

Cardiovascular REPORT

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS MEDICINE

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Save the Root, Spare the Valve

For patients with aortic aneurysms, surgery preserves aortic root and quality of life.

Cardiac surgeon Duke Cameron has had three decades of success with valve-sparing aortic root surgery.

When a fluke of circumstances revealed that 52-year-old Manny Orosco had an aortic aneurysm, he was little prepared. He was even less primed for the solution: traditional open heart surgery and replacement of his aortic valve.

That was a no-deal for the Arizona rancher and outdoorsman, who couldn't fathom either life-long blood thinners required by a mechanical valve or the limited durability of a biological tissue valve.

A different choice

Instead, Orosco came to Johns Hopkins and its head of cardiac surgery, **Duke Cameron**. It was Cameron, he learned, who'd been doing valve-sparing aortic root replacements in Marfan syndrome patients, who are particularly vulnerable to aneurysm, or dilation, of the aorta. Unlike traditional aortic replacement in which the aortic valve is replaced, Cameron's technique—one that he's refined over the years—allows repair of the aneurysm while preserving the patient's native aortic valve.

"What that also means for patients," Cameron explains, "is there's no need for a lifetime of blood thinners and a reduced quality of life." The standard

for years has been to replace both the aneurysm wall and the aortic valve, he notes. In younger patients like Orosco, that's typically meant a mechanical valve within a Dacron conduit; thus the need for anticoagulation therapy. For older patients or ones who couldn't tolerate blood thinners, a bioprosthetic valve is the alternative.

"The problem with that," says Cameron, "is the almost certain need for another surgery 10 or 15 years later." So, the valve-sparing procedure has distinct advantages over its traditional precursor, he notes. But, up until recently, those advantages have been mostly theoretical because of the absence of long-term data.

Surgical outcomes strong

Not so today.

In fact, where outcomes of valve-sparing aortic root replacement are concerned, Cameron's got the data that show its success.

Last year, he reported on three decades of Johns Hopkins experience with aortic root procedures, specifically in patients with Marfan syndrome who underwent surgery for aortic root dilation. The most notable result was zero operative mortality among those patients who underwent elective prophylactic

surgery. And after 10 years, more than 90 percent of patients were free of thromboembolism and endocarditis, significant complications seen more commonly when the valve is replaced.

"Our experience with this operation has translated to strong outcomes," says Cameron. That's good news for eligible patients with aortic aneurysm like Orosco who want an alternative to traditional aortic root replacement. And, says Cameron, it opens up another door for the care of patients with the even more aggressive aortic root dilation seen in Loeys-Dietz syndrome.

Identifying aortic aneurysms early

Of course, the challenge is identifying aortic aneurysms in non-Marfan patients early enough to treat them. Often, there are no symptoms until an individual is suddenly struck with chest pain, taken to the hospital and dies before a diagnosis can be made.

Orosco's diagnosis came after his son—a Hopkins medical student—detected heart murmur. That prompted a visit to his cardiologist, a diagnosis and then his surgery.

"He was lucky," says Cameron, "not just because his surgery went well and he's back home now, but because the aneurysm was caught early." ■

Inside



2

Muscling in on Hypertrophic Cardiomyopathy



3

The Operation to Relieve Thoracic Outlet Syndrome



4

Unmasking the Genetics of SCD

These studies are recruiting patients.

Atrial Fibrillation

Ronald Berger is the principal investigator of a study investigating the safety and efficacy of the Ablation Frontiers Cardiac Ablation System in the treatment of permanent atrial fibrillation. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*

Coronary Artery Disease

To test the hypothesis that ICD therapy in combination with medical therapy in post-MI patients with an infarct size ≥ 10 percent of the LV mass improves long-term survival compared to medical therapy alone, principal investigator **Ronald Berger** is conducting a randomized study of patients with CAD and mild to moderate LV dysfunction. Patients who do not meet the EF or infarct mass criteria may be placed in the study registry. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*

