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Transplantation techniques remain the gold standard for advanced heart failure treatment. Pictured is Dr. Bruce Reitz, left, performing a heart-lung transplant. Dr. Norman Shumway, a transplant pioneer, is directly across the table, also holding a surgical instrument.



ADVANCED HEART FAILURE: TRANSPLANTS, HEART ASSIST DEVICES, AND THE FUTURE

HEART TRANSPLANTATION IS THE gold standard surgical treatment for patients with advanced heart failure. Unfortunately, there is a worldwide scarcity of donors for heart transplants. Over the past ten years, the number of heart transplants performed in the United States has remained relatively stable at between twenty-five hundred and thirty-five hundred annually. If there were enough donor organs, it is estimated that more than fifteen thousand, and perhaps as many as thirty thousand, heart transplants would be done each year. Patients of any age could theoretically undergo a heart transplant, but because of the scarcity of donors and a somewhat higher rate of complications after surgery, patients more than sixty-five years of age are generally not eligible.



The History of Heart Transplants

The technique for transplanting the heart and lungs did not rely exclusively on the heart-lung machine. The first transplantation was reported in 1905 by Drs. Alexis Carrel and Charles Guthrie. While at the University of Chicago, the pair implanted the heart of a small dog

into the neck of a larger dog by joining the heart of the smaller dog to the jugular vein and carotid artery of the larger animal. The animal's blood was not anticoagulated, and the experiment ended about two hours after circulation was established because of a blood clot in the cavities of the transplanted heart.

In 1950, Dr. Vladimir Demikhov, the great Soviet surgical researcher, described more than twenty different techniques for heart transplantation and published various techniques for heart and lung transplantation. He was even able to remove an animal's own heart and replace it with the heart from another animal before the heart-lung machine was developed. This was accomplished by placing the donor heart above the dog's own heart, and then with a series of tubes and connectors, rerouting the blood until he had the donor heart functioning in the appropriate position and the other heart removed. One of his dogs climbed the steps of the Kremlin on the sixth postoperative day but died shortly afterwards of rejection.

By 1960, Drs. Richard Lauer and Norman Shumway in the United States had established the foundation for heart transplantation as it is performed today.

Their method had also been used by Sir Russell Brock in England and Demikhov in the Soviet Union but became popular only after Lauer and Shumway reported it publicly. Shortly thereafter, Dr. James Hardy at the University of Mississippi attempted the first human heart transplantation. Because no human donor organ was available at the time, a large chimpanzee's heart was used. It was unable to support the circulation.

The first human-to-human heart transplant occurred December 3, 1967, at Groote Schuur Hospital in Capetown, South Africa. A surgical team headed by Dr. Christiaan Barnard transplanted the heart of a donor, who had been certified dead after there was no heart activity for five minutes, into a fifty-four-year-old man named Louis Washkansky, whose heart had been irreparably dam-

aged by repeated heart attacks. This first transplant captivated the world's imagination, and Barnard's name quickly became one of the most recognizable names in medicine. Interestingly, Barnard himself did not think the operation was revolutionary. Not a single picture was taken during the entire procedure. In a recent interview, Barnard talked about the conditions that led to the first transplant:

"Heart transplantation was successful because it was virtually just another heart operation. We had experience in major heart surgery. We knew how to prepare a patient for it. We know how to care for a patient during such an operation and how to care for the patient postoperatively. All we had to do was work out the surgical technique

THE FIRST HEART TRANSPLANT

DR. CHRISTIAAN BARNARD WILL always be remembered as the heart surgeon who performed the first successful heart transplant using a human donor heart. He attended medical school at the University of Cape Town, South Africa, where he received training in general surgery. Then, in 1956, he received a two-year scholarship to study surgery at the University of Minnesota in Minneapolis.

"I actually went to Minneapolis to study general surgery," Barnard recalled. "I was working in a laboratory one day in general surgery when I walked past one of the labs where Dr. Vince Gott was working with a heart-lung machine. [Gott later became professor and cardiac surgeon-in-charge at Johns Hopkins University.] He looked up and said, 'Listen, I'm working and I need a pair

of hands. Do you mind scrubbing and giving me some help?"

"It immediately fascinated me that we now had the ability to work inside the heart. I switched to cardiac surgery, and that's how I got involved in heart surgery. I trained under Dr. C. Walton Lillehei in Minneapolis, and I often went to Rochester, Minnesota, to watch Dr. John Kirklin work."

When his training was over, Barnard returned to South Africa, where he performed the world's first human-to-human heart transplant. In 1999, Barnard recalled that famous operation:

"When I was ready to take the heart out of the donor, who was brain dead, I disconnected the respirator and waited until the heart went into ventricular fibrillation (a fatal rhythm)

Dr. Christiaan Barnard earned worldwide fame when he performed the first human-to-human heart transplant in South Africa in 1967.



and see how we were going to monitor and treat rejection.”

Indeed, cardiac surgeons were clearly successfully tackling the demands of heart transplantation. Only three days after Barnard’s first transplant, the second human heart transplant using a human donor was performed on a child by Dr. Adrian Kantrowitz in Brooklyn, New York. Kantrowitz’ patient died of a bleeding complication within the first twenty-four hours.

Washkansky, meanwhile, died on the eighteenth postoperative day. At autopsy, the heart appeared normal, but pneumonia was present, possibly because of the methods used to treat rejection.

Barnard performed his second heart transplant on Philip Blaiberg on January 2, 1968. Blaiberg was discharged from

the hospital and became a celebrity for the several months he lived after the transplant. This highly visible success signaled that a heart transplantation was possible for humans suffering from end-stage heart disease.

In the first year after Barnard’s first heart transplant, about one hundred heart transplants were performed by cardiac surgeons around the world. However, by the end of 1968, most groups abandoned heart transplantation because of the extremely high mortality related to rejection. Despite the lack of interest, Shumway, Lauer, Barnard, and a few others persevered both clinically and in the laboratory. Their eventual discovery of better drugs for suppression of the immune system response established heart transplantation as we know it today.

before I opened the chest and took out the heart.

“The only moment that was an eerie moment was when I had taken the heart out of the recipient. That was the first time that I saw a human being without a heart but alive because he was kept alive by the heart-lung machine. That was the only moment of the operation I really, really remember.

“We did not consider the operation a big event. We realized we were doing a different operation, but we had done different operations before. We did not take a single photograph of the operation. In fact, I didn’t even inform the hospital authorities that I was doing the operation that night. I only told them afterwards, and we didn’t have press or anybody around. It was only the next day that the media found out that we’d done the operation.”

The celebrity surrounding that event changed his life and, in his own words, he found the publicity surrounding that event “disturbing for two reasons. It interfered quite significantly with my practice of surgery because there were always media around, and it also interfered with my family life.”

After this famous transplant, however, Barnard was often on the leading edge of organ transplantation. Even before the heart transplant, he performed the first kidney transplantation in Africa and, later on, the third heart-lung transplantation in the world. He also performed the world’s first **heterotopic transplant** (sometimes called the “piggy-back transplant”), an operation during which a donor heart is placed next to the patient’s heart and the two work in parallel. This operation, which is still used today, was developed for circumstances when the donor heart was either questionable or too small.

Heterotopic Transplant:

A transplant of an organ or tissue, usually from one person to another, when the organ or tissue is not put in the location where it normally resides.



Dr. Bruce Reitz performed the world's first successful heart-lung transplant in 1981. His first patient, Mary Gohlke, was a long-term survivor.

THE FIRST SUCCESSFUL HEART-LUNG TRANSPLANT

DR. BRUCE REITZ GRADUATED from medical school in 1970 in an environment that had been electrified by the first heart transplant.

"After Dr. Christiaan Barnard did that procedure, that's the kind of thing I was reading about every day as a medical student, and it really stimulated me," Reitz said. By the mid-1970s, working with Dr. Norman Shumway, Reitz was involved in a heart-lung transplantation program at Stanford University.

"Shumway suggested that I look at transplanting heart and lungs together," Reitz said. "He had done some work years ago, with a little bit of success. So we added a few things that got some successful results in the laboratory."

Building on this early work, Reitz performed the world's first successful heart-lung transplant. He recalled:

"Well, it was really a unique high-point of my career. First of all, it is a project that we had started in the lab about five years before. We had gone through some development phases and then through a phase when things started to click, and cyclosporine was an extremely ex-

citing compound that was so promising. Then we had thought that it was ready for patients, and I had Shumway's complete support and encouragement. Then to actually do the operation — Shumway was assisting me — was a really terrific experience.

