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Integrated Mayo Clinic Team Boosts Long-Term Cardiac Transplant Survival

Richard C. Daly, MD

Brooks S. Edwards, MD

More than 35 years ago, a team of South African surgeons shocked the world with the first human to human heart transplant. At that time, heart transplantation was viewed as a daring, revolutionary procedure with uncharted consequences and unknown results. Today, cardiac transplantation has become a nearly routine procedure with manageable complications and predictable outcomes. In the United States, more than 2,000 heart transplants are performed annually; the number of procedures is limited only by the scarce number of suitable donors.

Recipient Candidates

Because of the scarcity of donor organs, this precious and limited resource must be allocated in a manner that ensures maximum benefit. "The ideal cardiac transplant candidate is a patient with end-stage cardiac disease for whom conventional therapy is not likely to provide symptomatic benefit or satisfactorily improve life expectancy," according to Brooks S. Edwards, MD, Mayo Clinic transplant cardiologist. "Examples include inoperable coronary artery disease, multiple forms of cardiomyopathy, complex congenital heart disease, including hypoplastic left heart syndrome in infancy, and inoperable valvular heart disease."

Patients with infiltrative forms of cardiomyopathy such as amyloidosis and hemochromatosis have successfully received transplants at Mayo Clinic but are carefully selected. In some situations, patients with multiorgan disease may be considered for multiorgan transplants (heart-lung, heart-liver, heart-kidney, heart-lung-liver, or heart-stem cell). With no restriction on age for potential transplant recipients, patients from birth to their early 70s have benefited from heart transplantation at Mayo Clinic.

Once a patient is accepted as a candidate for transplantation, he or she is placed on a national waiting list administered by the United Network for Organ Sharing (UNOS). Patients waiting for donor hearts are listed in 1 of 3 categories, depending on the severity of their illness: Status 1A is the most critical; the patient requires intensive care, invasive hemodynamic monitoring, and multiple inotropic drugs or mechanical support. Status 1B patients may require intravenous inotropic support, may be stable recipients of ventricular assist devices, and may not require intensive care. All other transplantable patients are categorized as status 2.

Priority for placement of donor organs is given first to status 1A and then 1B patients before hearts are offered to those waiting as status 2. Because of the large number of patients waiting for heart transplantation (currently more than 3,700) and the priority system administered by UNOS, most donor hearts go to status 1A and 1B recipients. The organ donor shortage results in waiting times of many months for even high-status patients.

At Mayo Clinic in Rochester, patients with decompensated heart failure are admitted to the specialized inpatient heart failure service. Continuous intravenous inotropic therapy and support with an implantable left ventricular assist devise (LVAD) are available. Once stabilized, these patients may be managed as outpatients and retain their status 1B listing. Many patients may return home on these forms of support.

Several options are available for mechanical cardiac assistance, including uni- and biventricular assisted systems, implantable LVADs, and extracorporeal oxygenation (ECMO). ECMO can be used in selected situations, particularly in small children, but has limited durability. When an organ does become available, charter aircraft can return patients on home maintainence to Rochester for transplant in a timely manner.

Inside This Issue

Donor Candidates

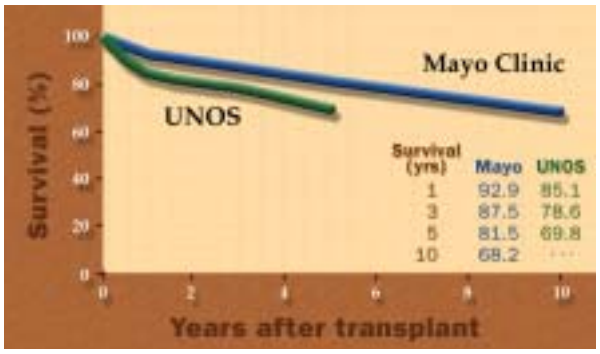
Deciding whether a donor and a recipient are a suitable match depends on many issues, including recipient factors (such as condition, size, previous surgery, and pulmonary vascular resistance) and donor factors (such as age, size, hemodynamics, inotropic requirements, echocardiographic results, recent cardiac resuscitation, and estimated ischemic time). The ischemic time begins with cross-clamp of the donor aorta and administration of cardioplegia and includes the time required for procurement, packaging, transportation, and implantation to the point when the cross-clamp is removed, and the heart is reperfused. "Risk of death with cardiac transplantation increases linearly as ischemic time increases up to approximately 4 hours, after which the risk increases exponentially with additional time," says Richard C. Daly, MD, Mayo Clinic transplant surgeon. "As donor age increases, that mortality curve starts its steep climb sooner." It is important to consider both donor and recipient factors when evaluating a donor for a particular recipient. For example, a recipient with high pulmonary vascular resistance requires a larger donor and shorter ischemic time in order to reduce the risk of donor right heart failure.

