

UH Heart & Vascular **Innovations**

University Hospitals Harrington-McLaughlin Heart & Vascular Institute



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Delivering Excellence



This inaugural issue of *UH Heart & Vascular Innovations* is a testament to the building of a first-class team of clinician-scientists who excel as much in scientific discovery as patient care. The University Hospitals Harrington-McLaughlin Heart & Vascular Institute boasts the best our country has in translational and clinical research activities that directly benefit patients. Our institute's 11 Centers of Excellence focus on cardiovascular medicine and imaging, interventional cardiology, heart failure and transplant, electrophysiology, and cardiac and vascular surgery.

I joined University Hospitals in 2006 with the vision of creating a premier institute for heart and vascular care distinguished by cutting-edge discovery and innovation.

UH Heart & Vascular Innovations marks some of our achievements to date. Our feature, "Successful Treatment of Atrial Fibrillation," profiles catheter ablation with UH's Mauricio Arruda, MD, a pioneer in advancing ablation techniques to successfully treat atrial fibrillation.

We also present the groundbreaking work of Carl Orringer, MD, in "Life-Saving Scorecard," who has shown how calcium artery scoring, early on, can measure the presence of coronary artery disease accurately, noninvasively and quickly.

Meanwhile, Alan Markowitz, MD, explains in "A Matter of Debate" how timely surgical intervention is key and how innovative techniques in valve repair now make it preferable to valve replacement.

This issue also spotlights UH's stem cell research by interventional cardiologist Marco Costa, MD, PhD, in "Limb-Saving Potential of Stem Cell Therapy." He has been developing CD34-positive stem cell therapy to treat critical limb ischemia, a technique using heart-specific stem cells harvested from patients' own blood that, when injected locally, promote new blood vessel growth.

I'm certain that reading this first issue will make you confident about UH's ability to deliver excellence and to remain unparalleled in patient care, physician education and clinical research.

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UH Heart & Vascular Innovations

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The commitment to exceptional patient care begins with revolutionary discovery. Faculty at the Case Western Reserve University School of Medicine, who also are physicians at UH Case Medical Center, are at the forefront of medical research and innovation. The School of Medicine is the largest medical research institution in Ohio and among the nation's top medical schools for research funding from the National Institutes of Health.

Among the nation's leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine. The Case Western Reserve University School of Medicine is a nationally recognized leader in medical research and education.

Limb-Saving Potential of Stem Cell Therapy

A pioneering treatment for vascular diseases may help to avoid amputation

Many patients with peripheral vascular disease and critical limb ischemia eventually require amputation. New stem cell therapy research being done at University Hospitals Case Medical Center that intervenes in vascular diseases early may help reduce the need for such drastic intervention.

“Any gain in this area would be a tremendous benefit,” says **Marco Costa, MD, PhD**, Director, Interventional Cardiovascular Center and Research & Innovation Center, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Professor of Medicine, Case Western Reserve University School of Medicine.

For patients who undergo amputation, multiple revascularization procedures with surgery or angioplasty have typically failed, making amputation the only remaining option. Any patient with advanced vascular disease who is no longer a candidate for standard therapies may qualify for stem cell therapy, which may help create new blood vessel pathways in the diseased limbs and prevent amputation down the road, Dr. Costa says.

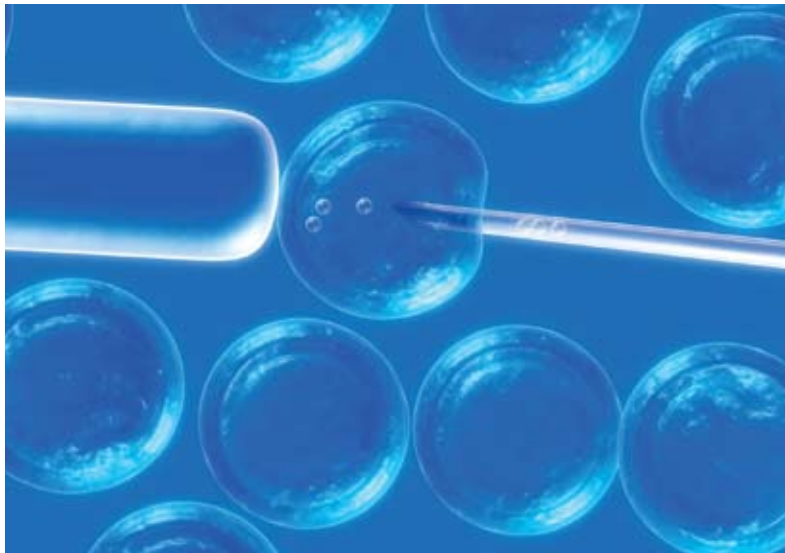
NEW BLOOD VESSEL GROWTH

About a year and a half ago, UH Case Medical Center began a comprehensive, translational stem cell program as part of the multimillion dollar EDUCATE program (turn to page 6 to learn more about this initiative), which will track heart disease risk in more than 5,000 patients over the next decade.