Heart Failure

- Principal investigator **Alan Cheng** is heading a randomized, double-blinded, non-significant risk, three-armed trial to investigate the effects of optimizing AV delay timing in heart failure patients receiving cardiac resynchronization therapy. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*
- **John Conte** is the principal investigator of an FDA trial evaluating the efficacy of the HeartWare left ventricular assist device for bridge to transplantation. *Info: Dzifa Dordunoo, 410-955-3597, edordun1@jhmi.edu*
- **Charles Henrikson** is the principal investigator of a study to determine if an algorithm can be developed based on pre-implant clinical variables to predict responses to cardiac resynchronization therapy. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*
- **David Kass** is the principal investigator of a phase 2 open-label study to investigate the effect of CK-1827452 injection on ventricular performance, myocardial oxygen consumption and myocardial efficiency in patients with heart failure and left ventricular systolic dysfunction. *Info: Barbara Peterson, 410-955-9864, bpeter21@jhmi.edu*
- **Stuart Russell** is the Johns Hopkins principal investigator for ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), a randomized, double-blind, parallel-group, multicenter outcomes trial of nesiritide versus placebo for the treatment of acute exacerbations of heart failure in hospitalized patients. *Info: Elizabeth Heck, 410-502-3173, eheck1@jhmi.edu*
- RESET (restoration of chronotropic competence in heart failure patients with normal ejection fraction), led by principal investigator **David Spragg**, is a prospective, randomized, multicenter U.S. clinical investigation designed as a double-blinded trial to assess the effect of rate-adaptive pacing in patients with heart failure, normal ejection fraction and chronotropic incompetence by evaluating functional capacity and quality-of-life changes. *Info: Barbara Peterson, 410-955-9864, bpeter21@jhmi.edu*

Ischemic Heart Disease

Led by principal investigator **Jon Resar**, the Spirit Small Vessel Registry Study is evaluating the safety and effectiveness of the 2.25 mm XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) in improving coronary luminal diameter in subjects with ischemic heart disease due to a maximum of two de novo native coronary artery lesions in small vessels, each in a different epicardial vessel. *Info: Kathleen Citro, 410-955-7377, kcitro@jhmi.edu*

Sudden Cardiac Death

Gordon Tomaselli is the principal investigator of a study examining the role of genetic, protein and electrocardiographic markers measured longitudinally in predicting the risk of SCD and overall mortality in patients with implantable defibrillators placed for primary prevention. *Info: Barbara Butcher, 443-287-3427*



Hypertrophic cardiomyopathy has a passionate foe in cardiologist Theodore Abraham.

Muscling in on Hypertrophic Cardiomyopathy

Cardiologist **Theodore Abraham** has seen his share of young patients with HCM. The inherited condition, which causes thickening of the heart's wall muscle, is the leading cause of sudden cardiac death in people under age 30.

"You usually hear about it occurring in young athletes," says Abraham. "They're caught literally off guard on the field, and end up in an ER or dead."

Abraham's out to change that trend.

As head of the Johns Hopkins Athletic Heart Clinic—a center for research, diagnosis and treatment of HCM—he's focused on educating, raising awareness and increasing screening in young people to avoid field fatalities.

"Death is preventable through early detection," he says. "The problem is that you won't find HCM through a regular physical exam." Not only that, sometimes even when you are looking for it, the heart may appear completely normal. Abra-

ham, who has special expertise in cardiac imaging, says you have to know what you're looking for, and when and how far to take it.

While the news isn't always great once identified—some athletes with HCM may have to alter their lifestyles significantly—the condition can be treated successfully. While milder cases can be treated medically with beta-blockers or calcium-channel blockers, more severe

"If you know there's a family history of HCM or there have been symptoms like chest pain or palpitations, it shouldn't be a question."

ones may require surgery or ICD implantation, or both.

There's a wide degree of variability, Abraham notes. And, that's why it's so important to be vigilant.

"When you see it day in, day out," he says, "you've got to do something." Anyone who participates in sports no matter what the age, he says, should be screened. When it's a high-intensity sport, that's even more reason. And, if you know there's a family history of HCM or there have been symptoms like chest pain or palpitations, it shouldn't be a question.

"If you've been seen and told there's no problem," Abraham says, "get another opinion." For him, it's that serious. Besides the regular clinic, Abraham is also the brainchild behind Hopkins Heart HYPE, an education and awareness program geared toward Baltimore-area schools.

"What we really want," says Abraham, "is to avoid the after-the-fact scenarios." ■

The Operation to Relieve TOS

Among the challenges of thoracic outlet syndrome is first getting it properly diagnosed, says Department of Surgery Director **Julie Freischlag**.

The telltale symptoms that include neck pain, numbness and tingling, weakness or swelling in arms and hands, and headaches—among others—mimic problems like carpal tunnel, pinched nerves and even some heart conditions.

“That can make it confusing,” says Freischlag, whose specialty is vascular surgery. “Recognition is the first hurdle.”

