SynCardia Systems, Inc.
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August 28, 2007

*BY ELECTRONIC DELIVERY (*CAGinquiries@cms.hhs.gov*)*

Steve Phurrough, MD, MPA, Director
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop
7500 Security Boulevard
Baltimore, MD 21244

Re: Comments on National Coverage Analysis Concerning Artificial Hearts (CAG-00322N)

Dear Dr. Phurrough:

SynCardia Systems, Inc. ("SynCardia") appreciates the opening of a national coverage analysis that includes the CardioWest™ temporary Total Artificial Heart ("TAH-t") by the Centers for Medicare and Medicaid Services ("CMS") in response to our request. While we believe our request included the information needed for CMS to determine that the TAH-t is reasonable and necessary as a bridge to transplant for patients in biventricular failure, we provide this comment during the initial public comment period to offer additional information that we believe to be relevant to the national coverage analysis. Below we identify the information attached to this letter and the relevance to the CMS analysis.

- **Appendix 1**: In Section II(F) of our reconsideration request, we noted that a number of prominent cardiac transplant institutions have expressed strong interest in participating in the clinical trial SynCardia intends to conduct on a new driver for the TAH-t. We included the letters in our possession at that time, but have since obtained additional letters. We are providing these letters to CMS because they bear on the issues in which CMS has indicated an interest, pursuant to the tracking sheet for the artificial heart national coverage analysis. Specifically, they discuss hospital staffing of their individual cardiac programs and their experience with heart transplants.

- **Appendix 2**: The information contained in this article by Dr. Arabia concerns TAH-t patients that were included in the reported studies that we identified in our request for reconsideration of the national coverage decision for the artificial heart. Even so, because this article arrays the information differently and has been published, we wanted to provide it to you for your consideration. It discusses the feasibility clinical study of the TAH-t, in which 23 of 24 patients were successfully bridged to transplant and 22 of them survived for at least a year (compared to the control group in which 10 of 18

patients died while awaiting a transplant). The article also provides a snapshot of the first 100 TAH-t patients.

- **Appendix 3**: Similar to the article from Dr. Arabia, this article by Dr. Copeland and others discusses results of 62 TAH-t patients who were included in studies identified in our reconsideration request. Although this does not break new ground, since it is a published peer reviewed article, we wanted to ensure that we provided it to you

- **Appendix 4**: This article from Dr. El-Banayosy and others offers additional information on use of the TAH-t in Europe. It reports on the use of the TAH-t in 42 patients whom the authors characterized as the "sickest patient cohort receiving mechanical circulatory support ever reported, as shown by their pre-implant hemodynamic and laboratory data." Even in that population, the overall survival rate was 48%, which the authors termed a "favorable result."

- **Appendix 5**: We believe that this article (lead author, Leprince) contains a helpful discussion of the appropriate size of the pericardial cavity for implantation of the TAH-t. We discussed this issue in Section II(C) of our request, but this article provides CMS with greater detail on the issue of the size of the chest cavity.

- **Appendix 6**: This chapter from an International Society for Heart and Lung Transplantation monograph series contains a more in-depth description of the device implantation procedure than was provided in our request and might be useful to CMS.

- **Appendix 7**: This contains three case reports (lead authors Leprince, Polito, and Smith) related to the use of the TAH-t. While we understand that CMS may put less weight on case reports, it is nonetheless useful for the agency to be aware of these reported uses of the TAH-t.

Again, SynCardia appreciates the opening of the artificial heart coverage analysis and the opportunity to comment. We hope that this additional information provided will be useful to the agency and we look forward to the issuance of proposed decision that will include affirmative coverage of the TAH-t as a bridge to transplant.

If you have questions concerning this letter, please do not hesitate to contact me at (520) 547-7467. Thank you for your consideration.

Respectfully,

Carole E. Marcot
Vice President
Regulatory Affairs and Quality

Attachments

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Appendix 1

Aurora St. Luke's Medical Center

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June 26, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
Centers for Medicare and Medicaid Services
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7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive:

Aurora St. Luke's Medical Center has a respectable history in the fields of heart failure management, heart transplantation and mechanical cardiac support devices. The Tendick Center for Heart Failure at Aurora St. Luke's supports patients throughout the various stages of heart failure. When a patient initially presents to the clinic, the Heart Failure team consisting of Heart Failure Cardiologists and Heart Failure RN Coordinators manages them. As the patient's condition deteriorates, the Heart Transplant Surgeons, Cardiologists and the Transplant RN Coordinators assess them. Depending on the patient's clinical situation, the patient is presented with the options of heart transplantation or mechanical circulatory assistance.

I was one of the Primary Investigators for both the Jarvick TAH and the CardioWest TAH clinical trials. I implanted my first artificial heart in 1986 and have done eight Jarvick TAHs and three CardioWest TAHs to date. In 2006, I implanted a 39-year-old gentleman with a CardioWest TAH due to his arrhythmias. Prior to the implant, he was required to stay in the hospital, attached to a defibrillation vest. This patient did exceptionally well on the TAH. Although he was a status 1A while on the TAH, he had an elevated PRA and it took six months to find an acceptable donor. Due to the limitations of the 450-pound console, he was confined to the hospital. While the hospital staff kept the patient busy with rehabilitation, visits to an in-house apartment and movie screenings in the auditorium, the large console significantly impacted his quality of life, along with his family's.

At our institution, we have 7 different types of ventricular assist devices and 1 TAH. The CardioWest TAH provides a unique niche to a subset of our patients. This device allows patients that are in bi-ventricular failure or have intractable, sustained arrhythmias to receive the cardiac output they need. While the Thoratec does offer support for those in biventricular failure or those with sustained arrhythmias, it is limited by the amount of cardiac output that the device offers. For a larger patient, the Thoratec does not offer as much flow as the CardioWest TAH. Our last TAH patient achieved flows of 6.5 to 8 LPM and the Thoratec would not have been able to provide that. The benefit of the Thoratec device is that they do already have a portable driver to send a patient home

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with. However, if it does not provide enough flow, then it can't be used on this subset of patients.

Our Cardiac Surgeons will continue to use the CardioWest TAH because of this unique niche that it fills. However, a case like the one mentioned above uses extensive resources of the patient, the hospital and the insurance company. These patients would benefit tremendously from the use of a portable driver to go home.

I anticipate that the CardioWest TAH could be used in 1-3 patients annually at our institution. While we do not currently have a patient on the device, we do have a potential patient. This patient is another candidate due to his arrhythmias. He is currently confined to the hospital, attached to a Lidocaine infusion. If he received the TAH and was afforded the opportunity for home discharge, he could potentially maintain a better quality of life than he currently has.

