The Johns Hopkins Heart and Vascular Institute

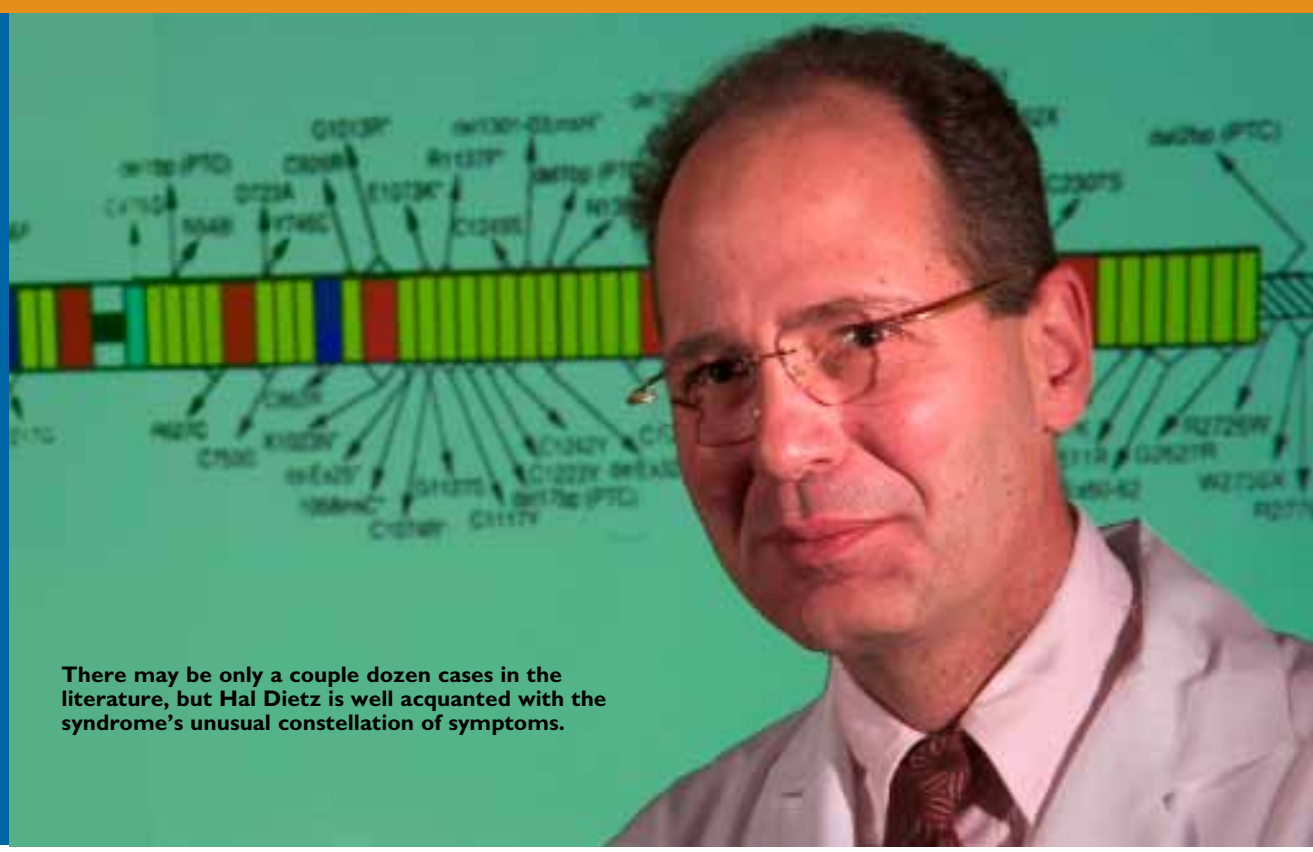
JOHNS HOPKINS MEDICINE

Cardiovascular REPORT

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS MEDICINE

Fall 2009

A Disorder Tortuous in More Ways Than One



There may be only a couple dozen cases in the literature, but Hal Dietz is well acquanted with the syndrome's unusual constellation of symptoms.

The infant's face suddenly turned pale; her lower extremities, beet red. Then she started tongue thrusting.

After being rushed to the emergency department of a local hospital, where imaging revealed a congenital hiatal hernia, the 1-month old was swiftly transferred to the neonatal intensive care unit at the Johns Hopkins Children's Center. There, the patient showed signs of hypertension in her upper extremities, while blood pressure in her lower extremities was normal. Even more unusual was what preliminary imaging of her head, neck and chest showed: hairpin turns and pigtail twists in her aortic arch and carotid and pulmonary arteries.