"When you take it all out like that (heart and lungs) and put it in, there are actually fewer connections. There's basically the blood coming into the heart and the blood going out that has to be hooked up, but the whole circulation to the lung and back to the heart remains attached, and you just connect the airway."

His first patient, and the world's first patient to have a successful heart-lung transplantation, was a woman named Mary Gohlke, who suffered from a lung disease that had damaged her heart. "We were fortunate because we had a good patient who needed it, and she got better and was a terrific spokesperson for transplantation," Reitz remembered.

Reitz' team also discovered that the risk of rejection remains the same for a complete heart-lung transplant as for a heart transplant.



Heart and Lung Transplants

Almost fifteen years after the first heart transplant, a team of doctors headed by Dr. Bruce Reitz began a clinical trial to transplant both the heart and the lungs. Operating at Stanford University in 1981, the team's first patient was dis-

charged from the hospital in good condition and was still healthy more than five years after the transplant.

This clinical success was partially due to the discovery of a potent antirejection drug. **Cyclosporine** was discovered by workers at the Sandoz Laboratory in Basel, Switzerland, in

Cyclosporine:

A drug used to help prevent organ rejection in patients who have transplants.

1970. Ten years later, it was introduced at Stanford for cardiac transplantation. The incidence of rejection and infection was not reduced. However, these two major complications of heart and heart-lung transplantation were less severe with cyclosporine. The availability of cyclosporine stimulated the development of many transplant programs around the world in the mid-1980s.

Today, some patients who might have previously received a heart-lung transplant now undergo a single or double lung transplant, and the heart is repaired, if practical. Dr. Joel Cooper and his colleagues at the University of Toronto in the early 1980s led the way to human lung transplantation as we know it today.

Heart Transplants

Heart transplants are recommended for patients with advanced heart fail-

ure. Because donors are hard to locate, candidates for heart transplant have to meet certain standards. They should be psychologically stable. Their other organ systems, such as their kidneys, liver, and lungs, should be in good condition. It is possible, however, for some patients with severe lung disease and heart disease to undergo heart/lung transplantation. Candidates for heart transplantation cannot have long-standing insulin-dependent diabetes with organ damage. They are screened for most types of cancers because the drugs they will need to take after the transplant to help suppress rejection can actually cause certain cancers to grow rapidly. There are certain blood disorders that are also affected by these drugs. The drugs can suppress some blood elements and worsen these disorders. Patients generally are not considered qualified candidates if they have active infections because the immuno-

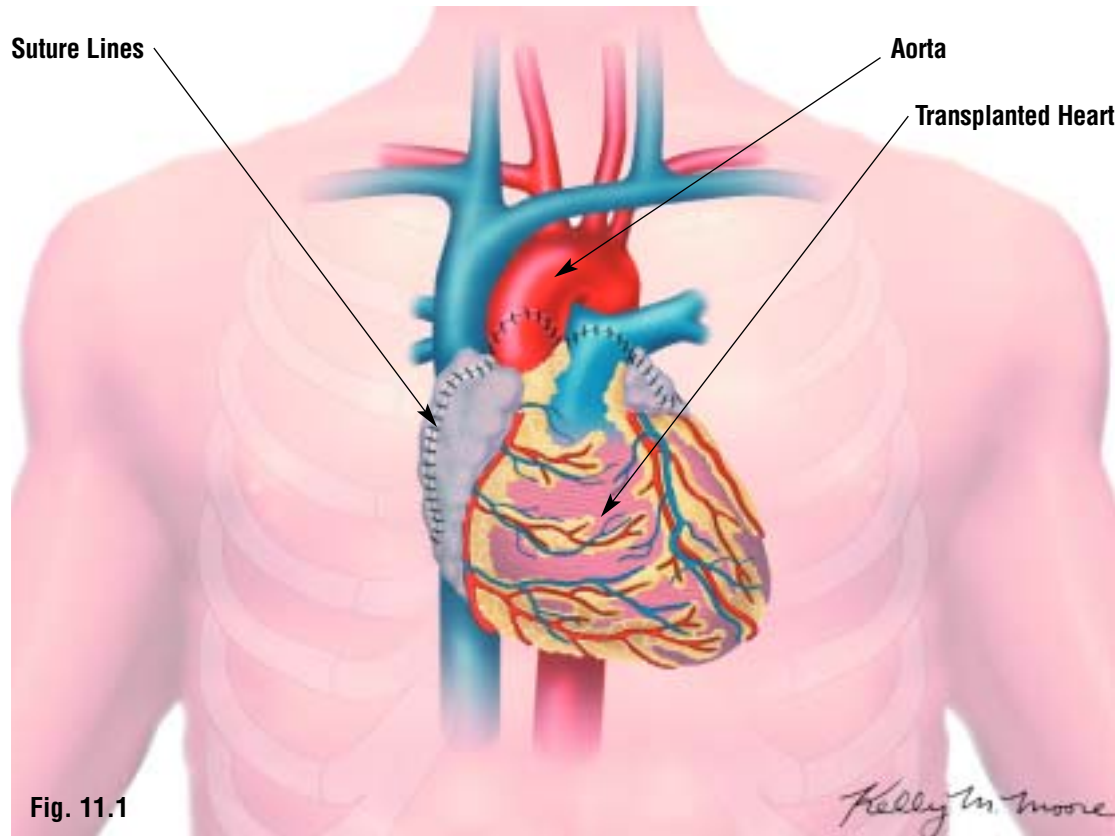


Fig. 11.1

Fig. 11.1: During heart transplantation, surgeons leave part of the native heart to sew onto the new, donor heart. The stitches show where the attachments are made during the operation.

suppression drugs make the body's immune system less effective in fighting infections and therefore can allow the infections to become worse.

Once it is determined that patients are candidates for a heart transplant, they are put on a waiting list for a donor heart that matches their blood and tissue type. When a match is found, the patient is admitted to the hospital.

The heart usually comes from a donor who has been in a traumatic accident and suffered fatal head injury and whose lung function was sustained by a ventilator. Frequently, the transplant team will have to go to another city or state, often traveling by private jet to retrieve the donor heart. The heart is removed from the donor. It is kept alive by using one of a number of techniques while it's brought back to the hospital where the transplant will take place. When the team bringing the donor heart is within a half hour of the hospital, the transplant patient is anesthetized and the chest is opened. When the team arrives with the heart, the patient is connected to the heart-lung machine. The diseased heart is then removed, and the new heart is sewn in (Fig. 11.1).

Portions of the transplant recipient's own left atrium with the four pulmonary veins and portions of the right atrium with the superior and inferior vena cava are not removed. The healthy donor heart is then sewn in. The left atrium and then the right atrium are connected to the remnants of the recipient's left and right atria. Next, the aorta and pulmonary arteries are connected. The clamp on the aorta is removed so the heart-lung machine, which had been supplying the body with oxygenated blood, can get blood to the recipient's new heart, and it will begin to beat.

After the chest is closed, the patient goes to the intensive care unit and usually spends at least a couple of days there followed by several more days in the hospital.

A number of powerful drugs are used to suppress organ rejection immediately after the surgery. When patients go home, they will typically be taking cyclosporine, prednisone, and azathioprine or tacrolimus. These drugs have side effects that can be harmful, and they have to be monitored carefully. In a successful transplant, some of these can be eliminated after a few weeks.

In an attempt to diagnose rejection even before there is clinical evidence, the patient must undergo regular heart **biopsy**. This is done with a special catheter that is introduced through a vein in the neck to obtain a small biopsy specimen of the transplanted heart muscle.

Most rejection episodes can be treated successfully with medications, but sometimes when they are severe the patient's circulation needs to be supported with a mechanical heart assist pump or even a second heart transplant.

The chance of surviving heart transplant surgery and leaving the hospital is greater than 90 percent. The chance that the patient will be alive one year after the transplant is about 85 percent, and there is about a 4 percent mortality rate per year after that as the survival rates decrease owing to complications related to the rejection process. Nonetheless, some patients now are alive twenty years after a heart transplant. Some patients have had more than one heart transplant during that period. Many heart transplant patients return to work and live a relatively normal life after their surgery.

Research continues on using animals as donors for human hearts. At this point, the rejection process continues to be much more severe when an animal's tissues are transplanted into an animal of a different species, for example, a dog's organ transplanted into a cat. If the rejection problem can be solved through research, organ shortage would no longer be a problem because animals such as pigs could be bred for organ donation.

Biopsy:

The process of removing tissue from a patient for examination.

