



Douglas L. Packer, MD

**2010-2011 President
Heart Rhythm Society**

Heart Rhythm Services





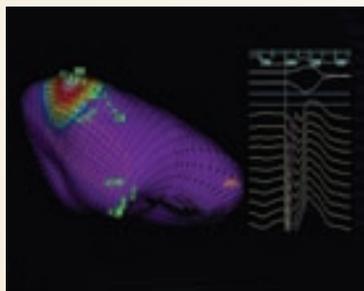
Dear Colleague:

On behalf of Mayo Clinic, I would like to take this opportunity to provide you with a review of the activities of our group. Our members have wide and varied areas of expertise, from basic molecular research to advanced ablative skills, with the goal to provide the highest quality care to each and every one of our patients. To that end, our practice integrates research, education, and clinical care to further the understanding of the pathophysiology of cardiac arrhythmogenesis and to develop data-driven, clinical best practices.

The future holds many challenges for the electrophysiology community, including the increase in the number of patients with chronic arrhythmias, the development of new technologies for treating arrhythmias, and cost constraints to providing care. We at Mayo Clinic are committed to providing leadership and innovation to the medical profession as we navigate these challenges, never forgetting the words of our founders: "The needs of the patient come first."

Douglas L. Packer, MD

2010-2011 President, Heart Rhythm Society
Director, Heart Rhythm Center, Rochester, Minnesota



2009 Electrophysiology Procedural Volumes

Diagnostic Studies

Diagnostic EP study	170
Head-up tilt	649

Ablations

Atrial flutter	140
Atrial tachycardia	62
AP/AVNRT	279
AVN	199
PVI	612
Ventricular tachycardia	193

Device Implants

Pacemaker implants	1,430
Bi-V pacer implants	24
ICD implants	692
Bi-V ICDs	239
ICD follow-up	112
Lead extraction	98
Loop recorders	84

Device Clinic

Transtelephonic checks	23,336
Pacemaker in-clinic checks	8,440
ICD in-clinic checks	6,816
Remote ICD checks	4,465
Remote Pacer checks	646
Implantable loop checks	130
Remote on-site checks	1,342

AP/AVNRT, accessory pathway/atrioventricular nodal reentry tachycardia; AVN, atrioventricular node; Bi-V, biventricular; EP, electrophysiology; ICD, implantable cardioverter-defibrillator

National Leadership



Douglas Packer, MD, 2010-2011 Heart Rhythm Society President
Stephen C. Hammill, MD, 2004-2005 Heart Rhythm Society President
David L. Hayes, MD, 1998-1999 Heart Rhythm Society President



Douglas L. Packer, MD

Director, Heart Rhythm Center

2010-2011 President,
Heart Rhythm Society

Continuing Evolution of Therapy for Atrial Fibrillation

Atrial Fibrillation: The Problem

Atrial fibrillation (AF) remains the leading arrhythmia in North America, both in numbers of patients affected and the frequency of accompanying sequelae. The prevalence continues to increase, despite progress in the treatment of contributing factors. Although 1% of individuals in their 60s may have AF, the prevalence increases to 10% to 12% in individuals older than 80 years. Currently 2.5 million Americans have AF, but with the aging population and improved cardiovascular survival, this number may increase to 5 million to 6 million by the year 2050. In most patients, AF is initially paroxysmal; other patients, particularly those with underlying heart disease, may have more persistent or even chronic AF. Nevertheless, the previously held belief that most paroxysmal AF ultimately progresses to a chronic form has been questioned. Recent studies have suggested that progression occurs in only 20% to 40% of patients over the course of 3 to 5 years, although longer-term data are lacking.

Nevertheless, AF becomes increasingly problematic because of the occurrence of AF-related thromboembolic events such as stroke, accompanying fundamental changes in thrombus formation, and changes in left atrial size, morphology, and function. Perhaps 15% to 30% of patients with an acute stroke have underlying AF. Patients with AF also have an increase in overall mortality risk (15% in patients without AF vs 35% in those with AF), attributable to stroke risk and comorbid conditions. In the Framingham and other studies, it has been demonstrated that this increase in mortality is attributable to AF as a risk factor, rather than simply being caused by the presence of underlying disease. Atrial fibrillation is an increasing burden on the global health care system because of the numbers of patients affected, the impact of stroke, and the cost of both inpatient and outpatient therapy.

Drug Therapy for AF

Because of stroke risk, most patients require some form of antithrombotic therapy in the form of aspirin or warfarin. Those patients with no risk factors may completely forgo antithrombotic therapy, while the recent ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation have suggested that therapy with aspirin alone is adequate in those at low risk with a CHADS score less than 1. Patients with several risk factors (age >75 years, hypertension, diabetes, prior stroke or transient ischemic attack, left ventricular dysfunction) are at higher risk, necessitating anticoagulation therapy with warfarin. This recommendation is based on an extensive series of large mortality studies consistently demonstrating the benefit of antithrombotic therapy. Despite clear guidelines and extensive experience with thromboembolic events, many patients who would benefit from antithrombotic therapy do not receive it.

Many patients have a rapid ventricular response rate during AF, which is responsible for symptoms. In some cases, rapid rates may also result in tachycardia-induced cardiomyopathy. While this occurs relatively uncommonly in the absence of other heart disease, the possibility of an AF contribution to ventricular dysfunction should be considered in patients who have a rapid ventricular response rate and reduced ejection fraction. As such, many patients require rate control to prevent these sequelae and improve overall quality of life. Establishing appropriate rate control, however, requires some assessment of rate during rest and exertion. Most guidelines and recent clinical trials recommend that resting rates during AF be less than 90 to 100 bpm, with exercise heart rates maintained at less than 110 to 120 bpm.

