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Preventing Sudden Cardiac Death in Patients with Ischemic Heart Disease

Evidence warrants implantation of defibrillators in those with depressed left ventricular ejection fraction.

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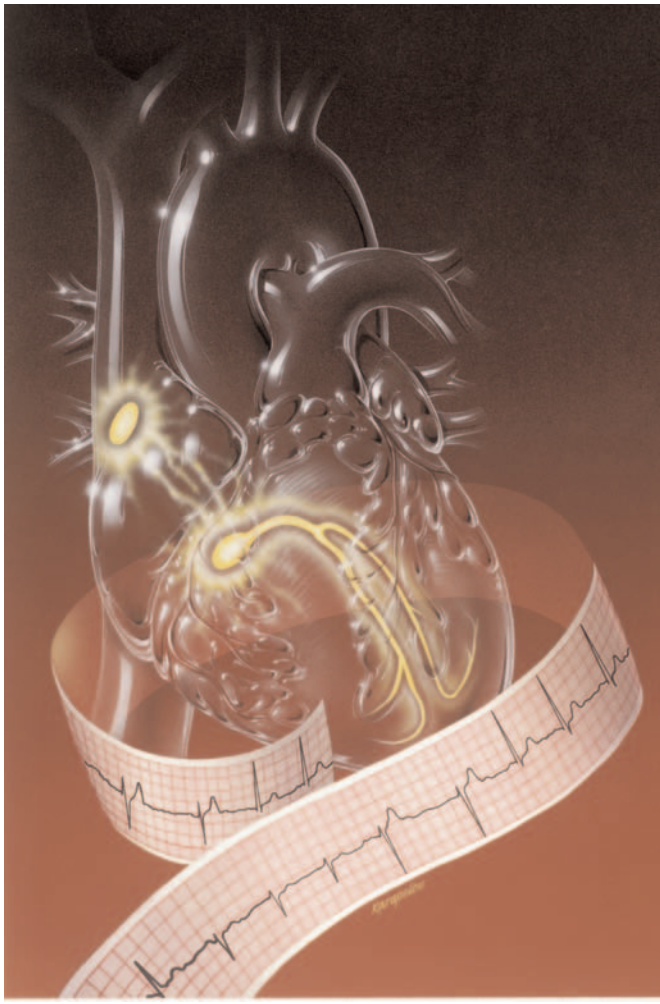
Patients with ischemic heart disease are plagued by a high risk of sudden cardiac death due to ventricular arrhythmias. Over 340,000 people die from sudden cardiac death (SCD) each year in the U.S., with ventricular tachyarrhythmias the culprit in at least 75-80% of these cases. Studies reveal that the most common mechanism is ventricular tachycardia caused by scarring from previous myocardial infarction. Given that approximately 14 million people in the U.S. have ischemic heart disease today, the ability to prevent SCD in this population would hold significant potential.

Yet until recently, physicians were largely unable to predict which patients with ischemic heart disease were at highest risk for SCD, as evidenced by a dismal survival rate (less than 30%). Despite great interest in anti-arrhythmic therapy to prevent ventricular arrhythmias in these patients, several trials have had disappointing results. The efficacy of preventing SCD with ICD implantation for secondary prevention was demonstrated in the AVID trial, but researchers still faced the challenge of identifying which patients should be targeted for primary prevention.

Studies including the Multicenter Automatic Defibrillator Implantation Trial (MADIT) I and the Multicenter Unsustained Tachycardia Trial (MUSTT) demonstrated the benefits of ICD implantation in patients with reduced left ventricular ejection fraction (LVEF) and sustained ventricular tachycardia (VT) at electrophysiology (EP) testing. The MADIT II and SCD-HeFT trials then demonstrated that just a reduced LVEF could be used to risk stratify the patients who would benefit from ICD implantation.



"Reduced LVEF is now considered the single best predictor of who is most likely to suffer SCD," says Bindi K. Shah, MD. Armed with this knowledge, physicians are now able to proactively address the risk of SCD in ischemic patients for the first time.

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Managing the acute MI patient

Innovative protocols reduce "door-to-balloon" time at NewYork-Presbyterian Hospital.

