CARDIAC BIOENGINEERING

New Devices Are Helping Transform Coronary Care

A year ago, Albert Williams lay in bed at the Texas Heart Institute in Houston, barely alive after a mysterious decline in his heart function. He prayed that a transplant would save him. Today, the 43-year-old still hasn't received a new heart, but he is often seen washing his car or mowing his lawn outside his Houston home. When strangers ask about the cassette-sized box strapped to his waist or the battery pack slung over his shoulder, the affable Texan explains frankly, "It's a pump for my heart."

The experimental pump is also part of a revolution in cardiovascular research: the design of a vast array of new devices that provide life-saving help to patients with diseased hearts. The novel gadgets range from the seemingly simple, such as small metal tubes called stents that keep coronary arteries open after balloon angioplasty, to complex, implantable microelectronic machines that watch for and correct abnormal heart rhythms. Even the simple tubes carry hefty price tags, resurrecting worries about skyrocketing medical costs. But cost issues are unlikely to seriously slow the pace of innovation, propelled by ever-increasing clinical need and rapid advances in electronics and other technologies. "The area of cardiovascular devices is extremely active at this time. ... Real progress is currently being made in a number of important areas," says cardiologist Myron Weisfeldt of Columbia University College of Physicians and Surgeons in New York City.

Mechanical hearts

The design of "heart pumps," such as the one Williams wears, is one of the areas seeing this rapid progress. Known as a left-ventricular assist device (LVAD), it's used to treat heart failure, in which a heart attack, infection, or other disease leaves the heart too weak to pump all the blood the body's tissues need. LVADs take over the functions of the heart's main pumping chamber, the left ventricle, to push oxygen-carrying blood from the lungs to the tissues.

Right now, almost all LVADs are used only as "bridges" to heart transplants. But newer models, now in clinical testing, give patients a freedom not possible with bulkier early models, says Matthias Loebe, a cardiac surgeon at the German Heart Institute in Berlin: "These devices allow patients to go home and do everything they normally do—drive a car, have a girlfriend—everything."

And the future may be even brighter, as researchers race to develop the next generation of LVADs, which promise to be smaller, more convenient, and safe enough for permanent use. Indeed, Patrick McCarthy, director of the assist device program at the Cleveland Clinic, predicts that "LVADs will eventually be better than a heart transplant." If so, that would be a major advance, given that each year, only about 4000 of the approximately 150,000 people in the industrialized world who need new hearts get them. The rest die waiting for a donor.

McCarthy's vision is not assured, but the best current models have already come a long way from the first implantable heart-assist device, which was born almost 30 years ago, in the shadows of flashier—and largely unsuccessful—attempts to create a total artificial heart. Realizing that 80% of heart-failure patients need help only for their left hearts, a team of engineers led by Victor Poirier at Thermo Electron Inc. in Waltham, Massachusetts, took a simpler approach and built half a heart—an LVAD.

After Poirier's group tested a primitive prototype in a human in 1975, officials at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Maryland, were sufficiently encouraged to sponsor a program to develop implantable LVADs that could serve as long-term alternatives to transplants. Two promising devices emerged from this initiative: the HeartMate, developed by Poirier's team and approved for human use by the Food and Drug Administration (FDA) in October 1994, and an LVAD made by Novacor in Oakland, California, a portable version of which is now in clinical trials.