Surgical Technique

The atria and great arteries are procured along with the donor heart, although the recipient's left and right atria are often left in place. The implant procedure involves anastomosis of donor and recipient atrium to atrium and great artery to great artery for each side of the heart. Alternatively, a bicaval technique may be used, which involves excision of the recipient right atrium with anastomosis of the donor and recipient venae cavae and left atria, in addition to the great arteries. "It had been hoped that the bicaval technique would result in reduced tricuspid insufficiency and improved cardiac efficiency with smaller atrial sizes," says Dr Daly. "It has not been possible to show significant improvement in cardiac efficiency, but there is a small reduction in the need for a pacemaker postoperatively." Approximately 10% to 12% of patients require pacemakers postoperatively with the standard surgical technique, and this may be reduced to approximately 5% to 6% with a bicaval technique. This small advantage has to be balanced against the increased surgical time required for the bicaval technique as well as the potential for superior vena caval stenosis or kinking and subsequent interference with cardiac biopsies.

Postoperative Care

The most frequent cause of early postoperative death after heart transplantation is right ventricular failure. A high pulmonary vascular resistance in the recipient may exceed the capacity of the donor right ventricle to function normally. Careful donor-recipient matching helps to reduce the risk of this potential. Unexpected ventricular dysfunction after transplantation is also more common on the right, perhaps because of preservation issues. If unexpected left or right ventricular failure occurs after



Patient survival after cardiac transplantation at Mayo Clinic Rochester (as of January 1, 2001) compared with United Network for Organ Sharing (UNOS) data.

transplantation, patients are supported with inotropic medication, balloon pump, or ventricular assist devices until ventricular recovery occurs. According to Dr Daly, recovery of ventricular function under these circumstances is common, particularly when the donor was younger.

Standard early postoperative inotropic support includes administration of isoproterenol, dopamine, and nitroprusside to provide inotropic and chronotropic support of the transplanted heart and to promote pulmonary vascular dilation. Other support is similar to that provided for other cardiac surgical patients. Exceptions to this include the need for immunosuppression after transplantation and the understanding that the heart is denervated when drugs are chosen to treat postoperative arrhythmias. Additionally, if hemodynamic deterioration develops, the possibility of rejection must be considered along with the other usual postoperative concerns such as tamponade.

Postoperative Immunosuppression

At Mayo Clinic, the main immunosuppressant administered in the early postoperative period is OKT3, a murine monoclonal antibody directed against the CD3 receptor of T cells. Immunosuppression with this agent is very reliable, and early rejection is rare. OKT3 is usually given for the first 7 to 14 days after transplantation. "Cyclosporine is not started until several days after surgery when renal function has stabilized; this has resulted in a low instance of posttransplant renal insufficiency," says Dr Edwards.

Chronic immunosuppression after heart transplantation typically consists of 3 drugs—a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolic acid), and corticosteroids. Many patients can be weaned gradually from corticosteroids in the early

months after transplantation. In some situations, sirolimus is administered after heart transplantation to prevent rejection, preserve renal function, and limit graft vasculopathy. This new use for sirolimus is being investigated.

Because cardiac transplant patients may develop a variety of chronic complications, including infectious diseases, neoplasms, hypertension, and graft coronary artery disease, an integrated multidisciplinary system is important for early identification and effective treatment of potential complications. The Mayo Clinic Transplant Center provides such a system for patient care after organ transplantation.

Transplant Outcomes

After receiving their transplants, patients follow a lifelong medical regimen; however, most can return to an active, productive lifestyle. Transplant outcomes vary from center to center. Aggregate data from UNOS show that the 1-year average survival after cardiac transplantation in the United States is 85%. At Mayo Clinic, the 1-year survival is 93%, and this excellent rate extends to the 10-year period and beyond (see Figure). The excellent results achieved by the Mayo Clinic Cardiac Transplant Program, believe Drs Edwards and Daly, are attributable in large part to the integrated practice. The transplant team meets daily and includes dedicated specialists in cardiology, cardiovascular surgery, infectious disease, and pulmonary medicine, as well as dedicated transplant nurses, social workers, and other experts as necessary.