Approximately 1.5 million people suffer myocardial infarction (MI) every year in the U.S. Among those suffering acute MI, about one third die – half of these before reaching the hospital.

"Physicians face two main challenges in treating ST elevation MI (STEMI)," according to Dr. Robert Campagna, MD. "We must determine the correct treatment plan of medications or procedures, and we must administer this treatment in a very timely manner. Most places know how to treat acute MI properly, but many places may not be able to do it quickly enough."

The mainstays of treatment include either primary angioplasty in the cardiac catheterization laboratory or thrombolytic therapy. Angioplasty is generally considered the treatment of choice, so patients will typically undergo the procedure if the hospital is equipped.

For the past eight years, patients arriving at NewYork-Presbyterian Hospital/Weill Cornell Medical Center have always received expedited angioplasty, 24 hours a day, seven days a week. A new protocol is now in place to ensure that for patients coming in through the ER, "door-to-balloon" time is even faster. A "virtual" chest pain unit follows newly-established protocols for patients arriving at the ER with chest pain and chest pain equivalents. Patients get an EKG within five minutes, and it is read by a physician within five minutes. If there is evidence of MI, a five to six member MI team is paged and the patient is brought to the catheterization lab for immediate angioplasty.

"Although most centers have clinical pathways to address incoming patients with MI, dedicated chest pain units with allocated physical space have not worked for most centers because of their inflexibility with staffing and resources," says Dr. Campagna. The new virtual unit at NewYork-Presbyterian/Weill Cornell, consisting of protocols without dedicated space, provides for more flexible use of resources to adjust for variations in patient flow.

For those patients arriving by ambulance, a pilot project is aimed at further reducing door-to-balloon time. NewYork-Presbyterian Hospital's EMS personnel are now trained to do 12-lead EKGs on patients suspected of acute coronary syndromes. In a new system of pre-hospital notification, the EMS crew sends EKG results via digital cell phone to the ER for immediate interpretation while the patient is en route, so that the catheterization laboratory can be ready the moment the patient arrives. NewYork-Presbyterian Hospital is the first in the New York area to implement this type of system.

If a hospital is not equipped for angioplasty, patients are likely to receive thrombolytic therapy or be transferred to a hospital that has a catheterization laboratory, according to Dr. Campagna. The choice of therapy should depend on how quickly the transferring hospital can get the patient to the catheterization laboratory. "Angioplasty should be performed within 90 minutes from the time of presentation, but many places do not have procedures in place to achieve this," says Dr. Campagna.

While speed in administering coronary intervention is clearly paramount, proper medical followup is also critical to patients' long-term health. A standard regimen after STEMI may include aspirin, beta-blockers, ACE inhibitors, statins, clopidogrel, and counseling for smoking cessation. Yet research has demonstrated that in many hospitals, a surprisingly low percentage of patients receive appropriate medical therapy upon discharge. To address this issue, the protocols and procedures of the virtual chest pain unit encompass post-hospital care as well. ■

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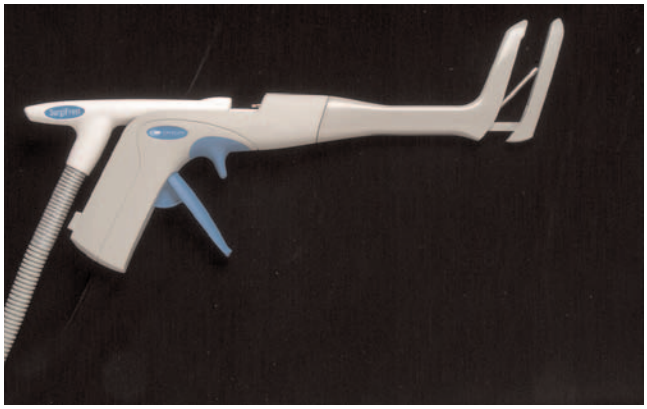
Cryoablation's Next Step

Versatile cryoablation technology broadens the spectrum of patients who can undergo ablation for atrial fibrillation.

The benefits of using cryoablation to treat atrial fibrillation (AF) have been clearly demonstrated during the last several years. Increasing numbers of surgeons have used cryoablation to create endocardial lesions during concomitant cardiac procedures, and have appreciated its unique advantages of efficacy and safety. Now, a two-in-one device featuring a detachable clamp and the well-established SurgiFrost® probe, offers further benefits yet.