Aurora St. Luke's Medical Center would be excited to participate in the IDE Discharge Study. We believe that it would offer the patient the opportunity to go home and improve their quality of life while minimizing costs at the same time. We realize that there are currently no associated reimbursements from CMS for this program, however it will be extremely beneficial to our program and others like ours when these reimbursements are available.

If you have any questions, please contact me in my office at (414) 649-3780

Sincerely,

Alfred J. Tector

Alfred J. Tector

Cleveland Clinic

Nicholas G. Smedira, MD
Surgical Director
Cardiac Transplant/Mechanical Circulatory Support
The Kaufman Center for Heart Failure

May 11, 2007

Marcel Salive, MD
Director, Division of Medical and Surgical Services
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Blvd.
Baltimore, MD 21244-1849

RE: IDE Discharge Study of the Syncardia Cardiowest temporary Total Artificial Heart

Dear Dr. Salive:

Since 1984, the Cleveland Clinic has had an active heart transplant program and has been involved with mechanical circulatory support since 1991. In May of 2007 at the American Association of Thoracic Surgery meeting I presented the cumulative experience of the Cleveland Clinic with multiple circulatory support devices. The total number of devices utilized over the 16 years of the study was 375, with 262 or 70% of the patients being successfully bridged to transplant. We are also involved with permanent therapy and have actively supported device patients as outpatients both as a bridge to transplantation and for long term support.

We have utilized the Total Artificial Heart-t in 6 patients and believe we can support more patients and improve their quality of life if they can be discharged.

Another advantage of hospital discharge is some patients requiring biventricular support have psychosocial issues and/or drug and alcohol use and need to undergo 6 months of therapy before being considered transplant candidates. It has been difficult to do this while the patient is sequestered in the hospital.

We anticipate that approximately 3-5 patients will be treated with the total artificial heart, and would think that 50% of these, or 1-2 patients, will require discharge.

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As I mentioned earlier the TAH is utilized for biventricular support and the other support device most commonly used is a left ventricular assist device. The indication for TAH use is fulmanant mycocarditis, acute myocardial infarction and decompensated heart failure with difficult to control ventricular arrhythmias.

While our objective is to provide the best mechanical circulatory support for the patient independent of reimbursement, the financial well being of the device program will be annually assessed.

Thank you for your time and consideration. If you have any further questions, please do not hesitate to contact me,

Sincerely,

Nicholas G. Smedira, MD

NGS:cmv

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Milton S. Hershey Medical Center
College of Medicine

Heart & Vascular Institute
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Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
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7500 Security Boulevard
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Dear Dr. Salive,

Penn State Milton S. Hershey Medical Center has a long history of Circulatory support experience dating back to the 1960's with the development of the Pierce-Donnachy design LVAD (currently marketed by Thoratec Corporation). With those beginnings came the first human implant of that device by Dr. William Pierce in 1976. Since that time this program has implanted more than 330 circulatory support devices for advanced heart failure. PSMSHMC in conjunction with Penn State Artificial Organs department, had developed and trialed our own version of a Total Artificial Heart which is now owned and being further developed by Abiomed, Inc.

Penn State Milton S. Hershey Medical Center has been a cardiac transplant center since 1984. Since that time we have completed 367 cardiac transplants and continue to have a very active program.

Our Heart Failure program continues to grow. We currently have in excess of 2500 outpatient visits annually for heart failure. With four dedicated heart failure cardiologists, a heart failure fellowship, Nurse Practitioners, Physician Assistants, Transplant Coordinators, dedicated artificial organ NPs and social workers we continue to provide care to a growing number of class III and IV heart failure patients on an outpatient and inpatient basis.

Our cardiology and surgical staff work closely together to provide patients with a multidisciplinary approach to heart failure. We currently evaluate and treat the heart failure patient through a multifaceted approach including oral and home IV medications, electrophysiological intervention, surgical heart failure intervention including cardiac restraint devices, circulatory support devices including the Syncardia TAH-t, and cardiac transplant.

Circulatory support devices have become a cornerstone for advanced heart failure treatment at PSMSHMC. Waiting times for cardiac transplant donors has remained substantial in this region. For that reason we have been aggressive in the use of

circulatory support devices to allow the cardiac transplant candidate to remain as healthy as possible while waiting for an appropriate donor organ. We have a long history of use of the Pierce Donnachy (Thoratec) pneumatic pump. For this reason we have used this pump in the past for patients with biventricular failure. With the acquisition of the Syncardia CardioWest TAH-t we have been able to transition to the use of a total artificial heart for these patients. It has allowed us to treat patients with intractable arrhythmias and profound shock with a higher level of control.

The current requirement that TAH-t patients remain in the hospital represents a significant financial commitment for the institution. With the ability to discharge the patient to home with the IDE driver, it has the potential to become psychologically beneficial for the patient, and economically beneficial for the patient and the institution by allowing the patient to live at home with their families while waiting for transplant.

In the northeast region of the country the waiting time for an organ exceeds 90 days. At PSMSHMC 45 % of our cardiac transplant patients are medicare recipients. In light of this it would be beneficial for both the institution and for CMS, from many aspects, to enable the patient to be discharged to a home environment with the use of the portable device.

Penn State Milton S. Hershey Medical Center has a long history of participation in heart failure and circulatory support trials. We have a dedicated research staff that is experienced with both large and small scale trials.

Thank you for your time and consideration in this matter. Please feel free to contact us if you have any further questions.

Sincerely,

Walter E. Pae, Jr., M.D.
Chief Cardiothoracic Surgery
Penn State Heart and Vascular Institute

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM | HOSPITAL of the UNIVERSITY of PENNSYLVANIA

Office of Clinical Research and
Mechanical Cardiac Support Program
Department of Surgery
Division of Cardiac Surgery

June 25, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive,

The Heart Failure and Transplantation Program at the Hospital of the University of Pennsylvania, currently under the direction of Rohinton J. Morris, MD and Mariell Jessup, MD, is one of the busiest programs in the country, ranking 6th nationally in 2005. We were concurrently the busiest adult cardiac transplant center in the Philadelphia and Southeastern PA region, servicing patients from Northeastern PA, Central and South New Jersey, Delaware and Northeastern Maryland. We have maintained our leadership over the last six years, continuing to be the busiest transplant program, in spite of expansion in Philadelphia from 3 to 5 transplant programs. Since 1987, approximately 600 heart transplants have been performed at HUP, and the use of ventricular assist devices (VAD) has become a significant part of our program with over 275 device implants since 1995.

