



## When the Left Ventricle Fails

Cardiologists and surgeons of the cardiomyopathy team weigh the options.



Beth Ann Rhoades of Frederick, Md., returned home in September after receiving a Thoratec biventricular assist device at Johns Hopkins this summer. With her are Stuart Russell and John Conte.

**THE CASE:** On the day after Christmas, **Stuart Russell** and the cardiomyopathy team he directs were asked to consult on a 17-year-old who had been admitted to the pediatric intensive care unit. The patient had been a healthy high-school student, actively participating in sports until the previous spring, when she was found to have acute myelogenous leukemia.

During chemotherapy, she had received adriamycin, an anthracycline drug with potential cardiac muscle toxicity. Four months after completing chemotherapy, she presented to a hospital in her home town, Virginia Beach, Va., complaining of shortness of breath and nausea. Physicians there diagnosed heart failure and recommended that the teenager be transferred to Johns Hopkins.

Echocardiography showed severe left ventricular dysfunction with an ejection fraction of 10 percent. We performed an endomyocardial biopsy, a procedure commonly done at Hopkins to evaluate cardiomyopathy. Based on histologic examination of the tissue, we

ruled out myocarditis; based on electron microscopic examination, we confirmed the clinical suspicion of anthracycline toxicity.

Initial treatment for severe heart failure included diuretics and milrinone, a drug that increases cardiac output. She improved, but each time we reduced the dosage of milrinone, she experienced profound fatigue and abdominal bloating. Furthermore, when we performed a right heart catheterization while she was receiving milrinone, we found high cardiac filling pressures and low cardiac output, indicating heart failure despite these drugs.

**TREATMENT DECISION:** Heart transplant guidelines require that patients be at least five years past treatment for their malignancy and considered “cured.” Because of our patient’s recently diagnosed and treated leukemia, we could not consider her a candidate for heart transplantation. We examined two other treatment possibilities: sending her home with a constant infusion of milrinone, or implanting a left ventricular assist device

(LVAD) for either long-term support (so-called destination therapy) or as a “bridge to transplant” if she is cured of her leukemia for five years.

**DISCUSSION:** Five years ago, the RE-MATCH trial compared LVADs with optimal medical therapy in heart-failure patients who were not eligible for heart transplantation. Results showed that the use of LVADs was associated with a 48 percent reduction in the risk of death compared with medical therapy at one year. Although this was quite promising, LVADs were associated with infections, strokes, peripheral emboli, bleeding, and prolonged hospital stays. At one-year follow-up, only 52 percent of the LVAD patients were alive; by the end of two years, the number had dropped to 23 percent. Further analyses of this study (*N Engl J Med* 2001;345:1435-1443) have shown that the patients who benefited most from placement of an LVAD were the ones dependent on inotropic drugs—such as our patient.

*Continued on next page*

# Consultation: Stuart Russell

Clinical Director of Cardiomyopathy Service, Johns Hopkins Heart Institute



Stuart Russell and clinical exercise physiologist Lisa Garcia monitor a patient undergoing a metabolic stress test. While exercising, the patient is being monitored through a breath analysis that determines aerobic capacity and anaerobic threshold.

## What are the current indications for heart transplantation?

Today, patients up to age 70 who have end-stage heart failure despite being on maximal medical therapy can be listed. Many already have a biventricular pacemaker or automatic defibrillator. To undergo successful transplantation, they should be free of other major medical problems. Diabetes, for example, is not a contraindication to transplant, but organ dysfunction—renal insufficiency, retinopathy, peripheral neuropathy—is. One of the most important requirements is that patients have an adequate support network.

After we do the complete medical evaluation, we meet as a team to decide whether to list the patient for a transplant. Once listed, the patient must wait until a heart becomes available.

## With all the improvements in medical therapy, how can you determine if someone will really benefit from a heart transplant?

We evaluate clinical symptoms and test results, and when they indicate a poor prognosis despite medical therapy, we consider transplantation. Hyponatremia, for example, is a powerful marker of poor outcomes. And we rely heavily on hemodynamic measurements from right heart catheterization, plus metabolic exercise testing. Among the findings that indicate a poor prognosis on medical therapy are high cardiac filling pressures despite our best efforts at diuresis, and peak VO<sub>2</sub> less than 12 to 14 ml/kg/min on a metabolic exercise test. VO<sub>2</sub>, a measurement of oxygen consumption, is a surrogate for cardiac output and cardiac output reserve. We also use other markers from the metabolic stress test (MST), such as the slope of ventilation to carbon dioxide production.