Restoration of normal sinus rhythm may be the most effective means of rate control. A number of studies over the past 30 years have also shown the usefulness of membrane-active, antiarrhythmic drug therapy for maintaining sinus rhythm. Approximately 30% to 40% of patients treated with antiarrhythmic therapy are controlled over the course of 1 year of follow-up. These data have been validated by larger comparative clinical trials such as the AFFIRM trial. Similar results have been reported in RACE, STAF, and other studies designed to compare rate and rhythm control therapy. Although an increase in mortality may accompany AF, comparative studies examining the utility of rate vs rhythm control therapy have had disappointing results.

The AFFIRM trial, for example, showed no difference in overall mortality over the course of long-term follow-up with either treatment strategy. Similarly, the RACE, PIAF, and STAF studies yielded similar findings.

Additionally, the AF-CHF trial, which involved 1,376 patients with AF, also failed to demonstrate any difference in the end points of total mortality, worsening heart failure, or the composite of cardiovascular mortality, stroke, or worsening heart failure. In addition, bradycardia and rehospitalization were more common in those treated with antiarrhythmic drugs intended to maintain sinus rhythm. These findings may have been attributable to the following scenarios:

1. Other factors, including underlying disease, were responsible for the morbidity and mortality in AF patients, such that AF was a risk marker for mortality, rather than a risk factor.
2. A benefit from treatment with antiarrhythmic drug therapy may have been masked by the occurrence of organotoxicity or proarrhythmic events.
3. Silent AF in patients treated with rhythm control or undetected sinus rhythm in those treated with rate control drugs may have decreased the ability of the AF-CHF trial protocol to detect real differences in overall outcomes.

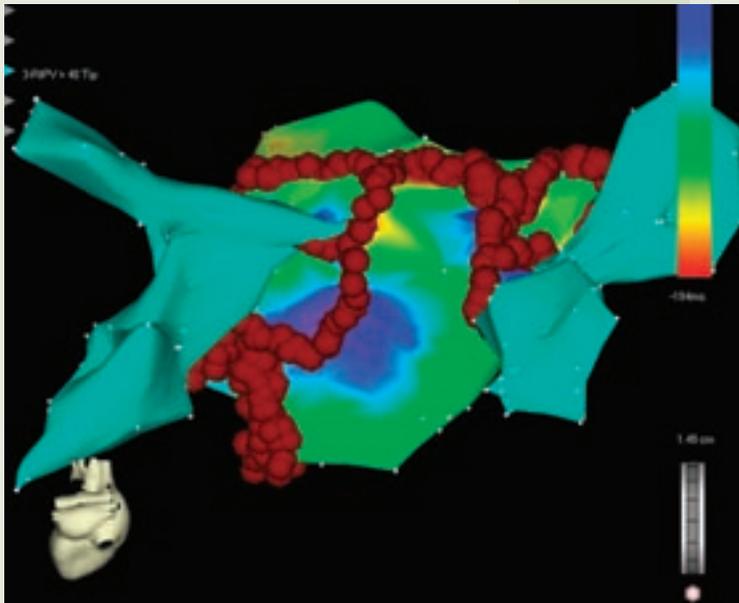


Figure. Computer-generated map of left atrial activation. Red dots indicate ablation sites.

Despite the pessimism generated by these studies, the results of the recent ATHENA trial have encouraged reconsideration of drug therapy for AF. In comparing the class III antiarrhythmic agent dronedarone with placebo in more than 4,500 patients, this study showed a 24% reduction in cardiovascular hospitalization or mortality, a 29% decrease in cardiovascular mortality, and a 26% decrease in cardiovascular hospitalization with active therapy at 22±5 months of follow-up. There were significantly lower rates of acute ischemic

syndrome and stroke with dronedarone therapy when rates of proarrhythmia and heart failure were also low. These data support the potential for cancellation of benefit from drug therapy by untoward toxicities of drug interventions, although the control rate with this drug is less than that of amiodarone.

Nonpharmacologic Therapy for AF

The escalation of AF occurrence, the efficacy limitations of drug therapy, and the adverse effects and toxicity from drug therapy have provided the incentive for the continued implementation of nonpharmacologic therapy over the last decade. Atrial fibrillation ablation has been shown in a number of observational studies to be of benefit in eliminating AF, reducing its frequency, and improving patients' quality of life. In most studies, 75% to 85% of patients with paroxysmal AF have been rendered free of this arrhythmia over the course of 1 year of observation. In patients with persistent or chronic AF and those with underlying disease, AF is decreased in 10% to 20% of patients. After longer-term follow-up, the ablation of patients with more advanced underlying disease, and a more critical view of treatment benefit without additional antiarrhythmic drugs or repeat ablative intervention, these overall success rates are lower than the more optimistic values touted in the first part of this decade.

Douglas L. Packer, MD, director of the Heart Rhythm Center in Rochester, Minnesota, and the 2010-2011 president of the Heart Rhythm Society, reviewed outcomes of ablation at Mayo Clinic. He found that over 2 years of long-term follow-up the response to ablation was excellent in more than 75% of patients with paroxysmal AF. Patients with persistent and chronic AF likewise have shown enhanced benefit, although a more aggressive ablative approach has been required. In those with paroxysmal AF, ablation for the isolation of pulmonary veins may be sufficient, while wider-area circumferential ablation with additional linear ablation or energy delivery directed at the underlying substrate has been required (Figure). Additional review demonstrated notable benefit in patients with underlying dilated cardiomyopathies. In many patients, not only was AF eliminated, but a substantial improvement in ejection fraction was observed, particularly in those with nonischemic left ventricular dysfunction.

Several recent studies have gone beyond observational reports to compare the efficacy of ablative vs drug therapy in patients with paroxysmal AF. The

CACAF, RAAFT, APAF, and A4 trials demonstrated a 76% recurrence rate in patients treated with drug therapy vs 24% recurrence in those treated with ablative intervention. These studies were limited, however, because of shorter-term follow-up and the exclusion of patients with underlying disease or advancing age. The impact of ablative therapy on the overall cost of health care is less certain.