Future Alternatives

Unfortunately, the supply of donor organs is inadequate to meet the need of all potential recipients who qualify for and would benefit from cardiac replacement. Alternative treatments include advances in medical therapy, alternative surgical approaches (ie, revascularization, mitral repair, ventricular remodeling), and mechanical LVADs as destination therapy. Mayo Clinic in Rochester has active clinical programs in all these therapeutic modalities. Xenotransplantation and other biological replacement therapies such as cell transplantation and angiogenesis are experimental options that may have future applications for treatment of heart failure. Mayo Clinic has active experimental xenotransplantion and angiogenesis programs that will be featured in future issues of this newsletter.

More information about heart transplantation can be obtained at the UNOS Web site: http://www.unos.org/ and at http://www.organdonor.gov/opo.htm.

Carotid Stenting May Help High-Risk Patients

David R. Holmes, Jr, MD
Timothy M. Sullivan, MD

Proceduralists

Harry Cloft, MD, PhD
David F. Kallmes, MD
Timothy M. Sullivan, MD

Cerebrovascular accident is the third leading cause of death in the United States, surpassed only by heart disease and malignancy. Stroke accounts for 10% to 12% of all deaths in developed countries. As the population ages, the total number of people afflicted with stroke will continue to rise.

Surgical carotid endarterectomy (CEA) of high-grade carotid lesions, both symptomatic and asymptomatic, is preferable to "best medical therapy" (ie, risk factor reduction and administration of antiplatelet agents) for stroke prophylaxis. CEA has been performed in increasing numbers of patients and now represents the surgical procedure most commonly performed by vascular surgeons. The results of this procedure continue to improve. In 1 reported series of 2,228 consecutive isolated CEA procedures, the overall stroke rate was 1.8% (1.3% for asymptomatic patients), and the mortality rate was 0.5%. "Despite the proven efficacy of CEA in the prevention of ischemic stroke, great interest has been generated in carotid angioplasty-stenting (CAS) as an alternative to surgical therapy, especially in high-risk patients," according to Timothy M. Sullivan, MD, vascular surgeon at Mayo Clinic in Rochester.

Indications

The indications for CAS do not differ from those for standard CEA:

- Asymptomatic lesions in the "70% to 99%" range on duplex ultrasonography, which correlates with an angiographic stenosis of at least 60%. (Most clinical trials of CAS in asymptomatic patients require angiographic stenosis of at least 80% for study inclusion.)
- Symptomatic patients (ie, those with hemispheric transient ischemic attack, amaurosis fugax, or stroke with minimal residua) with at least 70% angiographic stenosis. Patients with symptomatic, ulcerated stenoses greater than 50% may benefit from CEA.

Until now, many physicians have reserved CAS for patients considered at "high risk" for surgical therapy (Table 1). With the development of new approaches and the

findings of recent clinical trials, the role of CAS is rapidly changing (Figure 1).

Results

The short-term results of CAS depend on the presence or absence of cerebral embolization. With the addition of cerebral protection to the procedure, associated stroke risk seems to have decreased. Admittedly, however, improvements in devices and technology have created a "moving target," making evaluation of results difficult. A comprehensive list of CAS trials is provided on the *Cardiovascular Update* Web site (www.mayoclinic.org/cardionews-rst); however, several merit further discussion:

Table 1. Possible Indications for Carotid Angioplasty in High-Risk Patients

1. **Severe cardiac disease**
   a. requiring percutaneous transluminal coronary angioplasty or coronary artery bypass grafting
   b. history of congestive heart failure
2. **Severe chronic obstructive pulmonary disease**
   a. requiring home oxygen
   b. FEV_1<20% predicted
3. **Severe chronic renal insufficiency**
   a. serum creatinine>3.0 mg/dL
   b. currently on dialysis
4. **Prior CEA (restenosis)**
   a. contralateral vocal cord paralysis
5. **Surgically inaccessible lesions**
   a. at or above the 2nd cervical vertebra
   b. inferior to the clavicle
6. **Radiation-induced carotid stenosis**
7. **Prior ipsilateral radical neck dissection**

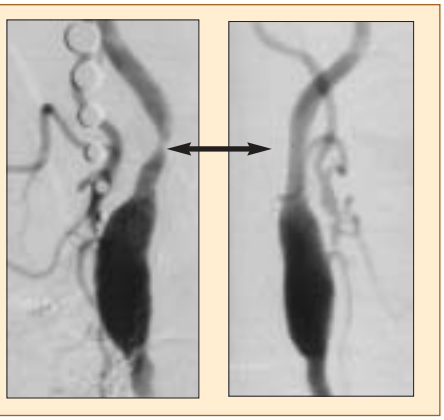


Figure 1. ***Before (left),*** **Recurrent, symptomatic left internal carotid stenosis 9 months after CEA with patch angioplasty. Lesion noted to be "high" at the time of operation.** ***After (right),*** **Completion arteriogram after angioplasty and stenting of recurrent internal carotid stenosis, performed under local anesthesia via a No. 6F sheath.**

The first large cohort of patients was described by Yadav et al in 1997 from the University of Alabama at Birmingham. A total of 107 patients (126 arteries) were treated; 59% were symptomatic, and many were referred from local vascular surgeons. All had preprocedural neurological assessment, and all were treated with balloon-expandable stents without cerebral protection. Amazingly, there were only 2 major strokes, 7 minor strokes, and 1 death at 30 days, for a combined stroke mortality of 7.9%.