## Are there other indications for a metabolic stress test?

In our new lab, we often use the test to determine why patients have limitations to exercise, to pinpoint the causes of dyspnea, and to assess the effects of various therapeutic interventions. For example, we frequently see patients who have exertional dyspnea that seems out of proportion to their lung or heart disease. The MST helps us differentiate between heart and lung limitations, which can help when choosing therapies. The test also helps us assess functional capacity and set exercise guidelines. ■

## What should my patients expect when they are evaluated?

First they are seen by a heart failure cardiologist whose focus will be to optimize medical therapy, rule out other medical problems, evaluate the immune system, and detect prior infectious exposures. Patients meet with a cardiac surgeon, a transplant nurse, and a social worker, and receive financial counseling so they know exactly what to expect both before and after the transplant.

## Left Ventricle

*Continued from previous page*

Since the publication of REMATCH, both LVAD devices and surgical techniques have improved. In one recent study, one-year survival was 61 percent in patients treated at high-volume centers who received an LVAD as destination therapy (*Congest Heart Fail* 2005;11:133-138).

Today's devices are smaller, more durable, and associated with lower infection rates. The older pulsatile LVAD pumps were large, noisy, and subject to deterioration of their valves. Newer continuous-flow devices (based on a rotor system spinning at 8,000 to 12,000 rpm) do not require valves and thus avoid the deterioration problem entirely. Indeed, many patients who have received a continuous-blood-flow device do not have a pulse, even though they have adequate cardiac output and blood pressure. The team at Johns Hopkins recently began enrolling patients in a clinical trial of a new continuous-flow device (the Heartmate II).

Because of our patient's youth and active lifestyle, and the likelihood that her leukemia could be cured, her family agreed with us that an LVAD was the best option for her.

**THE HOPKINS APPROACH:** With the patient on cardiopulmonary bypass, cardiac surgeon John Conte implanted a valveless pump through a standard midline sternotomy incision. Although first-generation LVAD pumps had to be placed in the abdomen because of their large size, the new pump is placed in the chest. Conte connects one end of the pump to the heart through an opening he creates in the left ventricle, then sutures the other end to the ascending aorta. The pump thus moves blood from the left ventricle, through the valveless pump, and out to the ascending aorta. Flow is regulated by the spinning of the pump rotor. At lower flow rates, some blood remains in the left ventricle, which ejects it normally, producing a palpable pulse. With higher flows, the ventricle is emptied, and the blood pressure may be non-pulsatile.

**OUTCOME:** Our patient's early postoperative course was made more complicated by pulmonary hypertension and right ventricular failure. She responded well to treatment with milrinone and sildenafil (Viagra). Cardiologists and pulmonologists at Hopkins have accumulated substantial experience using sildenafil for refractory pulmonary hypertension. As our patient continued to improve, we were able to wean off both agents over the next month. We taught her about how her device works and how to manage any problems (such as low battery or low pump flow alarms) that might occur. And, to be sure that she could manage on her own, she went on two field trips with her family.

About two months after her surgery, we discharged our patient to her home in Virginia. She now returns to Hopkins once a month for routine clinical follow-up. Although she missed out on graduating with her class, she is finishing her remaining courses at home with a tutor and is on track to graduate in the spring. Her outlook has consistently been positive, and if she remains free of the leukemia, we will recommend that she be listed for a heart transplant. ■

## Genetic Testing for Cardiomyopathy—Who? When? Why?



Daniel Judge and Nicole Johnson.

we now discuss the option of clinical genetic testing.”

With a long tradition in the study of genetics in cardiovascular diseases, the Hopkins approach is to offer patients and families an opportunity to meet with a genetic counselor who works primarily with inherited cardiomyopathies. **Nicole Johnson** is a board-certified genetic counselor who co-

ordinates the Familial Cardiomyopathy Initiative. She explains issues of inheritance, penetrance, and genetic susceptibility so that at-risk family members can undergo proper cardiac screening. When a genetic mutation is identified in a family, a negative test result can reassure an individual that repeated lifelong cardiac screening and uncertainty are not necessary. In contrast, for a family member who does have a genetic predisposition to cardiomyopathy, frequent cardiac screening and early use of medications and other therapies may slow disease progression and in some families, prevent unexpected sudden death. ■