Dr. Costa’s team is examining both the treatment and diagnostic potential of CD34-positive stem cells. One goal is to develop a stem-cell-based signature that may be used in combination with a calcium score to predict the likelihood of future heart attack and stroke. Results from clinical trials in “no-option” patients with severe coronary artery or peripheral vascular disease show tantalizing signals that injecting CD34-positive stem cells locally into heart or skeletal muscle reduces angina and claudication, respectively, and is accompanied by evidence of improved blood flow in approximately six months.

“We have very encouraging data which shows that by injecting cells, you improve symptoms and the ability of patients to exercise,” Dr. Costa says.

The UH Case Medical Center research builds on the pioneering work of Japanese scientist and collaborator, Takayuki Asahara, MD, at the Riken Center in Kobe, Japan. Dr. Asahara identified bone marrow-derived endothelial progenitor cells and demonstrated their role in generating new blood vessels. He discovered that CD34-positive cells are cardiovascular-committed stem cells, which, once injected, multiply and promote the development of new blood vessels and heart muscle.



THE BEST STEM CELLS FOR THE JOB

Harvesting stem cells from the patient’s own body sidesteps the issue of rejection. But today, the only way to harvest a large number of these specialized cells is through bone marrow aspiration, Dr. Costa says.

Dr. Asahara has found that CD34-positive cells also circulate in the blood. A cell-mobilizing agent called G-CSF (granulocyte colony-stimulating factor) is administered for five days to stimulate the release of more progenitor cells. Together with Dr. Asahara’s group, UH investigators are developing a new method for harvesting and expanding stem cells that only requires taking a 20 cc blood sample.

Success is about more than the right number of cells, Dr. Costa says. “Let’s say you take stem cells from a patient with severe illness, but the cells are sick, too. In the process of selecting and multiplying stem cells, you also make them healthier before putting them back into the patient.” Dr. Costa likens the process to a “spa treatment” for cells, so they can regroup and recharge.

With phase 2 trials wrapping up, Dr. Costa is hopeful that stem cell therapy will receive approval in three to five years. “It’s a huge opportunity for clinical application, such as heart attack, chronic coronary artery disease and critical limb ischemia.”



Marco Costa, MD, PhD, Director, Interventional Cardiovascular Center and Research & Innovation Center, University Hospitals Harrington-McLaughlin Heart & Vascular Institute

Meet Us Online

To get an inside look at University Hospitals Harrington-McLaughlin Heart & Vascular Institute through an online video, go to UHhospitals.org/heart.

Successful Treatment of Atrial Fibrillation

University Hospitals leads the way with a center devoted to this complex disease



Mauricio Arruda, MD, Director, Electrophysiology Center and Atrial Fibrillation Center, University Hospitals Harrington-McLaughlin Heart & Vascular Institute

The personal and societal impact of atrial fibrillation (AF) is undeniable: It's a cardiovascular disease that accounts for significant morbidity, mortality and health care costs. More than 2 million Americans have AF, and the condition will affect an estimated 14 million people by 2050.

"AF is the most common form of arrhythmia, yet it remains one of the most difficult to treat and among the least understood. Medical therapies remain suboptimal with significant side effects and often fail to suppress episodes," says **Mauricio Arruda, MD**, Director, Electrophysiology Center and Atrial Fibrillation Center, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Associate Professor, Medicine, Case Western Reserve University School of Medicine. The Atrial Fibrillation Center is making progress in research and clinical care and provides state-of-the-art therapies, including catheter ablation.

CUTTING-EDGE TECHNOLOGY

The Atrial Fibrillation Center offers access to the latest interventional therapies and patient-tailored treatment strategies, such as catheter ablation. "We have a team of cardiac electrophysiologists [EP], nurse practitioners, research coordinators and the EP lab staff who are dedicated to the treatment of atrial fibrillation. Our state-of-the-art electrophysiology laboratories, equipped with the latest technologies, including 3-D mapping systems and stereotactic remote magnetic navigation, are evidence of the Institute's strong commitment to the care of patients with AF," Dr. Arruda says.