Indications for Ablative Intervention

Even in the absence of cost data, there is sufficient information from observational studies, meta-analyses, and comparative studies to support more widespread application of AF ablation in patients failing a single antiarrhythmic drug because of AF recurrence or intolerability. The Guidelines for the Management of Patients With Atrial Fibrillation, endorsed by the American Heart Association and the American College of Cardiology, recommend this nonpharmacologic approach as second-line therapy. Similarly, the Expert Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-up, developed by the Heart Rhythm Society and endorsed by the AHA and ACC, comes to a similar conclusion. A number of centers are moving toward a primary therapy role for ablation, as success rates increase and complication rates decline.

In clinical practice, it is important to be clear on the indication for any intervention in AF patients. Of primary importance is the need to prevent stroke or other peripheral thromboembolic events. Warfarin therapy has been best demonstrated to reduce this risk. Additional studies will be required to establish a benefit in this area with membrane-active drug therapy or ablation. The role of therapy to establish and maintain sinus rhythm in patients with left ventricular dysfunction is acceptably clear-cut in recent ablation studies. Of greatest importance is the need to reduce or eliminate AF in symptomatic patients. This remains the primary indication for ablative intervention. Patients who have failed to respond to 1 drug may be good candidates for intervention, although the anticipated success rate depends on the type of AF and the presence of underlying left ventricular or left atrial dysfunction. Age appears to be a less important issue than previously thought. Patients with underlying valvular heart disease and hypertrophic cardiomyopathy have excellent short-term outcomes although much more aggressive procedures are

required.

Experience With Pulmonary Vein Isolation at Mayo Clinic

Since 1997, more than 2,500 pulmonary vein isolation procedures for the treatment of AF have been performed at Mayo Clinic's campus in Rochester. In the most recent review, 73% of patients with paroxysmal AF and 66% of patients with persistent AF maintained sinus rhythm for 1 year after the procedure without antiarrhythmic drug therapy. Another 10% of patients with paroxysmal AF and 11% with persistent AF were able to maintain sinus rhythm with previously ineffective antiarrhythmic drug therapy. The procedure was repeated in 13% of patients. Complication rates have been low, with severe pulmonary vein stenosis occurring in 0.8% and cardiac tamponade occurring in 2.1%. There have been 2 atrioesophageal fistulas. The majority of patients (71%) were younger than 65 years.

Ongoing Large Multicenter Trials

While observational studies and limited randomized comparisons demonstrate symptomatic improvement in patients undergoing ablation and early data suggest a cost benefit, larger long-term studies are required to establish a mortality benefit and a reduction in stroke risk. As a result, the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy in Atrial Fibrillation) trial was designed. This study, originating from Mayo Clinic, will examine the benefit of ablation vs drug therapy in 3,000 patients with AF enrolled in 140 centers around the world. Mayo Clinic recently received \$48 million in grants from the National Institutes of Health and from industry to lead this collaborative effort. The study will also establish long-term complications of AF treatment and their prevention by appropriate ablative or drug therapy. Importantly, this study will also establish the actual impact of the arrhythmia and its treatment on a patient's quality of life and health care costs.

Until these studies are completed, the application of ablative intervention will continue to be guided by a decade of observational studies and smaller randomized clinical trials, as well as information coming from national and international ablation registries.



Thomas M. Munger, MD

Operations Manager, Heart
Rhythm Center

Epicardial Radiofrequency Catheter Ablation for Ventricular Arrhythmias

Since the release of enhanced indications (earlier in the past decade) for implantable cardioverter-defibrillator (ICD) placement, patients at risk for ventricular arrhythmias have received life-extending device therapies. Thus, tertiary electrophysiology centers across the country are faced with an increasing number of patients who have ICD/drug-refractory reentrant ventricular arrhythmias and electrical storm (ES).

From prior studies, it is believed that more than 10% of ICD patients experience ES within 2 years of implantation. Further, with the introduction in the past 15 years of nontransplant strategies such as left ventricular assist devices and cardiac resynchronization therapy (CRT) for management of drug-refractory congestive heart failure (CHF), additional patients who would otherwise have died from CHF are experiencing ES, requiring medical attention.

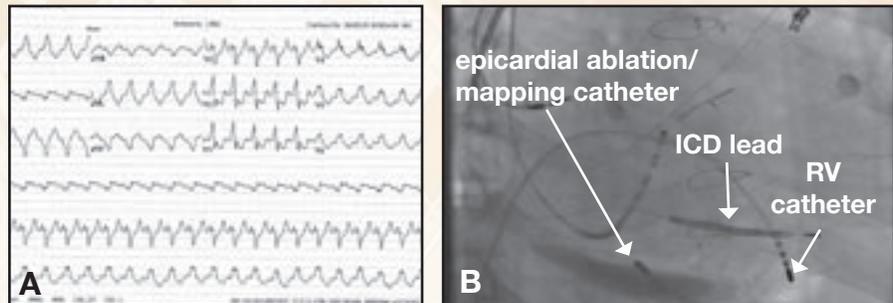


Figure 1. (A) The electrocardiogram of the VT is consistent with an inferior wall exit. (B) Right anterior oblique fluoroscopic projection. An ICD lead and an endocardial apical RV catheter are present. Contrast dye within the inferior pericardial space is shown as well as the epicardial sheath and ablation/mapping catheter.

For patients with ES, Class I–indicated treatments (according to the ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) include coronary artery bypass grafting, percutaneous coronary intervention, intravenous β -blockers, and intravenous amiodarone. The major Class II treatment is radiofrequency ablation (RFA), used as a required modality in at least 10% of ES patients presenting to large tertiary centers.