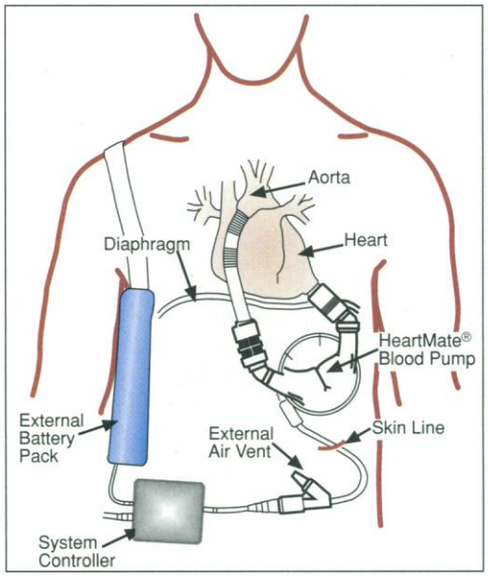
Both pumps, which are roughly the size of a slightly flattened grapefruit, are embedded in the abdominal wall and then linked, via two tubes, to the top and bottom of the left ventricle. With each heartbeat, the diseased ventricle sends blood through the bottom tube into the pistonlike pump, which squeezes the blood out the other tube and into the aorta. Both devices also require exterior connections. The FDA-approved pump is powered by air, while other models are electrically driven, sporting wires that penetrate the skin as well as a percutaneous air-vent tube to prevent a vacuum from developing. But despite their clumsiness—both are controlled by large external consoles that can't leave the hospital grounds—these early models proved to be successful bridges to heart transplants.

Now, though, a lucky few patients like Williams are receiving portable versions of these LVADs that are powered by two lightweight batteries in a case half the size of a videotape and controlled by a box no bigger than a deck of cards. Although portable LVADs are still restricted by supply and stringent FDA rules for clinical testing, experts predict that is about to change. "We're at the launching pad for widespread use," says McCarthy.

Researchers caution, however, that not all the questions about the devices have been answered. "We've seen LVADs improve patients' quality of life, but we don't know what the long-term outcome will be," says Robert Kormos, director of the artificial heart program at the University of Pittsburgh.

One worry is infection, which can develop where the wires and air tube penetrate the skin. In addition, the size of the pumps makes them difficult to implant even in men, and impossible in small women and children. That's why the NHLBI is now sponsoring efforts to design next-generation LVADs, one of which is spearheaded by bioengineer Robert Jarvik of artificial heart fame. "Our objective is a booster pump that is totally implantable, with no air tube or wire punching through the skin," says Jarvik, who is working with scientists at Transicoil Inc. in Norristown, Pennsylvania, and the Texas Heart Institute.

To achieve that goal, the team designed a pump that is roughly the size of a C-cell battery and will sit inside the left ventricle, connected to the aorta by a synthetic blood vessel. It has just one moving part, a rotor



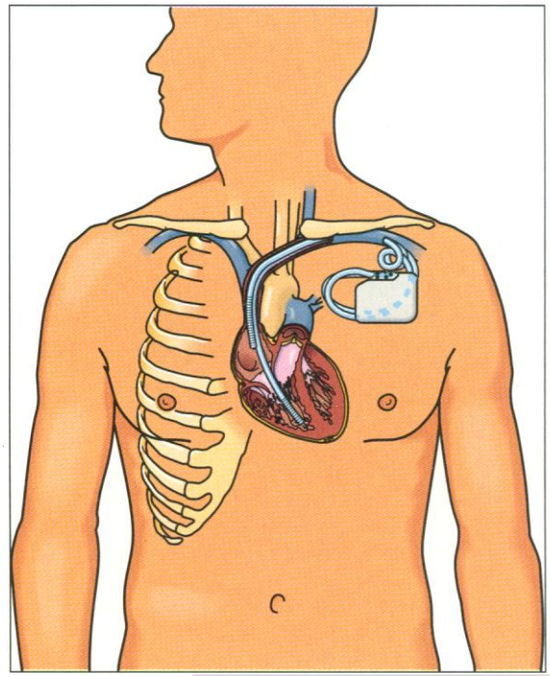
Heart assist. The diagram shows how an LVAD "heart pump" is hooked up to the heart and to its external controller and power supply.

that spins at about 10,000 rpm to force blood into the aorta. And instead of using a wire through the skin, the pump will drain power from coils implanted just beneath the skin that pick up electromagnetic energy from lightweight batteries worn in a thin vest.

Although the device has kept calves alive for up to 5 months, human trials are at least 5 years away, Jarvik says. Among other things, the researchers will have to prove that their high-speed pump doesn't damage blood cells. But even if Jarvik's device passes that test, it will need batteries that must be changed one or more times a day. Robert Whalen's group at Whalen Biomedical in Cambridge, Massachusetts, along with scientists at the University of Utah, Salt Lake City, is working on a radical way to eliminate this problem: by eliminating the motor.

