VIEWPOINT

Mechanical Circulatory Support—a Long and Winding Road

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The highly public reintroduction of the total artificial heart last year has prompted renewed interest in mechanical circulatory support systems for the treatment of end-stage heart disease.

Heart transplants are thought of as miracles because of their impact on length and quality of life. Unfortunately, like miracles, they are all too rare. Each year in the United States, about 2000 patients with end-stage heart failure receive heart transplants. Yet 400,000 or more individuals develop heart failure annually, of whom 30,000 to 100,000 potentially could benefit from a transplant. This has led to a system of rationing where committees have to determine whether a candidate is eligible for a transplant. Many patients have to be rejected because of advanced age, other medical conditions that limit life expectancy or quality of life, poor medical compliance, or bad habits such as smoking or alcohol abuse. Physicians strive to give the limited number of hearts to those who will best take care of this gift. No one wants to be in the uncomfortable position of rationing access to heart transplants, so physicians have worked for decades to develop complex machines that, like cardiac pacemakers or heart valves, can save desperately ill patients. The ultimate goal is to develop a machine that is as good as or even better than the donor heart, avoiding the need for a transplant altogether.

As a result of the highly public reintroduction of the total artificial heart (TAH) in July 2001, the interest of the medical community and the public has been drawn again to mechanical circulatory support systems for the treatment of end-stage heart disease (see page 1000) (*1*). A TAH implant is a dramatic event that removes the patient's heart and results in complete dependence on the most sophisticated technology ever implanted in humans. A TAH must "beat" approximately 35 to 40 million times a year, providing a cardiac output of 5 to 6 liters/min of blood (*2*). Current design goals are 90% reliability after 5 years of operation, which is comparable to the 70% 5-year survival for current heart transplant patients. The AbioCor TAH that has made news headlines is a titanium and polymer construct that uses an electrohydraulic actuator system to shuttle blood alternately between the right and left pumps (*3*). Currently under development are electromechanical TAH devices that directly convert electrical energy into mechanical action. A recent improvement has been the use of a transcutaneous energy transmission system (TETS) that transmits power through intact skin, eliminating the risk of infection entering the body along the percutaneous power line that was used with earlier implanted blood pumps. A rechargeable implanted battery provides brief periods of freedom from the external battery and electronics associated with the TETS, allowing the patient to shower or, theoretically, even to swim.

A TAH presents many design challenges. In all probability the patient will die very rapidly should the machine malfunction. Therefore, it must perform flawlessly. A major potential problem are blood clots that form around the four artificial plastic valves and in response to the synthetic material with which the blood is constantly in contact. Pulmonary problems may develop from a mismatch between right and left blood flows. Existing TAHs are large and do not fit many male candidates, most females, or any children. Should the TAH become infected, even intravenous antibiotics may not be effective. Despite these problems, the TAH is a desirable device for certain patients with severe heart muscle damage, or for those where the continued presence of the native heart is a liability (*4*). However, because of the inherent limitations in current TAH technology, there is wide agreement that only about 10% of the patients with end-stage heart disease (approximately 5000 to 10,000 U.S. candidates per year) should be treated with this radical approach (*5*).

Most clinicians believe that 90% of end-stage heart disease patients can be managed with a ventricular assist device (VAD) that supports the left ventricle, the locus of the most critical heart damage (*6, 7*). With a VAD, the right ventricle benefits from reduction of left atrial and pulmonary arterial pressures and the heart can start to repair itself. While "resting" during VAD support, damaged cardiac muscle starts to repair itself and to contract with more vigor. The benefit of a VAD versus a TAH is that the natural heart remains in place—if the VAD is stopped or removed, the patient's heart can still support the circulation. Clinical experience has demonstrated that once a damaged heart is "rest-

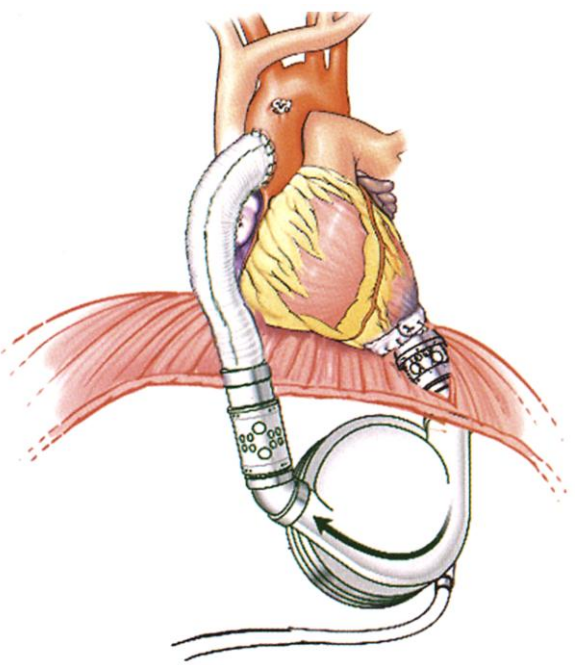

Fig. 1. The implantable HeartMate VAD, a pulsatile-flow device that supports the left ventricle of the damaged heart. Blood flows from the left atrium through the left ventricle and the pump inflow valve into the VAD, which then pumps the blood into the aorta. [Image courtesy of Cleveland Clinic Foundation]

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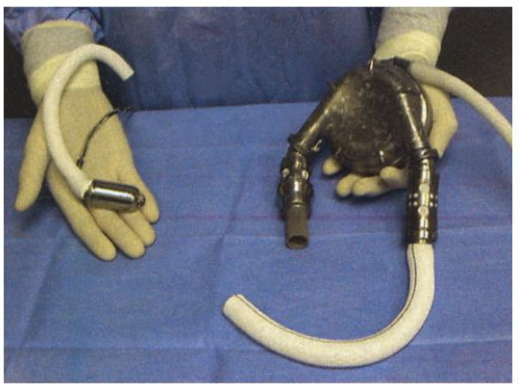