More than 7,500 patient visits occur annually in the Penn Heart Failure and Transplant Center, and our clinicians manage patients in all stages of heart failure. Patients are initially managed with pharmacologic support, and as the disease progresses, they may require surgical and electrical intervention. In the final stage of heart failure, patients are considered for cardiac transplantation. Some of these patients may require mechanical cardiac assist devices to survive to transplant, and some may receive a device (LVAD only) in lieu of a transplant. The devices traditionally used are left ventricular and biventricular assist devices. Since receiving FDA approval in 2004, the SynCardia CardioWest™ temporary Total Artificial Heart is also available for use as a "bridge" to cardiac transplant.

As the patients' treatment needs unfold, close collaboration between our heart failure cardiologists and cardiac surgeons allows us to optimize treatment of our patients using medical and surgical approaches. Joining these physicians in providing comprehensive care is a multidisciplinary team that includes nurse practitioners, transplant and VAD

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coordinators, social workers, financial counselors, and rehabilitation specialists. We also collaborate with specialists in cardiac imaging, arrhythmia management, cardiac anesthesia, infectious disease, and immunology. Select members of the team meet weekly to discuss patient eligibility and management for both transplant and device implantation.

Approximately 50 patients are transplanted at HUP each year, and roughly 40% of those patients survive to transplant because they were supported with a cardiac assist device. Since 1995, approximately 30% of the patients receiving devices have required biventricular support. It is this group of patients, transplant eligible with biventricular failure, who will benefit from our use of the TAH-t. The TAH-t replaces the native heart and all of the valves, which eliminates the potential for many complications we see with biventricular assist devices. Two patients have been successfully implanted with the Total Heart at HUP in the last three months. The first was successfully transplanted and the second is currently supported and doing well. We estimate that the TAH-t program will expand to support five to eight patients per year.

The FDA currently requires that patients supported by the TAH-t remain in the hospital, but it will benefit the patients and our institution greatly if we can discharge these patients to home while they await transplantation. The patients initially recover in the cardiac surgical intensive care unit and are then transferred to the cardiac intensive care unit (CICU) once they are stable. In the CICU, the patients undergo regular physical therapy, and both patients have been able to tolerate multiple walks throughout the day in addition to their therapy sessions. They have been able to function with minimal assistance, with their primary limitation being the enormous heavy console to which they remain attached.

We have an active discharge program for our other VADs, with three dedicated VAD coordinators who manage both bridge-to-transplant and destination therapy. We were the first center in the region to discharge a patient on an LVAD. The VAD coordinators and nurses provide extensive education to the patient and ensure readiness for discharge. The patients are given passes to leave the floor followed by a 6 hour "home pass" to develop a comfort level outside of the hospital prior to discharge. When possible, the VAD coordinators perform a home visit to verify the safety of the environment and any barriers to safe transition home. Additional preparation involves education of local emergency medical personnel and home care nurses, assessment and emergency planning for utility usage, and close communication with the patient's local physician. The same processes will be utilized in the discharge of patients with the investigational portable console used in the "IDE Discharge Study."

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There are substantial financial costs associated with implantation of mechanical cardiac assist devices, including the TAH-t, and the subsequent hospitalization. As an institution, HUP would require approval for payment by insurance companies prior to enrollment in the Discharge Study.

Thank you very much for your time and consideration. Please fell free to contact us if you have any questions or concerns.

Sincerely,

Michael A. Acker, M.D.
Chief, Division of Cardiovascular Surgery
Hospital of the University of Pennsylvania

Rohinton J. Morris, M.D.
Associate Surgical Director,
Heart Transplantation and Mechanical Cardiac Assist Device Program
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Cardiomyopathy Treatment Program

August 2, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
Centers for Medicare and Medicaid Services Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive:

Program description and the role of mechanical circulatory support: The University of Iowa's Cardiomyopathy Treatment Program is a well-established multidisciplinary program that provides treatment for patients with advanced heart failure and pulmonary hypertension. Our medical and surgical services have traditionally worked very closely together to provide outstanding service to the people of our rural state. We have evaluated and treated approximately 3,000 people over the past two years and currently have over 1,000 patients under active management. This letter will focus on two pertinent components of our program: heart transplantation and mechanical circulatory support. UIHC is a public institution and the only heart transplant and ventricular assist device (VAD) implanting center in the state of Iowa. We are dedicated to providing critical access to these services for all Iowans, including those who have limited resources. We have been performing adult and pediatric cardiac transplantation without any period of inactivity since 1985. Our heart transplant outcomes consistently meet or exceed the national average, and we are a certified transplant center by UNOS and CMS. In addition, the University of Iowa is a CMS certified center for the implantation of ventricular assist devices for both bridge to transplant and destination therapy indications. We have a long tradition of scholarly achievement and maintain a robust clinical trials program within the Cardiomyopathy Treatment Program. UI participated in the REMATCH trial evaluating the HeartMate LVAS against optimal medical management, and we currently participate in eight trials evaluating diverse drug and device treatments for heart failure. We also contribute to the Cardiac Transplant Research Database (CTRD) and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).

Patients referred to the program are evaluated first by one of three faculty cardiologists specializing in advanced heart failure: Drs. Barry Cabuay, John Chase and Frances Johnson. The minimum experience is 8 years in this subspecialty at the faculty level. There is a dedicated inpatient cardiology service for acute heart failure or transplant associated care. Outpatient heart failure subspecialty clinics are open Monday through

Friday. There is close collaboration with the electrophysiology group, and patients are routinely treated with bi-ventricular pacing and receive defibrillators as needed. Three cardiothoracic surgeons are available and experienced in pediatric and/or adult heart transplantation and mechanical circulatory support: Drs. James Davis, David Helman, and Wayne Richenbacher. In addition, we have an adult ECMO program lead by thoracic surgeon Dr. William Lynch for patients in shock needing urgent circulatory support. Patients who fail optimal medical therapy are presented urgently to our surgical team or, more commonly, at our weekly multidisciplinary conference for consideration of all appropriate surgical therapies including heart transplantation and temporary or permanent mechanical circulatory support.

The benefit of TAH-t to the UIHC Cardiomyopathy Treatment Program: There are a variety of factors leading us to seek acquisition of a reliable and effective biventricular circulatory support device (VAD). The first is a general increase in the proportion of patients with chronic biventricular dysfunction after many years of "effective" medical therapy for heart failure. Another is new UNOS organ allocation rules for heart transplantation that appear to be exacerbating the problem of long transplant waiting list times, especially for larger blood type O recipients. The requirement for high acuity before an organ is offered increases the likelihood that the patient will require life-saving treatment with a VAD or suffer the consequences of progressive multi-organ failure. Our current VAD bridge to transplant rate is near 35% and we expect this percentage to increase significantly in the next three years. We have studied reports of SynCardia CardioWest™ temporary Total Artificial Heart (TAH-t) recipient outcomes and bridge to transplant rates, reviewed INTERMACS data, and have personally discussed device use with medical staff at centers using the TAH-t. We believe that it is a treatment advance for selected patients in our program, and we are committed to adding it to our suite of available devices even if patients are confirmed to hospital while awaiting transplantation. The advantage of a portable driver that allows for discharge of a patient is enormous. Because Iowa is a rural state, we have considerable experience caring for patients who have been discharged to home on the HeartMate LVAS, and also with patients who were confined to hospital for months while awaiting transplant because they needed biventricular support with paracorporeal VADs. It is our opinion that the home environment improves overall health and rehabilitation in addition to improving quality of life. Our team is experienced in preparing patients, families, local EMS personnel, and local physicians in home care.