Two important trials of ventricular tachycardia (VT) ablation for secondary prevention of ES in patients with structural heart disease have appeared recently in the literature. These studies used saline-irrigated, cooled-tip RFA devices to create deeper endocardial lesions. Nonetheless, only 60% of patients in each trial were “free” of shocks at 6 months of follow-up. Multiple VT circuits, CHF, age, and lack of an incessant, hemodynamically well-tolerated VT to map were predictive of recurrence. Many left ventricular (LV) walls have a muscle thickness of more than 1 cm, beyond the lesion field depth of current catheter technologies. Furthermore, patients with dilated cardiomyopathy may have a higher scar density appropriate for anchoring linear RFA lesions on the outside of the heart, rather than the endocardial surfaces. Such is the case with a disease of the Amazon jungle, Chagas disease, caused by the parasitic protozoan *Trypanosoma cruzi* and transmitted by the blood-sucking assassin

bug (“kissing bug”). Chagas disease causes heart failure, conduction system disease, and ventricular arrhythmias. South American medical colleagues were quick to discover that the scars that produced the VT in these patients were chiefly epicardial, not endocardial, and could be more readily mapped and ablated from outside the heart rather than from the inside. While this could be accomplished surgically, a less invasive percutaneous approach was needed.

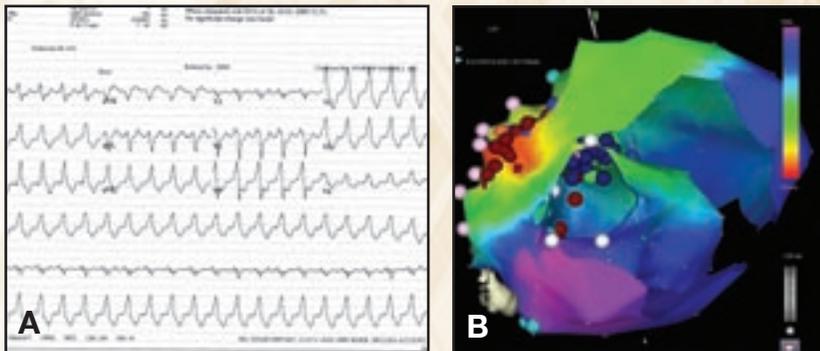


Figure 2. (A) Lateral exit is suggested by QRS morphology on this electrocardiogram. (B) This location is confirmed by simultaneous epicardial and endocardial activation maps, demonstrating an early breakout on the epicardial lateral left ventricle.

The initial experiences with epicardial mapping and ablation using a percutaneous approach were developed

by Dr Eduardo Sosa and colleagues at the Heart Institute (InCor), University of São Paulo Medical School in Brazil. They reported a percutaneous epicardial approach for placement of electrophysiologic hardware in 1999. This technique involves the subxiphoid placement of sheaths into an intact, closed pericardial space. The pericardium typically contains 30 to 50 mL of straw-colored fluid and as such is a virtual space. By accessing the pericardial space, electrophysiologists can map and ablate simultaneously from the endocardial and epicardial surfaces, thus facilitating full-thickness lesion generation in the left ventricle. Additional care must be taken in the epicardial space to avoid adjacent structures that are normally protected from thermal trauma on the inside of the heart (coronary arteries, phrenic nerve, pulmonary tissues). Several groups in Europe, Asia, and North America have visited São Paulo to gain experience with this important technique.

The percutaneous epicardial ablation program at Mayo Clinic began in 2004. Multiple patients have undergone endocardial mapping and ablation with no obvious scar even being noted; subsequent epicardial mapping demonstrated a definite epicardial scar substrate to which ablation could be applied, alleviating the patient's ventricular arrhythmia. While the typical patient has underlying structural heart disease, many patients with normal hearts and highly symptomatic premature ventricular contraction (PVC) or VT foci in the left ventricle (which cannot be accessed from traditional approaches

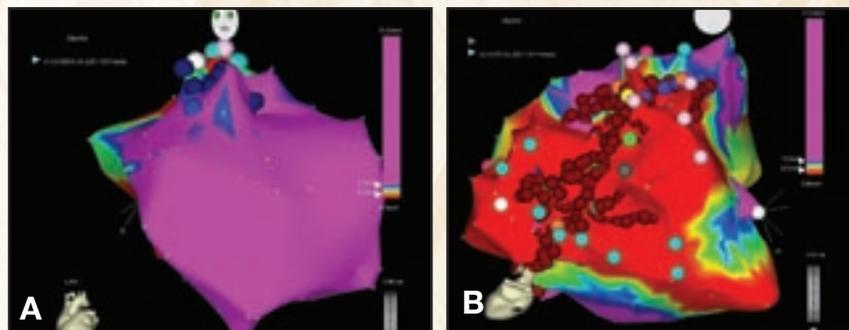


Figure 3. Voltage maps of the endocardial (A) and epicardial (B) surfaces are shown with the voltage sites in red. A large epicardial scar is shown with normal voltages inside the left ventricle.

using the LV outflow tract or the aortic cusp) are presenting for epicardial treatment.

Both fluoroscopic and echocardiographic imaging with contrast dye is used to facilitate access to the pericardial space. Most patients have the pericardial sheath removed either the evening of the procedure or within 48 hours after placement. The images shown in Figure 1 on page 10 are from a 57-year-old man with prior inferior myocardial infarction, ICD placement for recurrent VT, shocks despite amiodarone, and 2 prior endocardial mitral isthmus ablations.

Another example is a 48-year-old man whose VT is shown in Figure 2 on page 11. He had dilated cardiomyopathy, LV ejection fraction of 25%, an ICD enabled with CRT with multiple ICD shocks, and 2 prior unsuccessful ablation attempts.

Figure 3 shows voltage maps of the endocardial and epicardial surfaces, illustrating catheter positions in the same patient shown in Figure 2. Figure 4 shows fluoroscopic views of the endocardial and epicardial ablation catheters across from each other at anterolateral LV sites in the same patient.