Their plan is to construct a pump powered by muscle tissue taken from the patient's back. The muscle will be wrapped around a fluid-filled cylinder placed under the ribcage and connected to a blood pump placed between the left ventricle and the aorta. When the muscle is stimulated to contract, it will squeeze the cylinder, driving fluid into the pump's housing. There, the fluid compresses a blood-filled bladder, forcing the blood into a conduit leading to the aorta. The muscle stimulus will come from an implanted, low-energy trigger resembling a pacemaker, which could be powered, just as pacemakers are, by long-lasting batteries inserted under the skin.

Critics doubt, however, whether muscle tissue can ever be made strong enough to drive an LVAD. "There's a limit to the amount of power you can train muscles to produce," says Leonard Golding of the Cleveland Clinic, who is developing a device similar to Jarvik's. Undaunted, Whalen predicts he'll have a system in clinical trials within a decade. Even if he doesn't, most LVAD recipients consider battery packs a minor inconvenience, given what's at stake. Take Williams, the Houston implant patient, who's simply happy to be alive. "It's a miracle," he says.



PAUL STRANDOO

A shock in time. Implantable defibrillators, such as the one shown here, are already saving lives.

Personal shock therapy

While heart failure happens gradually, damage to the heart muscle can kill far more suddenly, if it interferes with the normal flow of electrical impulses controlling the heartbeat. This can cause abnormal heart rhythms, including, in some cases, ventricular fibrillation (VF), in which the heart beats so chaotically that it stops pumping blood, causing death within minutes. To make matters worse, many patients with arrhythmias do not respond to drug treatments, or find their side effects intolerable. "There's been no significant progress in drugs for arrhythmias since the 1920s," says Pierre Galletti, a biomedical engineer at Brown University.

But recent advances in devices called implantable defibrillators, which can sense when the heart is beating erratically and shock it back to its normal rhythm, are providing new hope. "What we have now is light-years ahead of what we had before," says Morton Mower, a cardiologist at Cardiac Pacemakers Inc. in Baltimore and co-inventor of the implantable defibrillator. Cardiac surgeon Levi Watkins Jr. of Johns Hopkins Hospital, who implanted the first one in a human in 1980, adds that 50,000 to 80,000 devices have been implanted worldwide and have saved the patient's life at least once in the "overwhelming majority" of cases.

And implantable defibrillators may have an even greater life-saving potential in the future. So far, the devices have been given mainly to people who have survived a VF attack, about 32,000 people in the United States each year. But physicians are beginning to give them to other people who have not yet had a VF attack, but are at high risk of one. These include patients with ventricular tachycardia—a type of arrhythmia in which the heart races faster than 100 beats per minute—and also some heart-attack survivors. As a result, up to 180,000 more people could become eligible annually for the devices, which cost about $23,000.

The original implantable defibrillator was the brain child of cardiologist Michael Mirowski, who got the idea back in the mid-1960s after his mentor died suddenly from VF. Then in Israel, Mirowski began dreaming of small gadgets that could be implanted inside people's chests to detect and correct life-threatening arrhythmias. Lacking resources in Israel to realize his dream, he landed a job at Sinai Hospital in Baltimore. There, he met Mower and proposed his project. "He asked me if I thought it was possible," Mower recalls, "and I couldn't see why not."

Within 3 months of teaming up with engineer William Staewen, the two doctors had a working model. It consisted of a box containing four wire-strewn, 8-by-10-centimeter boards supporting the circuitry needed to recognize abnormal rhythms and shock the heart back to life. This apparatus was linked to a sensing and shocking lead that was sewn to the outside of a heart. It took nearly a decade more, however, to craft the first defibrillator suitable for human use, which was introduced commercially in 1985 by Cardiac Pacemakers Inc.