Estimated TAH-t volume: The University of Iowa has recently made key recruitments in Cardiology and Cardiac Surgery that are expected to increase our program volume. Although it is difficult to accurately predict any growth curve, heart transplant referral and listing rates have increased several-fold in the past 9 months. Historically 3-5 patients are sent out of area for VADs each year due to size and/or need for bi-ventricular support. It is our opinion that having devices that support a wider range of patients will reduce the export of donor hearts from Iowa and increase our transplant volume to 20-25 transplants per year in the next 3-5 years. An estimate for TAH-t use in the first year of use is 1-2 devices based on our current activity, with increases to 5-7 per year by year three.

How the TAH-t will augment UIHCs current program: UIHC is currently implanting FDA-approved Thoratec pVADs, iVADs, and HeartMate XVE LVADs in eligible patients for bridge to transplantation. The SynCardia CardioWest™ temporary Total Artificial Heart would immediately replace biventricular implantation of the pVAD and iVAD in patients with bi-ventricular failure who are large enough to accommodate the device. Advantages of the TAH-t include elimination of an abdominal pocket, better flow rates, reduced resistence to venous return and thus improved organ perfusion. Available data suggests that hepatic and renal function improves much more rapidly with a TAH-t than with an LVAD. For this reason, the TAH-t may also replace the use of LVAD support in patients who have moderate RV dysfunction and/or secondary pulmonary hypertension.

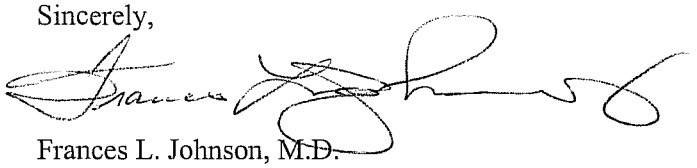
Hospital commitment: UIHC has identified cardiac care as an area of significant need in the next decade and has committed sizable resources to the development of a new University of Iowa Heart and Vascular Center, an integrated service-line that encompasses Cardiothoracic Surgery, Vascular Surgery, and Cardiology. The treatment of end-stage heart disease with therapies like heart transplantation and VAD

implantation is a high priority for both the UIHC and the School of Medicine. Signs of this commitment include approvals for key recruitments of physicians, physician scientists, and bioengineers in this area, appropriation and renovation of hospital and research space, and the allocation of funds for capital equipment and clinical program growth. We are more than willing to participate in the IDE Discharge Study following IRB approval.

Use independent of CMS reimbursement: The SynCardia TAH-t represents a significant financial commitment, although it is felt that with the potential for discharge in the present study, the total monies spent will probably be less than that for a prolonged BiVAD hospitalization. However, this financial commitment could not be borne by the hospital, and UIHC would not be able to enroll Medicare patients in the IDE Discharge Study for whom there is no insurance coverage, such as by Medicare or a private insurer.

Thank you for your consideration. Any further inquiries can be addressed to my office at (319) 356-4489 or by email at frances-johnson@uiowa.edu.

Sincerely,



Frances L. Johnson, M.D.
Clinical Associate Professor of Medicine
Division of Cardiovascular Disease
Medical Director, Cardiomyopathy Treatment Program

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June 01, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
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Dear Dr. Salive:

Mayo Clinic has a long and distinguished history in the field of cardiac transplantation. The Heart Transplantation program began in Rochester in 1988, where greater than 300 heart transplants have taken place. In Jacksonville, there have been 59 heart transplant and in Arizona 22.

Our outpatient Heart Failure clinics are fully staffed with cardiologists dedicated to this area of medicine. In 2006, more than 300 heart failure patients were seen in this clinic; in Jacksonville, 1400 were seen and in Arizona 339 patients. The advanced Heart Failure clinics are well-integrated into the Heart Transplant Programs at all three sites, incorporating Transplant, Cardiothoracic Surgery and Cardiology. This close collaboration allows advanced heart failure care to be delivered in an efficient manner. These entities allow for a wide spectrum of heart failure that includes optimal medical management, ventricular assist device implantation and cardiac transplantation.

Our cardiothoracic surgery teams at all three sites are well-trained in mechanical assist devices. In Rochester, the team of 11 surgeons implanted an average of 10 devices annually. In Jacksonville, the cardiothoracic team implanted 10 devices. In Arizona, the surgical team of 4 implanted 15 devices during 2006.

The accessibility of the Total Artificial Heart will complete the spectrum of artificial cardiac support available to our patients. The availability of a range of devices enables us to provide optimal care to the individual patients. Some patients are best served with a ventricular assist device, while very ill patients may need a TAH. A discharge program will allow a higher quality of life for patients as well as reducing costs.

Mayo Clinic is estimating that there may be an average of 8 -9 patients treated annually with a TAH, across the three sites. Currently, patient with severe biventricular failure and secondary systemic organ dysfunction who are suitable for heart transplantation are

potential candidates for the TAH. Some patients who are currently treated with biventricular assist devices might be better treated with a TAH-t.

Mayo Clinic would be most interested in participating in the IDE Discharge Study. In the circumstances of no CMS reimbursement, patients would be booked on an individual basis. Consideration would be given to following a protocol requesting charity care in specific circumstances.

Thank you in advance for your time and consideration.

Most respectfully,

Francisco Arabia, M.D., MBA
Chair, Division of Cardiothoracic Surgery

THE OHIO STATE UNIVERSITY Medical Center

Division of Cardiothoracic Surgery

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May 18, 2007

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Baltimore, MD 21244-1849

Dear Dr. Salive:

The Ohio State University Medical Center has developed a world class mechanical circulatory support and heart failure program over the last 5 years. At this juncture we are active in implanting 10 different mechanical circulatory support systems and are one of the busiest if not the busiest implantable device program in the country currently. Our experience has also involved implantation of the SynCardia Total Artificial Heart Systems of which we have had 2 implants recently. We feel that this technology is an important component of the future of mechanical circulatory support and has enormous potential. One of the concerns that we have had as a device was the limitation of the patients from leaving the hospital. This certainly puts a financial burden on the institution as well as a psychologic burden on these patients.