Adding versatility to earlier cryoablation probes, the new FrostByte™ includes a clamp that secures and freezes the pulmonary veins epicardially. The clamp improves adhesion of the probe and precision during ablation. In cases where a clamp cannot be used, surgeons may easily remove the flexible probe and use it alone to create linear lesions such as across the mitral annulus, and connecting lesions to the right and left pulmonary veins.

According to Charles A. Mack, MD, who developed the new device in conjunction with CryoCath Technologies Inc., FrostByte™ can be used to create epicardial as well as



endocardial lesions, in either open or closed approaches. Until now, cryoablation procedures have predominantly been done endocardially in an open heart, during mitral valve repair or other procedures. This increased versatility will particularly benefit patients with AF who are undergoing closed cardiac procedures, such as coronary artery bypass grafting, aortic valve replacement, and others. Lesions such as the mitral annulus and coronary sinus can now be performed epicardially with the same two-in-one device. Lesions connecting the right inferior pulmonary vein to the left inferior pulmonary vein can also be done epicardially without opening the heart. "This is truly a step forward," says Dr. Mack. He expects that with further use, surgeons will also find FrostByte™ useful during a minimally invasive approach.

Research has consistently demonstrated the safety and efficacy of cryoablation for AF. Unlike hyperthermic ablation methods such as microwave, radiofrequency, and laser, cryoablation leaves the cardiac tissue architecture intact. In addition, cryoablation poses no risk of injury to adjacent structures. In the largest study of cryoablation in the surgical treatment of AF during concomitant cardiac procedures, Dr. Mack's team demonstrated an 88.5% freedom from AF at 12 months (Circulation, September 2005). This compares quite favorably to other studies. Results of an animal study led by Dr. Mack have shown the efficacy of epicardial lesions using this two-in-one device, and will be published in the *Journal of Thoracic and Cardiovascular Surgery.* ■

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Deciphering PPCM

Although heart failure associated with pregnancy is typically labeled peripartum cardiomyopathy (PPCM), its causes, severity, and duration may vary dramatically.

A rare but potentially devastating condition, peripartum cardiomyopathy (PPCM) is defined as the onset of heart failure associated with pregnancy. It strikes previously healthy women during the last trimester of pregnancy or first three months postpartum. Outcomes of this condition vary dramatically, with some women declining rapidly within months, others successfully treated and stabilized with heart failure therapy, and still others experiencing abrupt improvement after delivery. "Pregnant women with heart failure are often labeled as having PPCM for lack of any other name," says Evelyn M. Horn, MD, "yet not all instances of left ventricular (LV) dysfunction are PPCM."

What we know about PPCM

We know that PPCM is a form of dilated cardiomyopathy. Having had no demonstrable heart disease prior to pregnancy, women with PPCM suddenly experience heart failure during the months immediately before or after delivery.

Risk factors include multiparity, multiple gestations, hypertension, advanced maternal age, and African American race. Because symptoms such as dyspnea, fatigue, and edema may mimic those associated with normal late pregnancy, PPCM may progress undetected, and diagnosis by echocardiography of left ventricular systolic dysfunction is imperative. Treatment consists of standard therapies for heart failure with the exclusion of drugs contraindicated during pregnancy (ACE inhibitors, Angiotensin receptor blockers, and aldosterone inhibitors) and breastfeeding as necessary.

According to Dr. Horn, "About one third of patients improve fairly quickly and ultimately have resolution, one third stabilize on medical therapy, and the remaining third may require either immediate or subsequent support with a left ventricular assist device (LVAD) or possible cardiac transplantation. For those women who have persistent LV enlargement, ongoing aggressive therapy with best heart failure treatment needs to be pursued, and an early referral to a heart failure center with expertise in advanced heart failure is recommended."

Among those whose LV size returns to normal, there is wide variation in response time, with some women improving within six weeks and others improving more gradually over the course of a year. For some, exercise intolerance may persist despite normalization of ventricular function, and some data show that once a patient has had PPCM, she remains at risk for recurrent myocardial dysfunction with subsequent pregnancies. "Heart failure therapy should likely be continued in this population for a period of time beyond early improvement of left ventricular function," says Dr. Horn.