Albert L. Waldo, MD, Associate Chief for Academic Affairs, Division of Cardiovascular Medicine, University Hospitals Case Medical Center, and The Walter H. Pritchard Professor of Cardiology, Professor of Medicine, and Professor of Biomedical Engineering, Case Western Reserve University School of Medicine, is a pioneer in understanding the basic mechanisms of AF, having developed animal models and a new multielectrode array to map the disease in patients undergoing heart surgery.

His epicardial mapping system uses special software that involves the placement of more than 500 electrodes on the heart. "After extensive experimental work, the system is now available for evaluation of AF patients undergoing open-heart surgery," Dr. Waldo says.

Bruce Stambler, MD, Senior Electrophysiologist, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Professor of Medicine, Case Western Reserve University School of Medicine, is involved in research that shows it may be possible to prevent and

"Innovative technologies and ablation strategies have evolved that target not only the triggers initiating AF but also the substrate thought to be responsible for the maintenance of persistent forms of AF."

reverse atrial fibrosis (a common component of AF) in congestive heart failure.

"Interventions that are capable of preventing and reversing atrial fibrosis are useful in preventing AF occurrence and the associated electrical abnormalities," Dr. Stambler says. "My laboratory is continuing to explore these areas. A better understanding of the role of fibrosis will likely result in improved care."

INDIVIDUALIZED TREATMENT

Dr. Arruda is at the forefront of advanced research and clinical experimentation in ablation technologies. The S.T.O.P. AF @ UH program, which he leads, offers patients the latest therapies, including medical, ablative and surgical treatments.

"We have the ability to measure and compare outcomes of different AF treatment modalities, as well as to enhance our clinical and translational research programs in atrial fibrillation," Dr. Arruda says. The center helps evaluate patients' eligibility for ablative therapies that may eliminate AF or decrease the consequences of AF. "We believe that each patient should receive an individualized treatment plan, taking into account the severity and frequency of symptoms, risk of thromboembolic events [stroke] and overall cardiac functional status," Dr. Arruda says.



Albert L. Waldo, MD, Associate Chief for Academic Affairs, Division of Cardiovascular Medicine, University Hospitals Case Medical Center



Mauricio Arruda, MD, performs a catheter ablation. He has helped this procedure emerge as a potentially curative therapeutic option for atrial fibrillation.

USING ABLATION

Dr. Arruda is a pioneer in using catheter ablation to treat AF. The procedure, which is showing great promise, involves guiding a catheter into blood vessels and delivering radiofrequency energy to heart tissue, which disrupts the erratic electrical signals.

“Innovative technologies and ablation strategies have evolved that target not only the triggers initiating AF, but also the substrate thought to be responsible for the maintenance of persistent forms of AF,” Dr. Arruda says.

While the ablation approach has usually targeted pulmonary vein isolation (PVI), it has been modified to encompass the left atrial myocardium surrounding the PV ostia, namely the LA-PV antra.

“This has likely accounted for higher success rates by electrically isolating further AF trigger sites, modifying the substrate required for AF self-perpetuation and possibly by modulating the autonomic cardiac nervous system,” Dr. Arruda says.

During PVI, several catheters (thin, flexible tubes with platinum rings and tips) are inserted into blood vessels (at the groin and sometimes at the neck) and advanced to different locations in the heart. The procedure is guided by intracardiac echocardiography and 3-D mapping systems, minimizing the use of X-rays. One of the catheters has a larger tip and is used to deliver radiofrequency energy to each opening of the pulmonary veins (PVs). After several

weeks of healing, the lesions form a permanent circular scar that blocks the abnormal electrical impulses from the PVs, preventing AF. So PVI may potentially cure AF. Moreover, the procedure no longer requires general anesthesia and most patients are discharged home in 24 hours, Dr. Arruda says.

ONE STEP FURTHER

For ablation to gain more recognition as a viable first-line therapy, evidence from large, randomized, multicenter clinical trials will need to show that the procedure stops AF’s complications and not just its symptoms.

Some large clinical trials, such as the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study, are already under way. This randomized, three-year clinical trial will follow 3,000 patients with AF to compare survival rates in those receiving ablation versus drug treatment.

