

Perspectives on Long Term Mechanical Circulatory Support for the Failing
Heart

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*Dr. Domonochi - This is very
good - see only minor suggestions*

Claude

The National Heart, Lung, and Blood Institute (NHLBI) has a continuing program of support for the development of mechanical circulatory support systems. Started as the Artificial Heart Program in 1964, it has resulted in a number of significant advances, including the hollow fiber membrane oxygenator and the intra-aortic balloon pump. Today, the primary focus of the program is the development and testing of a fully implantable, tether-free, left ventricular assist system (LVAS) intended for long-term use in patients with severe, medically intractable, heart failure.

The continued clinical need for, and progress toward, development of implantable devices for circulatory support will be discussed. Important clinical results will be noted and the NHLBI plan for clinical evaluation of an implantable LVAS will be described. Implantable artificial hearts to be used in the future will be briefly discussed. Of necessity, efforts in the last 25 years have focused primarily on technical development. The science has now matured to a point where evaluation of the safety and efficacy of fully implantable systems can begin. Preliminary information about the impact of these systems on quality of life will be a focus of this evaluation.

Need. Heart failure is a worldwide problem. In the United States, alone, 3 million people suffer from congestive heart failure (CHF) (1). CHF develops in 400,000 people each year and it is the most common hospital discharge diagnosis in patients older than 65 (1). At a time when death

from heart disease is declining (2), the prevalence of CHF is increasing (1).

Government Accounting Office

in full, budget don't know what it is

GAO report on cardiac transplantation in the United States also provides some insight regarding donor heart availability (7). During 1988, 1,529 transplants were performed, there were 929 patients on the waiting list, and 297 of these have been waiting for 6 months or longer. Additionally, 515 patients died while awaiting a donor organ.

two thousand

or 2,000

A potential solution to the problem of donor heart availability would be advances in manipulation of the immune system that would permit xenografting. *Although* Such advances do not appear likely in the near future, *it is an avenue of research which is being actively pursued.*

Because of a lack of alternative solutions, mechanical assistance for, or replacement of, a patient's heart may be an attractive therapeutic alternative for patients for whom a donor organ is not available. It is

for this reason that the NHLBI has pursued research aimed at the development of mechanical systems capable of supporting the failing circulation.

Artificial Heart Program. The Artificial Heart Program of the NHLBI has provided support over the years for research on circulatory support systems. A number of developments have resulted including extracorporeal systems for emergency cardiopulmonary bypass and left ventricular assist systems (LVAS's) for support of patients with post-cardiotomy ventricular dysfunction or as a bridge to transplant.

The ultimate goal of this program is the development of a totally implantable artificial heart. The attainment of this goal requires the solution of many complex problems related to both biomaterials and engineering design. The artificial heart program has utilized a step-by-step approach of research into and evaluation of progressively more sophisticated circulatory assist devices.

Devices. As the state-of-the-art advanced, devices in common use today were developed. The intra-aortic balloon pump, for instance, was made possible by the development of appropriate polymers and workable pneumatic actuators. During the 1970's, pneumatically powered ventricular assist systems came into clinical use. These devices were developed as part of the NHLBI research program (8,9). Several hundred have been used as a bridge-to-transplant or support post-cardiotomy patients who could not otherwise have been weaned from bypass. They have also been used, to a

lesser extent, to support patients following acute myocardial infarction. The biomaterials program has importantly influenced the development of materials used in these systems.

Bridge to Transplant. Because experience with ventricular assist devices used as bridges to transplant has motivated the current focus of the program discussed above, this use of LVAS's deserves special mention. The term "bridge-to-transplant" means that a mechanical device was used to support a patient requiring hemodynamic support while awaiting a donor heart. Most of the devices used have been pneumatically driven. About 40% of patients who received a mechanical device as a bridge were discharged alive (10). In 1988 the discharge rate was 50%. Though these data are uncontrolled, it is expected that without the placement of a mechanical support device mortality would have approached 100%. Experience with the current generation of temporary devices has led to the expectation that long term, fully implantable systems might be developed and this is now the primary objective of the Artificial Heart Program.

Long Term, Implantable Left Ventricular Assist System Development. Figure 1 is a diagram of an implantable LVAS of the type under development. In contrast to temporary devices, all of the major components of the system are implantable with the exception of the external batteries. Electrical power is transmitted across the intact skin by a belt-skin transformer. An electronic control package modulates the power to activate the blood pump. It also contains rechargeable nickel-cadmium batteries for brief periods of operation independent of the

external battery pack. The blood pump is positioned in the muscle sheaths of the left upper quadrant of the abdomen. The variable volume compensator maintains a low resistance to passive filling of the pumping chamber of the left ventricle. The system will deliver more than 10 liters per minute output at rates up to 180 beats per minute. The device will be placed chronically in patients who might benefit from transplant but who are unlikely to receive one. An engineering reliability testing program is being completed and human implants are expected to begin in 1991 following final animal testing.