What’s happening is the compression of the brachial plexus, subclavian artery or vein, which results in one of three types of TOS: neurogenic, venous or arterial. And, it’s typically people in their 20s and 30s who are the most likely candidates. Diagnosis means paying attention to that fact, what the symp-

toms are and finally to the patient’s lifestyle and activities.

People with neurogenic TOS, for example, are likely doing a lot of repetitive movements and may have had previous trauma to the neck or shoulder. Venous TOS, also called Paget-Schroetter syndrome, typically occurs in athletes or people who do consistent, strenuous work. Arterial TOS is rare, accounting for less than 1 percent of cases, and is usually the result of a cervical or other rib abnormality.

“Neurogenic is the most common type,” says Freischlag. “The combination of drug and physical therapy and lifestyle changes can help in about 60 percent of cases.”

For more complicated TOS diagnoses, arteriography, venography or other imaging may be options, or surgery can be done to relieve



compression of the neurovascular structures. Freischlag is among a handful of surgeons in the United States to perform transaxillary rib resection and anterior scalenectomy.

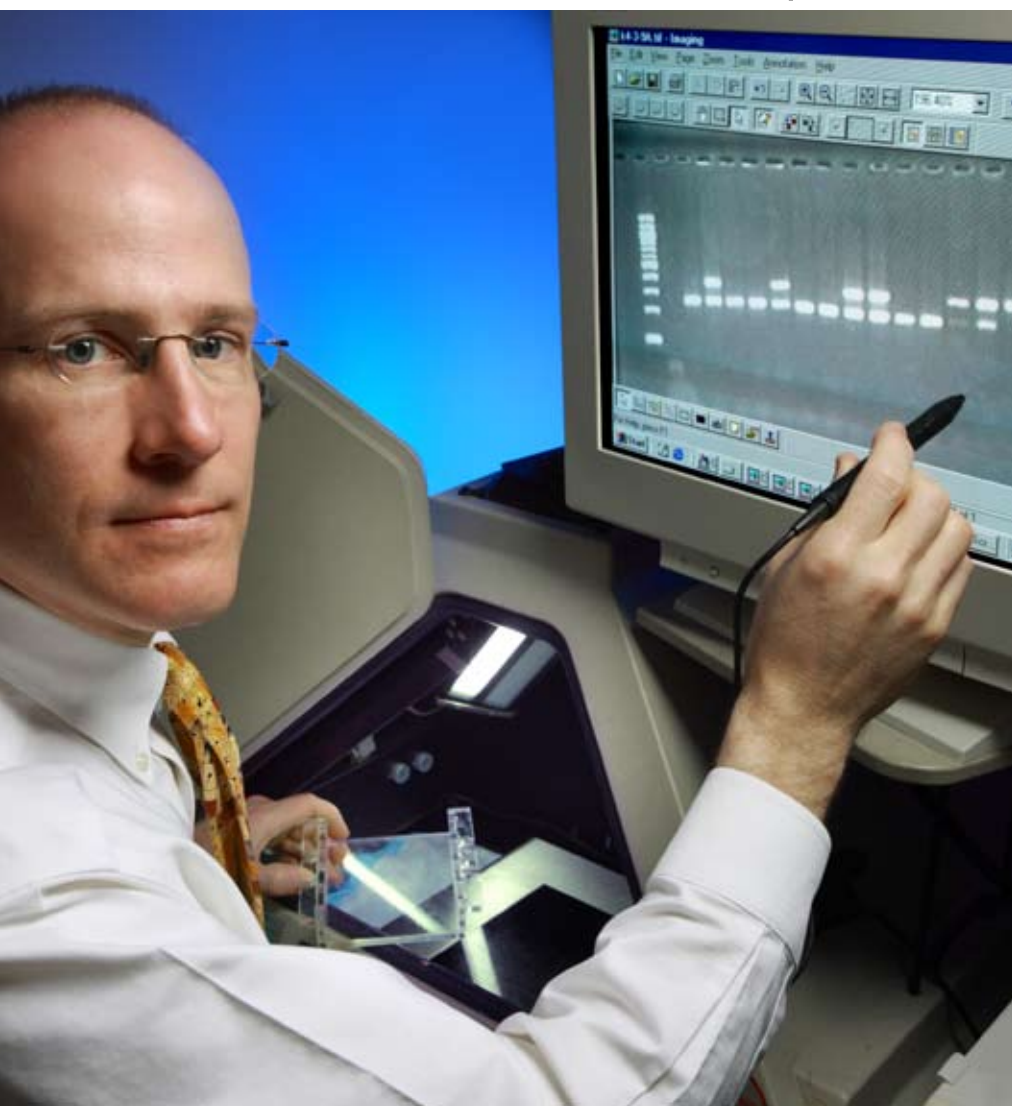
It’s important for physicians and their patients to know that TOS is both identifiable and treatable with very good outcomes, Freischlag notes.