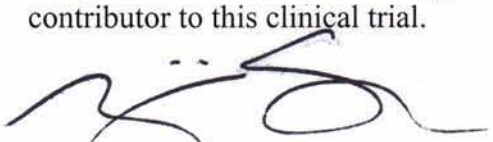
We have a large experience with outpatient management of mechanical circulatory support patients with over 20 patients currently at home under support. The ability for patients to leave the hospital facilitates substantial improvements in rehabilitation as well as a reduction of psychologic stress. They are home with their families and they are in there normal environments and work towards becoming normal individuals. Many patients return back to work despite the fact that they have mechanical circulatory support.

Having an outpatient component of a Total Artificial Heart System with SynCardia will certainly enhance this utilization as well as facilitate improved patient recovery. There is no doubt in my mind that this would facilitate improved outcomes over time as there is less of a "rush to transplant this patient". We would be able to maintain these patients for longer periods of time with better

physical recovery and removing some of the extra constraints of the financial burdens on the institutions and improve the patient overall well being. Our institution is experienced with multiple clinical trials in for the use of mechanical circulatory support and has the infrastructure teams and institutional support to support this clinical trial. Many of our team members (myself included) were investigators in the outpatient trials for the Thoratec TLC II portable driver in the past. That study will likely be very similar to this trial.

Currently we would estimate that at least 2-10 patients a year could be supported on this system at OSU. The current required for continued impatient use of this device with our bed constraints and others that it has handcuffed us to some small extent.

Thank you very much for your strong consideration for our institution to participate in this clinical trial. We feel we have the institutional support and a comprehensive mechanical support team who will be an active and important contributor to this clinical trial.



Benjamin Sun, M.D.
Chief, Cardiothoracic Surgery
Associate Professor of Surgery
Director of Cardiac Transplantation and
Mechanical Support

BS/msw

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UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

EASTMAN DENTAL CENTER
SCHOOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING
STRONG MEMORIAL HOSPITAL
UNIVERSITY OF ROCHESTER MEDICAL FACULTY GROUP

CARDIAC SURGERY

H. Todd Massey, M.D.
Surgical Director
Program in Heart Failure and Transplantation
Director
Artifical Heart Program
Associate Professor, Cardiac Surgery

Marcel Salive MD, MPH
Director, Division of Medical and Surgical Services
Centers for Medicare and Medicaid Services
Mail Stop C1-09-09
7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive:

The University of Rochester Medical Center's Artificial Heart Program at Strong Memorial Hospital is one of the nations leaders in mechanical circulatory support. The Heart Failure and Heart Transplant program has over X visits annually with Y patients currently awaiting heart transplantation. The primary service area for the heart transplant program is a population of 5 million. The program is directed by Leway Chen M.D,M.P.H, and has a staff of over 5 heart failure cardiologists. Mechanical Circulatory support has had a major role in our heart transplant program. Given the geography of Upstate New York in relation to Canada, the large medical centers in the northeast Unites States, and the increasing aging population with a decreasing youthful population translates into long wait times and over 70% of transplants requiring bridge to transplant VAD support. Mechanical Circulatory Support research has been a cornerstone of our program. The Artificial Heart Program has participated in the Thoratec TLC-II discharge to home study, Thoratec IVAD study, HeartMate II pilot and pivotal study, CentriMag AMI and PCCS study and The Momentum Trial. The program also has 3 basic science labs performing VAD research.

Safe and reliable discharge to home with Bi-VAD TAH-t support would benefit our patients thought decreased time away from family and social support as well as reduced in-hospital time associated with iatrogenic and hospital acquired complications and infections. Only one of the two Bi-VAD systems we currently use is cable of home discharge. The system that is capable has sub-optimal battery performance. This has a great effect on our patients that could easily have great then 14 feet of snow surrounding their house any give winter. It has been our experience that the Bridge to Transplant patients have less complications and do better at the time of transplant if they can rehabilitate in their home environment. We anticipate these better outcomes, improved quality of life and additional measures of safely and reliability will benefit our patients that receive the SynCardia TAH-t

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Strong Memorial Hospital annually places over 20 patients a year on long term bridge to transplant mechanical support. At least 10 of these patients would be of the body size and clinically indicated for a TAH-t device. These ten patients would be appropriately sized patients with extended wait times for transplant due to blood type, anti-bodies, or deferred wait times to measure compliance with a medical regimen or abstinence. The ability to discharge patients with the device would greatly affect our intent to use the device since it would permit us to decrease length of stay and potentially improve outcomes.

The currently employed treatments have been supporting patients with the Abiomed AB ventricle or Thoratec IVAD/PVAD systems, prolonged ICU stays on IABP or inotropes or transitioning the patient to palliative care because of inability to provide support. Some patients with preexisting mechanical aortic valves that could not undergo replacement of valve with LVAD or Bi-VAD placement have not been offered support because of the surgical barriers that this situation presents. There is also a group of patients who require bridging with temporary RVAD support following LVAD placement that may benefit from placement of a total support system such and the SynCardia TAH-t.

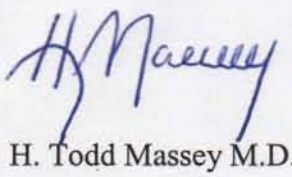
It is my strong belief that due to the improved outcomes and survival demonstrated by the SynCardia TAH-t, the availability of a discharge unit would only increase the survival, reduce complications and improve the quality of life of these patients. The Artificial Heart Program at Strong Memorial Hospital is ready and willing to participate in the IDE Discharge Study.

The advancements in circulatory support technologies have always translated into lower costs and decreased length of stays. Our own LVAD average length of stay has decreased from 74 days to 28 days in the last few years as pump technology has changed. Given the superiority of this technology as well as the ability to discharge, I believe this will also decrease length of stay and costs.

Strong Memorial Hospital has a commitment to providing the best technology and care to our patients, but cannot burden this charge alone. Without insurance coverage Medicare patients would not be able to be enrolled in the Discharge Study of the SynCardia Cardiowest™ TAH-t

Thank you for your time and commitment to mechanical circulatory support.

Sincerely,



H. Todd Massey M.D.

Surgical Director; Artificial Heart Program

STANFORD UNIVERSITY SCHOOL of MEDICINE
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May 21, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive:

This letter is to express the interest of Stanford University Medical Center (SUMC) to participate in the "IDE Discharge Study" of the SynCardia CardioWest™ temporary Total Artificial Heart. Stanford has a very long history of pioneering studies in heart transplantation and the use of mechanical ventricular assist devices. Dr. Norman Shumway began the clinical heart transplantation program in 1968, following many years of laboratory research investigations. As such, it is the longest continually active heart transplant program in the world today. In addition, development of the Novacor left ventricular assist system led to the world's first successful bridge to heart transplantation in 1984.

