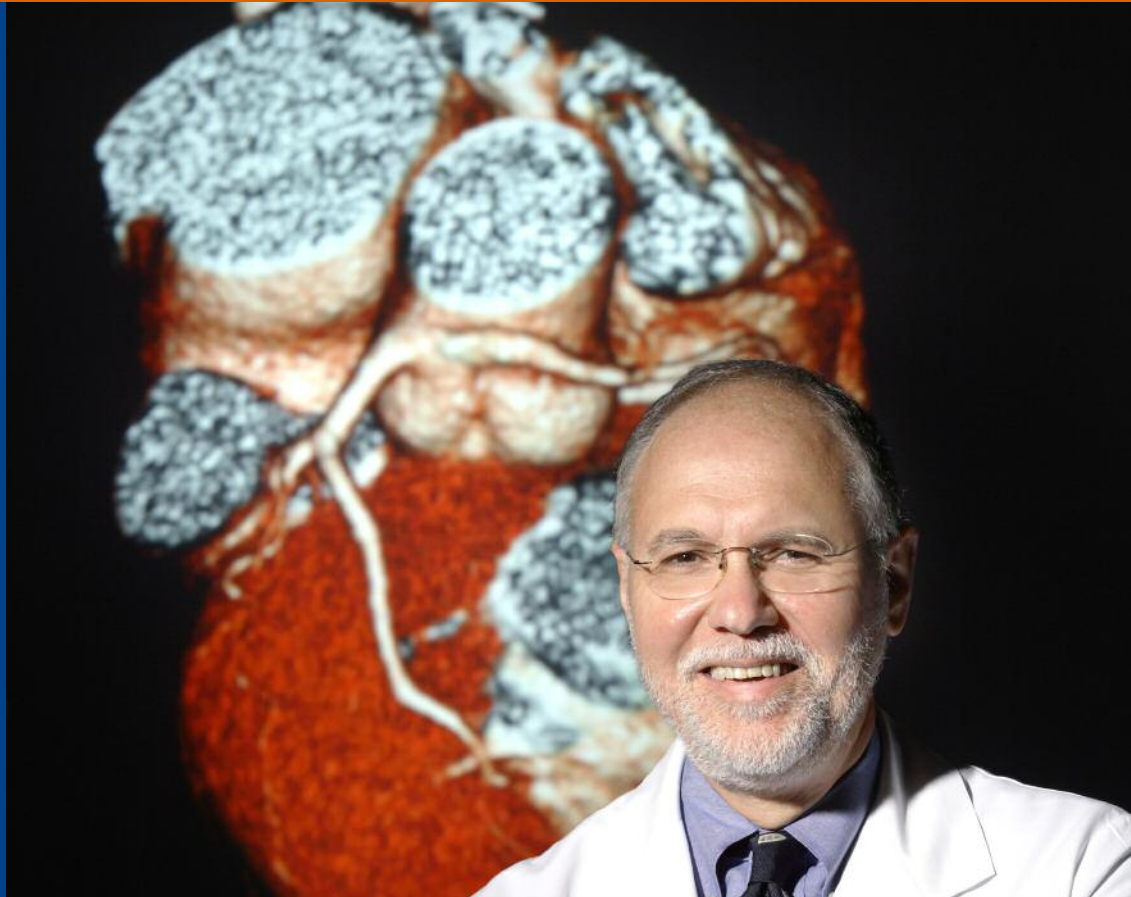


## To Make the Haystack Smaller

Using powerful biological, genetic and epidemiologic tools, Hopkins cardiologists hunt the origins of fatal arrhythmias.



“If we can understand why specific patients have arrhythmias,” says Cardiology Chief Eduardo Marbán, “we can target those patients while sparing others.”

**THE CASE:** Despite the myocardial infarction he'd had the previous year, the 45-year-old man who arrived in August 2005 for an evaluation with cardiology chief **Eduardo Marbán** reported that he was feeling fine. During his examination of the patient, however, Marbán found significant pulmonary congestion. He ordered an echocardiogram, which showed left ventricular dysfunction with an ejection fraction of 25 percent.

Marbán immediately started the patient on an ACE inhibitor and diuretic. But after three months of treatment, the ejection fraction increased to only 30 percent.