What we don't know

Researchers have yet to uncover why, fundamentally, PPCM occurs. "Anyone short of breath will have an evaluation by echocardiogram," according to Dr. Horn. "If the test shows that heart function is diminished, the condition will likely be called PPCM. Yet a range of disparate factors may be at play."

Theories of underlying etiologies are complicated. Acute left ventricular dysfunction may be caused by pregnancy-related issues such as hypertension, preeclampsia and eclampsia, conditions associated with systemic vascular dysfunction in which the heart may be an innocent bystander. Because fertility drugs are associated with multiple gestations, there may also be an increased incidence of preeclampsia in patients who use them. In other women, the hemodynamic stress of pregnancy may unmask previously undetected forms of ventricular dysfunction — conditions such as cardiomy-

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opathy, hypertensive heart disease, valvular heart disease, or coronary disease.

"Histologically, PPCM may look like acute myocarditis with a lymphocytic infiltrate reflecting an immunological mechanism," explains Dr. Horn. "This may reflect maternal autoantibodies against cardiac-specific tissue proteins that are stimulated by the response to the fetal antigen." However, lymphocytic infiltrates could also indicate the presence of viral myocarditis. Release of the inflammatory cytokines, which are implicated in acute myocarditis, idiopathic dilated cardiomyopathy, and likely PPCM, may be associated with acute left ventricular dysfunction.

"For most women, pregnancy is an interesting immune-tolerant state, one in which fetal foreign antigens are not rejected," says Dr. Horn. "But women who have chronic non-cardiac diseases with an immunological basis (such as systemic lupus erythematosis or inflammatory bowel disease) have a varied response during pregnancy, with some improving and others experiencing an exacerbation of these diseases. In general, the immunological response is not predictable, and the specific immunological trigger that may lead to acute peripartum cardiomyopathy is not yet defined. Pregnancy is also a hypercoagulable state, and it could be that a hypercoagulable condition, such as the presence of a lupus anticoagulant, may have brought on the cardiac disease." Patients found to have a truly hypercoagulable condition may require long-term anticoagulation.

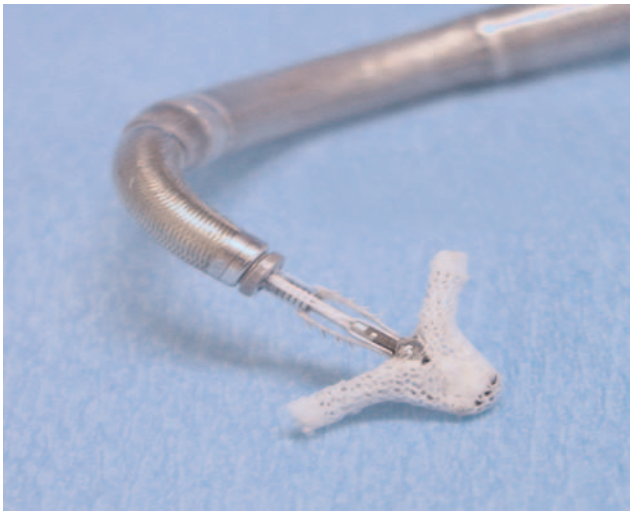
Dr. Horn differentiates patients in whom the hemodynamic changes of pregnancy exacerbate some subtle pre-existing LV dysfunction—such as in the obese diabetic patient with hypertension and shortness of breath—from another set of patients who may have acute pregnancy-related conditions such as hypertension, preeclampsia or eclampsia, and who typically experience abrupt improvement after delivery. Women with rapidly reversible LV dysfunction from these latter conditions may not have the same risk in future pregnancies, assuming that the pregnancy-related issues such as preeclampsia do not recur. The presence of underlying disease or the presence of preeclampsia or eclampsia excludes these women from a true diagnosis of PPCM.

The risk associated with future pregnancies for women who truly have had PPCM remains debatable, according to Dr. Horn. "Some physicians find such patients remain at higher risk, while others are safely managing the NYHA Class I and II patients at high-risk perinatal centers that coordinate obstetrical, cardiology and obstetrical anesthesiology support."