Although this device saved lives, its design left much to be desired. Larger and fatter than a pack of cigarettes, its sensing abilities were so crude that it couldn't distinguish between a true arrhythmia and the rapid heartbeat of exercise, and it delivered only one level of therapy—a literally hair-raising shock.

Since then, advances in electronics have shrunk the devices by more than half—to just slightly larger than a pager. In addition, their leads are now threaded through blood vessels and into the right side of the heart, making surgery far less invasive. "Fifteen years ago, we cracked the chest; today, we thread a vein," explains Watkins.

But the biggest advance comes from the microprocessors that perform sophisticated diagnostic and sensory functions and can be programmed to respond to each patient's heart. For instance, defibrillators can now distinguish an exercising heart from one going into arrhythmia by ignoring the gradual heart rate increases typical of exercise but responding to sudden jumps in heart rate. They also monitor, second by second, the results of their shocks—allowing them to begin with very mild shocks and then, if sensors reveal that a heart is still malfunctioning, to step up the treatment to higher voltages. Medtronic pioneered this technique, known as tiered therapy, in the early 1990s with their "PCD" defibrillator. And now, several companies have introduced devices that record the heart's activity during each arrhythmic episode, enabling more precise diagnosis and treatment.

Still, all these devices have a serious shortcoming: They ramp up to deliver a monstrous shock, because that's the only surefire way to reset the heart. William Ditto and his colleagues at the Georgia Institute of Technol-

ogy are exploring a way of doing that with a lot less firepower, based on a careful analysis they made of the arrhythmic heart.

When the Georgia Tech researchers, along with Francis Witkowski of the University of Alberta in Canada, used electric current to throw the hearts of dogs into VF, they found that the heart muscle behaves chaotically, in mathematical terms, meaning that it rapidly switches between numerous different electrical patterns, many of which are regular. These results suggest, Ditto says, that a low-energy stimulus might be able to lock the arrhythmic heart onto one of its component rhythms and thus trick it into defibrillating itself.

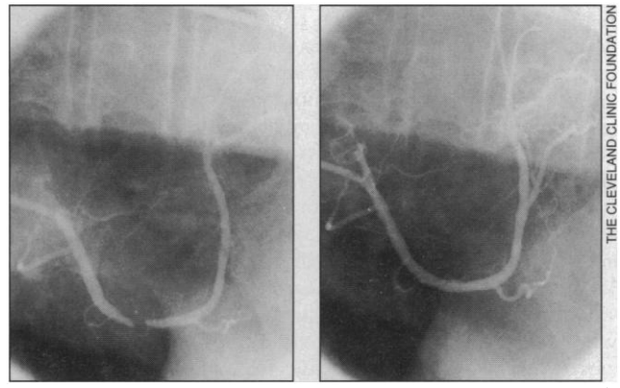
In practice, Ditto explains, this would mean applying "small tickles of electric current" at precisely timed intervals dictated by a chaos-control algorithm he and others developed in 1990. The Georgia Tech team, working with researchers at the University of California, Los Angeles, has found that the method works on disembodied rabbit hearts; in a few months they'll test the technique in whole dogs. If it worked in people, Ditto's invention would be a boon for patients such as 71-year-old Salvatore Viviani, who received seven shocks soon after his defibrillator was implanted last December. "My whole body jumped, and I was hollering pretty loud," he recalls. "But at least those shocks saved my life."

Armor for arteries

The new LVADs and implantable defibrillators depend on advances in microelectronics and other sophisticated technologies. But even the simplest devices can have enormous life-saving potential. Take the tiny metal tubes called stents. In the past 20 years, balloon angioplasty—which uses an inflatable balloon to open coronary arteries clogged with atherosclerotic plaques—has become a mainstay of treatment for coronary artery disease. Indeed, at least 400,000 people undergo balloon angioplasty each year in the United States alone. But the procedure is far from perfect. Blockages re-form within 6 months in up to 40% of patients, as scar and muscle tissue gradually grow into the vessel in a process called restenosis.