In these examples, epicardial activation, voltage mapping, and epicardial RFA were critical and necessary to achieve the desired clinical effects. Both ventricular rhythms terminated with epicardial energy delivery.

As experience with ablation of patients with structural heart disease and reentrant VT, as well as younger patients with focal epicardial VT or PVC foci and associated tachycardia-induced cardiomyopathy has widened, electrophysiologists and cardiologists are exploring other areas that could prove fruitful if assisted by this valuable percutaneous epicardial access technique. In the future this approach will include devices for left atrial appendage occlusion, reservoirs for drug delivery, epicardial pacing, and genotherapies.

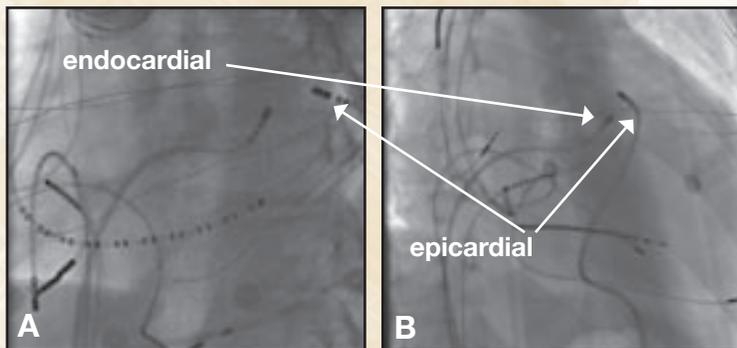


Figure 4. Left (A) and right (B) anterior oblique fluoroscopic views of the endocardial and epicardial ablation catheters across from each other at anterolateral LV sites.



Yong-Mei Cha, MD

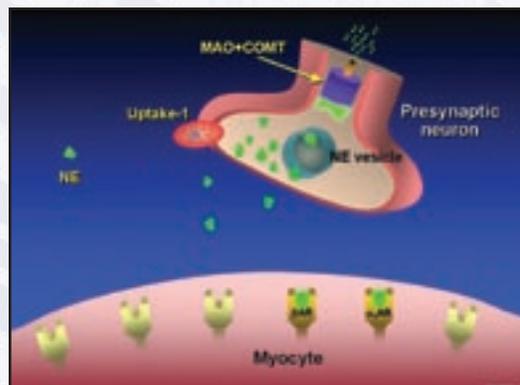
Electrophysiologist at Mayo Clinic

The Vital Role of Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) benefits a subset of patients with congestive heart failure, improving symptoms, quality of life, and survival and providing an effective alternative treatment for this disease. Correction of biventricular electrical and mechanical dyssynchrony is considered the underlying beneficial mechanism of CRT. Although heart failure is associated with an abnormally activated sympathetic nervous system, manifested by increased concentration of circulating catecholamines, attenuated cardiovascular reflexes, impaired cardiac vagal reflexes, and downregulation of adrenergic nerve terminals, the effect of CRT on cardiac neurohormonal function has not been well characterized.

Cardiac adrenergic control is governed by norepinephrine, a sympathetic transmitter, which is synthesized within neurons and released to the synaptic cleft. Most norepinephrine undergoes reuptake into presynaptic nerve terminals by the uptake-1 mechanism (Figure 1). Nerve growth factor belongs to a family of proteins termed neurotrophins that play a critical role in the development of sympathetic innervation.

Figure 1. Schematic of norepinephrine reuptake into presynaptic nerve terminals by the uptake-1 mechanism (β AR, β -adrenergic receptor; α 1AR, α 1 adrenergic receptor; COMT, catechol-O-methyl transferase; MAO, monoamine oxidase; NE, norepinephrine).



Several radiolabeled compounds have been synthesized for noninvasive imaging of cardiac neuronal function. The catecholamine analogue 123 iodine metaiodobenzylguanidine (123 I-MIBG) is the most commonly used tracer for mapping myocardial presynaptic sympathetic innervation and activity (Figure 2), and carbon-11 hydroxyephedrine (11 C-HED), an alternative norepinephrine analogue, is used

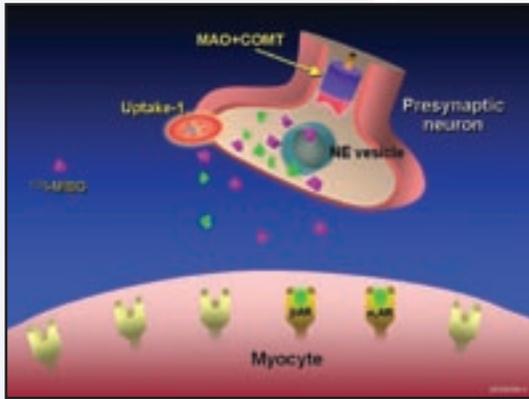


Figure 2. Schematic of ¹²³I-MIBG used as a tracer for assessing presynaptic uptake-1 transport function (βAR, β-adrenergic receptor; α₁AR, α₁ adrenergic receptor; COMT, catechol-O-methyl transferase; MAO, monoamine oxidase; NE, norepinephrine).

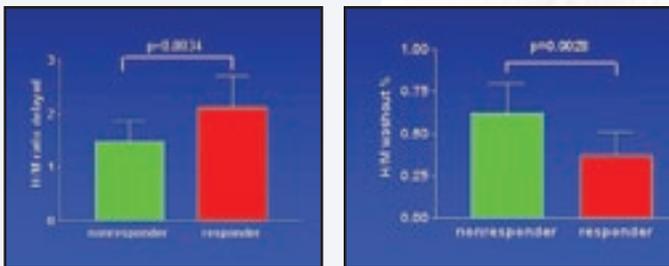


Figure 3. Delayed H/M ratio (left) and washout rate (right) determined by ¹²³I-MIBG in CRT responders and nonresponders (H/M, heart/mediastinum).

as a positron emission tomography (PET) tracer for assessing presynaptic uptake-1 transport function. Mayo Clinic researchers, led by Yong-Mei Cha, MD, have examined the effect of CRT on neuronal integrity, the cardiac presynaptic sympathetic function determined by these nuclear cardiac imaging modalities. Furthermore, they are evaluating whether neurohormonal profiles and sympathetic function can predict the likelihood of response to CRT.