More research needs to be done to discover what causes AF, but UH is working on that part of the puzzle as well. “Most patients with paroxysmal [sudden] AF benefit from an empiric ablation strategy designed to electrically isolate the PV myocardial extensions from the left atrial myocardium,” Dr. Arruda says. “Further investigation may help us to better understand the complex pathogenesis leading to AF and hopefully to develop simpler and more specific treatment approaches.”

Life-Saving Scorecard

Calcium scoring improves cardiovascular risk prediction



Carl Orringer, MD,
Director,
Preventive
Cardiovascular
Medicine,
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McLaughlin Heart
& Vascular Institute

Risk factors such as hypertension, diabetes, cholesterol and smoking have long played a role in predicting the risk of future heart attack, stroke and cardiovascular death. But now another tool – calcium artery scoring (CAS) – is emerging as a valuable addition to identify high-risk patients. And this is particularly true for those living in Northeast Ohio, as a result of a new program at University Hospitals Harrington-McLaughlin Heart & Vascular Institute.

This noninvasive, five-minute CT scan measures calcium deposits in coronary artery walls. No IV line or contrast test material is used, and patients are exposed to only a low dose of radiation.

PREVENTING FUTURE EVENTS

“The idea is to detect CAD before it becomes clinically apparent,” says **Carl Orringer, MD**, Director, Preventive Cardiovascular Medicine, Lipid Clinic and LDL Apheresis Program, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Associate Professor of Medicine, Case Western Reserve University School of Medicine. He is also the leader of a research initiative called the Early Detection Using Calcium Scoring for Treatment and Elimination of Coronary Heart Disease (EDUCATE) program.

“An assessment using traditional risk factors alone has significant limitations in predicting heart disease risk. In about 25 percent of people, traditional risk factors fail to pinpoint high-risk individuals,” Dr. Orringer says. Identification of the high-risk individual is critical because it allows the physician to intervene and prevent a future heart attack by starting, for example, aspirin and cholesterol-lowering therapy, he adds.

THE RIGHT TIME

Dr. Orringer recommends calcium scoring for men 45 and older and women 55 and older with one or more risk factors. For individuals with a first-degree relative who has had a heart attack or stroke, testing is recommended five

years prior to the index event (for example, if a brother had a heart attack at 45, then test at 40).

The process benefits patients by improving physicians’ assessments. “Calcium scoring makes sure you’re not under- or over-treating patients. It helps ensure that you are treating patients in a way that’s appropriate to their risk, which is especially relevant if it means a patient taking medication for life,” Dr. Orringer says.

ACCURATE INFORMATION

The test can diagnose and quantify coronary atherosclerosis and provides accurate prognostic information beyond traditional assessment. It also helps to measure risk in groups that typically fall under the radar, such as those with type 2 diabetes, younger patients and females.

The test typically costs from \$300 to \$500 and isn’t covered by insurance in most parts of the country; but at UH, the doctor-referred test is \$99.

By the Numbers

Calcium scores of 0 correlate to a 0.1 to 0.2 percent risk of heart-related death or heart attack per year for the next five years.

“Those patients can be reasonably treated with a long trial of diet and exercise. Medication may be used only with very high cholesterol levels,” says Carl Orringer, MD.

Scores from Dr. Orringer’s research:

- **9 percent** of the first 4,000 patients were high-risk (10-year event rate approximately 25 percent).
- **20 percent** were intermediate risk (10-year event rate approximately 13 percent).
- **44 percent** had scores of 0, indicating very low risk.



A patient undergoes a calcium scoring test, which is noninvasive and helps provide physicians with information for better assessments.

A Matter of Debate

Surgery vs. watchful waiting for asymptomatic mitral regurgitation: What would you do?

Mitral valve repair surgery has become the gold standard for correcting the effects of a leaking valve, something that more than 2 million people in the United States have. Despite this preferred treatment, the timing of the surgery for an important group of patients, those with asymptomatic mitral regurgitation, is still being debated. The various causes of mitral valve dysfunction and the lack of a universally accepted measure of disease severity contribute to split opinions among experts.

Many physicians favor watchful waiting, delaying surgery until the patient becomes symptomatic.

Alan Markowitz, MD, Chief Surgical Officer, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Director, Heart Valve Center, also of the Institute, and Assistant Professor of Surgery, Case Western Reserve University School of Medicine, suggests that earlier surgical intervention is likely better. Intervening before adverse physiologic changes occur, such as left atrial and ventricular enlargement, atrial fibrillation and pulmonary hypertension, can likely improve a patient's long-term prognosis, he says.