Enter the stents. These small metal devices—either coils or slotted tubes—are expanded inside an artery to hold the balloon-mashed plaque against the artery wall and open the vessel so wide that restenosis won't significantly impede blood flow. Ever since last year, when researchers found a way to dramatically reduce stents' most dangerous side effect, life-threatening clot formation, stent fever has gripped cardiologists. In the United States, these metal scaffolds were implanted in more than 110,000 patients in 1995, up from just a few thousand in 1994. "The stent is the first new technology that makes a real difference in restenosis," says Patrice Nickens of NHLBI.

However, major concerns about stenting remain, including whether they might have injurious long-term effects. Another concern is their whopping cost. On average, a stent implant costs about $2400 more than angioplasty—$1600 of that for the tube alone, says David Cohen, a cardiologist at Beth Israel Hospital in Boston.



Opening up. The coronary artery at left is blocked, but after angioplasty and stent placement the artery is open *(right)*.

But these concerns about stents are small compared to the one that surfaced in 1991, when Patrick Serruys at Erasmus University Hospital in Rotterdam, Netherlands, and his colleagues reported the results of early trials. The stents, they found, caused a high incidence of acute clotting, or thrombosis, occurring within days of the surgery; in 18% of patients, the clotting blocked the coronary arteries and led to heart attacks. The discouraging results hit the cardiology community like "a bombshell," says Serruys, squelching enthusiasm for stents.

Still, restenosis is such a serious problem that researchers persevered, beginning two large-scale randomized studies (known as the Benestent and STRESS trials) comparing coronary-stent placement with traditional balloon angioplasty. But unlike earlier trials, in these all the stent recipients got anticlotting drugs to combat thrombosis. And the results were more encouraging.

In the STRESS trial, only 30% of the 205 patients who got stents had restenosis, compared to 40% of the 202 angioplasty controls, and the larger Benestent trial found a similar drop. What's more, only 3% of the stent recipients experienced the sudden clotting that plagued earlier studies. This came at a cost, however. The potent anticoagulants, heparin and warfarin, used with the stents caused major bleeding problems and required week-long hospital stays, more than twice those needed after angioplasty alone. So most cardiologists stuck with the bare-bones balloon.

Meanwhile, though, rumors began to leak of findings that would obviate the need for such powerful anticoagulants. Using ultrasound to re-examine stents that had been placed in arteries, a team led by Antonio Colombo at Columbus Hospital in Milan, Italy, found large gaps between the edges of the stent and the artery wall—gaps that might, Colombo reasoned, encourage clot formation.

So Colombo's team began testing a new way of deploying stents in which a high-pressure balloon is used to expand the tubes to a larger diameter, wedging them more snugly against the artery wall. When used with aspirin and ticlopidine hydrochloride, oral anti-clotting drugs that are much less dangerous than heparin and warfarin, the new method produced spectacular results. "We achieved a thrombosis rate of less than 1%—less than one-third the rate others had reported using anticoagulants," Colombo recalls. The findings, which were published in the 15 March 1995 issue of *Circulation*, "opened the door" to widespread use of stents, Serruys says.

With acute clotting under control, researchers are now trying to make the stents even more effective against restenosis. In a pilot study of 207 patients, for example, Serruys's team has found that a stent coated with heparin—which inhibits clotting factors involved in both thrombosis and the wound-healing that leads to restenosis—slashed restenosis to about 13% after 6 months. And Eric Topol's team at the Cleveland Clinic has had promising results in animal studies with stents coated with polymers that slowly release various chemicals, including nitric oxide, known to inhibit body processes underlying restenosis.

It's too soon to tell, however, whether these stents will prove safe and effective over the long term. In fact, Serruys and others say that's a general concern about stents, as almost all the clinical studies so far have lasted just 6 months. "I'm concerned we'll see new atherosclerosis within the stent 5 to 10 years down the road," Serruys says. Other possible problems include infection and wear on the coronary arteries. Yet there's little sign that cardiologists will give up stents—or any of the other bits of wizardry that are reshaping the treatment of heart disease. Says Donald Baim, Beth Israel's chief of interventional cardiology: "The new device genie is clearly out of the bottle."

–Ingrid Wickelgren

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