While there have been many advances in the management of advanced heart failure and the sickest women are treated accordingly, better understanding of the nature of this disease may further elucidate the interaction between immunology and heart disease – understanding that could have implications far beyond PPCM. ■

Evalve update

EVEREST II, the first multi-center, randomized trial of a novel percutaneous valve repair therapy, is now enrolling patients at NewYork-Presbyterian Hospital/Columbia University Medical Center.



Since 2004, physician innovators at NewYork-Presbyterian Hospital/Columbia University Medical Center have been participating in the investigation of a nonsurgical technique for repairing the mitral valve. Under Principal Investigator Hal S. Wasserman, MD, the hospital was one of only seven initial sites to participate in the FDA approved EVEREST I (**E**ndovascular **V**alve **E**dge-To-Edge **RE**pair **ST**udy) clinical research study, the first U.S. clinical study of the Evalve® MitraClip™ Repair System. This system consists of several catheters and a small clip that is advanced percutaneously through the femoral vein, across the inter-atrial septum, and positioned on the mitral valve leaflets to reduce mitral regurgitation (MR). The procedure may be appropriate for selected patients with regurgitation caused by myxomatous degeneration of the valve that typically occurs in the central part (A2-P2) of the leaflets and for MR caused by ischemic heart disease.

One year follow-up of the first 27 patients enrolled in EVEREST I was presented in November 2005 at the American Heart Association meeting. Of those who received a clip, 75% remained free from surgery at one year. There were no deaths as a result of the procedure, and only a 4% major adverse event rate at 30 days. Over 90% of patients who experienced significant reduction in mitral regurgitation at one month maintained this improvement at one year.

Based on these promising results, the phase two study, EVEREST II, has been initiated and will randomize patients 1:2 between standard surgery (mitral valve repair or replacement) and the Evalve Percutaneous Mitral Repair procedure. Approximately 300 patients will be enrolled at over 30 North American centers.

"This is a pivotal trial, and we are optimistic regarding the outcomes based on our experience in EVEREST I," says William A. Gray, MD. "If successful, this will give patients access to the first non-surgical therapy for mitral valve repair." Dr. Gray, who served as Principal Investigator of EVEREST I at Swedish Medical Center in Seattle, WA, is now Principal Investigator of EVEREST II at NewYork-Presbyterian/Columbia.

NewYork-Presbyterian Hospital is now recruiting and screening patients. Other investigators of EVEREST II include Allan Schwartz, MD, Martin B. Leon, MD, Jeffrey W. Moses, MD, Michael Argenziano, MD, Nick Homma, MD and Marco DiTulio, MD. ■

KEY ELIGIBILITY CRITERIA:

- Moderately severe or severe mitral regurgitation (Grade 3 or 4)
  - With symptoms
  - Without symptoms but presence of left ventricular dilation or dysfunction
- Eligibility for surgical replacement of mitral valve, including cardiopulmonary bypass

KEY EXCLUSION CRITERIA:

- Ejection fraction £ 25%
- A history of endocarditis or rheumatic heart disease
- Significant renal insufficiency
- Need for other cardiac surgery

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Based on the strength of this evidence and consistent clinical experience, the electrophysiology laboratory at NewYork-Presbyterian Hospital/Weill Cornell Medical Center now implants ICDs in high-risk patients as a routine measure. "We no longer need to perform electrophysiology studies in all these patients," says Dr. Shah. "We are implanting defibrillators in more patients, and doing it empirically based on EF and clinical history because we believe this will prolong people's lives." Current criteria for implantation include cardiomyopathy of any cause and an LVEF £ 35%.

Patients who receive defibrillators are followed closely by Dr. Shah and colleagues in the electrophysiology clinic at NewYork-Presbyterian/Weill Cornell. Those with heart failure may receive a biventricular device to both reduce symptoms and prevent SCD.