**TREATMENT DECISION:** It is well accepted that post-MI patients with impaired left ventricular function are at markedly increased risk for ventricular arrhythmias and sudden cardiac death. Given the patient's past history of MI and his persistent low ejection fraction despite aggressive medical management, Marbán recommended placement of an implantable cardioverter defibrillator.

Three months after receiving the ICD, the patient reported being awakened during the night by a shock. When Marbán interrogated the device the next day, he learned that the patient had been shocked during an episode of ventricular tachycardia that probably would have been fatal.

**DISCUSSION:** Although the implanted defibrillator indeed proved to be life-saving in our patient's case, available data suggest that only a third of patients who get an ICD ever receive an antiarrhythmic shock. In one study of patients with impaired left ventricular function after an MI who were randomly assigned to receive either routine clinical care or an implantable defibrillator, the mortality rate was lower with an ICD, but the difference between the treatments was less than 5 percent.

There's little question that ICDs save lives. Yet what cannot be reliably predicted—even among patients with diagnosed atherosclerosis, much less in the general population—is which people are truly at high risk

for sudden cardiac death and are therefore likely to benefit most from intensive interventions. Severely reduced left ventricular ejection fraction—35 percent or less—is a predictor of SCD, but it lacks both sensitivity and specificity. Widespread prophylactic deployment of implantable defibrillators in large populations of at-risk patients is impractical and subjects a sizeable percentage of people who may never develop a life-threatening arrhythmia to an invasive procedure that's not without complications.

**THE HOPKINS APPROACH:** At the Johns Hopkins Donald W. Reynolds Cardiovascular Clinical Research Center, dozens of investigators whose expertise spans cardiology, genetic medicine, radiology, epidemiology, biomedical engineering, electrophysiology and biological chemistry are collaborating with each other and investigators at other institutions to discover novel genetic and structural risk factors for sudden cardiac death. They are

*Continued on next page*

# Consultation: Ronald Berger

Director of the Cardiac Electrophysiology Training Program, Johns Hopkins Heart Institute

## Can you provide a profile of the kind of patient who should be referred for ICD implantation?

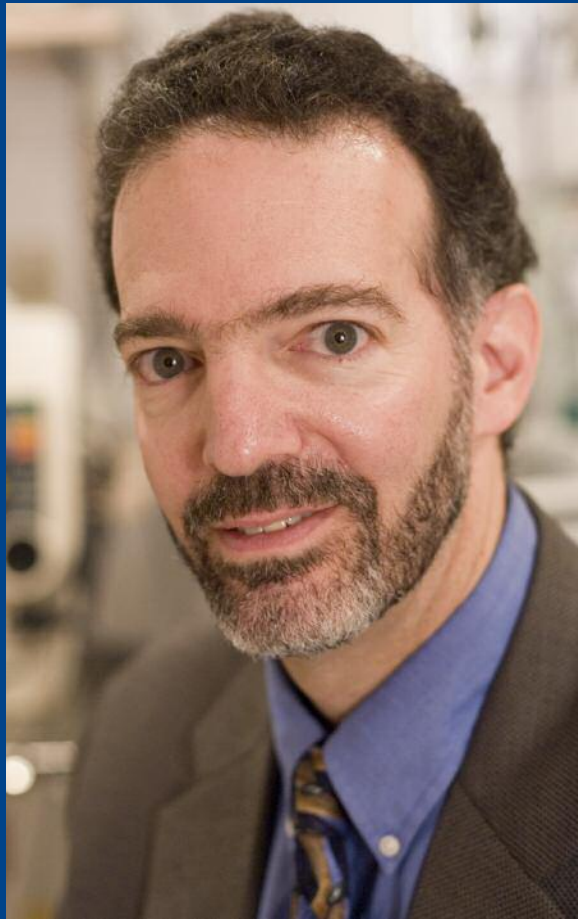
Patients with heart disease who experience a life-threatening arrhythmia are candidates for an ICD. The devices also have been shown to improve survival in “primary prevention” patients (those not yet having experienced VT or VF) who have either ischemic or nonischemic cardiomyopathy, with LVEF less than 35 percent and NYHA class II or III heart failure.