Genetic testing for hypertrophic, dilated, and restrictive cardiomyopathies has become clinically meaningful. Along with these recent advances have come questions about the risks and benefits of genetic testing. “It’s well recognized that hypertrophic cardiomyopathy runs in families,” says Hopkins cardiologist and genetic researcher **Daniel Judge**. “But we’ve found that dilated and restrictive cardiomyopathies also occur frequently in relatives of patients. Until recently, genetic testing for these conditions was considered a research tool without clinical application. However, for many families with these conditions,

### BEYOND ANEURYSM REPAIR

Surgical ventricular remodeling (SVR) is a procedure based on techniques for treating left ventricular aneurysms and is now being investigated as a treatment for patients with ischemic cardiomyopathy and advanced heart failure. Typically, patients with congestive heart failure after myocardial infarction have left ventricular dilation with large areas of akinesis or dyskinesis, often with associated mitral regurgitation. SVR addresses these changes by resizing and reshaping the ventricle, in combination with coronary bypass grafting and mitral valve repair. Cardiac surgeon **John Conte** and others here who’ve offered SVR for several years are participants in the NIH-sponsored STITCH (Surgical Treatment for Ischemic Heart Failure) trial comparing the procedure to other treatments for CHF.

“The usual candidates have had an anterior myocardial infarction,” says Conte. “We’ve been leaders in showing that patients with multiple areas of infarction or associated pulmonary hypertension can benefit from SVR as well.”

Conte and colleagues have presented their results at major meetings, including those of the International Society for Heart and Lung Transplantation, the American Association of Thoracic Surgery, and the Society of Thoracic Surgeons.

### VIAGRA FOR BIG FAILING HEARTS?

Sildenafil, which increases an arterial dilating molecule, is best known as a treatment for erectile dysfunction. But cardiologist **David Kass** and his research team have discovered that it also may have potent and potentially important beneficial cardiac effects.



David Kass

Comparing the drug with no treatment in mice with cardiac muscle enlargement, Kass’s group found that Viagra blocked adrenergic stimulation and not only prevented but reversed hypertrophy and its resulting dysfunction (see Image Gallery, page 4). Even more encouraging, says Kass, is that “subsequent research suggests these effects will likely translate to humans, potentially offering a major new treatment for patients with hypertension, cardiac hypertrophy, and heart failure.”

A large clinical trial testing the efficacy of drugs like Viagra in improving heart function and reversing ventricular hypertrophy is expected to start later this year.

## Teaching Rounds

### Tissue Doppler Echocardiography

For patients with congestive heart failure, cardiac resynchronization therapy (CRT, also known as biventricular pacing) reduces symptoms, promotes favorable reverse remodeling of the left ventricle, reduces heart failure hospitalizations, and may reduce mortality. CRT re-coordinates contraction of both ventricles, electrically pacing not only the right ventricle (as a standard pacemaker does) but also the left. The biventricular pacemaker is considered for patients who have refractory heart failure despite optimal medical therapy, particularly those with low ejection fraction and electrocardiographic QRS prolongation. However, about 30 percent of patients who meet these criteria do not respond to CRT. Novel imaging techniques such

as tissue Doppler echocardiography may enable better patient selection for CRT.

The dyssynchronous heart is characterized by an initial septal contraction while the lateral wall is not yet activated, and lateral wall contraction while the septum is relaxed—a pattern that leads to inefficient expulsion of blood from the left ventricle. “With tissue Doppler echocardiography, we track myocardial motion,” says cardiologist **Ted Abraham**, who studies this highly sensitive technique. “Patients who have a septal-to-lateral systolic motion delay exceeding 65 msec are those likely to benefit from CRT. Even in patients without QRS prolongation, we’ve been able to identify ventricular dyssynchrony.” ■



Sections of mice hearts show the protective effect of sildenafil (Viagra). Cardiac hypertrophy and remodeling is induced by an operation to constrict the aorta. Top row: Normal (left), and 3 weeks (center) and 9 weeks (right) after surgery. Bottom row: Treatment with sildenafil prevented cardiac enlargement.

Top right cover image: A set of pressure-volume loops representing left ventricular work through 10 cardiac cycles as pre-load is reduced.

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### Cardiovascular Topics at Johns Hopkins

February 23–25, 2006

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# Cardiovascular REPORT

The quarterly Johns Hopkins Heart Institute *Cardiovascular Report* is one of many ways the Institute seeks to recognize and enhance its partnership with its thousands of referring physicians. Comments, questions and thoughts on topics you would like to see covered in upcoming issues are always welcome. © The Johns Hopkins University, 2005

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