NEWS

A Space Age Vision Advances in the Clinic

The total mechanical heart is making headlines, but many say a less radical technology—the heart assist device—is leading the revolution

After barely surviving for nearly 2 decades, efforts to build a "total artificial heart" have gained a new lease on life. Surgeons in Louisville, Kentucky, removed the failing heart of a 59-year-old man last July and replaced it with a machine. Indeed, they implanted a whole network of machines: a 1-kilogram pump, a computer, a battery, a power converter, and cables to link them all together.

It was a dramatic procedure, the first total heart implant in the United States since the mid-1980s. The patient, Robert Tools, had been facing certain death and was too sick for a donor heart. He agreed to be the first to try a new mechanical replacement heart made by Abiomed Corp. of Danvers, Massachusetts. And it was a success, at least in some respects: Tools survived the implantation at Louisville's Jewish Hospital and later gained enough strength to venture outdoors a couple of times. But he suffered a stroke—caused possibly by a clot that formed in the artificial heart. On 30 November he died after 151 days on the machine.

Tools's experience was certainly better than that of his famous predecessor—Barney Clark, the Seattle dentist who in 1982 was the first to receive the celebrated "Jarvik-7" heart, named for its designer Robert Jarvik. Clark lived 112 days tethered to an external power unit the size of a washing machine, never able to leave the hospital room. In news clips he appeared miserable and uncomfortable. Even though another patient with a Jarvik-7 lived for 620 days, the artificial heart became linked in the public mind with Barney Clark's ordeal.

Hoping to erase those memories, Abiomed took a different tack. It created a more user-friendly device, called AbioCor, in which the pumping components are fully implanted, powered by radio-frequency energy transmitted through the skin. Doing away with connector lines may lower the risk of infection and frees the patient to walk around for several hours with batteries. Company president and CEO David Lederman also sought to protect patients' privacy and limit harsh publicity: Hospitals agreed not to give daily reports on medical details. And he lowered expectations, telling reporters that they should consider it a success if the first patients lived 60 days. At this writing, four of six had passed that mark and three were still living. *Time* magazine dubbed AbioCor "the invention of the year."

The AbioCor trials have gone "remarkably well" considering how sick the patients are, says John Watson, the senior official at the National Heart, Lung, and Blood Institute (NHLBI) who oversees this area. But that success has rekindled a debate about the best way to meet the needs of the estimated 100,000 people in the United States who, like Tools, face heart failure each year yet have little prospect of obtaining one of the 2200 donor hearts available for transplant.

AbioCor's comparative success has led supporters to argue that it could eventually

Heart of the heart. The AbioCor pump is controlled by a small computer and power supply system, all implanted.

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be an alternative to transplantation. But critics dismiss the totally implantable heart as "obsolete," a hugely expensive technology that may never deliver an acceptable quality of life. Many experts, including Watson, believe that, at least in the near term, desperate patients are more likely to be helped by machines known as ventricular assist devices (VADs). These mechanical pumps, in use since the early 1990s, boost rather than replace the ailing heart by increasing blood flow through a single chamber, or ventricle, and may even help the heart get stronger.

All these devices are now just stopgaps. The U.S. Food and Drug Administration (FDA) has approved them only as a "bridge to transplant," not as a permanent solution. But supporters of AbioCor and VADs are both hoping to gain FDA's blessing for far more extensive use of these ultimate bionic devices.

Aerospace baby

The U.S. effort to build artificial hearts began in 1964 when NHLBI established the first R&D program, with a budget that rose to $10 million a year by 1970. Contracts, mainly with aerospace firms, yielded several test devices, including the Jarvik-7. Developed at the University of Utah under the direction of Willem Kolff, it was the first artificial heart implanted in a human with FDA's approval. Kolff recruited Utah heart surgeon William DeVries to lead the clinical work and in 1982 won FDA's consent to treat five patients. DeVries and others reported results in 1988. An accompanying editorial in the *Journal of the American Medical Association* noted "many complications" that "seem to be related specifically to the design of the Jarvik-7," such as blood clots and infections along the skin-penetrating power lines.