## And who should get a cardiac resynchronization (CRT) device?

CRTs have been shown to improve heart failure symptoms and survival in patients with a dilated heart of either ischemic or nonischemic etiology who have LVEF less than 35 percent, LV dyssynchrony, and NYHA class III or IV heart failure. Dyssynchrony has been traditionally defined as QRS width greater than 130 ms, but recent studies support the use of echocardiography as a better means to establish the presence of intraventricular mechanical dyssynchrony.

## If a patient already has a standard ICD or pacemaker but has ventricular dyssynchrony, can the device be upgraded to a CRT system?

Yes, this is a common scenario. In fact, chronic RV pacing by an existing device is often the very cause of dyssynchronous LV contraction and heart failure symptoms. By upgrading to a CRT device and lead system, we can often provide substantial



improvement in the patient’s heart failure symptoms.

## How worried should we be about the recent series of ICD recalls?

The recent recalls and associated press coverage have brought to light the fact that ICDs (and pacemakers) all have the potential for random component failures. Current ICDs have an expected failure rate of roughly one in 200, so we shouldn’t be surprised by an occasional cluster of similar failures that leads to a recall. However, the term *recall* does not mean that elective replacement of these devices is mandatory or even recommended. In each case, the small risk of device failure has to be weighed against the small, but non-zero, risk associated with device replacement.

## Can patients with a pacemaker or ICD get an MRI scan if needed to evaluate a clinical problem?

Current labels for pacemakers and ICDs state that MRI scans are contraindicated due to concern that the electromagnetic fields of MR scanners can cause device malfunction. Nonetheless, recent clinical investigation at Hopkins has shown that

many patients with modern pacemakers and ICDs can undergo MR scanning safely and without damage to their devices, as long as appropriate precautions are taken. Device patients needing MR scans can be referred to our electrophysiology service for imaging under an IRB-approved research protocol. ■

## Smaller Haystack

*Continued from previous page*

enrolling patients who meet the current criteria for a prophylactic ICD but have not had a sudden cardiac death episode. By comparing patients who subsequently receive a shock from the device to treat a lethal arrhythmia to those who are never shocked, they’re aiming to pinpoint functional and metabolic features that explain why some in this high-risk population experience SCD and others don’t.

Marbán, who directs the Reynolds Center, points to existing evidence that SCD includes a still poorly understood heritable component. In one study, having one parent who died of cardiac arrest increased the child’s risk for SCD by 70 percent to 80 percent. In another study, the risk was increased 900 percent if both parents died of SCD.

Building on these observations, researchers

here are working with Hopkins’ Institute for Genetic Medicine to look at hundreds of thousands of genetic markers in the population to find those associated with SCD. But instead of relying on the time-consuming and haphazard gene-mapping approach, they’re using the whole-genome association method, which taps chip-based technology to rapidly detect subtle genetic deviations. They’ve already found one candidate gene, called *CAPON*, whose common variant explains normal variations in the QT interval and shows that there are heritable differences in cardiac electrical activity (see Research Notes, page 3).

On another front, Reynolds Center investigators are conducting detailed studies of overall cardiac function using magnetic resonance imaging to focus on zones of scarring which often are the sites where arrhythmias originate. In one study, believed to be the first to examine cardiac architecture in patients

with nonischemic cardiomyopathy, subjects whose myocardium contained more than 25 percent scar tissue were approximately nine times more likely to have ventricular arrhythmia than those with less or no scarring.

**OUTCOMES:** Seeking to prevent SCD in the general population, especially among patients whose first manifestation of heart disease is a fatal arrhythmia, amounts to looking for a needle in a haystack. But by making the haystack smaller—by providing state-of-the-art care for known high-risk patients while simultaneously enrolling them in prospective studies—Reynolds Center researchers expect that potent new biological tools, phenotyping methods and population science resources will make it possible to devise new, effective ways to identify and treat SCD patients, including those not suspected of having heart disease. ■

## Closing Gaps in Resuscitation Science



CPR team director **Henry Halperin**

When Hopkins engineering dean William Kouwenhoven and neurologist Orthello Langworthy showed in 1933 that an electric shock could restore normal sinus rhythm and contraction to a fibrillating heart, they launched one of the 20th century's greatest achievements: cardiopulmonary resuscitation. By the 1950s, Kouwenhoven and an eclectic mix of engineering and medical colleagues had developed the first closed-chest defibrillator, discovering along the way that chest compression, by restoring blood flow, is critical to cardiac-arrest survival. Treating victims of halothane-induced ventricular fibrillation, Kouwenhoven's team achieved a

survival rate of 70 percent in a series of 20 patients. Their study\* is still cited as the seminal article in the development of modern CPR.