Early results indicate that CRT reverses cardiac autonomic remodeling by upregulating presynaptic receptor function, with increased ¹²³I-MIBG uptake and ¹¹C-HED retention index at the sympathetic terminal level in parallel with improvements in heart rate variability, indicating a favorable rebalance of cardiac sympathetic function. The study results suggest that CRT improves cardiac presynaptic sympathetic activity similar to pharmacologic therapy with β-blockage or renin-angiotensin-aldosterone axis inhibition.

Furthermore, cardiac sympathetic reserve assessed by ¹²³I-MIBG scintigraphy appears to be a potential predictor of clinical response to CRT (Figure 3). The baseline sympathetic uptake function in patients who responded to CRT was similar to that in controls, representing a preserved sympathetic function. Conversely, those with severely impaired baseline sympathetic function were less likely to benefit from CRT. Mayo researchers speculate that in responders the cardiac sympathetic ending might be “hibernating” as an adaptation to elevated sympathetic control (functional deactivation), whereas nonresponders may have structural deficits in the cardiac sympathetic neurons due to scarred myocardium or anatomic cardiac denervation. This hypothesis appears to be supported by these early findings and is being examined in larger-scale studies.



Michael J. Ackerman, MD, PhD

Director, Long QT Syndrome Clinic

Director, Windland Smith Rice Sudden
Death Genomics Laboratory

Long QT Syndrome Clinic and the Windland Smith Rice Sudden Death Genomics Laboratory

Long QT syndrome (LQTS) affects 1 in 2,500 people. In 5% to 10% of cases, the first symptom is sudden death, often related to physical exertion or auditory triggers such as an alarm clock. However, many cases can be diagnosed following warning signs such as sudden fainting spells or a family history that suggests its potential presence and from objective data derived from electrocardiography, exercise or epinephrine QT stress testing, and genetic testing. The condition was first clinically described in 1957, but the first LQTS genes were not identified until 1995. The first genetic test for LQTS became clinically available in North America in 2004.

Hundreds of mutations have now been identified in 12 LQTS-susceptibility genes. Of these 12 genes, 9 are minor contributors to the disease, collectively accounting for less than 5% of LQTS. The 3 canonical LQTS-susceptibility genes cause about 70% to 75% of LQTS:

- LQT1 (*KCNQ1*-encoded potassium channel [IKs] mutations)
- LQT2 (*KCNH2*-encoded potassium channel [IKr] mutations)
- LQT3 (*SCN5A*-encoded sodium channel mutations)

Given the potential risk of sudden cardiac death and the genetic nature of this collection of familial heart rhythm syndromes known as the cardiac channelopathies, the challenge is to incorporate and decipher the information derived from all the available clinical tools to accurately diagnose disease, predict risk, and develop a personalized treatment plan.

Currently, 40% of patients who come to Mayo Clinic's campus in Rochester with the diagnosis of LQTS leave the clinic having been reclassified as otherwise normal. Others come having been advised of an urgent need for an implantable defibrillator and leave the clinic effectively managed without a device for their low-risk substrate. Still others have received videoscopic denervation therapy as a potent antifibrillatory intervention as part of their personalized treatment program. Genetic tests are interpreted comprehensively, and the probabilistic nature of genetic testing has been brought into sharp focus here. Identification of the subset of patients with a negative genetic test has enabled the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory to discover the last 4 of the 12 LQTS-susceptibility genes.

Since its inception in 2000, Mayo Clinic's Long QT Syndrome Clinic has provided comprehensive evaluations for more than 1,000 unique patients and actively manages the care of more than 500 patients with genetically proven LQTS, making Mayo one of the most experienced centers in the world. The Long QT Syndrome Clinic and the Windland Smith Rice Sudden Death Genomics Laboratory at Mayo Clinic in Minnesota have one of the most comprehensive "bedside-to-bench" programs internationally for families affected with this condition, and it is one the premier research laboratories for this syndrome worldwide.



Timothy M. Olson, MD
Director, Cardiovascular
Genetics Research Laboratory

Hereditary Component of Atrial Fibrillation Revealed

A Mayo Clinic study published in 2003 revealed that lone atrial fibrillation (AF) is a familial disorder in at least 15% of patients with AF, highlighting the pathogenic role of hereditary factors. The Human Genome Project, completed in the same year, has provided a comprehensive roadmap to facilitate discovery of the genetic underpinnings of AF. Last year more than 2,000 patients with AF were referred to Mayo's Heart Rhythm Center in Rochester for evaluation and management of this arrhythmia. This large referral base has served as a rich resource for recruitment of familial cases of lone AF, under the auspices of an ongoing National Institutes of Health-sponsored study. The study cohort comprises more than 250 unrelated individuals with structurally normal hearts who lack traditional risk factors for AF. Their AF was diagnosed at a mean age of 44 years.

Initial investigations at Mayo and other research centers have implicated AF as a channelopathy in a subset of patients. Indeed, mutations within some of the same genes responsible for long QT syndrome and ventricular arrhythmia have been identified in patients with AF, indicating that distinct chamber-specific rhythm disorders could share similar genetic origins. In vitro modeling of mutant channels showed that the extremes of atrial action potential shortening or lengthening were arrhythmogenic substrates for AF. Further investigations have revealed a synergistic gene-environment mechanism for AF and a common risk-conferring functional polymorphism.