Heart Assist and Artificial Hearts

Beyond heart transplantation, physicians have a number of mechanical options to assist failing hearts. One particularly useful device is called the **intra-aortic balloon pump**, which is used temporarily to treat patients with failing hearts and more commonly to help wean some patients from the heart-lung machine.

Intra-Aortic Balloon Pump

The intra-aortic balloon pump consists of an external pump unit, a catheter slightly larger than a piece of spaghetti,

and an inflatable balloon that's about the shape and size of a bratwurst (Fig. 11.2).

The catheter and the balloon pump are usually inserted into the femoral artery in the groin area and guided up into the aorta. The outside end of the catheter is attached to an external pump. The balloon is then synchronized to inflate and deflate with the cardiac cycle. This action pumps blood and helps the failing heart in a number of ways. For this machine to work appropriately, the heart has to do some of the work, but the device is capable of doing about 20 percent of the heart's work. In many cases, it can make the difference between life and death.

ADRIAN KANTROWITZ: INTRA-AORTIC BALLOON PUMP

DR. ADRIAN KANTROWITZ'S MANY contributions to heart surgery — early pacemakers and heart transplantation, for instance — include the most practical heart assist device in use today: the intra-aortic balloon pump. This novel device likely saves more than one hundred thousand lives every year worldwide.

Kantrowitz developed the device with his brother Arthur, a Ph.D. physicist and former rocket scientist. Shortly after returning from service in World War II, Kantrowitz worked in the laboratory at Case Western Reserve University in Cleveland. There, he coauthored a paper with his brother on arterial counterpulsation.

“We showed you could increase coronary blood flow and unload the left ventricle. We published this as a theoretical thing because I couldn't figure out how to do it practically. Then Dr.

Dwight Harken, professor of surgery at Harvard Medical School, did his work.... It was really Harken who put the word to it — counterpulsation.

“But the problem was you couldn't move enough blood. You had to move it through a small tube. My brother and I thought the way to do it was to put a balloon in — we literally thought of a balloon. We discussed this at our mother's house.”

They soon learned that Dr. Willem Kolff had published a paper in which he actually tried a balloon pump in human cadavers but never in living humans. The brothers then developed a device that, in 1967, Kantrowitz tested in living humans.

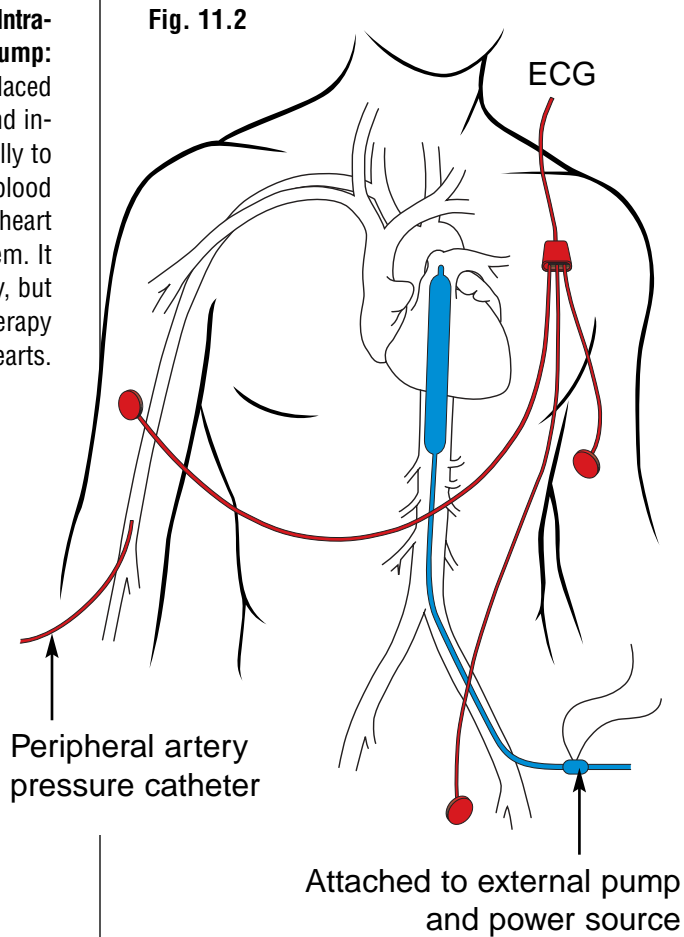
“These were patients who were in cardiogenic shock,” Kantrowitz recalls. The results in their first three patients were published in the *Journal of the American Medical Association* in 1968.

Dr. Adrian Kantrowitz, working with his brother, developed the **intra-aortic balloon pump**, which is used to help support the circulation with weakened hearts.



Fig. 11.2: The Intra-Aortic Balloon Pump:

This device is placed into the aorta and inflates rhythmically to help maintain blood pressure in the heart and arterial system. It is a temporary, but very valuable, therapy for weakened hearts.



The concept of aortic counterpulsation (as used with the intra-aortic balloon pump) was first described by Dr. Dwight Harken in 1958. In 1962, Dr. Willem Kolff's group introduced a balloon catheter into the aorta of an animal. In 1967, Kantrowitz and associates reported the first use of the intra-aortic balloon pump in three patients. All were in shock but improved during balloon pumping. One survived to leave the hospital.

Nowadays, most hospitals in the United States and virtually all large hospitals around the world, particularly those that have a cardiac center, use the intra-aortic balloon pump. According to Kantrowitz, the intra-aortic balloon pump is used in the United States in about one hundred thousand patients every year.

Kantrowitz's team has also been approved by the FDA to surgically implant a permanent version of the intra-aortic balloon pump in a limited number of select patients.

 **Early Artificial Hearts**

Doctors also continue to work with the concept of implanting totally artificial hearts, which would alleviate the shortage of donor organs. Before this becomes a practical reality, however, there are several obstacles that need to be overcome.

The heart was first replaced with a mechanical device by Dr. Tetsuzo Akutsu and Kolff at the Cleveland Clinic in 1957. Working in animals, these two researchers implanted an artificial heart in a living dog. The animal survived for ninety minutes.

In 1966, a team of Houston doctors under the leadership of Dr. Michael DeBakey used a left ventricular assist device in a woman who could not be weaned from the heart-lung machine after having two heart valves replaced. After ten days of circulatory assistance with the pump, she was weaned successfully from the device and recovered. This woman was probably the first patient to be weaned from a heart assist device and leave the hospital alive.

The first artificial heart in a human was implanted in 1969 by Denton Cooley, who used it as a bridge to heart transplantation for a patient who would most likely have died if Cooley hadn't used it to support the patient's failing heart until a donor heart was found. Cooley's team performed the operation on a patient who could not be weaned from the heart-lung machine after heart surgery. After sixty-four hours of support with the artificial heart, heart transplantation was performed, but the patient died of an infection thirty-two hours after the heart transplant.

The first two patients successfully bridged (kept alive by a mechanical heart

assist device) to heart transplantation were bridged at almost the same time and in the same metropolitan area but by different surgical teams. On September 5, 1984, in San Francisco, Dr. Don Hill implanted a Pierce-Donachy left ventricular assist device in a patient in cardiogenic shock. The patient's heart was replaced successfully two days afterward, and the patient was later discharged. Two days later, a team of surgeons at Stanford

University successfully replaced the heart of a patient who had been maintained with an electrically driven Novacor assist device.



Recent Artificial Hearts

The first implantation of an artificial heart, called the Jarvik-7, that was meant to be permanent (as opposed to a bridge to heart transplantation) was performed

DENTON COOLEY

DR. DENTON COOLEY, WHO WAS one of the physicians working toward successful heart transplantation in the late 1960s, vividly remembers the excitement at the dawn of heart transplantation:

“Many of us in the United States, maybe four or five surgeons that I know of, were challenged by the idea of a heart transplant. I’m not sure what stopped the others. But what delayed me was trying to identify a donor. I could not quite understand how we were going to get a good donor heart.”

In 1968 and 1969, with those hurdles overcome, Cooley performed twenty-two heart transplants.

“Nothing for me could compare with the excitement of that first cardiac transplantation I did in 1968,” he said in a recent interview. “It was very thrilling, but I felt a lot of pressure. I’ve never been more exhilarated than I was to see that heart begin to work and see the patient recover.”

Although Cooley was at the very cutting edge of early transplantation, the first human-to-human heart transplantation was performed by another

doctor, who shouldered the immense responsibility of showing that the concept was practical. “It is to Dr. Christiaan Barnard’s enduring credit that he showed a beating human heart could be removed from one individual and implanted into another,” Cooley said. “Prior to that, we weren’t quite certain of the ethics of taking out a beating heart because in those days, we always thought that life continued until the heart stopped beating. We didn’t quite understand the fact that sometimes with brain injuries, the heart would keep working long after the patient was clinically dead.”