Today, advanced cardiovascular life support combines fundamentals like chest compression with more complex elements, such as pressor and antiarrhythmic drugs. Yet even under good circumstances, says electrophysiologist **Henry Halperin**, the current survival rate is less than 20 percent: "There's a lot about the mechanics of cardiac arrest that we still don't understand."

Halperin, the 2000–2002 chairman of the American Heart Association's ACLS committee, points out, for example, that ventricular fibrillation (VF) is a less common cause of cardiac arrest than pulseless electrical activity (PEA)—a situation in which defibrillation is useless. "So at Hopkins, we're looking at the basic scientific differences between VF and PEA," he says, "and we've made a lot of progress. We're also building on the known benefits of hypothermia by developing new ways to lower body temperature during cardiac arrest treatment.

"CPR and ACLS do save lives," he adds. "But of the 200,000 potentially salvageable people each year, only about 20,000 survive. That's what keeps me motivated."

\* Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed-chest cardiac massage. *JAMA*. 1960;173:1064-1067.

### RHYTHM IN THE GENES

In the search for sudden cardiac death's genetic underpinnings, rare mutations in ion channel genes have surfaced that are associated with long- and short-QT syndromes. Trouble is, most people at risk for SCD don't have these mutations. So where else in the human genome's 3 billion nucleotides could trouble be lurking? Instead of focusing on genes already known or suspected to influence cardiac rhythm, Hopkins-led researchers have applied a new technique, genome-wide association, to unearth subtle variations that could contribute to lethal arrhythmia. "This approach," says senior author **Aravinda Chakravarti**, who heads Hopkins' McKusick-Nathans Institute of Genetic Medicine, "allows us to find targets that we never would have imagined."

Their work has turned up a common variant in the nitric oxide signaling 1AP gene that correlates with QT interval. Also called CAPON, the gene regulates nitric oxide signaling but had never been suspected of having a role in cardiac repolarization. "Our finding," says Chakravarti, "opens a completely new area of cardiac biology."

### MOOD AND MORTALITY

Until a few years ago, cardiologist **David Bush** was more than a little skeptical about a purported relationship between depression and heart disease. "I thought, how could feeling depressed possibly increase mortality fivefold? Then we did our own prospective study in patients with acute myocardial infarction," says the director of the cardiac catheterization lab at Johns Hopkins Bayview Medical Center. "And we found that when depressive symptoms are present, four-month mortality is significantly higher."

In subsequent studies looking for relevant markers such as ejection fraction, Bush and colleagues noted that although the mechanism of death isn't clear, depression still emerges as an independent risk factor for increased mortality. Furthermore, he says, the deaths tend to be sudden, supporting the hypothesis that arrhythmia is involved.

Last year, the Agency for Healthcare Research and Quality issued a report on post-MI depression, which Bush and others at Hopkins' Evidence-Based Practice Center prepared by reviewing the relevant literature. Intrigued by evidence pointing to a variety of biological pathways as possible etiologies, they're now testing the possibility that the neurotransmitter serotonin increases platelet stickiness.



