

Cardiovascular Report

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS MEDICINE

Winter 2016

Toward Better Treatment for Heart Failure with Preserved Ejection Fraction

Her repeated encounters with fluid-overloaded patients gasping for breath led Kavita Sharma to specialize in advanced heart failure and transplant cardiology.



It was a scenario cardiologist **Kavita Sharma** encountered time and again during her residency at Johns Hopkins. The patient, usually a woman, typically in her 50s or 60s, would present with textbook signs of heart failure—shortness of breath, edema, fatigue, orthopnea—but a remarkably robust ejection fraction. Yet the patient was clearly in serious, often advanced, heart failure with a constellation of companion disorders including hypertension, diabetes, atrial fibrillation and kidney disease.

Heart failure with preserved ejection fraction, or HFpEF, accounts for nearly half of the 6.6 million cases of heart failure in the U.S. and kills nearly half of people diagnosed with it within five years. Although there are at least nine well-studied treatments for heart failure with reduced ejection fraction, HFpEF has poorly understood pathophysiology and virtually no proven therapies.

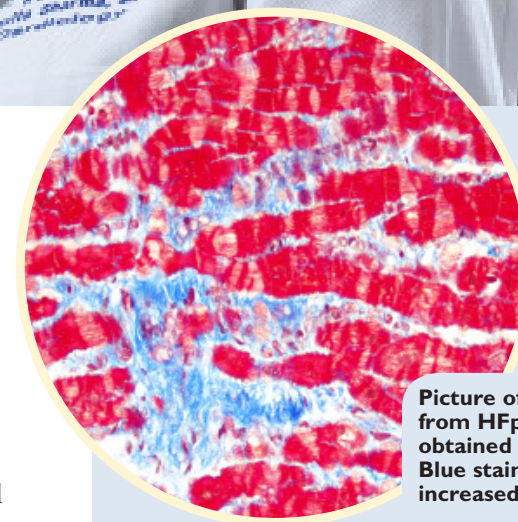
The mysteries of the condition intrigued Sharma, and within months of finishing her cardiology fellowship in 2014, she launched the Johns Hopkins HFpEF program—one of only a handful in the country. The centerpiece of the program is a clinic dedicated to diagnosis and treatment. The clinic actively follows about 150 HFpEF cases; Sharma sees about four to five new patients a week.

All patients admitted to the hospital in acute heart failure with left ventricular ejection fraction greater than 50 percent are referred to the clinic,

where they undergo echocardiograms with strain analyses and pulmonary function and cardio-metabolic stress tests. Some patients also get right-heart catheterizations and heart biopsies.

Ruling out underlying pathologies that can lead to secondary HFpEF is vital, Sharma says. A handful of patients, for example, have cardiac amyloidosis, which can often manifest as HFpEF. On the flip side, nephrologists and pulmonologists refer many patients who initially present with kidney disease or pulmonary hypertension, all of which makes interdisciplinary crosspollination key.

Clinical management focuses on removing fluid, reducing recurrent edema and treating comorbidities including secondary hypertension, atrial fibrillation, diabetes and chronic kidney disease, all of which are commonly seen in HFpEF patients. These therapies are also the cornerstones of treating classic heart failure, but HFpEF may require modifications that address its idiosyncrasies. For example, a recent study led by Sharma showed that patients with HFpEF are more vulnerable to acute kidney injury as a result of standard fluid-removal therapies when admitted to the hospital and require more delicate approaches to fluid removal. The Hopkins group is using low-dose intravenous dopamine experimentally. Some evidence suggests that dopamine promotes blood flow to the kidneys, and the strategy, Sharma says, may help mitigate injury.



Picture of heart muscle from HFpEF patient obtained from a biopsy. Blue stain shows increased fibrosis.

What Are Cardiac Cells Doing in HFpEF?

Johns Hopkins is the only site in the United States performing cardiac biopsies to better define the morphology of cardiac cells in HFpEF and glean insights about any molecular aberrations that account for the signature myocardial stiffness seen in HFpEF. The investigators are also performing genetic analyses seeking to pinpoint any DNA alterations that might illuminate heritable patterns of disease behavior.

“Much of our insights into human heart failure come from studies of muscle tissue from explanted hearts, but because HFpEF patients are generally not transplanted, our understanding of this disease is far more limited,” says **David Kass**, director of Johns Hopkins’ Center for Molecular Cardiobiology. “Cardiac biopsies will give us much-needed information about the characteristics and behavior of cardiac cells in HFpEF.”