TIMELY INTERVENTION IS KEY

"When we assess a patient, we ask two things about mitral regurgitation: What toll is it taking on the patient, and what toll is it taking on the heart?" Dr. Markowitz says.

Measuring the diameter of the atrium is the initial step since the size of the left atrium is the first to be affected. If the left ventricle starts to enlarge (because it has to eject an even larger volume of blood), that signifies that the condition has advanced.

"Echocardiography is more accurate than cardiac catheterization in the evaluation of valve function for this," Dr. Markowitz says. "Echo allows you to take measurements unavailable in other ways and has removed much of the guesswork so we can target patients more precisely."

The solution? The default method has been valve replacement, but valve repair is gaining ground as the preferred surgical option, Dr. Markowitz says. Replacement requires either a biological or mechanical prosthesis – or removing leaflets and occasionally the valvular attachments. Repairing the valve preserves the patient's own leaflets, creating less demand on the heart (cardiac contraction is more efficient), on the patient (long-term anticoagulation is unnecessary and fewer medicines are needed), and better long-term survival. "Now we know that almost all cases of degenerative mitral valve regurgitation can be repaired," Dr. Markowitz says.



Alan Markowitz, MD, performs a mitral valve repair surgery.

PATIENTS BENEFIT

Advances in the way mitral regurgitation is assessed and treated have changed the prognosis for asymptomatic patients.

"We've really progressed, and we have many methods at our disposal for repairing valves that we used to think could only be replaced," Dr. Markowitz says.

Case Study: Repair Results

An asymptomatic male in his 50s had mitral regurgitation for 15 years when he first went to see Alan Markowitz, MD.

An echocardiogram revealed severe mitral regurgitation with some chamber remodeling including enlargement of the left atrium and left ventricle.

With the new evidence indicating changes in the size of the heart chamber, Dr. Markowitz recommended repair. He repaired his patient's mitral valve uneventfully, and the individual was able to resume work after six weeks.



Alan Markowitz, MD, Chief Surgical Officer, University Hospitals Harrington-McLaughlin Heart & Vascular Institute, and Director, Heart Valve Center, also of the Institute, and Assistant Professor of Surgery, Case Western Reserve University School of Medicine



CME CREDITS

4th Annual Cardiovascular Disease Update

Date: Tuesday, Oct. 20, 2009

Time: Reception, 5-6 p.m. Dinner & CME Presentations, 6-9 p.m.

Place: Landerhaven, 6111 Landerhaven Drive
Mayfield Heights, OH 44124

Case-based presentations will include:

- **Acute coronary syndromes:** Are aspirin and heparin old-fashioned?
- **Abdominal aortic aneurysm:** How do we screen, diagnose and treat?
- **Lipid treatment:** What is the best approach for low HDL and elevated triglycerides?
- **Heart failure:** When should you worry?

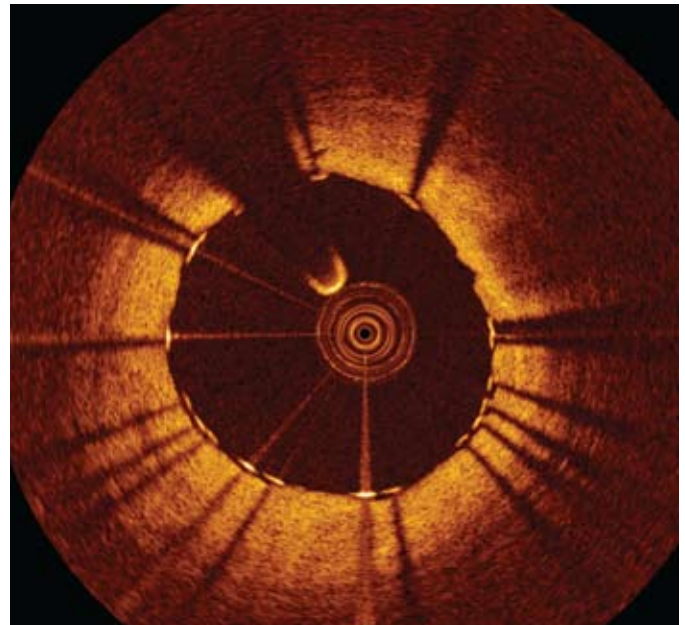
Plus

Lively Debate: The pros versus cons of percutaneous aortic valve replacement in treatment of aortic stenosis

And

Case studies with expert panel

This activity has been approved for *AMA PRA Category 1 Credit™*



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