Fig. 2. Size comparison of the HeartMate pulsatile VAD (right) with the newer and much smaller continuous-flow (nonpulsatile) Jarvik 2000 VAD (left). Continuous-flow VADs are currently in clinical trials. [Photo courtesy of Cleveland Clinic Foundation]

ed" through VAD support, the heart can repair itself and its function improves. In a few cases, the VAD was removed and the patient no longer needed a transplant. The goal is for wider application of VAD support so that heart failure patients are supported for weeks or months until cardiac damage has been repaired sufficiently such that a transplant is not necessary.

Design of the VAD began as early as 1963 but did not progress rapidly until the 1990s. Since then, thousands of patients have been successfully supported, sometimes for years (*8*). The most commonly used VAD is the HeartMate, a rotating torque motor and cam system that displaces 75 cc of blood from the left ventricle into the aorta (Fig. 1). The control system can increase or decrease the pump rate to match demand. The surfaces that make contact with blood are textured so that an adherent layer of blood cells settles on the surface, enabling blood to flow smoothly. Blood is directed through the pump by inflow and outflow valves made of pig tissue (*9*). In the Cleveland Clinic experience, the incidence of emboli (blood clots) or stroke is very low, about 2%, using only aspirin as an anticoagulant.

A new type of VAD—in which rotary dynamic pumps produce a continuous nonpulsatile flow of blood—is currently in clinical trials. In some situations, patients with this new VAD have a normal cardiac output of 5 to 6 liters/min, but no palpable pulse or measurable blood pressure! There was concern that this would cause physiologic abnormalities, but experience with animal models and early clinical results suggest that the difficulties may have been overestimated (*10, 11*). These continuous-flow devices are much smaller and simpler than the pulsatile pumps (Fig. 2) and thus fit the majority of adults and children. They may also be less expensive. Most current designs use highly polished titanium surfaces that appear to be compatible with blood, at least for the short residence times during which blood is in contact with the pump. As a "partial" assist VAD that elevates the total cardiac output of a weak heart closer to the normal range, these devices show tremendous potential.

Prototypes of the continuous-flow VAD include the Jarvik 2000 (Fig. 2), Micro-Med DeBakey pump, and HeartMate II pumps, all now in clinical trials. Each of these devices has an axial flow impeller supported on blood-lubricated pivot points. So far, the devices have been implanted with a percutaneous wire that connects the device to an external controller and battery. Nothing prevents the use of a TETS system in future versions, although this would add hardware to the implant. The next generation of VAD blood pumps (still being tested in the laboratory) use three-dimensional magnetic suspension of the pump rotor (*12, 13*). These pumps address residual concerns regarding friction, wear, and the crevice-like geometry of the pivot supports (which trap blood cells), and are predicted to remain reliable for 10 years or more. This technology, the prototype of which is hopefully to be launched this year, brings us much closer to the day when small reliable blood pumps with few complications become as common as pacemakers and heart valves.

The future most likely includes two scenarios: small, magnetically suspended blood pumps that are completely implanted and powered through transcutaneous energy sources; and the "synergistic" combination of these pumps with new biological therapies. Such therapies include gene therapy, transplants of muscle stem cells or cardiac myocytes, and treatment with drugs such as the beta-agonist Clenbuterol. Patients on VAD support who are treated for several months with Clenbuterol show physiologic hypertrophy (thickening) of their heart muscle, which contracts more vigorously (*14*). A patient could receive a small blood pump to "rest" the heart, meanwhile being treated with biological therapies to promote healing of the cardiac muscle. Once the heart is repaired, the pump would be removed. Already an oxygen-starved heart has been induced to grow new blood vessels through injection of the gene encoding vascular endothelial growth factor directly into the damaged cardiac muscle (*15*). Recently, new heart muscle cells grown from a patient's own skeletal myoblasts have been injected into the damaged heart, improving local cardiac function and abrogating the problem of rejection associated with a heart transplant (*16, 17*). Gene therapy can be combined with cell therapy such that the muscle cells to be transplanted are engineered to carry genes encoding proteins that will promote muscle cell survival and growth. These clinical efforts toward cardiac repair are not science fiction; they have already begun and show encouraging early results.

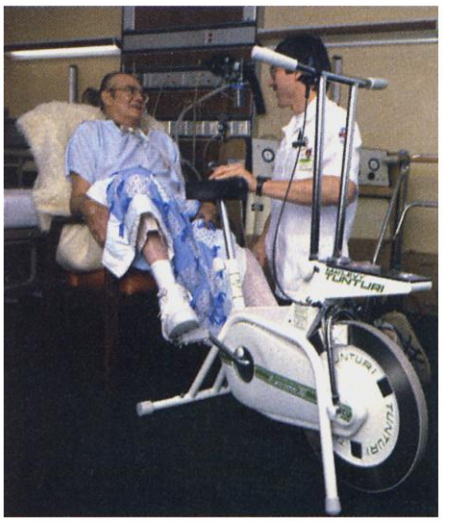

Fig. 3. Barney Clark was the first patient to receive the Jarvik-7 total artificial heart. Clark, implanted with the Jarvik-7 in 1982 and shown here pumping an exercycle under the watchful eye of his physical therapist, lived for 112 days after the operation. [Photo courtesy of Brad Nelson/University of Utah Health Sciences Center]

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