**David Bush**

### Bench to Bedside

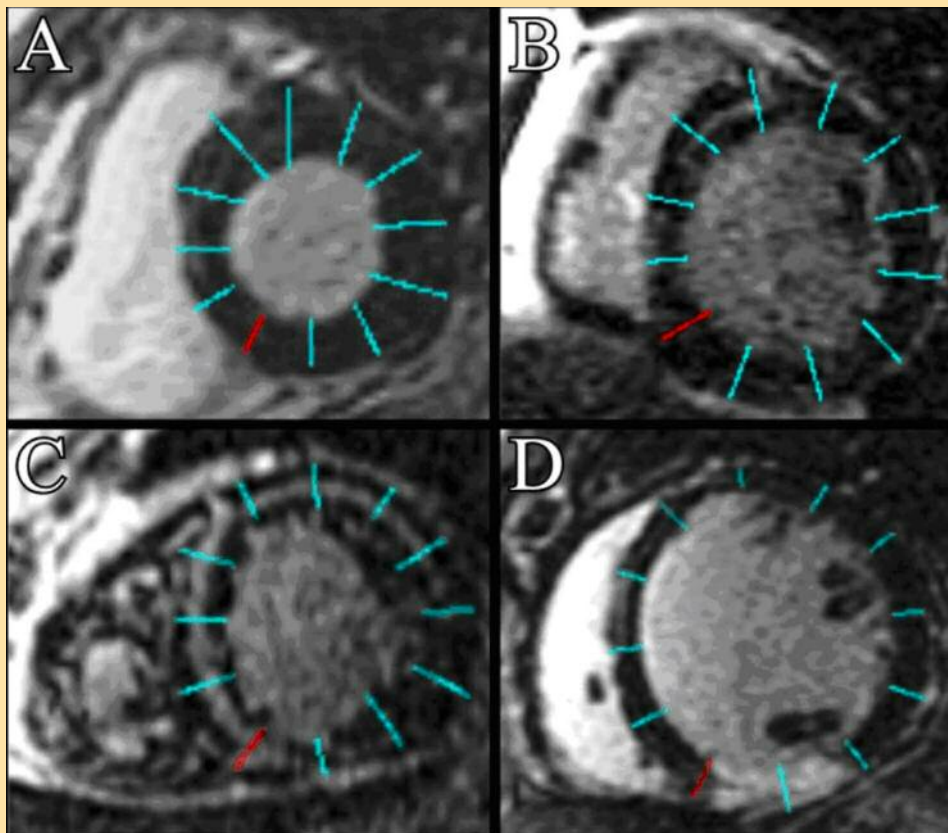
## Cardiac MRI—Window on the Risk for Sudden Cardiac Death

Left-ventricular systolic dysfunction after myocardial infarction increases the risk for arrhythmia-related sudden cardiac death because patchy fibrosis at the borders of the healing infarct creates regions of electrical conduction block. This slows conduction through the myocardium and helps to initiate and perpetuate reentry-type tachyarrhythmias induced by the appropriate triggers. The question, says cardiologist **Katherine Wu**, is how the size, geometry and transmural of the infarct and its borders influence SCD risk.

For answers, Wu and colleagues are using magnetic resonance imaging to phenotypically characterize patients

with prior MI and LV dysfunction who've been referred here for prophylactic insertion of an automatic implantable cardioverter defibrillator. MRI, she says, can accurately measure ejection fraction, LV volumes and infarct size. Furthermore, because it's non-invasive, MRI can also safely generate serial images for following the course of LV remodeling.

By looking at LVEF, LV volumes and mass, total infarct size, and a novel measure of tissue heterogeneity in the infarct periphery, Wu's team is prospectively relating these variables to appropriate ICD firings and clinical outcomes. ■



Mid-ventricular short axis MR images from patients with reduced ventricular function but without coronary artery disease (nonischemic cardiomyopathy). The four panels represent different transmural extents of scar (as percent of wall thickness). The characteristics of the scar in terms of both transmural extent and the number of sections showing scar influence the probability of inducible arrhythmia and by inference, sudden cardiac death.

**A: No scar**  
**B: 1% to 25%**  
**C: 26% to 75%**  
**D: 76% to 100%**

### Contact Information

#### Cardiology Access Line (CAL)

For physicians or their agents to refer an outpatient to cardiology  
410-502-0550 or [CAL@JHMI.EDU](mailto:CAL@JHMI.EDU)

#### Hopkins Access Line (HAL)

24/7 connection between a referring physician and Johns Hopkins full-time faculty in any subspecialty  
410-955-9444 or 800-765-5447

#### Cardiac Surgery

410-955-2800

#### CME courses

For details on cardiovascular CME courses, go to [www.hopkinscme.org](http://www.hopkinscme.org) or call 410-955-3169

## Mark Your Calendar

### Cardiovascular Topics at Johns Hopkins

February 22–24, 2007

[www.hopkinscardiologycourse.com](http://www.hopkinscardiologycourse.com)

# Cardiovascular REPORT

The quarterly Johns Hopkins Heart Institute *Cardiovascular Report* is one of many ways the Institute seeks to recognize and enhance its partnership with its thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome. © The Johns Hopkins University, 2006

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