Since that first transplant, technology and medicine have made great leaps in the treatment of failing hearts, including ventricular assist devices, pacemakers, and defibrillators. Said Cooley:

“If we had the donors, I think we would be able to forget about the mechanical replacement of the heart. But we’re never going to have enough donors to meet the need. So we have to have some mechanical support devices, although many of these devices will be used as a bridge to transplantation.”

Dr. Denton Cooley performed twenty-two heart transplantations in 1968 and 1969, making him the most prolific transplantation surgeon in the world at that time.



Dr. Willem Kolff was a true pioneer in artificial organ technology. His models for artificial hearts inspired the original Jarvik hearts that were implanted into human patients in the mid-1980s.



THE MECHANICAL HEART

AFTER THE HEART-LUNG MACHINE had proved that people could live while being supported by a machine, it was a short and logical jump to a completely artificial heart. Working first at the Cleveland Clinic and later at the University of Utah, Dr. Willem Kolff became one of the leading doctors in the development of artificial hearts and other organs. Kolff, in fact, had invented the artificial kidney in the 1940s in Nazi-occupied Holland.

“I went to Berk EnamelWorks and spoke to Mr. Berk and explained the principal of the rotating drum artificial kidney to him,” Kolff recently remembered about that first artificial kidney.

“Berk EnamelWorks began making artificial kidneys for me. When it came time to pay, it turned out they were only allowed to work for the German Wehrmacht, that is, the German army, so I never got a bill. We would, of course, have gone to concentration camps if we had.”

Kolff used fifteen artificial kidneys during the war, and this invention went on to provide long-term benefits for thousands of patients. Like a real kidney, the artificial kidney is connected to the patient’s circulation, except that it is done through small tubes. When blood flows through the machine, it cleanses the blood of the waste products that

by a group including Kolff, Dr. William DeVries, and Dr. Robert Jarvik at the University of Utah in 1982. By 1985, they had implanted the Jarvik heart in four patients, and one survived for 620 days after implantation. The Jarvik-7 heart was based on long-standing research by Kolff and his team at the University of Utah and earlier at the Cleveland Clinic.

All of these mechanical artificial heart devices required tubes running through the skin to an external power source and drive unit. Although the machines that powered the hearts were external and relatively large, they also had smaller portable drive units so patients could get up and walk around.

Over time, all of their patients suffered complications related to their artificial hearts, including blood clots and infections, which are particularly prone to occur with these types of devices. Any device that breaks the skin’s natural barrier poses a danger of infection because the skin is such an effective barrier against bacteria. When tubes and wires go through the skin, bacteria can

eventually get into the body and infect these devices.

One of the patients who had such a device — Barney Clark — became somewhat of a celebrity. His device functioned for more than a year. One might consider these short-lived clinical research trials as failures. Nevertheless, much important information was learned and shared from having these devices in humans (as opposed to animals). At the University of Utah and other centers, laboratory research continues on various types of artificial hearts and ventricular assist devices.

Currently, however, there are no permanent, implantable artificial hearts being placed in humans worldwide.

Ventricular Assist Devices

Short of a totally artificial heart, the FDA has approved devices that are designed to help the heart’s ventricles pump blood, called ventricular assist devices (Fig. 11.3). In most cases, these devices are used only as a bridge to heart

the patient's own kidneys would normally remove. Renal dialysis, or mechanical blood cleansing, is now used all over the world to treat patients with kidney failure and is based on concepts initially developed by Kolff. In fact, Kolff estimates that approximately half a million people in the United States alone are treated each year with renal dialysis.

After the war was over, Kolff moved to the Cleveland Clinic, where he began researching the heart-lung machine and artificial hearts. In 1957, he and a colleague, Dr. Tetsuzo Akutsu, removed the heart from a dog and implanted the first artificial heart, which kept the dog alive for ninety minutes with its circulation totally supported by the device. Although the device was implanted,

tubes ran through the skin to the power source.

Soon after this, Kolff moved to the University of Utah, where he began to build an artificial organ program. It was in this program and under Kolff's leadership that Dr. Robert Jarvik began his research into the artificial heart that would later bear his name and be implanted into Barney Clark in 1982.

"Although it was not a clinical success, the procedure was an important milestone," remembered Kolff. "We knew from animals that we could sustain the circulation, but from Barney Clark, we learned that he still loved his family, that his mind was okay, that his sense of humor was okay, that he still wanted to serve his fellow man. All of the important things were retained."

Fig. 11.3:

The Jarvik 2000, a left ventricular assist device, is used to aid a failing left ventricle. It is thumb-sized. The controller and battery are the size of a portable telephone and worn externally.

transplantation and usually remain implanted for a few days up to several weeks. However, some patients have had these ventricular assist devices for more than a year.

When the devices are used as a bridge to heart transplantation, the results are good. The devices do not appear to affect long-term survival after heart transplantation, which is about the same in patients who needed the devices as in those who did not.

At some centers in Europe, ventricular assist devices are being implanted in patients who are not being considered for heart transplantation. Doctors are hoping that the sick heart will recover during several months, at which point the device can be removed. So far, however, it's been found that most of these patients do not recover enough to allow the devices to be removed.

One major drawback of the assist device is that it requires tubes that run through the skin to external power sources. Portable machines allow the

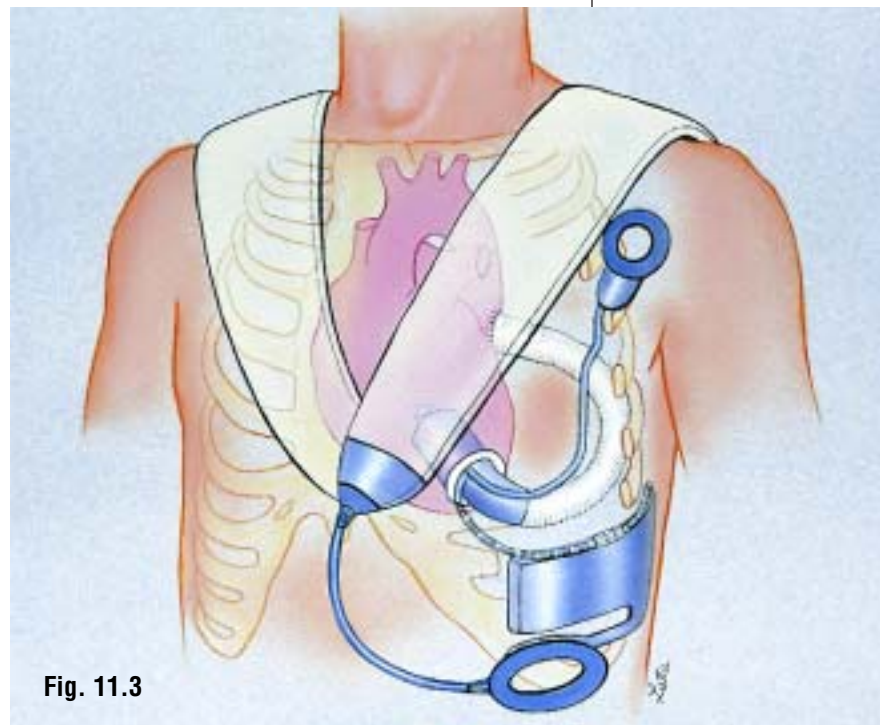
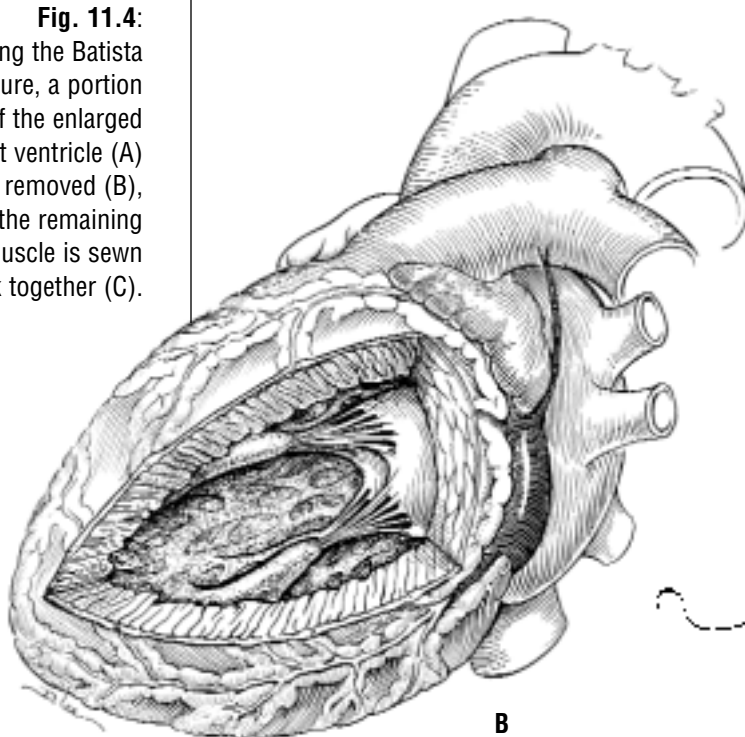
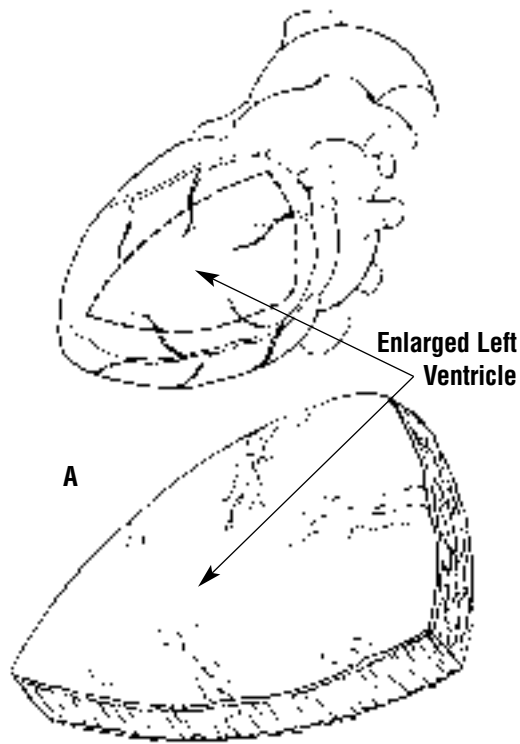