Roubin et al subsequently reported a series 528 consecutive patients (604 carotid arteries) treated over a 5-year period. This group included patients treated with both balloon-expandable and self-expanding stents, with and without cerebral protection devices. The overall 30-day combined stroke-mortality rate was 8.1% (for 528 patients) and included a 5.5% rate of minor stroke, 1.6% rate of major stroke, and 1% rate of nonneurological death. When divided into yearly intervals, the risk of stroke and death reached a maximum of 12.5% in the period ending September 1997 and declined to a minimum of 3.2% the following year. "This rather dramatic change in results likely represents improvement in equipment as well as an improved ability of the investigators to select appropriate patients for intervention," suggests Dr Sullivan.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), published in June 2001, reported the results of a randomized trial of CEA versus angioplasty (with and without stenting) for the treatment of patients with symptomatic carotid and vertebral artery stenosis. A total of 251 patients were randomly assigned to the endovascular arm, and 253 were randomly assigned to the surgical arm. Although the 2 procedures were essentially equivalent in their abilities to prevent (or cause, as it turned out) stroke, both treatments did so at an unacceptably high level; the combined end point of death or any stroke was achieved in 10% of patients in both groups. In addition, 20% of patients treated with angioplasty or stenting had severe restenosis or occlusion at 1 year.

"This trial had several flaws that make the results essentially irrelevant in current clinical practice," says Dr Sullivan. "It was selective and nonconsecutive, and only 26% of the patients in the endovascular group had stents placed; the majority had angioplasty alone. No cerebral protection devices were used. As such, the conclusions reached are not applicable to current, state-of-the-art carotid angioplasty practice."

Finally, a recent report by Criado et al describes their CAS experience in a vascular surgery practice. Between 1997 and 2001, a total of 135 CAS procedures were performed, the majority (60%) in asymptomatic patients. The rate of complications was relatively acceptable at 2%, and only 1 patient had a serious restenosis at 16 months of follow-up. Perhaps more importantly, these patients represent 41% of those being treated for carotid disease in their vascular-endovascular practice.

"Embolic stroke is the most common serious complication reported for CAS; its incidence may be greatly reduced by the use of cerebral protection devices," according to Mayo Clinic interventional cardiologist David R. Holmes, Jr, MD. Early in the development of interventional cardiology, embolization was not believed to be an important consideration because the mechanism of dilation was thought to be only plaque compression and not disruption. Subsequent pathology studies demonstrated that not only was distal embolization present, it occurred quite commonly in some scenarios.

Awareness that distal embolization has varying consequences in different vascular beds led to the development, testing, and clinical release of a group of CAS distal protection devices, including filters and distal occlusion devices. Early experiences with carotid intervention (initially percutaneous transluminal coronary angioplasty and subsequently stent placement) were associated with a small but measurable incidence of both major and minor strokes. Since the introduction of distal protection devices, there appears to have been a substantial

Table 2. Limitations and Relative Contraindications to CAS

- Inability to obtain femoral artery access
- Unfavorable aortic arch anatomy
- Severe tortuosity of the common carotid artery
- Severely calcified or undilatable stenoses
- Lesions containing fresh thrombus
- Extensive stenoses (>2 cm)
- Critical (≥99%) stenoses
- Lesions adjacent to carotid artery aneurysms
- Contrast-related issues
- Chronic renal insufficiency
- Previous life-threatening contrast reaction

decrease in the incidence of strokes. Additionally, the recent Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial demonstrated marked reduction in the incidence of overall major adverse cardiac events with CAS compared with CEA.

"The whole field of distal protection continues to evolve, but it clearly is an essential component of CAS," says Dr Holmes (Figure 2).

Advanced age and the presence of long or multiple lesions have been implicated as independent predictors of stroke.