Three months later, NHLBI director Claude Lenfant announced that he was ending the total artificial heart program because NHLBI couldn't afford it, and many clinicians believed that VAD systems then under development were closer to practical use. But two powerful senators—Edward Kennedy (D–MA) and Orrin Hatch (R–UT)—got NHLBI to reverse that decision and renew funding.

Over the years, NHLBI has spent about $100 million on the total artificial heart, Watson estimates. By the late 1990s, however, only two competitors remained: Abiomed and a group led by William Pierce, Walter Pae, and Gerson Rosenberg of Pennsylvania State University's Hershey Medical Center. Penn State lost the race to the clinic, Rosenberg says, when its industrial backer, 3M Corp., pulled out. In 2000 the university sold the "Penn State Heart" to Abiomed, which plans to develop it.

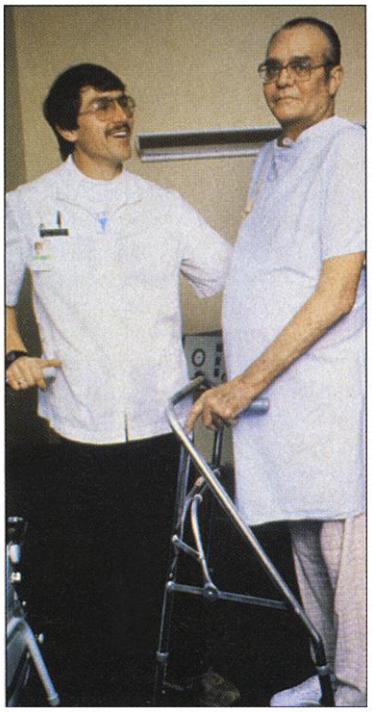
Survivor

What makes AbioCor exceptional, says company vice president Edward Berger, is that the system fits within the body. Unlike predecessors, it doesn't require a line into the body for pressure relief or power supply. It relies on a quiet centrifugal electric pump that shuttles hydraulic fluid alternately between two chambers that press on blood sacs corresponding to the left and right sides of the heart. In addition to reducing infection risks, according to Abiomed, this should enable the patient "to remain mobile and continue a productive lifestyle."

The AbioCor has not been priced yet, Berger says, although many predict that it will cost about $75,000. Berger notes: "Our goal is to eventually sell it for less than half that amount," assuming manufacturing can be improved. The implantation procedure might

cost $150,000, observers say. The heart would be offered to patients with moribund left and right heart chambers who could not be saved by a VAD. No one is sure how many people might be candidates; Abiomed estimates "many thousands" per year in the United States, whereas an executive at a VAD manufacturing firm doubts that the number would reach 3000. VADs, by contrast, are thought to have a potential market of 30,000 to 100,000 per year.

Before Abiomed can sell this product, however, it must demonstrate to FDA that its device will extend and improve a patient's life. Jarvik thinks this will be hard. The AbioCor system "represents old technology," Jarvik argues. It uses a displacement diaphragm pump that requires artificial heart valves, he adds, making for a complex system that's likely to cause clots and infections. Jarvik predicts that fiscal managers will balk at total replacement hearts: Because they are intended for the sickest heart patients, Jarvik predicts that implanting them will often be traumatic, leading to "million-dollar patients."



Pioneers. Robert Jarvik (left) and Barney Clark, the patient who received the first Jarvik-7 heart, in 1982.

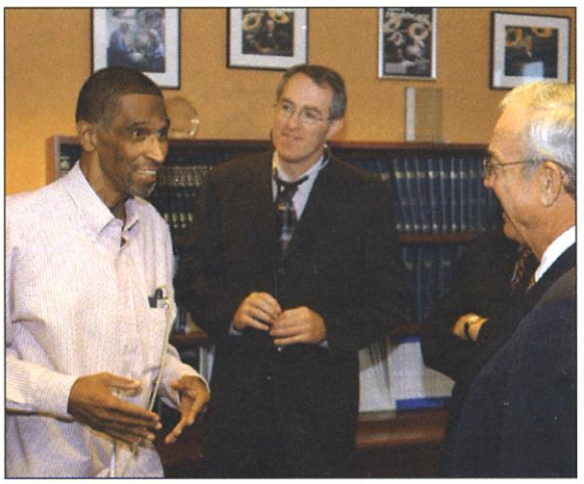
Abiomed's Berger rejects this skepticism, noting in an e-mail that "reliability testing in the laboratory leads us to think … we may already have an AbioCor that will sustain a patient for more than a year." It is too early to tell whether blood clots will be a problem for the first-generation AbioCor, he says, although results so far suggest that "the issue is addressable through anticoagulation management" similar to that already given to patients with artificial heart valves. Recently Abiomed announced that it is removing an outer "cage" to lower the risk of clots in future trials. Eventually, 5 to 10 years from now, Abiomed hopes its device will run for 5 years and be an alternative to heart transplantation.