Fig. 11.3

patients to be fairly active or mobile so they can improve their physical condition over time. Unfortunately, infection often occurs over time with this type of device because of



the tubes and wires that have to cross the skin barrier.

Patients who are having mechanical assist devices implanted on a permanent basis should consider this as clinical research. It's likely that with time and research, there will eventually be assist devices and artificial hearts commonly available at all hospitals where heart surgery is performed. Some will most likely be totally implantable so no tubes or wires will cross the skin. The surgery done to implant these devices will become routine.

Batista Procedure

Dr. Randas Batista, a heart surgeon in Brazil, has recently developed a heart surgery procedure for certain patients with substantially enlarged, failing hearts. In the Batista procedure, the doctor removes a piece of the enlarged left ventricle and sews the remaining edges of the cavity back together (Fig. 11.4). After the size of the chamber is reduced, the left ventricle seems to function better and more efficiently. Batista has often found, however, that he has to either repair or replace the mitral valve because part of the muscle that controls it frequently has to be removed as part of the procedure.

The early mortality for this procedure, both in Brazil and in centers in this country, has been about 20 percent. By about

Fig. 11.4



Fig. 11.4: During the Batista procedure, a portion of the enlarged left ventricle (A) is removed (B), and the remaining muscle is sewn back together (C).

two years after the procedure, about 40 percent to 50 percent of the patients die; however, some of the patients who survive the procedure seem to do quite well and are relieved of their symptoms of heart failure for at least two years after the procedure. At this point, it is unclear how these patients will do long term or if the heart will expand again.

More information needs to be obtained, particularly from long-term follow-up, before this operation can be recommended as a routine form of surgery for treating patients with considerable heart failure.

Skeletal Muscle Cardiac Assist

The final form of heart assist involves neither mechanical devices nor donated organs but uses part of the patient's own anatomy to bolster the heart's function. This approach was pioneered in animals by Kantrowitz in 1959 when he wrapped the diaphragm muscle around the heart and stimulated the muscle to contract in synchrony with the animal's heart. This

worked, but only for several seconds until the muscle fatigued.

The problem of muscle fatigue was solved in 1969 when Drs. Stanley Salmons and Greta Vrbova from London, England, discovered that certain types of skeletal muscles, which are attached to the bones in our arms, legs, and elsewhere, could be electrically conditioned and made more fatigue resistant.

This observation led me and colleagues at the University of Pennsylvania to develop an electrical conditioning protocol for fiber transformation of animal muscles. Meanwhile, Dr. Ray Chiu and associates at McGill University developed the concept of burst stimulation to increase the force of muscle contraction.

These advances in muscle conditioning prompted several surgeons to wrap the back muscle, or latissimus dorsi, around the failing ventricles and stimulate the muscle to contract during contraction of the heart muscle. This procedure, which is known as **cardiomyoplasty**, was first performed in a human by Dr. Alain Carpentier in 1985.

Cardiomyoplasty:

A surgical procedure using a muscle, usually the latissimus dorsi muscle in the back, to wrap around a failing heart. The muscle is then electrically stimulated so it will contract in synchrony with the failing heart and hopefully improve the signs and symptoms of heart failure.

CARDIOMYOPLASTY AND AORTOMYOPLASTY

By

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AN ALTERNATE FORM OF cardiac assistance is known as dynamic cardiomyoplasty (DCMP), a promising but unproven surgical treatment for patients with end-stage heart failure (Fig. 11.5). The procedure was first performed in a human by Drs. Alain Carpentier and Juan Carlos Chachques of Paris, France, in 1985.

It involves freeing up a back muscle called the latissimus dorsi. The main blood supply and nerve supply are left intact. The muscle is then placed inside the chest and wrapped around the heart, where it is stimulated with a pacemaker for several weeks to make it more fatigue resistant. After this period, the muscle is stimulated with a special type of pacemaker so it contracts in synchrony with the heart in hopes of helping the function of the patient's own failing heart muscle.

Over the last fourteen years, more than one thousand patients worldwide have had dynamic cardiomyoplasty performed. The



vast majority have demonstrated substantial improvement in symptoms of heart failure.

Despite this dramatic improvement, however, consistent evidence of improvement in heart function has not been found. Also, there is no good evidence that patients undergoing this procedure live longer than similar patients who have not had dynamic cardiomyoplasty. Lack of clear survival advantage and ongoing misunderstanding of the procedure's mechanism of action has so far hindered dynamic cardiomyoplasty's ac-

ceptance as a treatment alternative for patients with end-stage heart failure.

In more than six hundred cardiomyoplasty patients implanted with Medtronic electrical stimulators, clinical improvement in signs and symptoms of heart failure has been noted in 80 percent to 85 percent of surgery survivors. Improvement in symptoms of heart failure usually begins within the first six months after the surgery. In addition, the number of hospitalizations for heart failure decrease. A similar clinical improvement was found in a Phase II trial of cardiomyoplasty in the United States conducted under the auspices of the FDA.

During the recently completed Phase III trial, patients undergoing cardiomyoplasty had an operative mortality of less than 3 percent.

Today, the sickest patients who have heart failure symptoms at rest or who are confined to bed or to sitting in a chair are considered at too high a risk for