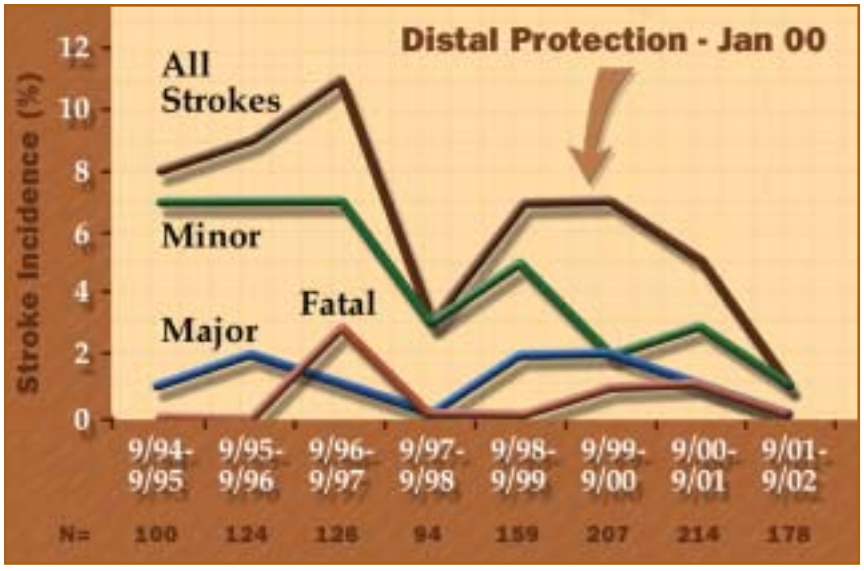


Figure 2. Outcomes of more than 1,000 carotid artery stenting procedures performed by a single group of operators at Lenox Hill Heart and Vascular Institute. Data were derived from a presentation by New et al at the American College of Cardiology 52nd Annual Scientific Session (*J Am Coll Cardiol.* March 19, 2003;41[no. 6, suppl A]:79A, abstract 868-2).

Other complications have also been cited, including prolonged bradycardia and hypotension, deformation of balloon-expandable stents, stent thrombosis, and Horner syndrome. Cerebral hyperperfusion with associated seizures and intracranial hemorrhage has also been reported. The incidence of restenosis probably ranges from 3% to 10% at 1 year. If restenosis occurs, most patients can be treated safely with repeat angioplasty.

Preliminary (30-day) results of the SAPPHIRE study suggest that CAS may be superior in high-risk patients. The purpose of the study was to compare outcomes in 307 high-risk patients randomly assigned to CAS or CEA (156 to CAS , 151 to CEA). In addition, 409 patients thought not to be surgical candidates were entered into a CAS registry. Enrollment of randomized patients required consensus from a multidisciplinary team consisting of a neurologist, surgeon, and interventionist. At 30 days, there was no difference between the 2 groups with respect to death or stroke (5.8% CAS vs 6.6% CEA). With use of a combined end point of death, stroke, and MI, however, a statistical difference favoring the CAS cohort was found (5.8% vs 12.6%; *P*=.047). Of the 409 patients who were thought not to be surgical candidates, the majority underwent stent placement and did well (the combined risk of stroke and death in the CAS registry arm was 6.9%). Early results suggest that, in high-risk patients, stent placement is marginally superior to surgery when combined with a distal protection device. One-year follow-up data should be available by the end of 2003.

Enrollment in the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) has begun, and a multidisciplinary team from Mayo Clinic will be involved. This study, sponsored by the National Institutes of Health, will randomly assign symptomatic patients with high-grade carotid stenosis to CEA or CAS with a self-expanding (nitinol) stent and a cerebral protection device. Primary end points include stroke, myocardial infarction, and death within 30 days and ipsilateral stroke up to 4 years. Secondary outcomes include the differential efficacy in men versus women, 30-day morbidity and mortality, restenosis rates of the 2 procedures, cost and quality of life, and identification of subgroups at differential risk for CEA and angioplasty. A parallel registry arm of the study, Carotid Revascularization With Endarterectomy or Stenting Systems (CARESS), will run simultaneously with the parent study. In addition, a number of industry-sponsored trials of various stents and protection devices are studying the procedure in high-risk subsets.

Conclusions

CAS is an evolving technique that shows considerable promise in the treatment of patients with carotid occlusive disease, although CEA remains the treatment of choice for most patients with bifurcation disease, both symptomatic and asymptomatic. Certain high-risk subsets of patients, especially those with cardiopulmonary and renal disease and those with surgically unfavorable lesions, may benefit from endovascular therapy. Ongoing trials are carefully designed to answer the questions of clinical efficacy and safety.

While tremendous enthusiasm has been generated for CAS, especially by nonsurgeons, it remains an investigational / experimental procedure and has yet to be proven equivalent or superior to CEA in head-to-head comparison (Table 2). "Only through carefully designed clinical trials with dispassionate oversight can we determine the ultimate role of CAS in the treatment of carotid disease," agree Drs Holmes and Sullivan.