Currently, the Division of Cardiovascular Medicine and the Department of Cardiothoracic Surgery collaborate in a large coordinated program of heart failure management with multiple surgical options, including transplantation and a spectrum of assist devices. Information about the hospital's programs is found at http://www.stanfordhospital.com.

Although a number of mechanical assist options are available for our patients, we have not previously utilized the SynCardia CardioWest™ temporary Total Artificial Heart. The excellent results obtained by the team at the University of Arizona, as well as other heart transplant groups worldwide, lead us to the conclusion that it is an excellent option for bridging patients with combined end-stage right and left ventricular failure to heart transplantation, and, in fact, is superior to our own experience with separate biventricular assist device utilization. Currently, we avoid biventricular assist whenever possible and find ourselves utilizing a left ventricular assist device with inotropic augmentation for right ventricular support, although utilizing BVADs when absolutely necessary. We have had extensive experience in managing Novacor LVAS recipients out-of-the-hospital, both at a nearby family residence (to ensure self-care competence and confidence with the designated caregiver before final discharge), and then at their homes, for periods up to and exceeding a year. – an experience that can be readily translated to recipients of the CardioWest™ temporary Total Artificial Heart. We estimate that the temporary Total Artificial Heart could be utilized in as many as four patients per year at our center.

However, the SynCardia CardioWest™ temporary Total Artificial Heart represents a significant financial commitment, and SUMC would not be able to enroll Medicare patients in the IDE Discharge Study without insurance coverage. It is essential for our institution's participation in the proposed trial to have CMS coverage available for our Medicare patients.

Thank you very much, and please let me know if I can supply any other information or be of help.

Sincerely,

Bruce A. Reitz, M.D.

University Medical Center

1501 North Campbell Avenue
Tucson, Arizona 85724

Artificial Heart Program
(520) 694-6455

June 27, 2007

Marcel Salive, MD, MPH
Director, Division of Medical and Surgical Services
Center for Medicare and Medicaid Services
Mail Stop C1-09-06
Baltimore, MD 21244-1849

RE: National Coverage of the SynCardia Systems, Inc. CardioWest TAH-t System

Dear Dr. Salive:

UMC is a pioneer and leader in the cardiac transplantation and mechanical circulatory support device fields. We were one of the first six heart transplant centers in the United States, founded in 1979. In 1987, UMC became one of the first three heart transplant centers in the nation authorized to receive Medicare funds for heart transplants. Approximately 800 heart transplants have been performed at UMC, with some of the highest survival rates in the world.

Our mechanical circulatory support experience began in 1985 with the world's first successful "bridge to transplant" (BTT) using a total artificial heart (Jarvik-7). Since then the "Artificial Heart Program" has implanted approximately 100 total artificial hearts as BTT, which is the largest experience in the United States, over 100 left ventricular assist devices (LVAD) as BTT, bridge to recovery (BTR) and destination therapy, and 65 biventricular implants (BIVAD). UMC is routinely rated as one of the best hospitals for heart and heart surgery (U.S. News and World Report 16th in 2006), and is one of CMS's device destination therapy centers. The UMC program has dedicated staff (8 FTE) and space (2500 sq ft), with experience with device studies and patient discharge on devices.

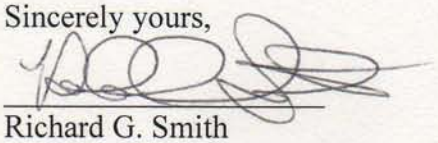
The capability of discharging TAH patients will benefit both the patient and hospital. Our TAH patients are the fastest to recover, but are limited to the hospital at present. Discharge will provide the patient with a better quality of life outside the hospital and reduce the cost of waiting for heart transplantation, both for the hospital and insurance companies.

We anticipate that by having the opportunity and option to discharge stable recovered patients on the TAH that our implant rate will increase. We expect to increase to at least

one implant per month on average. Since the recovered patient on the TAH is stable, adding discharge capabilities will increase the use of the TAH in areas previously treated with BIVADs, which allowed discharge, though with poorer overall outcomes.

Upon review of our TAH experience at UMC we note that more than one third of patients treated are Medicare-eligible. As such reimbursement from CMS is important to UMC. In addition, some private insurance companies use CMS approval as a gating factor for coverage. Historically therapies that have no possibility of reimbursement are used only in a very limited way. Thus, patients that are not covered by private insurers, CMS or other programs would not be able to receive a TAH or participate in the IDE discharge study.

Sincerely yours,



Richard G. Smith
Technical Director
Artificial Heart Program
University Medical Center

Washington University in St. Louis
SCHOOL OF MEDICINE

Department of Surgery
Division of Cardiothoracic Surgery
Nader Moazami, M.D.
Assistant Professor of Surgery
Director of Cardiac Transplantation

June 26, 2007

Marcel Salive, MD, MPH
Director, Division of Medical & Surgical Services
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1849

Dear Dr. Salive:

I am writing this letter as a formal commitment of Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, Missouri to participate in "IDE Discharge Study" of SynCardia CardioWest™ temporary Total Artificial Heart.

The Heart Failure Service at Washington University and Barnes-Jewish Hospital is one of the leading programs in the State of Missouri, offering the most advanced treatments for heart failure. This Division, under the direction of Dr. Gregory Ewald, has been involved in all aspects of heart failure management and offers a structured approach to treatment of heart failure, which encompasses the most advanced options available currently available including cardiac transplantation and mechanical circulatory support.

The Heart Transplant Program at this institution has been active since 1985 and over 500 heart transplants have been performed with results that are comparable to national survival rates for heart transplant patients.

In addition, our center has been heavily involved in offering the most advanced mechanical circulatory support systems for patients who are either deemed too unstable to wait for a transplant or those in whom we believe mechanical support offers the best permanent therapy. The center has a large experience with mechanical assist devices that have been approved by the FDA and these include the Thoratec pneumatic VAD, Heartmate VE device, Novacor device, Abiomed temporary device, as well as various percutaneous circulatory support systems such as the Tandem Heart device.

In addition, our program has been involved in the clinical evaluation of patients that are using the HeartMate II device that is currently in an investigational trial.