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When the Patient with Congenital Heart Disease Is Mom

Thirty-five-year-old Esther Martin of Harrisburg, Pennsylvania, was born with Shone's anomaly, the constellation of left-heart defects that include aortic and mitral stenosis and coarctation of the aorta. By age 10, she had had four repairs, followed by aortic valve replacement as an adult along with pacemaker implantation for heart block. So when newlywed Martin and her husband wanted to start a family, the decision was anything but casual. "I've always wanted to have kids but wasn't really sure it would be possible," she says.

Martin's uncertainty was amplified when a regularly scheduled follow-up only a few months before her wedding—revealed a severely regurgitant mitral valve. That unexpected twist sent the couple to the altar months earlier than planned.


Within a few weeks of her wedding, Martin was at Johns Hopkins undergoing mitral valve replacement by cardiac surgery director **Duke Cameron**. Mere weeks post-surgery, she was talking baby with pediatric cardiologist **Jane Crosson**, director of the adult congenital heart disease program at Johns Hopkins.

Martin is among the growing number of women born with cardiac defects who attempt pregnancy and successfully carry to term—a testament to parallel successes in pediatric and adult cardiology, cardiac surgery, diagnostic imaging and maternal-fetal medicine. Even so, pregnancy in such patients is always

deemed high risk.

Because congenital heart defects are spectrum disorders and because no two pregnancies are alike, the need for a tailored approach is that much more vital in women with heart defects. "Most can have successful pregnancies provided they have careful preconception counseling and assessment, their condition is well controlled, they are in good overall health and followed carefully," Crosson says. Pulmonary hypertension, she adds, including cases due to Eisenmenger syndrome, is the only condition that definitively rules out pregnancy because it carries risk of complications—chiefly heart failure and death—as high as 50 percent and up for the mother.

Martin's case illustrates the complexities. For starters, Martin's artificial aortic and mitral valves require lifelong anticoagulation, a challenge during pregnancy given the teratogenic potential of some blood thinners and the possibility for placental hemorrhage inherent in all anticoagulation treatment, Crosson says. Even though warfarin offers optimal protection for patients with artificial valves, it can have devastating effects on the fetus, so during her first trimester, Martin received injections with enoxaparin, a type of low-molecular-



Despite her history of complex cardiac anomalies, repairs and treatments, Esther Martin delivered a healthy baby.

weight heparin that doesn't cross the placenta. During the second trimester, she switched back to warfarin and then to regular heparin at week 35.

To ensure that the heart is coping with the substantially higher cardiac output of pregnancy, exercise stress testing is essential, Crosson says, yet Martin's pacemaker would have rendered such testing less useful. Instead, she had periodic echocardiograms.

Women with congenital heart disease have a small but real risk of giving birth to a baby with a heart defect—about 5 to 7 percent, compared with 1 percent for the general population. In September 2014, Martin gave birth to a healthy boy. She and her husband are already trying for baby number two. ■

CARDIAC SURGERY

A Bloodless Tetralogy Repair

More than half of cardiac surgeries require blood transfusion—a lifesaving measure but one that nevertheless could fuel short- and long-term complications ranging from temporary immune suppression to graft-versus-host disease.

For several years, use of blood-conservation techniques in cardiac surgery has been gaining momentum, and Johns Hopkins is among the hospitals that have launched protocols to reduce the use of blood products. Even so, totally bloodless heart operations in infants remain rare.

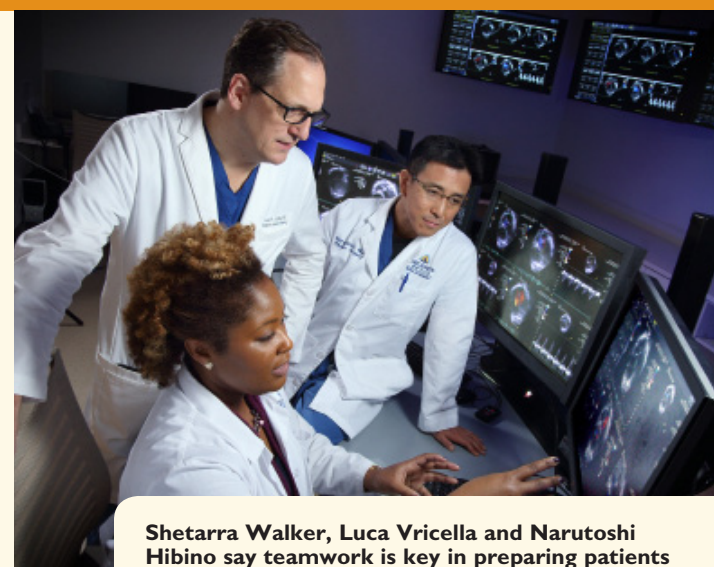
Recently, Johns Hopkins cardiac surgeons performed a totally blood-free tetralogy of Fallot repair in a 2-month-old, 6-kilogram infant—the youngest and smallest in the institution's history to undergo heart surgery without a single drop of foreign blood. The baby was discharged home on day six following the operation and has had a smooth, complication-free recovery.