Mayo Clinic Sudden Death Genomics Lab Uncovering Clinical Implications of Long QT Syndrome

Michael J. Ackerman, MD, PhD

More than 1,000 sudden deaths occur each day in the United States. The majority of these sudden deaths result from ventricular tachyarrhythmias secondary to coronary artery disease. However, some sudden deaths are unexplained, unexpected, and without a trace of evidence left at autopsy. "In some of these cases, a 'molecular autopsy' may establish a cardiac channelopathy and 'fingerprint' long QT syndrome (LQTS) as the likely cause of sudden death," according to Michael J. Ackerman, MD, PhD, director of Mayo Clinic's Long QT Syndrome / Inherited Arrhythmias Clinic and Sudden Death Genomics Laboratory.

Congenital LQTS affects approximately 1 in 5,000 persons and constitutes a primary repolarization disorder, often but not always manifest on a 12-lead electrocardiogram with notable QT-interval prolongation (QTc≥460 ms). Symptoms result when the long QT heart electrically degenerates into its trademark polymorphic ventricular tachycardia of torsades des pointes and range from syncope and seizures to sudden death. Triggers to perturb the long QT heart include exertion, emotion, and auditory signals. Actually, for many patients (if not the majority), LQTS constitutes a "dud" rather than the "ticking time bomb." However, the diagnostic challenge is to determine which patient will have 80 or more asymptomatic years and which patient will die suddenly. The comprehensive evaluation for LQTS includes 12-lead electrocardiography, 24-hour ambulatory Holter monitoring, and an exercise treadmill stress test. These standard tests attempt to document the electrocardiographic presence of LQTS. However, it is critical that the results of these standard tests be interpreted by physicians with expertise in LQTS to detect subtle QT abnormalities. In addition, the LQTS evaluation at Mayo Clinic includes provocative catecholamine challenges aimed at unmasking the long QT heart that is concealed at rest. Preliminary evidence suggests that such provocative testing may help identify patients at greatest risk. The comprehensive evaluation also includes a mutational analysis of the cardiac channel genes implicated in LQTS.

Heart Rhythm Services

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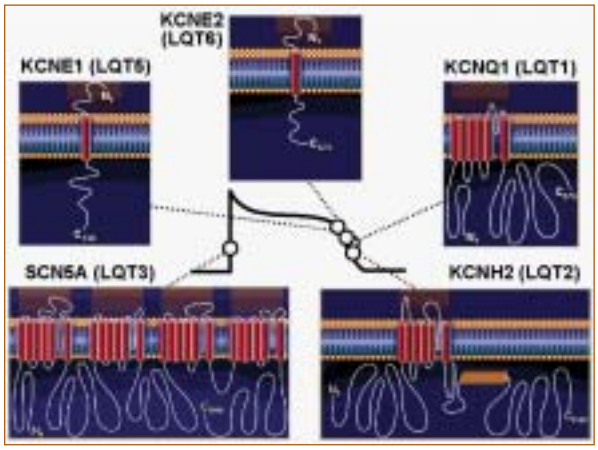

Ion channel mutations, their associated LQTS subtypes, and the affected portion of the cardiac action potential.

Congenital LQTS has been recognized for more than 40 years as a cause of sudden death. First described in 1957 by Jervell and Lange-Nielsen, the autosomal recessive form of LQTS has a severe cardiac phenotype, and affected patients also have hearing loss. In the early 1960s, Romano and Ward described the autosomal dominant form. Thus, LQTS may be referred to by its eponyms—Romano-Ward syndrome or Jervell and Lange-Nielsen syndrome.

Today, rather than by eponym, LQTS is recognized increasingly by its different genotypes. Increasingly, it is appreciated that the varying genotypes are associated with different arrhythmogenic triggers and different responsiveness to β-blocker therapy, the standard medical treatment for LQTS. At Mayo Clinic, we have determined that patients with LQTS who experience a cardiac event while swimming almost always have LQT1. More recently, Priori and colleagues in Italy described a risk-stratifying score based on the patient's genotype, sex, and baseline QTc.

At least 6 distinct genetic types of LQTS are now known. To date, hundreds of mutations scattered among 5 genes that encode critical ion channels in the myocardium appear to account for approximately 60% of families with LQTS. The gene encoding ankyrin B (a non–ion channel protein) has been established recently for the chromosome 4 locus of LQTS (LQT4). In addition, mutations in the inwardly rectifying potassium channel (IK1) encoded by the gene KCNJ2 are responsible for Andersen syndrome (periodic paralysis, facial stigmata, and often QT-interval prolongation). KCNJ2 has been labeled by some as LQT7. Recently, Mayo Clinic's Sudden Death Genomics Laboratory determined that 5% of infants with sudden infant death syndrome had genetic defects in myocardial ion channels.