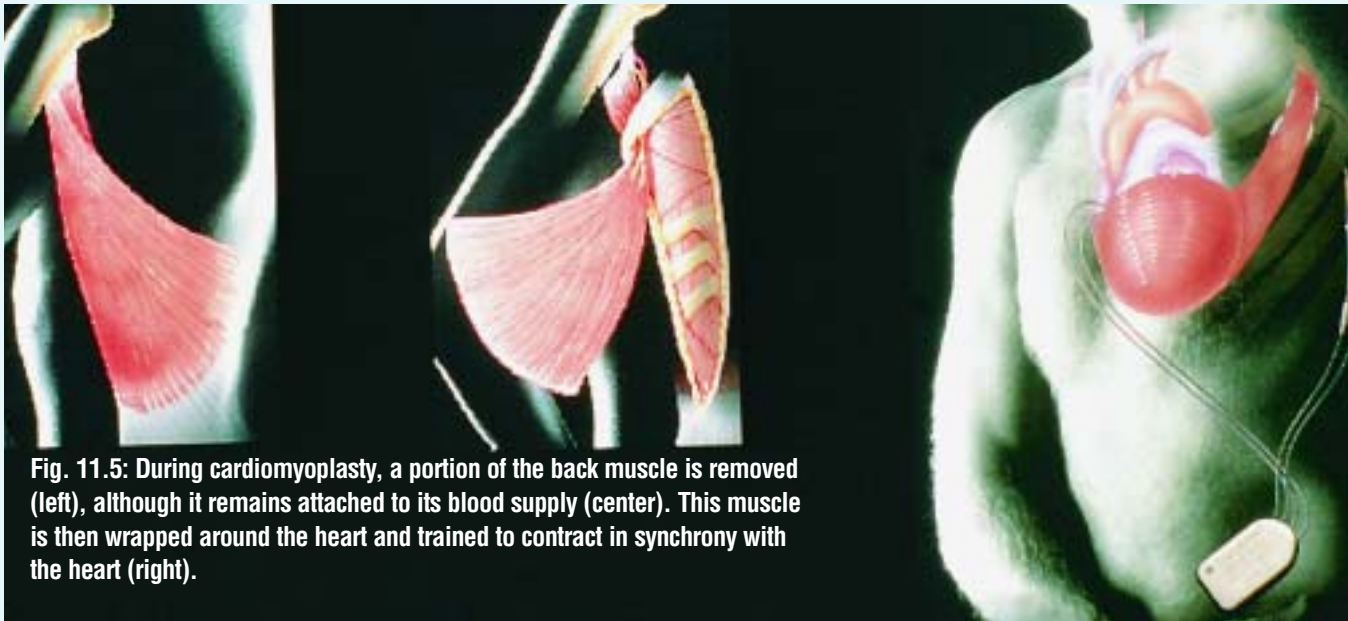


Fig. 11.5: During cardiomyoplasty, a portion of the back muscle is removed (left), although it remains attached to its blood supply (center). This muscle is then wrapped around the heart and trained to contract in synchrony with the heart (right).

cardiomyoplasty, so those patients are more likely to be referred for a heart transplant.

The Phase III randomized, clinical trial, again under the auspices of the FDA, commenced in June 1995 and was finished near the end of 1998. Slightly more than one hundred patients entered the study. It was a study designed to determine the safety of cardiomyoplasty as a treatment for heart failure due to dilated cardiomyopathy or ischemic cardiomyopathy (secondary to coronary artery blockages). In both dilated cardiomyopathy and ischemic cardiomyopathy, the main problem is that the heart muscle itself is failing. The study was designed to provide a clearer picture of the role of cardiomyoplasty as a treatment alternative for patients with end-stage heart failure.

Legitimate doubts about the efficacy of dynamic cardiomyoplasty remain. Although patients improve and have less severe symptoms of heart failure, no

consistent improvement in heart function or survival benefit has been demonstrated.

Although many heart failure patients can be managed effectively with medicine alone, there are clearly many other patients receiving medical therapy whose quality of life and exercise capacity have worsened yet who are not sick enough to be considered for transplantation. It is clear that a more potent treatment alternative for these patients must be sought. Unfortunately, recruitment into this Phase III randomized trial, which perhaps would have been the definitive study, was too slow to allow definitive data to be collected.

With the trial's termination in the United States, cardiomyoplasty's potential clinical benefit may never be totally known. Its ultimate role in the treatment of heart failure depended on the outcome of a properly designed, controlled study with a minimum of four hundred patients. Clinical cardiomyoplasty has

ceased being done in the United States, although in Europe, the procedure is still performed. The lessons learned from cardiomyoplasty, however, may still prove to be of greater significance.

Aortomyoplasty

A similar surgical procedure, in which the skeletal muscle is wrapped directly around the aorta, is called aortomyoplasty (Fig. 11.6). This operation has been performed in more than twenty-eight humans worldwide and shows some promise.

The difference between aortomyoplasty and cardiomyoplasty is that the latissimus is wrapped around the aorta instead of the heart. In some of these procedures, it has been wrapped around the ascending aorta just as it comes out of the heart. In other procedures, it's wrapped around the descending aorta after the major blood vessels to the head and to the upper extremities branch off it.

CARDIOMYOPLASTY AND AORTOMYOPLASTY

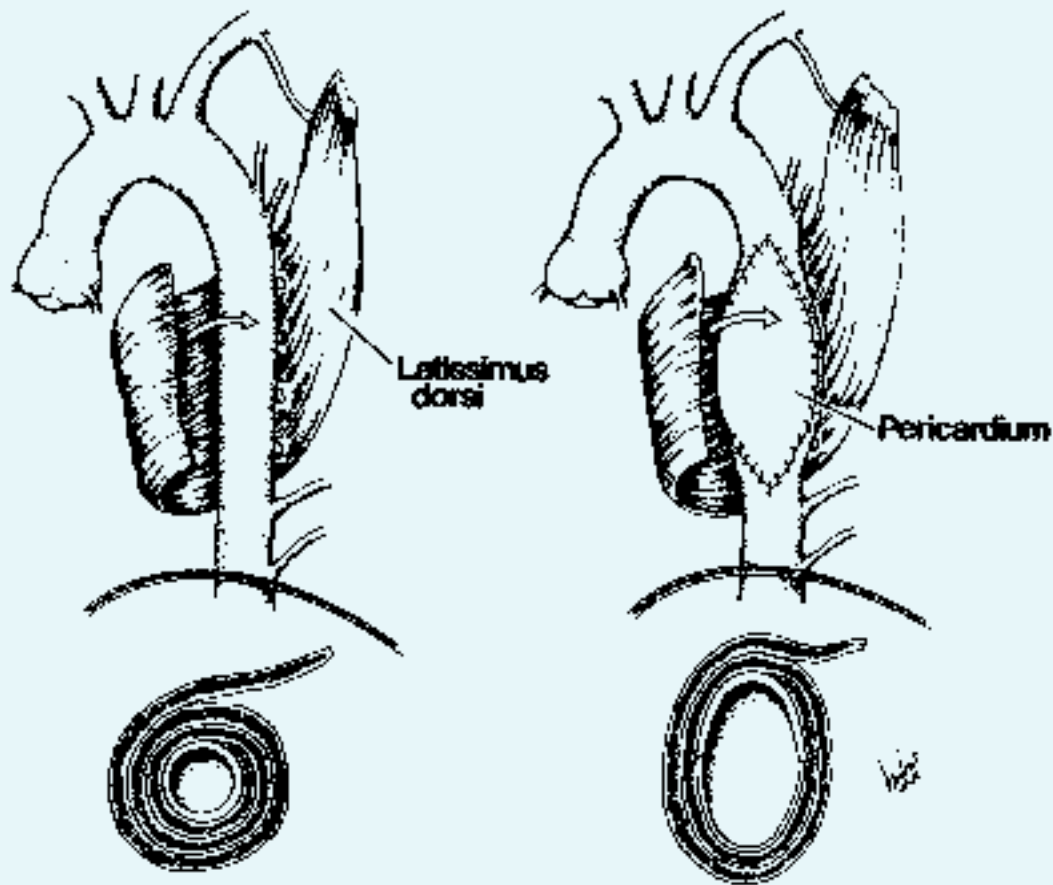


Fig. 11.6: During aortomyoplasty, a section of back muscle is wrapped around the aorta and trained to contract, easing the work load on the heart. In some cases, the aorta is also enlarged with pericardium.

Because the two procedures work on different parts of the anatomy, the muscle is trained to contract at different times. In cardiomyoplasty, the muscle is stimulated to contract at the same time as the heart ventricles. In aortomyoplasty, the latissimus muscle is stimulated to contract while the heart ventricles are relaxing. If the muscle was stimulated to contract to compress

the aorta at the same time the heart ventricles were contracting, it would be working against the heart because they'd both be trying to pump blood in different directions at the same time.

One advantage this procedure has over cardiomyoplasty is that the sick heart itself does not need to be manipulated. In some cases, the heart is so large that the latissimus muscle can-

not even be wrapped around it. In this case, cardiomyoplasty would not be performed, but an aortomyoplasty could be performed.

Although there are reports that patients with failing hearts have benefited from this procedure, it should be considered experimental, particularly until more long-term information is obtained.

BUILDING A HEART PUMP FROM YOUR BACK MUSCLE

By

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PHYSICIANS ARE CURRENTLY considering another alternative method of assist for congestive heart failure called the skeletal muscle ventricle procedure. In this novel approach, a pumping chamber is formed from the latissimus dorsi, which is a muscle located in the back that has been freed up and moved to the chest. The muscle is formed into a “pump” about the same size and shape as the left ventricle.

After the muscle pump is made, it is electrically stimulated for several weeks to make it fatigue resistant. During a second operation, the new pump is connected to the circulation and used as an assistive pump to help the heart.