Recruitment and phenotypic characterization of large, multigenerational families have enabled a powerful strategy for AF gene discovery that complements a direct candidate-gene approach—linkage analysis. The ability to precisely map the genomic location of an unknown disease gene provides a unique opportunity to identify unsuspected molecular bases for AF. Two Mayo Clinic studies illustrate this point.

- Review of genealogic and medical records of a 6-generation family revealed progressive sinus node dysfunction and AF restricted to 4

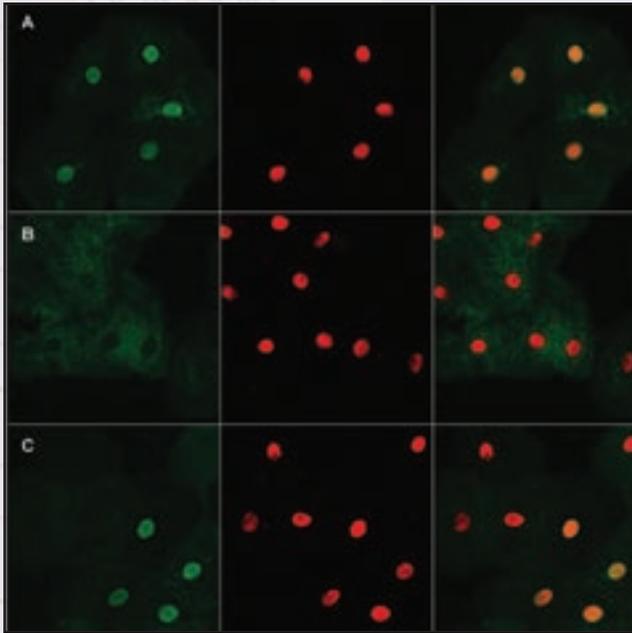


Figure. Immunocytochemistry. The EMD-Lys37del mutation impaired nuclear localization of the mutant protein. Left panels, emerlin staining (green); middle panels, chromatin staining (red); right panels, combined emerlin and chromatin staining. (A) In a normal female control, nuclear membranes of exfoliated oral epithelial cells showed robust staining with an antiemerlin antibody. (B) Buccal cell nuclei from an affected male exhibited lack of emerlin staining. (C) A female carrier heterozygous for the Lys37del mutation demonstrated staining of about 60% of nuclear membranes. Reprinted with permission from Karst ML, Herron KJ, Olson TM: X-linked nonsyndromic sinus node dysfunction and atrial fibrillation caused by emerlin mutation. *J Cardiovasc Electrophysiol* 2008; 19:510-515.

males related through maternal lineages. Suspecting a sex-linked basis for the disorder, targeted X chromosome genotyping mapped the disease locus to chromosome Xq28. This led to discovery of a single amino acid deletion in the nuclear protein emerlin, which impaired its localization to the nuclear membrane (Figure). Unlike prototypical null mutations in emerlin that underlie Emery-Dreifuss muscular dystrophy, this unique mutation caused a cardioselective phenotype without skeletal muscle involvement.

- In a different family with 11 clinically affected members, AF was inherited as an autosomal dominant trait. A genome-wide mapping study localized the culprit gene to chromosome 1p36-p35, leading to identification of a frameshift mutation in the atrial natriuretic peptide gene that segregated with AF. The mutation resulted in a circulating chimeric peptide, made up of ANP with an anomalous 12-amino acid tail, which shortened the atrial action potential in an isolated heart model. Discovery of mutant ANP thus uncovered an unexpected association between a defective hormone and susceptibility to arrhythmia.

Collectively, research studies have established lone AF as a genetically heterogeneous disorder resulting from distinct molecular defects. Lone AF remains an idiopathic condition, however, in the vast majority of patients. Under the direction of Timothy M. Olson, MD, efforts are under way to discover novel genes for AF, to gain new insights into the pathogenic mechanisms of this common arrhythmia, and ultimately to develop improved diagnostic, therapeutic, and preventive strategies.



Win-Kuang Shen, MD

Director, Electrophysiology
Research Program

Treatment of Atrial Fibrillation in the Elderly Population

Treatment of patients with symptomatic atrial fibrillation (AF) for whom antiarrhythmic drug therapy and/or pulmonary vein isolation procedures are either inappropriate or ineffective centers around relieving symptoms and controlling rate to prevent the development of tachycardia-induced left ventricular dysfunction. Rate control can often be achieved with the use of atrioventricular nodal blocking drugs such as β -blockers and calcium channel blockers. In some patients, adequate rate control cannot be achieved even with high-dose combination regimens, medications are not tolerated, or adequate rate control results in symptomatic bradycardia. Some patients are uncomfortable with the irregularity even when ventricular rates are ideal. Atrioventricular node ablation and pacemaker placement have long been treatment considerations for these individuals.

The aging of the population and the increasing prevalence of AF in the elderly population has complicated the overall approach to treatment in the elderly population. Comorbid conditions and polypharmacy in these patients often limit therapeutic options. Successful rhythm control does not obviate the risk of stroke. The cost to the health care system is considerable and growing. While national efforts are under way to reduce known risk factors for the development of AF, optimal management of this medically complex population is not yet clear. Whether there are specific, identifiable subsets that derive clear benefit from any particular strategy is also not apparent.

Win-Kuang Shen, MD, is principal investigator in the Pacing and AV Node Ablation Compared to Drug Therapy in Symptomatic Elderly Patients With Atrial Fibrillation Clinical (PACIFIC) Trial. This national clinical trial will explore approaches to treatment of AF in the elderly population. Specifically, this trial will compare atrioventricular node ablation and pacemaker implantation with pharmacologic rhythm or rate control. End points include all-cause mortality, cardiovascular hospitalization, quality of life, and overall resource utilization.

Other questions being addressed by Dr Shen's clinical research program include optimal pacing modes, specifically right ventricular apical pacing vs cardiac resynchronization therapy (CRT), in elderly patients with AF receiving device treatment. Limited data thus far suggest that CRT improves left ventricular ejection fraction and reduces all-cause mortality, but large-scale randomized studies are needed to identify patients who will benefit from more aggressive CRT.