The program recently acquired the Syncardia total artificial heart system and has subsequently implanted one device. Part of the reason that this device was acquired by our program was

Washington University School of Medicine at Washington University Medical Center, Queeny Tower, Suite 3106, One Barnes-Jewish Hospital Plaza, St. Louis, Missouri 63110-1013, Phone: (314) 362-8008, FAX: (314) 747-4216, e-mail: *moazamin@msnotes.wustl.edu*

because we thought that there are a group of patients who require more advanced therapies for their bi-ventricular dysfunction which was not being met by currently available LVAD technologies. Given that our hospital has had a vast experience with mechanical circulatory support, acquiring this system and familiarizing our team was not a difficult process. We believe that overall three to four patients per year will require implantation of this system for continued support.

At this time, our hospital has a large artificial heart program that includes dedicated nurses, coordinators, physicians, social workers, and transplant financial specialists who work together to oversee the total management of these patients. Our dedication to the continued advancement of the mechanical circulatory support program requires that we be involved in the Syncardia IDE Discharge Study. We believe that home discharge for patients on mechanical circulatory support is an important advantage in the overall treatment of patients with endstage heart failure. Unfortunately, up until this date, this technology has not been available for the total artificial heart and the requirement has been that patients should stay in the hospital while awaiting an appropriate transplant. Our past experience with home discharge of device-supported patients has proven to be extremely successful in terms of overall recovery of patients, both in terms of their physical and psychosocial well-being. The home discharge program at Washington University and Barnes-Jewish Hospital has been very well developed and is coordinated and handled by our three ventricular assist device coordinators with Ms. Kimberly Shelton, RN, our senior Program Director, having had extensive experience in this field. In addition, the multiple medical advantages of a home discharge program, we sincerely believe that this will also lead to significant cost reduction for these patients.

Once again, I would like to reiterate that we are committed to participating in this trial and we believe that this system adds yet another improved dimension for the care of these critically ill patients. Without CMS coverage of this device a large portion of this patient population may go unserved. As I mentioned previously, I believe that overall we will be placing the total artificial heart in three or four patients in whom the current technology with left ventricular assist devices is not adequate and this treatment modality should significantly augment the services that we can provide to our patients with end stage heart failure.

Please do not hesitate to contact me if you have any further questions.

Sincerely,

Nader Moazami, M.D.
Director of Cardiac Transplantation

NM:bjw

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1992 E. Silverlake Rd.
Tucson, Arizona 85713
Telephone: 520.545.1234
Facsimile: 520.903.1782

Appendix 2

Update on the Total Artificial Heart

Francisco A. Arabia, M.D.

The Marshall Foundation Artificial Heart Program, University of Arizona Sarver Heart Center, Tucson, Arizona

ABSTRACT **There has been a quest for an artificial organ that can replace the heart for decades. Remarkable advances were made in the second half of the twentieth century in the fields of medicine and engineering that led to the development of several devices with the intention of totally replacing the human heart. Some of these devices, like the Jarvik artificial heart, were utilized initially as a permanent replacement for the failing heart. It became more successful as a bridge to heart transplantation (BTT) in the years that followed its introduction. Currently the CardioWest total artificial heart (TAH) is the only device in clinical use with the intention of bridging patients to heart transplantation. Two new TAHs are being developed with the intention of being used as an alternative to transplantation (ATT) or on a permanent basis. The next 100 years will bring revolutionary new designs and advances in the field of end stage heart disease that may only be ideas at the present time.** *(J Card Surg 2001;16:222-227)*

BRIEF HISTORY

The development of the technology for the invention of the total artificial heart required many discoveries during many centuries. Description of the function of heart valves by Leonardo DaVinci was necessary to understand how the heart maintains unidirectional blood flow. The understanding of the circulation by William Harvey provided the basis of how the heart maintains the internal environment that provides nutrients to a multicellular organism.

The twentieth century saw the development of new ideas and machines as well as a better understanding of biology and medicine. One of the first designs of an artificial heart was proposed by the young aviator Charles Lindbergh and Nobel laureate Alexis Carrel. They came together as a result of Lindbergh's interest in medicine and experimental biology. In the early 1930s, they designed an "artificial heart" made out of glass that worked as a perfusion pump outside the body. Lindbergh's association with Carrel continued for many years, and he went on to modify the perfusion pump. His interest in experimental biology continued to expand in the years that followed and included the fields of genetics and immunology.[1]

The next major advance occurred in 1937 when a Russian surgeon named Demikhov replaced a dog's heart with two prosthetic ventricles. This historic event apparently went unknown for many decades and was not recognized until later. The next recorded landmark did not take place until 1953 when John Gibbon reported the use of the heart lung machine. This tool to maintain circulation while stopping the patient's heart opened the field of open-heart surgery.

The first successful use of an artificial heart in this country occurred in 1957 when Willem Kolff and Tetsuzo Akutsu implanted a pneumatic TAH that kept a dog alive for 90 minutes. In 1965, Yukihiko Nose's Green Heart kept a sheep alive for the record time of 50 hours. The Clifford Kwan-Gett TAH was another design that kept a calf alive for 2 weeks in the early 1980s.

The first clinical use of an artificial heart was performed in 1969 by Cooley[2] when he implanted

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the Liotta Heart. This design was pneumatically driven, used Wada-Cutter hingeless valves and had Dacron diaphragms and conduits. The Liotta heart was used to support a patient for 64 hours until a donor heart became available for transplant. However, the patient succumbed after the transplant. Twelve years passed before the next TAH was used. The Akutsu-TAH was first implanted in 1981 as a bridge to transplantation. It supported a patient for 2 days. However, the patient died 7 days after transplantation.

History was written in 1982 when the first TAH, the Jarvik-7 TAH was implanted with the intention of permanently sustaining life in a human.[3] Dr. Barney Clark, a dentist with end-stage heart disease, who had been turned down as a candidate for heart transplantation, became the first recipient. He became an instant symbol of modern medical technology and provided hope for patients with end stage heart disease. Dr. Clark survived for 112 days as the world watched the medical drama evolved. His course was complicated with renal failure, seizures, device failure, and pneumonia. The Jarvik-7 TAH was implanted in four more patients on a permanent basis, the longest surviving 620 days. The first successful use of the Jarvik-TAH as a bridge for heart transplantation was performed in 1985.[4] This event expanded the use of the Jarvik-7 TAH in this country and abroad as a bridge to heart transplantation. Also in that year the Penn State heart, a pneumatically driven TAH, was implanted in four patients as a BTT.

JARVIK-SYMBION TAH YEARS

The Jarvik TAH, manufactured by Symbion, Inc., continued to be used through out the world as a bridge to heart transplantation between 1985 and 1992. Data on the first 100 patients had been accumulated by 1988. A total of 68 patients had survived to reach transplantation. Forty-seven patients survived 30 days and 31 of them survived long term.[5] Several other total artificial heart were designed and implanted through out the world, primarily in Europe. All were utilized with the intention of bridge to heart transplantation (Fig. 1), but none had accumulated patient data as much as the Jarvik-7. At the end of 1992, 198 of these devices had been implanted as BTT.[6] Of the 198 patients, 143 (72%) were transplanted. Eighty-five patients were discharged home (43% of the total, 59% of those transplanted). Incidence of major complications included infections 9.4%, stroke 5%, and transient ischemic attacks in 4%.