These pumps have not been used in humans, although the re-



sults have been extremely encouraging in animals. In fact, one of these pumps has pumped blood effectively in the circulation of a laboratory animal for more than four years. In other cases, these pumps have been connected to the circulation with valves similar to those

in the heart and have pumped blood for more than a year.

One of the advantages of a skeletal muscle ventricle compared with heart assist devices is that everything is implantable, including the special stimulators (which are identical to those used in cardiomyoplasty and aortomyoplasty). The procedure also has potential advantages over cardiomyoplasty and aortomyoplasty in that almost all of the latissimus muscle is used for the pumping action, and therefore, much more effective support of the circulation can be obtained. In addition, the potential advantage of the procedure over a heart transplant is the absence of rejection because the patient's own tissues are used.

Although the research is promising, the procedure is not yet ready for human trials.

STATE OF THE ART IN MECHANICAL HEART ASSIST DEVICES

By

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HEART TRANSPLANTATION has remained the best available option for some patients with terminal heart failure since its introduction in 1967. Despite this encouraging fact, however, the survival rate after transplantation is limited, and there is a wide gap between the number of available donor hearts and the number of patients who need them. Because of these limitations, researchers are always looking for better ways to help patients dying of heart failure. These efforts include the development of mechanical circulatory devices such as the total artificial heart and the left ventricular assist device (LVAD).

Patients usually die of heart failure because the left ventricle, the heart's primary pumping chamber, does not function properly. Researchers therefore have directed their efforts at developing the LVAD, which takes over the function of the left ventricle. In the early 1970s, research efforts, supported by the Device and Technology Division of the



National Heart, Lung, and Blood Institute (NHLBI), were directed toward producing devices for long-term support (greater than two years).

The pumps were also used for short-term support in the hope that they would provide the necessary time for recovery of heart function. These pumps were pulsatile: The pump's action created a pulse similar to that of the natural heart and could draw blood from either the left ventricle or the left atrium and discharge it into the aorta.

In 1978, the Texas Heart Institute began using LVADs as bridges to transplantation. The devices were able to support patients during the time gap between imminent heart failure and heart transplantation. A similar device was implanted in 1984 at Stanford and again in 1986 at the Texas Heart Institute. Today, these large devices require an external connection to a battery pack. Despite this inconvenience, these devices have successfully supported many patients who otherwise would have died.

Over time, researchers observed that hearts that were supported by the LVAD and allowed to rest for longer time periods actually recovered some cardiac function; some patients have avoided transplant altogether. In turn, transplant surgeons have come to realize that long-term LVAD support improves the function of the body's other organs, leading to better outcomes when and if patients undergo transplantation. In the future, such devices may be

implanted permanently in some patients as an alternative to cardiac transplantation.

Alternative designs for mechanical circulatory devices are also being investigated. These include continuous flow pumps, which are considerably smaller than other assist devices currently in use. There is no need for valves because the blood flow is continuous.

The first temporary continuous flow pump, the Hemopump®, was successfully used in 1988 at the Texas Heart Institute. Continuous flow pumps offer great promise of widespread application, and the first clinical trials of the newest version were scheduled to begin in 1999.

In some cases, the heart is so damaged by disease that adequate support can only be obtained with a total artificial heart. Earlier versions of the total artificial heart included two single pumps, one to replace the right ventricle and one to replace the left ventricle, and the power source was outside the body. The first totally artificial heart was implanted at the Texas Heart Institute in 1969, followed by an-



The Abiomed total artificial heart.

other implantation in 1982. Other implantations of permanent artificial hearts soon followed. These implantations were fraught with complications, and the devices and power consoles were large and cumbersome.

However, continued NHLBI funding from the mid-1980s enabled researchers to develop a smaller implantable device in which electrical power is transmitted across rather than

through the skin. These pumps are quieter and appear to be less likely to create the blood clots that plagued recipients of the earlier devices. Because this newly developed totally artificial heart can be nearly, if not completely, implanted under the skin, the risk of infection should be lower. These artificial hearts are currently being tested at the Texas Heart Institute and at Penn State, Hershey. They are almost ready for initial clinical trials and should be ready to implant in patients by the early part of the twenty-first century.

Many advances have been made in the field of mechanical circulatory support, and future generations of these devices hold great promise. Although heart transplantation remains an alternative for a select group of patients, it is currently not available to the vast majority of patients who are dying from heart failure. In the next millennium, a long-term device should be widely available for the treatment of heart disease and terminal heart failure, hopefully sparing many of these patients from an untimely death.

CARDIAC RECONSTRUCTION FOR HEART FAILURE

By

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FOR DECADES HEART SURGEONS have opened the left ventricle to “reconstruct” the damaged heart muscle. This has typically been used for cardiac aneurysms, or areas of scarred heart muscle that bulge out when the heart contracts and cause heart failure, blood clot formation, and heart rhythm problems. In recent years, this operation has been extended beyond classic aneurysms to include patients who have damaged hearts from heart attacks and in whom the weakened heart can be improved by reconstructing the heart muscle. In most instances, the scar is removed or reconstructed, blocked heart arteries are bypassed, and leaky valves are repaired.

A highly celebrated Brazilian surgeon, Dr. Randas Batista, extended this concept to hearts damaged not just from heart attacks but also from viral illnesses, valve problems, and a parasitic disease common in Brazil. The “Batista procedure” was popularized in the United



States on many television network shows such as 20/20, NOVA, The Learning Channel, CNN, and all the network news stations. In this procedure, some of the heart muscle in these “flabby” hearts is removed, resulting in significant improvement in cardiac function in some patients. However, long-term follow-up is limited, and the results are unpredictable. Some patients had excellent results for years,

whereas in others, treatment failed, and their weakened hearts required heart transplantation.

At the Cleveland Clinic, we have been working on reconstructing the heart with both the Batista procedure and also using methods for hearts scarred from heart attacks. These scarred hearts generally improve significantly after reconstruction often coupled with coronary bypass surgery and frequently with valve surgery.

Although the number of Batista procedures performed now is far less than two years ago, we think that it was a useful step along the way. We are currently developing a device that can recreate the improvements seen with the Batista procedure, but without having to use the heart-lung machine, open the heart, and cut out and remove a large portion of the heart muscle. This new device should pose a much lower risk than the Batista procedure and provide a more predictable success rate.

GENE THERAPY

By

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THERAPEUTIC ANGIOGENESIS is a promising new treatment for artery blockages typically caused by atherosclerosis. Angiogenesis means the "formation of new blood vessels." In angiogenesis, a naturally occurring protein called a growth factor, or angiogen, is used to stimulate blood vessel growth. This enhances blood flow to tissues that are jeopardized by a blockage.

In the laboratory, therapeutic angiogenesis has been shown to help blood vessels develop. Among other actions, angiogenesis might reduce the effects of atherosclerosis, enhance wound healing, and promote tissue growth. It may be particularly useful for patients with such severe or widespread atherosclerotic disease that they cannot be fully helped by conventional therapies like angioplasty or bypass surgery.

Besides using growth protein, we are also considering gene therapy. To do this, we transfer genes directly into a targeted tissue, where the gene "turns on"



DNA that causes cells to produce the proteins that cause growth of new blood vessels. Genes can be transferred on genetically engineered viral particles. The adenovirus (Ad) is one such viral particle that efficiently transfers genes to tissues such as the myocardium, or heart muscle. Genes transferred by Ad remain in the tissue they are sent to and are active for only one or two weeks. This is important because it potentially prevents the overproduction of a protein that

might cause abnormal blood vessel growth.

We have so far tested the Ad protein transfer technique in twenty-one patients. These patients had not responded to coronary bypass surgery or coronary balloon dilatation because of the severity of their coronary artery disease. To date, the gene therapy appears to be well tolerated, and we plan to move into larger-scale human studies. Similar positive results have been reported by other investigators using a "naked" DNA segment that was not incorporated into a viral particle like Ad.

It is unknown which, if any, gene therapy strategy will work best, or whether they will be superior to the use of angiogenic proteins themselves instead of the genes for these proteins. Finally, it is unknown which, if any, of the many angiogenic proteins will work best, or which delivery method will be most beneficial. Preliminary studies and the promise of future advancements are, however, very encouraging.

THE FUTURE IN ARTIFICIAL HEART TECHNOLOGY

By

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CURRENTLY, THERE ARE more than three million heart failure patients in the United States, with more than four-hundred thousand new cases every year. Treatment of heart attack has come a long way. Today, physicians are able to use clot-busting drugs and catheters to save thousands of lives. There is, however, an unfortunate consequence of this rapid advance. Some of these people who are saved, particularly patients with coronary artery disease, develop heart failure.

