Percutaneous Valve Repair and Replacement

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Hundreds of thousands of patients in the United States, including a large share with congestive heart failure, might benefit from heart valve repair or replacement. Catheter-based approaches to the management of valvular heart disease are in a stage of rapid evolution and development. The goal of these approaches is to minimize the morbidity and mortality associated with open-heart surgery.

Percutaneous mitral valve repair

In the United States alone, about 250,000 people develop significant mitral regurgitation (MR) each year, with almost 50,000 undergoing surgery. Surgical repair of a diseased mitral valve has become the treatment of choice for patients with significant MR. Since there is no single therapeutic approach for every etiology of MR, surgical mitral valve repair includes a variety of techniques that are applied depending on the etiology and pathology of the mitral valve. One of the techniques is called edge-to-edge repair, wherein the scallops of the mitral leaflets are sutured together at the origin of the MR, leading to stabilization of the incompetent segment and the creation of a competent double-orifice mitral valve. The success of this surgical repair technique inspired the development of the MitraClip® system, a catheter-based repair system developed by Evalve, Inc. The percutaneous procedure is performed in the catheterization laboratory under general anesthesia using fluoroscopic and transesophageal echocardiographic guidance.

Experience with the MitraClip system

The first mitral valve repair procedure at Cedars-Sinai was completed in October 2005. Today, the Medical Center is enrolling patients in a randomized, Phase II, multi-center clinical trial comparing percutaneous mitral valve repair using the MitraClip device to standard surgical open-heart mitral valve repair or replacement in patients with moderate to severe or severe MR (IRB # 6381). The Phase II Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) is the first-ever prospective, randomized and core lab-monitored study of percutaneous and surgical therapy for MR. Preliminary data from an initial cohort of 107 non-randomized patients from the EVEREST I and EVEREST II studies have demonstrated the initial safety and efficacy of this first-in-class device in selected MR patients. Early data suggests that the device may be a viable therapeutic option for a spectrum of patients suffering from MR.

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Figure 1: The MitraClip system prior to clip deployment from the delivery catheter. Blood flows normally on both sides of the clip.

Figure 2 illustrates the reduction in MR and the MitraClip device securely attached to both leaflets of the mitral valve.
Emerging Therapeutic Paradigms for Management of Atherosclerosis
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Atherothrombotic cardiovascular disease remains the leading cause of mortality and morbidity in much of the Western world and is becoming a global problem with the increasing prevalence of obesity, metabolic syndrome and diabetes. Several novel and promising approaches for the management of atherosclerosis – including gene therapy and immunization – are currently being studied at the Cedars-Sinai Heart Institute.

Atheroprotective effects of a mutant gene
Since 1992, Cedars-Sinai researchers have been studying a mutant gene that produces a form of HDL with enhanced atheroprotective effects. Apolipoprotein A-1 Milano (Apo A-I Milano), the first naturally occurring mutant of Apo A-I – the major protein component of HDL particles – was identified in a small group of inhabitants of the lakeside town of Limone sul Garda in Northern Italy in the late 1970s. A middle-aged man living in the town was discovered to have very low HDL cholesterol and high levels of triglycerides, but no evidence of cardiovascular disease and a history of parental longevity. When blood tests were performed on nearly 1,000 inhabitants of the town, approximately 40 individuals were shown to have a unique alteration in their gene encoding Apo A-I. The mutation is characterized by an arginine-173 to cysteine-173 substitution leading to the formation of homodimers and heterodimers with wild-type Apo A-I in all carriers.

By 1994, my colleagues and I were able to demonstrate that an intravenous injection of a genetically engineered form of Apo A-I Milano complexed with a phospholipid carrier markedly reduced arterial plaque build-up in rabbits fed a high cholesterol diet by up to 70 percent without a significant reduction in circulating cholesterol levels.

Several subsequent laboratory studies substantiated significant and rapid onset anti-atherogenic and athero-regressive effects of recombinant Apo A-I Milano, including substantial lipid and macrophage depletion from advanced atherosclerotic lesions within 48 hours. Since these findings, we have provided further evidence, based on experimental studies done in genetically altered mice with high cholesterol levels, that repeated intravenous injections of Apo A-I Milano can halt the progression of plaque build-up and induce regression of pre-existing plaque within five weeks.

Based on these findings, Esperion Therapeutics, later acquired by Pfizer, initiated human trials of recombinant Apo A-I Milano in 2001. A small Phase II clinical trial demonstrated that weekly intravenous injection of recombinant Apo A-I Milano (ETC-216) for five weeks led to a significant and measurable shrinkage of human coronary artery plaques as measured by intravascular ultrasound technique. More definitive large-scale human trials over the next two to three years will be needed to validate the utility of this novel approach. The Cedars-Sinai Heart Institute is currently working with a new industry partner to achieve this objective.