As part of the comprehensive LQTS evaluation, the LQTS-causing genes are interrogated in suspected families according to a research protocol approved by the Mayo Foundation Institutional Review Board. The molecular diagnostic testing to "screen the genes" usually takes between 6 and 12 months. If a family's LQTS mutation is discovered, the genetic test result is offered to the family, now providing a diagnostic standard to determine whether any other family members are affected. Evaluation of family members is a critical component of a LQTS work-up because LQTS is generally inherited in an autosomal dominant manner, implying other relatives may harbor the defective cardiac channel that poses a potential risk. At present, a cardiac channel gene screen is not available as a clinical diagnostic test; however, this is anticipated in the next 12 months. When genetic testing becomes clinically available, proper interpretation of and genetic counseling regarding the genetic test results will be critical. "As we gain more information about the molecular and genetic basis of LQTS, it is hoped that we will be better able to estimate individual risk and someday implement successful treatment strategies to fully prevent sudden cardiac death in those with LQTS," says Dr Ackerman.

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Echocardiography in Congenital Heart Disease
Oct 12-15, 2003, Rochester, Minn

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Oct 25-26, 2003, Rochester, Minn

First Annual Echocardiography: From Pictures to Information
Oct 24-26, 2003, Phoenix, Ariz

Valvular Heart Disease: Case Studies
Nov 8, 2003, Orlando, Fla

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Feb 15-19, 2004, Phoenix, Ariz

Valvular Heart Disease
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Cardiac Device Therapy—2003: Update in Pacemaker, ICD and Cardiac Resynchronization Therapy
Aug 7-9, 2003, Chicago, Ill
Directed by: David L. Hayes, MD, FACC

Cases in Echocardiography: TEE, Doppler, and Stress—Interpretation and Clinical Decision Making for the Advanced Echocardiographer
Oct 30-Nov 1, 2003, Seattle, Wash
Directed by: Rick A. Nishimura, MD, FACC; Fletcher A. Miller, Jr, MD, FACC

Echo Hawaii 2004: Fourteenth Annual
Jan 26-30, 2004, Kohala Coast, Hawaii
Directed by: A. Jamil Tajik, MD, FACC; James B. Seward, MD, FACC

The 11th Annual Echocardiographic Workshop on 2-D and Doppler Echocardiography at Vail
Feb 23-26, 2004, Vail, Colo
Directed by: George M. Gura, MD, FACC; Thomas Ryan, MD, FACC

Cardiology at Cancun
Feb 23-27, 2004, Cancun, Mexico
Directed by: A. Jamil Tajik, MD, FACC; Guy S. Reeder, MD, FACC

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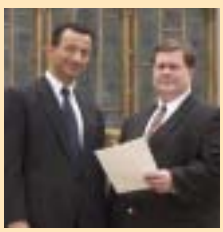
2003 Graduating Cardiology Fellows (and upcoming appointments): Back row *(left to right): Michael Wahl, MD (Aurora-Denver Cardiology, Denver); Michael Peterson, MD (DuPage Medical Group, Chicago); Paul A. Friedman, MD, and Andre Terzic, MD, PhD (program directors).* Middle row *(left to right): Calin Maniu, MD (University of South Carolina Medical School, Charleston); David Simper, MD (VA Hayden Medical Center, Phoenix); Ravi Kanagala, MD (Mayo Medical Center, Rochester); Arturo Valverde, MD (State University of New York, Buffalo); Nabil Nasir, MD (Lebanon); Martin Rodriguez-Porcel, MD (Mayo Foundation Scholar, Stanford); Kwan-Kin Law, MD (Hong Kong Tune Mun Hospital).* Front row *(left to right): Allison Pritchett, MD (Baylor University Hospitals, Houston); Bhavani Balaravi, MD (Cardiac Imaging Fellowship, Mayo Medical Center, Rochester); Guy Reeder, MD (program director); Lisa Erdmann (program coordinator); Patricia Best, MD (Mayo Medical Center, Rochester); Kristine Black (program coordinator).* Not pictured: *David Brosh, MD (Rabin Medical Center, Tel Aviv, Israel).*

2003 Graduating Cardiovascular Surgery Fellows: *Abbas E. Abbas, MD (left), will be assistant professor of thoracic surgery at Ohio State University, Columbus. David G. Cable, MD (right), is going into practice at CardioVascular Surgery of Alexandria LLC, Alexandria, Louisiana.*



Drug-Eluting Stents: 'Breakthrough' Over Bare Metal, But Questions Remain on Routine Use

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Since the inception of interventional cardiology, restenosis of treated coronary artery lesions has been a vexing problem. In one of the earliest reports from the National Institutes of Health percutaneous transluminal angiography registry in 1984, angiographic restenosis occurred in 33.6% of patients.