Reversing field

As Abiomed seeks to prove that its device can replace a failing heart, others—including Jarvik—are pursuing a different strategy. "Removing the natural heart is an obsolete approach," Jarvik says today. His own company in New York City is developing small, simple pumps that go inside the heart and potentially salvage it. He calls his new device the Jarvik 2000, or the "flow-maker," to suggest something as routine as a pacemaker. Jarvik argues that the risk of infection is greatly reduced because his device is one of several new models powered by a miniature rotary pump that generates no pulse and requires no artificial valves. The entire mechanism sits in the ventricle immersed in blood, an environment hostile to bacteria.

One surgeon pioneering the use of Jarvik 2000, Stephen Westaby of John Radcliffe Hospital at Oxford University, U.K., seconds Jarvik's views. "The total artificial heart puts us back 30 years," Westaby says. Instead, he praises the "thumb-sized" Jarvik 2000 because it is easy to sew inside the patient's left ventricle—and it can be removed just as simply if the natural heart improves. Already, Westaby says he is using the Jarvik 2000 experimentally as a permanent prosthesis: "I've had three in the community for 7 to 19 months now, and they're all doing terrifically well." The 19-month patient, Peter Houghton, who according to Westaby was "within a couple of weeks of death" before surgery, recently flew across the Atlantic Ocean on a commercial plane to see relatives and brief NHLBI on his health.

Researchers are surprised to discover that the use of VADs enables some patients' hearts to regain strength by resting the muscle. Westaby says he and colleagues at the Texas Heart Institute in Houston and the Cleveland Clinic in Ohio have all seen this phenomenon. This is "my biggest interest" now, Westaby says. "I intend to spend a lot of time on it." He imagines that it may be possible someday to routinely use small pumps, drugs, and cell therapy to restore sick hearts.



Next generation. Robert Tools (left), with doctors; Tools lived 151 days on the AbioCor device but suffered a stroke and fatal bleeding.

Many other VAD designers are also developing miniature rotary pumps. The biggest U.S. company in the field, Thoratec Corp. in Pleasanton, California, is working on several generations of VADs simultaneously. The newest, called HeartMate II and HeartMate III, will include small rotary pump devices. Terumo Corp. of Tokyo was among the first to use a levitating magnet system to eliminate bearings and friction that can damage blood cells, and similar designs are being developed by Thoratec and the Berlin Heart company in Germany.

Keith Grossman, CEO of Thoratec, claims that the HeartMate II VAD pump is designed to run for 5 to 8 years and HeartMate III, for up to 10 years. These goals are twice the design life of Thoratec's current standby, the HeartMate XVE. Grossman expects that a growing number of patients who cannot get donor hearts will use VADs as a permanent solution. Indeed, Thoratec has asked FDA for permission to begin marketing VADs as a therapy for heart disease, and FDA has already scheduled an advisory panel review for 4 March.

Thoratec and others plan to cite the REMATCH trial,* reported last November, as proof that mechanical hearts are robust enough now to be used as standard therapy. This trial of 129 patients showed that those with VADs were more likely to survive over a 2-year period, and to enjoy a good quality of life, than those on standard drug therapy. Eric Rose, lead author of the REMATCH study at Columbia University in New York City, predicts that an FDA policy change could come as early as this summer.

The major task after the FDA review, Rose says, will be to argue that Medicare should reimburse medical centers for VADs even if patients are not waiting for a transplant. Rose is already consulting with the Department of Health and Human Services about costs. If Medicare gives a green light, the artificial heart–makers will enter a brave new world.

–ELIOT MARSHALL

* E. A. Rose *et al.*, "Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure," *New England Journal of Medicine* **345**, 1435–1443 (2001).

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