Device Readiness Testing. The Device Readiness Testing program deserves special mention because it is likely to become a prototype for reliability testing of future (11,12) circulatory support systems. This program is the first NIH research activity to assess and enhance the reliability of a medical technology. It was undertaken to ensure the safety of the first generation of implantable devices before the start of clinical studies. The goal of the program is to demonstrate, with a high level of confidence, an 80% reliability for two years of continuous operation. Mock circulatory loops (Figure 2) were used to test the LVAS's. Operating characteristics were monitored 24 hours a day.

Although mock loops are useful for demonstrating engineering reliability, they have certain limitations. For instance, saline, rather than blood, was used. Also, mechanical, rather than bioprosthetic, valves were used because bioprosthetic valves are destroyed by microorganisms that proliferate in the mock loop.

National Institutes of Health

1st full time use

Animal Studies. Because of the limitations of the mock loops in demonstrating the interaction of the systems with a living organism and the need to assess circulatory performance, animal studies are being conducted. Previous criteria for testing in animals specified a period of testing twice as long as the intended implant period except for the temporary devices. This is impractical for chronic implants. The current NHLBI thinking is that tests of 4-6 months provide useful results regarding biocompatibility, bleeding, thrombosis, infection, embolism, and death.

Animal studies also have their limitations. There are substantial species differences between the animal model and the human being. Also, the implanted configuration of this system must be altered to fit an animal rather than a human being. Adverse events that occur during animal testing may or may not occur in humans because of the species difference. It is of interest that in testing the intra-aortic pump there were more complications in the animals than there were in humans (13). Animal studies, then, provide some indication of potential complications and hazards but it is felt that an implant period more than 5 months is not useful and that human implantation represents a major challenge that cannot be completely studied using animals.

Clinical Ventricular Assist Program. When animal testing is completed, it is expected that 2 clinical centers will be selected to implant a total of 20 LVAS's in 20 patients over a two year period. This program will focus on the many unanswered questions of device/patient interface. Each

patient will be followed for a minimum of 2 years or until death. The first implants are expected to begin in early 1991.

The formal organization of the study (14-16) (Figure 3) will include the two Clinical Centers, the Production Center, and a Data Coordinating Center. The trial will be administered by a Steering Committee composed of the investigators and by a member of the NHLBI Program Office. This Steering Committee will develop the collaborative protocols to be used in the study. It will be independently reviewed by a Safety and Data Monitoring Committee that reports to the NHLBI.

During Phase I of the program, the investigators will focus on patient entry criteria, protocol development and (FDA) investigational device approval. Patient implants will begin during Phase II after NHLBI approval of all aspects of the protocols.

The three phases of the study will evaluate the safety and efficacy of the LVAS over a protracted period of time. The device readiness testing program has previously demonstrated the engineering design, and the human investigation will study the long term response of the patient and the ability of the device to function appropriately in a human being following its implantation.

Patients for this study will have congestive heart failure and be severely symptomatic. They will be candidates for cardiac transplantation who are unlikely to receive transplant because of age or other factors.

(will be 27)
Expectations. This ~~is the~~ first time that a totally implantable LVAS has been used. Special consideration will be given to infectious and thromboembolic complications (17). The results of this sort of long term implant are not predictable, but a useful starting point is to examine some of the results from the bridge-to-transplant experience. For instance, in one series 72% of bridge patients were transplanted and 69% of them were discharged alive (10). This was a heterogenous patient population, studied at several different centers. Also, the data are uncontrolled but it is likely that all the patients would have died if a bridge had not been available. A particular concern is the fact that 17/40 patients developed serious infections and 9 died prior to discharge. Of the 8 patients who developed infections after implant, 2 died of infection, and 1 died of multiple organ system failure. The development of an infection in 20% of the patients after implant is of particular concern because the rate of infection is likely to increase as devices are left in place for longer periods of time. Additionally, the ability to eradicate a device based infection without device removal must be regarded as problematic. In addition, 7.5% experienced neurological events that were thought to be embolic in origin.

In summary, then, infection and thrombosis are problems of unknown but probably substantial magnitude. Recent clinical experience provides some encouraging, although limited, evidence of the potential viability of this type of technology. Fifty-seven "bridge" patients (18) were implanted with a ventricular assist system designed for long term use.

One system was electrically powered via a percutaneous lead, and the other was air driven. Thirty-three patients were transplanted and 27 were discharged alive.

Two of 57 patients with complex tissue matching requirements in another study (19) were successfully bridged to transplant after 125 and 132 days of support with an implantable ventricular assist system powered percutaneously. These two patients were ambulatory, exercised regularly, and previous organ dysfunction resolved after device implant. Patients enjoyed normal organ function and a reasonably good quality of life while confined to a hospital setting. These results are significant in that they are the longest use of devices specifically developed for chronic human use. Of note is the fact that these implants exceeded the 112 days that Barney Clark lived with the first chronic artificial heart implant (20).