“Not getting it taken care of can be a quality-of-life issue for these relatively young patients,” she says, “or worse, lead to a clot in the vein or artery that becomes life-threatening.” ■

Thoracic outlet syndrome is under-recognized but treatable, says vascular surgeon Julie Freischlag.

INHERITED CARDIAC DISEASE

Into the Heart of Amyloid



Dan Judge, director of Johns Hopkins' Center for Inherited Heart Disease, is working toward better drugs and earlier diagnosis of cardiac amyloid.

Ten years ago, a diagnosis of cardiac amyloid was a near-certain death sentence, its perpetrator often the rogue misfolding of certain proteins that cause organ failure. Since then, says cardiologist **Dan Judge**, most efforts have been focused on identifying the type of amyloid in order to make better treatment decisions.

“That’s helped,” says Judge. “But the condition is still under-recognized by many physicians.” And, that’s to the detriment of thousands of patients who might be helped by promising drugs currently in trials, particularly for the inherited type.

Part of the diagnostic challenge of cardiac amyloid is its presentation. Symptoms usually occur later in life and include shortness of breath, fatigue, leg swelling, weight loss, arm and leg numbness, and even carpal tunnel—which resemble a host of other medical problems. But, cardiologists may suspect the presence of amyloid in the heart if there is discordance between an echocardiogram and electrocardiogram.

“The echocardiogram shows enlargement of the heart but the electrocardiogram shows the opposite,” Judge explains.

Then, there are several different amyloid types, and that’s where specialists like Judge have been able to make some headway in the last decade.

“Today, we now make great efforts to sort out the type of amyloid and look into additional treatment depending on the cause,” he says. Some types of amyloid—including the light chain type that begins in the bone marrow, and another type caused by inflammatory disease—are treated very differently.

It’s the inherited or familial amyloid type that may primarily affect the heart that’s been the trickiest and has had the fewest treatment options, says Judge. Because it’s genetic and caused by a protein defect—in this case mutation-induced misfolding of a protein called transthyretin—the first line of defense is transplantation of the liver, which is where the mutant transthyretin is produced.

“The idea behind a liver transplant is to stop production of the bad transthyretin in order to prevent it from depositing into other organs like the heart,” says Judge. That’s not ideal and it’s difficult to do, but it’s been among the very few treatment options for this type of amyloid.

But researchers have been looking into drug therapies that can stabilize the mutant transthyretin protein. Judge is the principal investigator for Johns Hopkins in one of those drug trials, and he’s encouraged.

“This is extremely promising for patients with familial cardiac amyloid,” he says. “I’m very hopeful.” ■

Unmasking the Genetics of SCD



Aravinda Chakravarti and his team, along with other international researchers, have identified 10 genes that raise the risk of sudden cardiac death.

With no symptoms or known risk factors, sudden cardiac death is as unpredictable as a volcanic eruption. The result of an electrical timing abnormality that affects the heart's QT interval, SCD kills about 400,000 in the United States annually.

But, researchers **Aravinda Chakravarti** and **Dan Arking** have found 10 genes that raise the risk of SCD from QT abnormalities, which may be a significant step toward removing some of the guesswork.

The team, collaborating with other in-

ternational researchers, screened approximately 2.5 million markers in more than 16,000 people to detect subtle sequencing alterations in genomes that modify the QT interval and looked beyond known candidate genes. What they discovered represents a relatively small but extremely powerful screen that correlates genomic architecture with QT intervals, according to Chakravarti.

And, that basically suggests that the more of the 20 genetic variants at the 10 genes a person has, the greater the likelihood of having an abnormal QT interval. Also of interest were some of

“Almost half were new genes that no one would have guessed as being involved in cardiac biology.”

the study's more unexpected findings.

“Almost half were new genes that no one would have guessed as being involved in cardiac biology,” says Arking. “That just opens up a whole new world.”

The next step for Chakravarti and Arking will be to identify how big a player each individual gene is in raising SCD risk. Ultimately, the hope is to find drug targets.

“First, we must understand the science in a deep, meaningful way,” says Chakravarti. “If we understand, we can begin to intervene.” ■

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Cardiovascular REPORT

The Johns Hopkins Heart and Vascular Institute *Cardiovascular Report* is one of the many ways we seek to enhance our partnership with our thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome.

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