Apo A-I Milano gene therapy
Another approach currently being investigated with Apo A-I Milano is gene transfer, in which the actual DNA that codes for Apo A-I Milano, is transferred into the body and stimulates production of Apo A-I Milano by the host without need for exogenous repeated supply. In animal trials, it was shown that by using bone marrow cells transduced with a retrovirus carrying the Apo A-I Milano gene, atherosclerosis in genetically engineered mice can be reduced by as much as 70 percent (Figure 1). The Cedars-Sinai research team is also using an innocuous virus called the Adeno-associated virus (AAV) to ferry the Apo A-I Milano gene into the body of genetically altered mice. Results have shown that such gene transfer is feasible and can reduce atherosclerotic plaque buildup by up to 50 percent after a single intramuscular injection of the gene carried by the viral vector. Testing this approach in humans in the very near future is anticipated.

Immunization against atherosclerosis
Vaccines have successfully reduced deaths from infectious disease and have resulted in the global eradication of diseases such as smallpox and poliomyelitis. Vaccines are effective, specific, relatively inexpensive and generally well-tolerated. In recent years, the concept of vaccination has been extended to treat or prevent noninfectious chronic inflammatory or autoimmune diseases, such as Alzheimer’s disease and cancer, with variable results.

Identifying antigens and formulating a vaccine
The complex function that the immune system has in the pathophysiology of atherosclerosis is highlighted by the fact that both proatherogenic and atheroprotective effects of immune activation can be demonstrated. Several molecules have been identified as potential candidate immunogens in atherosclerosis.

My colleagues and I have been studying the structure of the ApoB-100 component of LDL to identify potential antigenic epitopes that could mediate the atheroprotective effects of immunization with oxidized LDL. In collaboration with Dr. Jan Nilsson of Lund University in Sweden, our team has generated a library of 302 peptide sequences spanning the entire structure of the human Apo B-100 molecule.


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Case Study: Use of the LVAD in Advanced Heart Failure

Sinan Simsir, MD

According to the American Heart Association, congestive heart failure contributes to some 300,000 deaths per year. For patients with end-stage heart failure, mechanical assistance has repeatedly shown a survival benefit.

The first widespread clinical application of left ventricular assist devices (LVADs) for patients with end-stage heart failure began in the late 1980s. Since then, major advancements have been seen in their design and the indications for use:

- As a bridge for patients awaiting heart transplant
- As a tool for patients who have had heart surgery and cannot be easily weaned from the heart-lung machine
- As a destination therapy for patients with end-stage heart failure who are unsuitable for cardiac transplantation

LVAD as destination therapy

Cedars-Sinai Medical Center began implanting LVADs in the early 1990s, and the first patient was discharged with a device in place in early 2007. In the past 17 months, 38 LVADs have been implanted at Cedars-Sinai, nine as destination therapy and 29 for bridging to transplantation. Of these, 24 patients have been discharged and nine have been successfully transplanted. The following case highlights a recent instance of LVAD implantation as destination therapy.

A 51-year-old male presented with HIV cardiomyopathy. He suffered from Class IV heart failure as defined by the New York Heart Association functional classification system, and he was found to be unresponsive to intravenous inotropes. Ineligible for heart transplantation, the choice was made to implant an LVAD in an attempt to improve his quality of life.

The implantation procedure

During surgery, a median sternotomy was performed under complete anesthesia and the patient was placed on cardiopulmonary bypass for approximately 35 minutes. An electrically powered, intracorporeal LVAD, called the HeartMate® XVE (Figure 1), was placed in the left upper abdomen beneath the rectus muscle but above the peritoneum in the preperitoneal space. The driveline of the LVAD, the only part that exists outside the body, was brought out through the right upper abdomen, underneath the ribs. One tube connects the LVAD pump to the left ventricle of the heart, while another returns the blood from the pump to the aorta. The electric power source pushes a plate within the pump that fills and empties it. This source can be provided from a power base unit while one is sitting up or laying down. It can also be attained from rechargeable batteries carried as a belt in case of ambulation or exercise. A smaller and smaller continuous flow pump, Heartmate II, is also available at Cedars-Sinai. This pump, however, has only been approved as a bridge to transplantation.

Postoperative care

Postoperative care for this procedure is often tenuous and intense. Patients with this level of heart failure usually have coagulopathy, and take-backs to the operating room are reported to be as high as 60 percent. Some other busy centers, which may perform the pump procedures differently, leave the patients’ sterna open for a day or two because of this potential. In the case of the patient discussed above, recovery went smoothly with no take-back for bleeding. It is currently one year since the LVAD was implanted and the patient is living his life normally, fully able to do anything he chooses. A pump change-out will most likely be considered in the near future.

Figure 1: illustration of the HeartMate® XVE, an electrically powered, intracorporeal LVAD. Reprinted with permission from Thoratec Corporation.
Revisiting Data Strengthens Evidence-Based Medicine
Sanjay Kaul, MD, FACC, FAHA

One of the goals of research at the Cedars-Sinai Heart Institute is to facilitate the translation of clinical trial evidence into pragmatic clinical practice.