Called in to consult, geneticist **Hal Dietz** suspected something that—in his experience, at least—wasn't so unusual. Given the child's symptoms, imaging results and small, wide-set eyes, Dietz surmised a rare vascular disorder called arterial tortuosity syndrome, or ATS. Indeed, follow-up cardiac catheterization showed severe lengthening, narrowing and twisting of all of the child's major arteries and severe hypoplasia of the aorta—hallmark signs of ATS that posed risks of aneurysm, infarction or stroke for the young patient.

Dietz found his way to ATS through his work with two related vascular disorders—Marfan syndrome and Loeys-Dietz syndrome (LDS), the latter characterized by the spiraling arteries, aneurysms and widely spaced eyes also found in ATS. In studying Marfan, Dietz learned that the disease is driven by too much activity of the growth-factor molecule TGF-beta, which was also found in the vessel walls of patients with LDS (named after Dietz and Belgian physician Bart Loeys). In looking at the vascular tissue in ATS patients who underwent surgery, they also saw a high expression of TGF-beta. More importantly, in studies of Marfan mouse models the researchers found that the hypertension drug Losartan had the ability to decrease the activity of TGF-beta, thereby reducing the risk of aortic aneurysm and other vascular complications seen in infants with ATS.

That's important because therapeutic options are limited for ATS patients. Surgery is complicated in these cases and requires a long time on cardiopulmonary bypass. Recent advances in endovascular techniques have enabled nonsurgical treatment of aortic coarctation by balloon dilatation, but these elongated vessels most often tend to be too narrow for stenting. As in this case, physicians typically decide to watch and wait for arteries to grow. But knowing the gene defect for ATS has allowed Dietz and Loeys to screen family members and better understand the clinical spectrum of severity in ATS, opening the door wider to improved outcomes.

> "Now we can at least offer families hope that their child will be able to survive and have a reasonable quality of life. With close follow-up and aggressive surgical interventions when appropriate, the chances for patients like this child are greatly improved."

"If you pooled the world's experience with ATS, as recently as three years ago you would have concluded that this condition is uniformly fatal in infancy or very early childhood," says Dietz. "Now we can at least offer families hope that their child will be able to survive and have a reasonable quality of life. With close follow-up and aggressive surgical interventions when appropriate, the chances for patients like this child are greatly improved." ■

Inside

These studies are enrolling patients.

Atrial Fibrillation

Hugh Calkins is the principal investigator of a study investigating the safety and efficacy of the BARD Magellan atrial fibrillation ablation system in the treatment of paroxysmal AF. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*

Carotid Artery Disease

Mahmoud Malas is the Johns Hopkins principal investigator for the ACT 1 study, a multicenter, prospective, randomized trial comparing the gold standard carotid endarterectomy versus minimally invasive carotid stenting under cerebral protection to treat carotid artery stenosis and prevent stroke. *Info: 410-550-1355*

Coronary Artery Disease

Ronald Berger, principal investigator for the DETERMINE study, is testing the hypothesis that ICD therapy in combination with medical therapy in post-MI patients with mild to moderate LV dysfunction improves long-term survival compared to medical therapy alone. Patients who do not meet the EF or infarct mass criteria as measured by CE-MRI may be placed in the study registry. *Info: Elizabeth Robinson, 410-502-0517, erobin26@jhmi.edu*

Coronary Artery and Valvular Disease

Charles Hogue is the principal Investigator of a randomized study looking at two different blood pressure management strategies during cardiac surgery to determine which is associated with a lower incidence of neurologic problems during or after surgery. *Info: Michelle Parish, 410-614-0891, maparish@jhmi.edu*

Heart Failure

- **John Conte**, **Stuart Russell** and **Ashish Shah** are the principal investigators 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
- 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*

Marfan Syndrome

Luca Vricella is the Johns Hopkins principal investigator of a multicenter study evaluating and comparing operative outcomes of the aortic valve-sparing and aortic valve-replacement surgical interventions in adult and pediatric patients with Marfan syndrome. *Info: Kimberly Behrens, 4105021914, kbehren1@jhmi.edu*

Metabolic Syndrome

Pamela Ouyang is the principal investigator of a placebo-controlled trial studying the effect of a range of doses of an oral antioxidant, alpha lipoic acid, on levels of oxidative stress and inflammation in patients with glucose intolerance/diabetes, hypertension, high lipids and moderate obesity. *Info: Jeanne Wingo, 410-550-4278,jwingo@jhmi.edu*

Peripheral Arterial Disease

Elizabeth Ratchford is the local principal investigator of the CLEVER study, a prospective, randomized multicenter clinical trial comparing the benefits of supervised exercise, endovascular revascularization and optimal medical care in adults age 40 and older with intermittent claudication due to aortoiliac peripheral arterial disease. *Info: Elizabeth Ratchford, 410-616-7225; eratchf1@jhmi.edu*

For details about these and other studies being conducted at the Johns Hopkins Heart and Vascular Institute, click on Clinical Trials at hopkinsmedicine.org/heart.