The Implantable Artificial Heart. Many of the patients who require mechanical circulatory support may require a complete replacement. In 1988 the NHLBI funded the first program targeted solely at development of an implantable artificial heart. These systems are to be electrically powered, tether-free and designed for 5 years of operation. These are rigorous requirements but are necessary if systems are to evolve which will benefit patients at a moderate price and have a truly long lifetime.

The targeted program to develop an artificial heart has followed many years of research aimed at solving basic problems involved in perfecting

this technology. It is only now that data suggest that the implantable artificial heart is feasible. Competing priorities limit fiscal resources available for artificial heart development but it is felt that the NHLBI is now in a position to move ahead with this program.

In order to provide a continuing evaluation of need for and feasibility of

a mechanical heart, the ~~US~~ Institute of Medicine has been asked to ~~study~~ *assess the many aspects of* the artificial heart program, ~~and their report is eagerly awaited.~~ *It is expected that their report will help the NHLBI to chart the course of the artificial heart program.*

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References

1. Mark M. Levinson, Richard G. Smith, Randall C. Cork, et al. Vol 10(3), page 236-244, 1986
2. Stamler J. Epidemiology, established major risk factors, and the primary prevention of coronary heart disease. In: Parmley WW, Chatterjee K, eds Cardiology, Vol 2, Ch1, Philadelphia: JB Lippincott Company, 1988
3. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316
4. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 1986;314:1547.
5. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: The Framingham study, N Engl J Med 1971;285:1441-6
6. Artificial Heart and Assist Devices: Direction, Needs, Costs, Societal and Ethical Issues, NIH Publication No. 85-2723;May 1985
7. Shikles JL, Schupp AR, Hogberg RB. Heart Transplants: Concerns about cost, access and availability of donor organs. Government Accounting Office Report, 1989, p. 21.
8. Assisted Circulation, Edited by Felix Unger, Springer-Verlag, New York, pages 87-95;1979
9. Bernhard, WF, Berger, RL, McCormick, N, Stety, JD, Klein, MD, Ryan, TH, and Carr, JG. Successful Use of a Paracorporeal Left Ventricular Assist Device in Man. JAMA 243:46-49, 1980
10. Farrar, DJ, Hill, JD, Gray, LA, et al: Heterotopic Prosthetic Ventricular as a Bridge to Cardiac Transplantation. N Engl J Med, 318:333-340,1988
11. RFP NHLBI 84-1; Device Readiness Testing of Implantable Ventricular Assist Systems
12. Altieri FD, Watson JT, Taylor KD. Mechanical Support for the Failing Heart. Biomaterials Applications, Vol 1, pages 106-157, 1986
13. Rosenweig J, Chatterjee S, Merino F. Treatment of acute Myocardial Infarction by Counterpulsation: Experimental Estimate and Clinical Experience, J Thoracic and Cardiovascular Surgery 59:243-250, 1970
14. RFP NHLBI HV-89-10: Clinical Center for the Evolution of

- Implantable Ventricular Assist Systems for Human Subjects with Chronic Refracting Heart Failure, 1989
15. RFP NHLBI HV-84-01 (R88): Clinical Ventricular Assist System Production, Support and Evaluation, 1988
 16. RFP NHLBI HV-89-9: Data Coordinating Center for the Evolution of Implantable Ventricular Assist Systems for Human Subjects with Chronic Refracting Heart Failure, 1989
 17. Paul Didisheim, Don B. Olsen, David Farrar, et al. Infections and Thromboembolism with Implantable Cardiovascular Devices
 18. Personal Communication: Summary Data provided by Dr. Peer Portner, Baxter-Novacor, and Mr. Victor Poirier, ThermoCardiosystems, Inc., Oakland, CA., and Woburn, MA.
 19. Personal Communications: Dr. Bartley Griffith, University of Pittsburgh School of Medicine, Pittsburgh, PA and Dr. O. Howard Frazier, Texas Heart Institute, Houston, TX
 20. W.C. DeVrie^s, the Permanent Artificial Heart: Four Care Reports. JAMA Vol. 259, No. 6, page 844-859, 1988

Legends

- Figure 1. Schmatic showing the major components of an implantable left ventricular assist system. BST = belt skin transformer, ECP = electronics control and power, EPSM = external power source and status monitor, VVC - variable volume compensator.
- Figure 2. Mock circulatory loop with left ventricular assist system in place. BST = belt skin transformer, ECP = electronics control and power, EPSM = external power source and status monitor, VVC - variable volume compensator.
- Figure 3. Organizational structure for the study of the implantable left ventricular assist system. NHLBI = National Heart, Lung and Blood Institute.