"It's a conditioned assumption that blood transfusions are unavoidable," says **Luca Vricella**, director of pediatric cardiac surgery. "In small babies,

it's medically, clinically and logistically challenging, but it can be done."

Identifying and treating anemia preoperatively is vital, says pediatric cardiologist **Shetarra Walker**. Patients get erythropoietin injections for several weeks leading up to surgery to enhance their hematocrit. Blood conservation is also done intraoperatively. Collecting blood from the patient before the surgery to fend off any blood loss is a common approach that can be modified for use in Jehovah's Witnesses patients by using a closed circuit technique that allows the blood to be recirculated directly back into the body. Any spilled blood is siphoned and reintroduced into the circulation, says pediatric cardiac surgeon **Narutoshi Hibino**, who operated on the infant with Vricella.

During surgery, triggers are established that signal the need for transfusion. For example, if brain oximetry starts trending downward, a transfusion is initiated promptly to prevent tissue hypoxia. The transfusion threshold must be individualized, because it's predicated on factors such as age, comorbidities and overall cardiopulmonary reserve.



Shetarra Walker, Luca Vricella and Narutoshi Hibino say teamwork is key in preparing patients for a transfusion-free heart operation.

"The question we ask is, what is the lowest level of hemoglobin a patient can withstand without compromising tissue oxygenation?" Hibino says. "That varies from person to person."

"All pediatric cardiac surgeries are ensemble pieces," Vricella says. "But nothing illustrates the power of teamwork like orchestrating bloodless surgery in a little infant." ■

A Lower Risk Threshold for TAVR?

Aortic stenosis affects about 12 percent of people over 75, about a fourth of whom have disease so severe it mandates surgical repair. Many, however, have intraoperative risk that renders them poor candidates for open-heart surgery, the gold standard approach.

For nearly a decade, the less invasive transcatheter aortic valve replacement (TAVR) has gained ground as the safer alternative for people at high operative risk, generally defined as 10 percent or higher. Many patients older than 80 will fall in that category, as will some younger patients with extensive comorbidities.

At 80 and otherwise healthy, Joyce Wetzler belonged in neither group. She was diagnosed at Johns Hopkins two years ago after experiencing increasing shortness of breath and worsening fatigue. After a series of echocardiograms, Wetzler was referred for evaluation to cardiac surgeon **John Conte** and interventional cardiologists **Jon Resar** and **Rani Hasan**.

Currently, the sole option for most people like Wetzler is open-heart surgery. At Johns Hopkins, she had the choice of enrolling in a clinical trial evaluating the efficacy and safety of TAVR for intermediate-risk patients. “I thought, I could die having open-heart surgery, and I could die having the minimally invasive one,” she says. “I figured if I had the second, I might help others and do my part for science.”

With Wetzler under light sedation, Hasan, part of a five-member clinical crew, performed the procedure in August 2015. After examining intraoperative images, Resar later told Wetzler that her native valve leaflets had been opening only a few millimeters. Without surgery, she would have likely died within the year.

Wetzler was discharged home two days after her procedure. A month later, she was running laps with her Old English sheepdog at a dog show. Save for a few hypertensive spikes, she’s been feeling great. “I remember walking toward Madison Square Garden last winter and barely catching my breath,” Wetzler says. “That’s all gone now.”

“Patients are up and moving around the same day. Most go home in two to five days.”
—Rani Hasan

A Study to Bring Clarity

Even though transcatheter aortic valve replacement (TAVR) carries a decidedly lower operative risk for older and/or medically frail patients than open-heart surgery, for intermediate-risk patients, the risks and benefits are less clear.