Thomas Reifsnyder: "I can't say 100 percent of the time, but 95-plus percent of the time, that limb can be saved."

Bypassing Amputations

"People have this idea that limb salvage surgery on the lower extremity is only a temporizing measure," says **Thomas Reifsnyder**. "They think that people who come in with gangrene or an infection in their foot are going to end up with an amputation."

But Reifsnyder, who heads vascular surgery at Johns Hopkins Bayview Medical Center, has made it something of a personal mission to not merely treat but actually save the limbs of patients with diabetes or other conditions that cause circulation problems in the legs and feet. In fact, he says, "95-plus percent of the time, that limb can be saved, and most of the bypasses we do actually outlive the patients."

That doesn't mean Reifsnyder considers effective limb salvage operations simple. "Sometimes," he says, "we have to get a little tricky with them, and unless you've done a lot of these procedures, they can seem pretty daunting. But if you can do them efficiently and with sophistication, you end up saving most—not all, but most—of those legs."

One element for succeeding that Reifsnyder considers key is having basic vascular surgery training.

Although guide wires, balloons and stents have made a significant difference in the way endovascular surgery and therefore limb salvage is being done, he says, "if you aren't trained and experienced in general vascular surgery, limb salvage operations that involve piecing together useable veins can take eight to 10 hours instead of three to five hours to complete."

Whether it's reconstructing the foot by rotating tissue flaps, artful transmetatarsal amputation or complicated bypass surgery to transplant veins from one portion of a patient's legs or arms to another, Reifsnyder believes that "it takes practice and a broader understanding of what might be involved" to keep operating time to a minimum and outcomes good.

"Most leg bypasses," he says, "should only take two to four hours, even if they're re-dos, even if you're using veins from patients' arms—they shouldn't be all-day cases. Patients do well with that. Frequently you can do these cases as quickly as you could do an angioplasty or a stenting."

Another reason Reifsnyder relies on his grounding in general vascular surgery when it comes to limb salvage, he says, is that endovascular techniques tend to be more appropriate for aneurysm disease or lower-extremity problems such as claudication or pain while walking. "In other words," he explains, "the limb wouldn't die if you didn't do anything. But most of the leg bypasses I do, if you don't do something, the patient is going to end up with amputation." ■

Anticoagulation in the Elderly

Older patients, says cardiologist **Susan Zieman**, are much more afraid of having a stroke than they are of dying. And because of that, when they're given the opportunity to make informed choices, more opt to take an anticoagulant than those who don't.

This expressed desire by older adults, plus the fact that 80-year-old atrial fibrillation patients have up to a 23 percent risk of stroke, is why Zieman advocates chronic anticoagulation therapy, which can reduce stroke risk by 60 percent.

Despite plenty of good data to support that approach, however, misperceptions still prevail.

One assumption, says Zieman, who specializes in treating patients age 70 and older, is that mature patients will inevitably fall and then be at risk for life-threatening bleeds. "Physicians tend to underestimate the risk of stroke in older patients by 22 percent and overestimate the risk of bleeding by 670 percent," she says, when in reality an older patient would need to fall nearly 300 times a year for warfarin not to be the optimal therapy for stroke protection in atrial fibrillation.

Bruising is likely to happen with falls, but not serious or life-threatening bleeding. "Because their center of gravity can shift behind the body's center with age," Zieman says, "these patients have low-velocity falls and tend to plunk down rather than fall forward." A simple home-safety check that results in getting rid of hazards such as throw rugs, installing cordless phones and enhancing lighting can go a long way toward reducing falls, as will screening for low vision.

Another stumbling block to using anticoagulation therapy—for everyone involved—is that patients who take anticoagulants (or their caregivers) need to be vigilant about what they eat, keep careful records of all other medications they take (including herbal remedies) and have their blood levels monitored regularly. Physicians, too, voice concerns about inconveniencing patients who, once starting warfarin, will need to be monitored at least monthly and perhaps as frequently as every three weeks.

This level of ongoing management may be inconvenient, but, says Zieman, it can be offset by rigorous patient education, home testing, and monitoring through an anticoagulation clinic.

Geriatrics specialist Susan Zieman

"As physicians, we need to be cautious about superimposing our own value system onto these patients," says Zieman. "We may think they hate to be monitored, but they generally enjoy getting out to see people and actively participating in preventing their worst fear from happening. ■

Myth-Busting Lung Transplantation

A key advantage with double-lung transplants, says Ashish Shah, is that residual disease is not left behind in the spared lung.