Patients who continue to experience ventricular arrhythmias and receive recurrent shocks after implantation with an ICD are initially managed with drug therapy, says Dr. Shah. Nevertheless, a small percentage of patients remains refractory to medication and continues to receive recurrent shocks. "NewYork-Presbyterian/Weill Cornell is well prepared to treat patients who continue to have a large burden of ventricular tachycardia," according to Dr. Shah. Physicians at the EP laboratory perform complex ablations both endocardially and, when necessary, epicardially. "In the era of defibrillators, more patients are living longer with ventricular tachycardias and may need further treatment," Dr. Shah explains.

Although these life-saving devices can terminate the tachycardia before it causes lasting harm to the patient, some patients are burdened by frequent shocks and syncope. This can cause significant morbidity and should be addressed with radiofrequency ablation. "We use three-dimensional mapping systems to locate the electrical circuit and the area of scar in the patient's ventricle, and can then eliminate the ventricular tachycardia," says Dr. Shah.

"Despite great advancement in the prevention in SCD," states Dr. Shah, "we have a long way to go with risk stratification to identify all patients at risk." Ongoing research at NewYork-Presbyterian/Weill Cornell includes T wave alternans and other methods of further risk stratification. ■

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REVIVAL:

Percutaneous Endovascular Implantation of Valves Trial

Cardiac surgeons and interventional cardiologists at NewYork-Presbyterian Hospital/Columbia University Medical Center are collaborating in a Phase I study of percutaneous aortic valve replacement for high-risk patients with aortic stenosis.

Using a percutaneous approach through the femoral artery, the surgeons are using a retrograde approach through the aorta. Under x-ray guidance they advance a large catheter through the artery to the aortic valve, where they position and deploy a tissue valve with metal stent scaffolding. The force of the expanding stent anchors the new valve in place without the need for sutures.

Patients must be at least 70 years of age and have critical aortic stenosis. At the time of press, six patients have undergone the procedure at NewYork-Presbyterian Hospital/Columbia, all with successful deployment of the replacement valve and no major complications. Without the need for cardiopulmonary bypass or open surgery, patients have recovered quickly and have been discharged as early as the second day after the procedure.

While percutaneous aortic valve replacement is currently available only for high-risk elderly patients, additional refinement and technological advances could eventually make it an option for patients at normal risk.

The REVIVAL trial is being conducted by Jeffrey W. Moses, MD, Martin Leon, MD, Susheel Kodali, MD, and Mathew Williams, MD. ■.

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NewYork-Presbyterian Heart is comprised of physicians of Columbia University College of Physicians and Surgeons and Weill Medical College of Cornell University representing medical and surgical disciplines working together with other health professionals in a collaborative process.

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Faculty Highlights

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Without the thoughtful leadership of William A. Gray, MD as an interventional operator and clinical trialist, the current FDA-approved carotid stent procedure would have been markedly delayed. He established two highly regarded carotid stenting programs, at Swedish Medical Center, Seattle, and at Presbyterian Hospital, Albuquerque, and has served as Principal Investigator of carotid stent trials at both national and local levels. Most notably, he was PI of the national ARCHeR trial, which formed the basis of carotid stent approval in the U.S. His work in device development and in advocacy for reimbursement has played a key role in gaining approval for coverage by the Centers for Medicaid and Medicare Services (CMS).

Protected Carotid Stenting in High Surgical Risk Patients: The ARCHeR Results, by Dr. Gray and coinvestigators, is currently in press.

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After completing his cardiology fellowship at Weill Medical College of Cornell University (2003) and a dedicated imaging research fellowship at Duke University (2004), Jonathan W. Weinsaft, MD was recruited to the NewYork-Presbyterian/Weill Cornell Medical Center Division of Cardiology in 2005. He has since directed the development of the cardiac MRI program, one of few programs nationwide to be structured in association with a Cardiology Division.

Current investigational focus of the cardiac MRI program includes delayed enhancement imaging for detection of left ventricular thrombi, and MRI imaging parameters in the post-myocardial infarction setting.

Recent publications include "Improved Detection of Coronary Artery Disease by Stress Perfusion Magnetic Resonance with the Use of Delayed Enhancement Infarction Imaging." *Journal of the American College of Cardiology* (in press), and "Anatomic Distribution of Myocardial Ischemia as a Determinant of Exercise-Induced ST Segment Depression." *American Journal of Cardiology 96*: 1356-60, 2005.

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