These results are surprisingly similar to those reported in 2001 from the largest restenosis trial to date, the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) Trial, which included approximately 11,500 patients in whom the restenosis rate was 33%. "Although angiographic lesion and patient selection criteria have certainly changed during the past 15 to 20 years, restenosis rates have not," according to David R. Holmes, Jr, MD, Mayo Clinic interventional cardiologist.

Given the magnitude of the problem of restenosis, it has been the object of intense investigation. Several mechanisms are implicated in the restenosis process, including acute recoil, negative remodeling, excessive matrix formation, and neointimal hyperplasia. Compared with conventional angioplasty, stents decrease restenosis by approximately 30%. "The mechanism for this reduction is prevention of negative remodeling. Stents do not decrease neointimal hyperplasia," according to Dr Holmes. "In fact, stents are associated with an increase in the amount of neointimal hyperplasia, but this effect is counterbalanced by a mechanical scaffolding effect." In-stent restenosis, depending on the specific angiographic pattern, may be recalcitrant to treatment. Treatment of in-stent restenosis has spawned the development of new approaches such as vascular brachytherapy.

One drug-eluting stent, the sirolimus-eluting stent, is now approved by the US Food and Drug Administration. A second, a paclitaxel-coated stent, is in the final phases of testing. These stents combine mechanical scaffolding properties with drugs to prevent neointimal hyperplasia.

The sirolimus-eluting stent has been studied in single-center registries (which now include careful follow-up for 3 years), multicenter registries, and randomized clinical trials. A relatively small randomized trial of 228 patients (the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions [RAVEL]) documented no subacute closure and no restenosis. The larger multicenter trial, the Sirolimus-Eluting Stent in Coronary Lesions (SIRIUS) trial, included 1,058 patients who were at higher risk for restenosis. The results of this trial showed that in-hospital outcomes with freedom from major cardiac adverse events were excellent and resembled those achieved in patients receiving conventional stents. Furthermore, the primary end point of target vessel failure at 9 months (defined as cardiac death, myocardial infarction, or target vessel revascularization) was dramatically improved (8.8% vs 21.0%) in patients who received the sirolimus-eluting stent.

This improvement was related to a reduction in the rate of target lesion revascularization from 16.6% to 4.1%; death or myocardial infarction was infrequent, and the rate was similar between the 2 groups. "Angiographic restenosis rates, both within the stent (3.2% vs 35.4%) and within the treated arterial segment (8.9% vs 36.6%), were much improved with the drug-eluting stent, and clinical improvement was sustained out to 1 year," says Dr Holmes. These data formed a major part of the evidence used for FDA approval. Despite these early encouraging results, several issues must be addressed before routine use of these types of stents in practice:

- ***Cost.*** Currently the sirolimus-eluting stent is approximately 3 times as expensive as a bare metal stent. Assessment of cost is complex—economic analysis of the SIRIUS trial documented that at 1 year, because of the decreased need for repeat procedures, the costs of drug-eluting stents were only approximately $300 more than those associated with use of the bare metal stent. From a global societal standpoint, use of the drug-eluting stent appears to be an effective strategy. However, the impact on hospitals may be different because of increased initial costs, a potential shift away from surgical procedures (a high revenue generator) to percutaneous coronary intervention, and fewer repeat procedures.

- ***Other patient and lesion subsets.*** At present, experience is limited, although further registries and trials are planned. Questions that remain to be answered are, for example, whether these stents will be effective for treatment of vein graft disease or in-stent restenosis.

- ***Multivessel disease.*** In the SIRIUS trial, the in-stent restenosis rate per lesion was 3.2% and the in-segment restenosis rate per lesion was 8.9%. In clinical practice, if 3 or 4 vessels are treated, the restenosis rate per patient may well exceed 15%. This may still be reasonable if the goal is to avoid surgery, although the costs associated with such a strategy may be prohibitive.

Drug-eluting stents represent a giant step forward in improving outcomes for patients undergoing percutaneous coronary intervention. "Our ability to use these devices will shift some patients who would have had coronary artery bypass graft surgery into the interventional laboratory and also may affect patients with serious coronary artery disease who in the past have been treated medically," says Dr Holmes. "These stents are really breakthrough technology."