable metal stent (AMS) to address these issues. Magnesium is an essential element for the human body, and the weight of the stent (~3 mg) appears to have no adverse effect. Biocompatibility of this stent was evaluated in porcine models; the majority of the stent was absorbed at 8 weeks. In addition, the magnesium alloy had less elastic recoil and foreshortening than the current DES platforms. Interestingly, the minimal lumen diameter (MLD) increased over time, whereas the area stenosis decreased over time, probably due to the positive vessel remodeling allowed by the AMS.

First in-man experience with the Biotronik magnesium AMS was demonstrated in 20 patients with critical limb ischemia, undergoing peripheral (below the knee) revascularization.[3] Primary and secondary patency rates were favorable, with no evidence of toxic behavior of the implant. Further clinical trials (Insight I and II) are evaluating angioplasty alone versus AMS for the treatment of infrapopliteal lesions in patients with critical limb ischemia. Preliminary data from the PROGRESS trial demonstrated safety and efficacy at 4-month follow-up in patients with de novo native coronary artery lesions treated with the AMS. Longer follow-up will be needed to further assess the clinical efficacy of the AMS in patients with coronary artery disease. Finally, Biotronik is also exploring the possibility of combining their magnesium AMS with controlled drug-eluting technology on next-generation devices.

Intrinsic Mechanisms of Vascular Repair

Doris Taylor, PhD, from the University of Minnesota in Minneapolis, presented intriguing information on evolving concepts surrounding vascular repair. Atherosclerosis is a chronic, immunoinflammatory, fibroproliferative disease fueled by lipid. This chronic vascular injury progresses with time in an unpredictable manner, probably due to genetic variability in an individual's susceptibility, as well as traditional risk factors. The effect of concomitant vascular aging on atherosclerotic disease progression remains incompletely understood.

Endothelial progenitor cells (EPCs) derived from bone marrow are involved in vascular homeostasis that normally repairs and rejuvenates arteries. In patients with known coronary artery disease, EPCs are a novel risk predictor for cardiovascular mortality and morbidity. Endogenous mobilization or injection of ex vivo–generated EPCs is associated with enhanced reendothelialization and improvement of endothelial function. In addition, endogenous mobilization of EPCs has been demonstrated with certain pharmacologic treatments (eg, statins, estrogens) as well as physical activity (which may partly explain their beneficial cardiovascular effects). Previous studies have demonstrated the ability to reverse the effect of atherosclerosis in a hypercholesterolemic mouse model with the infusion of bone marrow–derived EPCs from younger mice.[4] In contrast, treatment with

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bone marrow EPCs from older mice was much less effective. Progressive EPC deficits may therefore contribute to the development of atherosclerosis and the concept of vascular aging.[4,5]

Evolving concepts that have yet to be resolved include vascular senescence (loss of cellular function with aging) versus vascular obsolescence (loss of cells with aging), or whether vascular aging includes a component of both. Dr. Taylor also described recent studies demonstrating potential differences in this reparative ability by gender. Ongoing studies hope to further clarify this potential gender difference, which could have obvious implications for future treatment options. Only by understanding these evolving concepts and issues will we be able to fulfill the potential promise of cell-based cardiovascular repair that could attenuate or even eliminate atherosclerotic disease progression. ■

[John J. Young, MD, Jill Jesurum, PhD, Mark Reisman, MD, William A. Gray, MD]

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Main Points

- Radiolabeled tracer compounds capable of identifying important cellular or molecular processes may provide clinicians with a powerful imaging tool with which to identify vulnerable plaques and patients at high risk of atherosclerotic complications.
- Cardiac contractility modulation may be a treatment option for chronic heart failure patients independent of the degree of ventricular dyssynchrony.
- Bioabsorbable stent technology holds great promise in the treatment of atherosclerotic vascular disease, not only in the coronary arteries, but in other vascular beds as well.
- In porcine models of a new magnesium absorbable metal stent, the majority of the stent was absorbed at 8 weeks. In addition, the magnesium alloy had less elastic recoil and foreshortening than the current drug-eluting stent platforms.
- Endogenous mobilization or injection of ex vivo–generated endothelial progenitor cells is associated with enhanced reendothelialization and improvement of endothelial function.