Samuel J. Asirvatham, MD

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Radiofrequency Ablation of Complex Ventricular Arrhythmias

Complex ventricular arrhythmias are among the most difficult for electrophysiologists to manage. Ventricular tachycardia is potentially lethal and can result in frequent shocks in patients with defibrillators. Antiarrhythmic drugs are frequently incompletely effective and have potentially serious adverse effects. Radiofrequency ablation (RFA) of ventricular arrhythmias is typically complex with suboptimal efficacy. Fortunately, new techniques have made RFA an increasingly attractive treatment option for patients with symptomatic or refractory ventricular arrhythmias.

One important difficulty is the development of unstable hypotension when ventricular tachycardia is induced for mapping purposes, limiting the ability to accurately pinpoint the arrhythmogenic zones of slow conduction. Mayo Clinic is among the first institutions in the United States to use a microcirculatory axial blood flow pump in patients with hemodynamically unstable ventricular tachycardia (Figure 1). This pump is a miniaturized percutaneous cardiac assist device, providing circulatory support during sustained ventricular arrhythmias. This support permits prolonged mapping of the arrhythmia and increases the chances of a successful ablation.

The pump is placed via the femoral artery, across the aortic valve into the left ventricle with use of fluoroscopic and intracardiac ultrasound echocardiographic (ICE) guidance (Figure 2). ICE is particularly helpful in monitoring function of the aortic valve and position of the pump within the left ventricle. Forward flow in the systemic circulation is approximately 2.5 L/min. Although this is markedly less than normal cardiac output and vasopressors have been administered for additional hemodynamic support, patients have shown no signs of organ hypoperfusion despite lengthy procedures.

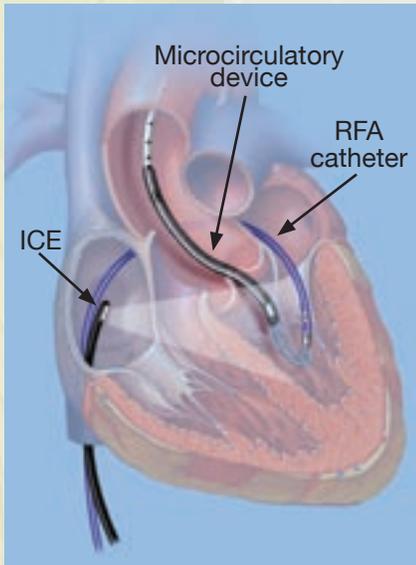


Figure 1. Placement of microcirculatory pump and intracardiac ultrasound.

Potential complications that may occur with use of this device include vascular damage, increased ectopy (including nonclinical ventricular arrhythmias), difficult catheter manipulation, aortic valve dysfunction, and thromboembolic events. This early experience has included younger patients without serious comorbid conditions such as renal dysfunction. Other factors may contribute to the success or failure of ablation attempts in these patients. This early experience at Mayo Clinic is encouraging, although wider application and long-term follow-up will be required to determine appropriate indications for this approach.

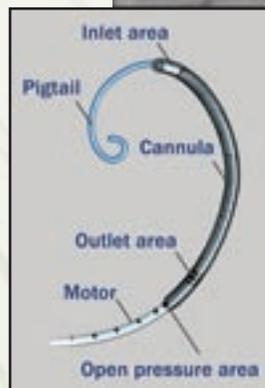
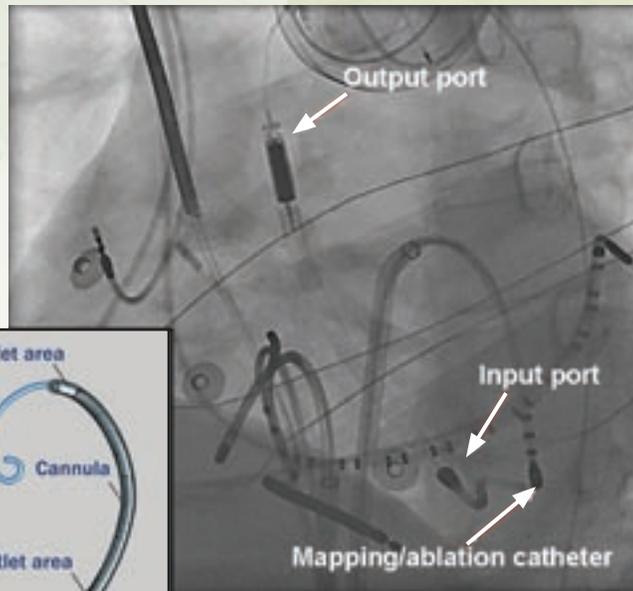


Figure 2. Fluoroscopic image obtained during complex ventricular RFA procedure. Arrows indicate input and output ports on the microcirculatory assist device.

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Heart Rhythm Services Team

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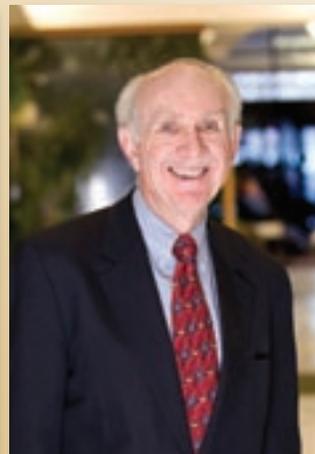
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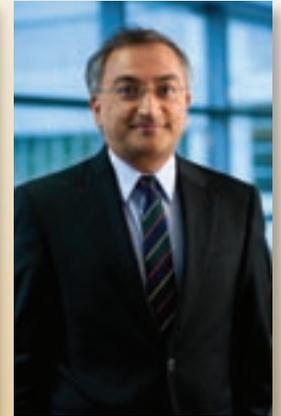
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