By analyzing and critically appraising clinical trials focused on management of chronic stable and acute unstable coronary artery disease, researchers are able to verify whether the data measures up to what is being claimed and, based on its findings, re-assess how the information should be applied in clinical practice. Most recently, the Cedars-Sinai Heart Institute has focused its research on three areas: drug-eluting stents, the risks associated with rosiglitazone and the Bayesian approach to analyzing clinical trial data.

Drug-eluting stents

Quite often, observations made in the course of clinical practice serve to target the subject of analysis. For example, when clinicians at Cedars-Sinai began to notice high numbers of complications with drug-eluting stents (DES), they sought a deeper understanding of their cause. After analyzing the data available in clinical trials, we concluded that while DES are effective in reducing restenosis, this benefit was overestimated and the risk of stent thrombosis, a potentially life-threatening complication, was underestimated, especially in more complex lesions and higher-risk patients than those evaluated in the pivotal clinical trials.

After an extensive evaluation of the data, we offered recommendations for regulatory reform at a special FDA Advisory Committee on DES, as well as recommendations for optimal use of DES in clinical practice so that its benefits outweigh its potential for harm and cost. In addition, three specific actions were recommended to encourage evidence-based patient management:

- Emphasize medical therapies with proven long-term benefit as a rational alternative to stenting
- Use novel modeling techniques to estimate long-term outcomes based on available near-term data
- Restructure reimbursement incentives to encourage the use of evidence-based therapies

It did not take long for the ramifications of the analysis to find their way into clinical practice. In January 2006, 95 percent of heart catheterization procedures at Cedars-Sinai utilized DES. By December 2006, that number had fallen to under 80 percent, and by June 2007 to under 60 percent—a trend also reflected in nationwide practice.

Re-analysis of rosiglitazone

Rosiglitazone, a drug marketed as Avandia® for the treatment of type 2 diabetes, came under fire after an article published by Dr. Steven Nissen and Kathy Wolski linked it to a significantly increased risk of heart attack and a nearly significant increased risk of cardiovascular death. In their study, data from wide-ranging clinical trials that were not necessarily designed to track heart attacks and cardiovascular death were pooled together. In addition, most of the trials did not report occurrence of any heart attack or cardiovascular death. In this type of “sparse data” situation, the statistical model employed by Nissen and Wolski tends to yield unreliable risk estimates. Using different statistical models, our re-analysis determined that although risks were increased, they were no longer statistically significant. We thereby concluded:

- The risk for myocardial infarction and cardiovascular death for diabetic patients taking rosiglitazone is uncertain: neither increased nor decreased risk is established
- Only prospective clinical trials designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone will resolve the controversy about its safety

The FDA Advisory Committee reviewed the data and heard testimony of two physician researchers from Cedars-Sinai. At the conclusion of the hearings, the panel recommended that rosiglitazone carry new risk warnings, but stopped short of calling for the drug to be removed from the market.

Bayesian analysis

Large, randomized clinical trials are key drivers of modern cardiovascular practice, as they are cited frequently as the authoritative foundation for evidence-based management policies. Cedars-Sinai researchers are interested in improving the process of generating and developing clinical practice guidelines based on an appraisal of the evidence using an alternative statistical paradigm based on Bayesian analysis.

The Bayesian approach calls for integrating “prior information” – knowledge gained from previous work – with “evidence” – empirical data obtained from new experiments – to generate “posterior” – updated knowledge, via a mathematical formula called Bayes’ theorem. Unlike conventional statistical methods which formally use prior information only in the design of a clinical trial, the Bayesian approach utilizes it throughout both the design and analysis stages of a trial. Additionally, the Bayesian approach:

- Provides direct probability statements – the probability that the study hypothesis is true given the observations – which are what most people wrongly assume they are getting from conventional statistics
- Allows for flexible, adaptive research designs and multiple interim looks at accumulating data
- Reduces sample size by using prior information and interim looks during the course of the trial
- Provides an exact quantitative estimate of “clinically important” therapeutic benefit or harm

The Bayesian method is particularly appealing because it is at the heart of the learning process by which we update our existing knowledge with new information in many facets of daily life, including the way doctors practice medicine. Although Bayesian designs are now widely used in everything from astrophysics to zoology, they’ve been slower to catch on in medical research, particularly clinical trials. However, that is beginning to change – and the FDA has recently begun to use the Bayesian approach in its device-approval process.

Working to improve care and outcomes

While both prior knowledge and new clinical trial data provide a strong foundation for clinical decision-making, the medical community should be cautious about clinging to old assumptions or prematurely leaping to new conclusions. Cedars-Sinai researchers will continue to participate in the collaborative development and refinement of best practices by critically analyzing information generated by clinical trials and observed clinical care outcomes. Our ultimate goal: continuous improvement in the quality and cost of care at the local and national levels.

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