By the 1990s, enough of the immunosuppressant and technical challenges had been conquered to make lung transplantation a viable option for high-risk patients with pulmonary fibrosis. And while **Ashish Shah** is careful to note that it's disingenuous to say lung transplantation is the perfect treatment for patients with end-stage lung disease, he's hopeful.

That optimism is part experience, part diving into data from the United Network for Organ Sharing (UNOS), which makes information about 10,000 patients in the United States available to researchers.

"The power of these big data sets that yield big subsets is huge," says Shah, surgical director of lung transplantation at Johns Hopkins. "We no longer have to rely on single-center research and are able to ask important questions about the biology of this procedure."

Conducting a detailed review of the patient records for all single- and double-lung transplants performed in the United States and Canada from 1987 to 1997 has enabled the Johns Hopkins researchers to challenge some of the major prevailing myths.

First among these myths is the long-held assumption that double-lung transplants are riskier, especially among older, sicker patients. Not necessarily, says Shah. In fact, double-lung transplants improve outcomes in the sickest patients. Moreover, when both lungs are replaced, the new lungs, which must breathe together as a pair, are already adapted to each other.

Another myth? Double lung transplants are too complex an operation for an elderly patient. Again, says Shah, not so fast.

"Through our analysis of the UNOS database, we've discovered that double and single-lung transplant patients over age 60 have the same short term and intermediate survival rate," he explains. In addition, having a double-lung transplant seems to be a contributing factor for patients who have survived for 10 years.

First among these myths is the long-held assumption that double-lung transplants are riskier, especially among older, sicker patients. Not necessarily, says Shah. In fact, double-lung transplants improve outcomes in the sickest patients.

But the data needs to be mined for more gems of information. For example, Shah and his colleagues are interested in knowing why some patients may survive a decade after receiving a lung transplant while others may not. Why do some patients quickly reject the new lung or set of lungs? It's clear that the biology of transplanted lungs is far more complex than that of other solid organs

"We're at the end of the beginning of a maturing field," Shah says. "We haven't yet seen full maturity in our understanding and practices, which makes it exciting and a little frightening at the same time." ■

Virtual Valve Repair

Mitral valve repair has no mercy. If it doesn't work the first time, cardiac surgeons usually have no other option but to put in a prosthetic valve. And that adds complication to existing complexity. What's been missing is a viable way to practice the procedure to get it as close to perfection as possible.

But cardiac surgeon **David Yuh** believes he's found part of that answer—virtually speaking.

For the past year, Yuh has teamed up with engineers from the Johns Hopkins Applied Physics Laboratory and Department of Biomedical Engineering to develop a better way to understand and plan these reconstructive operations.

> It provides a tool for trying and testing different surgical approaches.

"The mitral valve is a complex entity," says Yuh, who compares working on the valve, which is flat and flaccid when emptied of blood, to working on a deflated parachute. "It's like trying to cut up a parachute on the floor and then hoping it will deploy properly."

With NIH funding, Yuh and his team have found a way to combine real-time three-dimensional transesophageal echocardiographic (TEE) imaging with computational models of the mitral valve. Until now, two-dimensional TEE imaging has dominated as the gold standard for assessing valvular dysfunction and planning for repair. Yuh explains that adding computational modeling enhances predictive value.

"Three-dimensional echocardiography allows us to more accurately describe to our patients the likelihood of repair and why," he says.

More importantly, he notes, it helps surgeons plan more accurate repairs. The combined technology allows them to image the patient's own mitral valve and then navigate through the repair surgery. It provides a tool for trying and testing different surgical approaches, and then viewing the outcome on a computer monitor long before entering the operating room.

Yuh is quick to point out the challenges of working on the heart in general and the mitral valve in particular. But, modeling like this is useful, and his hope is that it will become applicable to other reconstructive heart operations such as aortic root replacement and aneurysm repairs, and ventricular remodeling operations. ■

David Yuh, director of cardiac surgical research

Your Vital Links

Cardiovascular Access Line (CAL)
To refer patients for cardiovascular services
410-502-0550 or cal@jhmi.edu

Cardiac Surgery
410-955-2800

Vascular Surgery and Endovascular Therapy
410-955-5165

Pediatric Cardiology
410-955-9714

Interventional Radiology
410-502-2835

Hopkins Access Line (HAL)
Your 24/7 connection with Johns Hopkins full-time faculty in any specialty
410-955-9444 or 800-765-5447

Online Referral Directory
hopkinsmedicine.org/doctors

www.hopkinsmedicine.org/heart

Mark Your Calendar

Cardiovascular Topics at Johns Hopkins

February 18–20, 2010
Johns Hopkins School of Medicine
Turner Auditorium
720 Rutland Avenue
Baltimore, MD 21205

Info: www.hopkinscme.net

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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