Because transplantation is limited, physicians have turned to mechanical hearts, a concept that has captured the imagination of cardiac surgeons, the public, and the media alike. Although there are no fully implantable mechanical hearts available, physicians do have mechanical treatment options for end-stage heart disease.

In fact, within the next ten years, a miniaturized blood pump is destined to become the treatment of choice to relieve symp-



toms and prolong life in older heart failure patients. Physicians have recently discovered that “resting” the heart with such a blood pump may promote recovery in some patients. This raises the possibility that circulatory support can be used as a therapy in conjunction with other treatments.

Left Ventricular Assist Devices

The totally artificial heart, which received much publicity in the 1970s and 1980s, was conceptually flawed. These unwieldy devices were acceptable as a

bridge to transplantation (when meant to keep patients alive until they could receive a heart transplant) but were never a long-term solution. To be successful, an artificial heart must be more than a reliable blood pump; it must be forgettable. That was something the big artificial hearts could never be.

In recent years, however, physicians have realized that whole-heart replacement may not be necessary. After all, more than 90 percent of heart failure patients can be sustained with left ventricular support alone.

Currently, left ventricular assist devices are used mainly as a bridge to transplantation. The modern left ventricular assist device consists of a blood sac that is compressed by a pusherplate mechanism that is either electrically or air driven. Artificial heart valves direct the blood flow. This system mimics the human left ventricle by providing pulsatile blood flow while taking the burden of pumping off the patient’s heart. This is a workable solu-

tion and saves many lives, but the serious problems of pump size, noise, driveline infection, and stroke remain. Nevertheless, some patients have had these devices in place for up to four years and enjoyed an acceptable quality of life. This has encouraged us to use the left ventricular assist device for long-term support in patients who are not eligible for transplantation.

The Next Generation of Assist Devices

The ideal treatment for chronic severe heart failure must be reliable, cost effective, easy to manage at home, and capable of providing adequate circulation. Keeping these goals in sight, another generation of heart assist devices called axial flow impeller pumps is on the horizon. These are compact, silent, nonpulsing blood pumps that provide up to eight quarts of flow per minute.

Among these is the thumb-sized Jarvik-2000, which fits within the failing left ventricle and pumps blood to the aorta. The impeller revolves at up to eighteen thousand rpm, moving blood so rapidly that the red cells remain undamaged. The controller and batteries are the size of a portable telephone and fit easily onto a normal belt.

Other ingenious blood pumps are under development, including some with magnetically suspended rotors. These fully implantable, miniature artificial hearts will greatly increase our

ability to treat heart failure, although we do not know their reliability and complication rate.

A recent revelation has been the effect of chronic rest on the failing left ventricle. For years, we have known that prolonged bed-rest, which reduces heart function, results in improvement. However, the benefits are limited by the negative effects of inactivity on the limb muscles, blood vessel tone, and nervous system.

Ideally, patients would be able to exercise their bodies while their hearts rested. This is now possible with long-term implantable blood pumps. When we compare the heart muscle at the time of blood pump insertion to the muscle during transplantation, there is often a shift in heart muscle cells towards normal, both in shape and function. This discovery that recovering hearts were being removed at transplantation, coupled with the shortage in donors, led to the use of blood pumps to induce heart recovery.

Although the benefits of this therapy are obvious, there are certain requirements that must be met before this strategy has a chance for success. The first is a user-friendly blood pump for patients of all sizes. This must be simple to implant and remove, without the risk of infection, and easy to control. Second, it must be implanted before the heart degenerates to a point at which the heart failure cannot be reversed.

In our limited experience with this approach, certain factors

are apparent that separate those with sustainable heart recovery from others who will slip back into heart failure. Patients with long-lasting recovery tend to be younger, have a shorter history of heart failure, show a more rapid improvement in heart performance, and require a shorter period of blood pump support.

The type of heart disease is also important to recovery. Coronary artery disease patients with large areas of dead muscle will not recover. However, young patients with viral infections involving the heart can often be supported with a blood pump until the inflammatory process completely resolves. Even those who require external cardiac massage and a heart-lung machine during blood pump insertion can be restored to nearly normal cardiac function.

A Look at the Future

The scope of mechanical heart failure therapy is developing rapidly as new blood pumps emerge from the bioengineering laboratories. These will eventually be used as often for heart failure as the pacemaker is for rhythm problems. The major issues are not ethical but economic. In the further future, new drugs, gene therapy, and tissue engineering with the patient's own heart muscle cells will be used to promote recovery of the patient's heart in conjunction with periods of mechanical circulatory support.

HEART CELL TRANSPLANTATION FOR THE FAILING HEART

By

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AN ESTIMATED 465,000 PATIENTS in the United States are diagnosed with congestive heart failure each year. For those patients with mild heart failure, medicine can often relieve their symptoms and improve their quality of life. However, for patients with severe heart failure, medicine may be insufficient, and heart transplantation may offer the potential for a better, longer life. Unfortunately, there is a limited supply of donor hearts, and less than 10 percent of patients needing a heart transplant will actually receive one.

This dilemma — what to do for patients with severe heart failure who are unable to receive heart transplants — stimulated our interest in heart cell transplantation, an exciting new field with the potential to improve the quality of life and lengthen the lives of patients who suffer from heart failure. We hope we can begin the first trials of heart cell transplantation in human patients within the next two years.



Terrence M. Yau



Ren-Ke Li

So far, our research group has succeeded in growing animal and human heart cells in cell culture, outside the body. It is a very painstaking and exacting process that was previously thought to be impossible. However, over the course of ten years, we have developed techniques that permit these cells to grow and reproduce in a culture dish while retaining most of the characteristics of heart muscle cells.

When transplanted into rat hearts that have been scarred by injury to the heart's main pumping chamber, the transplanted cells formed a block of muscle tissue within the scar tissue that can be easily identified under a microscope. Consequently, hearts that had been injected with the cultured muscle cells had better pumping function than those injected with only the solution the cells were grown in but not the cells themselves.

On the basis of this finding, we realized that injecting cultured heart muscle cells into an

injured heart had the potential to restore function. However, we also found that the rats developed an immune response to the transplanted cells, which were taken from a different rat, and the cells were gradually destroyed over about six months.

To avoid this immune response, we have taken heart muscle cells from one animal, grown them in the laboratory, and transplanted them back into the same animal. These cells, because they are recognized by the animal as its own cells, do not cause an immune response and are not destroyed. Again, these transplanted heart muscle cells improved heart function and blood flow to that area of the heart.

Within the next one to two years, we hope we will be able to use a similar approach in human patients undergoing heart surgery. At the time of their heart catheterization, patients with poor heart function would have a very small amount of heart muscle tissue removed. This tissue would be grown in the laboratory over several weeks to obtain a much greater number of cells. Then, during heart surgery, the cultured heart cells would be transplanted back into the patient's

heart. The resulting improved heart function will hopefully result in a greater exercise capacity, better quality of life, and longer life expectancy.

This form of therapy does not apply only to heart muscle cells. We have also examined the role of muscle cells from other parts of the body, the cells responsible for making fibrous tissue, and the cells that form blood vessels. When blood vessel cells were transplanted into the scar tissue, we found that the number of blood vessels in the area tripled.

Our research suggested that a combination of heart muscle cells, to improve heart function, and blood vessel cells, to improve blood flow to the heart, might be the best solution for failing hearts with inadequate blood flow. This is exactly the situation seen in many patients with advanced atherosclerosis.

We are also using our experience in culturing heart muscle cells to build a graft material that could be used to repair heart defects in children with congenital heart disease. The graft materials currently available for repair of these defects have no living cells and therefore do not grow after implantation. Inevitably, the

child outgrows the graft and usually requires a second or third operation to replace it. Each successive operation carries a greater risk.

A graft that grows with the child and does not require additional operations would be a significant advance. We have been able to grow heart muscle cells in a three-dimensional mesh, which is gradually dissolved by the body, leaving only the cells. When this mesh is seeded with heart muscle cells and implanted into the legs of rats, the graft can be seen to beat rhythmically just like normal heart muscle.

We hope to someday build a graft that can be used to repair heart defects and that will grow with the child. Although much more work is necessary to develop this kind of graft, our initial results have been very encouraging.

Heart cell transplantation is an exciting new technology with the potential to improve heart function and blood flow in patients with advanced heart failure and extensive atherosclerosis. It may also lead to the development of living graft materials that can be used to repair heart defects in children, avoiding the need for second or third operations.