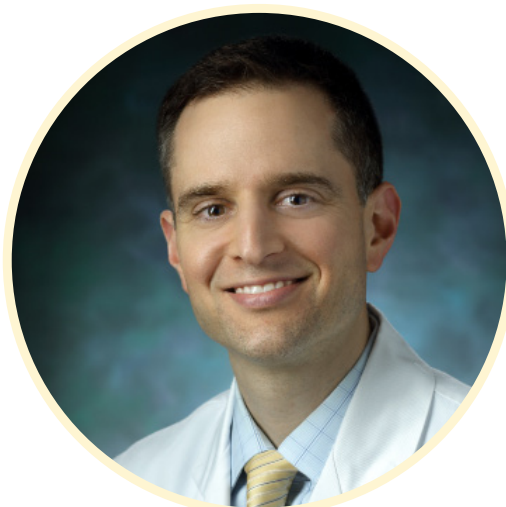
“Most patients with an intermediate-risk profile can undergo open-heart surgery relatively safely, but their risk is still a tad higher than we’d like it to be,” says Conte, who with Resar is heading the Johns Hopkins arm of an ongoing multicenter trial called SURTAVI. “Our current trial aims to gauge the pros and cons of either approach in this particular subset of patients.” The primary outcome measures of the study, which will include five-year follow-up, are all-cause mortality or disabling stroke at two years.

In high-risk patients, TAVR carries a notably lower mortality risk (14 percent versus 18 percent) at one year, and a comparable stroke risk. But TAVR patients are more likely to require a pacemaker due to conduction system damage during the procedure. Some 15 to 20 percent of TAVR patients end up needing a pacemaker around the time of the procedure, compared with 5 percent in open-heart surgery, but many of them have underlying conduction disease related to aging that requires pacing anyway, Conte says.

Eight out of 10 TAVR patients need only light sedation and are often able to go to a regular hospital unit rather than an ICU after the procedure. In addition, says Resar, Johns Hopkins experts typically opt for a percutaneous catheter insertion rather than a surgical cut-down to further minimize recovery time. Subclavian artery entry is always an option, but about 90 percent of Johns Hopkins cases are done using iliofemoral insertion because of its lower complication rate.

“Patients are up and moving around the same day,” says interventional cardiologist Rani Hasan. “Most go home in two to five days.”

Regardless of the trial outcomes, a



Jon Resar and John Conte are leading the Johns Hopkins arm of a study looking at the efficacy and safety of transcatheter aortic valve replacement in patients deemed at intermediate risk for open-heart surgery.

multidisciplinary, case-by-case assessment will remain the centerpiece to optimizing outcomes in individual Johns Hopkins patients, Resar says.

At Hopkins, the preoperative work-up involves two to three pre-procedure visits, an echocardiogram, a CT scan, a pulmonary function test and a carotid ultrasound. Each case is then discussed by a team of clinicians including a cardiologist, a surgeon and an interventional cardiologist. ■

Details: 410-955-3299; jresar@jhmi.edu

Heart Team Clinic

Patients in the Washington, D.C., region who have severe aortic stenosis can be evaluated for TAVR through the Heart Team Clinic at Suburban Hospital in Bethesda, Maryland. The clinic, a collaboration between the TAVR program based at The Johns Hopkins Hospital and the Hopkins-affiliated cardiac surgeons at the NIH Heart Center Suburban Hospital, also provides post-TAVR follow-up care.

Toward Better Treatment for Heart Failure... (continued from page 1)

The Johns Hopkins program is a main site in several ongoing federal studies to assess treatment strategies and disease progression. Sharma and colleagues are collecting demographic, lifestyle, risk factor and laboratory data to help clarify the pathophysiology of HFpEF and understand the mechanisms that fuel the racial and gender disparities observed in the condition.

“Our program goals are ambitious, but how could they not be?” says **Stuart Russell**, co-director of the HFpEF program and director the heart failure transplantation program at Johns Hopkins. “The challenges posed by this disease demand nothing less.” ■

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Johns Hopkins Medicine
Marketing and Communications
901 S. Bond Street, Suite 550
Baltimore, MD 21231

Heart and Vascular Institute

James Black III, M.D.; Duke Cameron, M.D.; Edward Kasper, M.D.;
Medical Editors

Marketing and Communications

Dalal Haldeman, Ph.D., M.B.A., *Senior Vice President*
Mary Ann Ayd, *Managing Editor*

Ekaterina Pesheva, *Writer*

Kristen Caudill, *Design*

Keith Weller, *Photographer*

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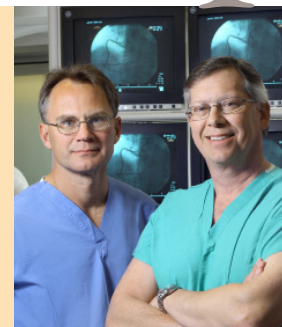
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