TAH IN HUMANS (SEPT 2000)

DEVICE	TIMEFRAME	CENTERS	IMPLANTS	TRANSPLANTS	DISCHARGED
LIOTTA	1969	1	1	1	0
AKUTSU	1981	1	1	1	0
JARVIK 7-100	1982-1992	10	44	26	16
PHOENIX	1985	1	1	1	0
PENN ST	1985-1989	1	4	1	0
JARVIK 7-70	1985-1992	30	159	120	69
BERLIN	1986-1990	1	7	2	0
UNGER	1986-1990	3	4	2	0
VIENNA	1989	1	2	1	1
BRNO	1988-1990	3	6	3	0
POISK	1987-1990	3	16	3	2
CARDIOWEST	1993-2000	9	169	109	95
PHOENIX-7	1998	1	2	1	1
TOTALS			416	271	184

Figure 1. *World Experience with total artificial heart in humans.*

In 1990, the U.S. Food and Drug Administration (FDA) withdrew permission from Symbion, to continue production of the Jarvik TAH in the United States. Although the device continued to be manufactured in Canada, the device was utilized in France but none were used in this country. One year later, CardioWest Technologies, Inc., (Tucson, AZ, USA) acquired assets and technology from Symbion, Inc. In 1992 the FDA granted limited clinical investigation to manufacture the Jarvik-7-70, now renamed the CardioWest C-70. The FDA granted an investigational device exemption to CardioWest Technologies in 1993 and first the TAH was implanted that year as a BTT.[7-10]

CARDIOWEST

The CardioWest is a pneumatically driven TAH that totally replaces the failing ventricles (Fig. 2). It is placed in an orthotopic position (Fig. 3) via a mediastinotomy. Each ventricle connects to its respective atrium and great vessel. Two Medtronic-Hall (Medtronic, Inc., Woodland Hills, CA) valves (size 27 mm, 23 mm) are placed at the inflow and outflow of each ventricle.[11] A four-layer diaphragm separates blood from compress air. A pneumatic drive line connects to each ventricle, exits the body below the left subcostal margin, and connects to the driving console. Each ventricle has a volume of about 70 cc and can provide flows up to 8-9 L/min under physiologic conditions. The pa-

J CARD SURG
2001;16:222-227

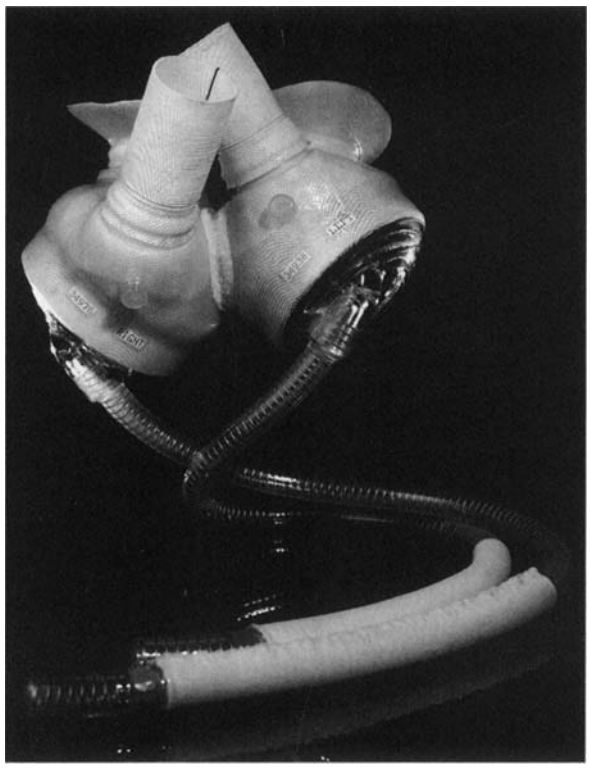

Figure 2. *CardioWest TAH.*

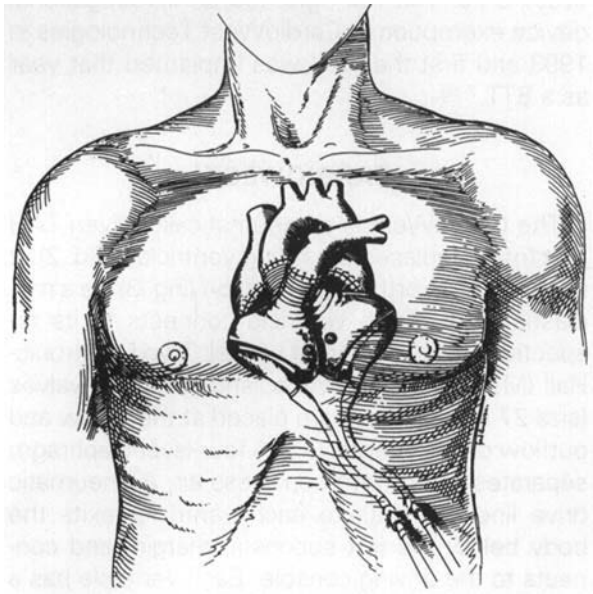

Figure 3. *Schematic of CardioWest TAH.*

tients are anticoagulated with a combination of persantine, aspirin, and warfarin.

Since 1993, a total of 169 CardioWest TAH have been implanted as a BTT in the United States, France, and Canada. The etiologies of the cardiomyopathies included: ischemic 40%, idiopathic 32%, and others (viral, postpartum, valvular) 28%. In the United States, all patients had been listed for heart transplantation prior to implantation. All had been on maximal medical therapy and had a very limited life expectancy.

WORLD EXPERIENCE

Indications

Patient selection is probably the most important factor in determining success with mechanical circulatory assistance. Early experience with the use of post-cardiotomy devices for cardiac recovery showed that patients younger than 60 years had a survival rate of 21-31%, patients older than 60 had a survival rate of 12%, and patients over 70 years had a survival rate of 6%. Other factors contributing to successful outcomes include: careful selection of assist device; the skill, experience, and judgment of the implanting team. When criteria for placement of ventricular assistance are met, prompt intervention is important as prolonged hypotension (greater than 12 hours) is associated with multisystem failure and poor recovery. Measurements of cardiac output and atrial pressures are necessary to assess the patient's need for a device. These parameters are also very helpful in the immediate postoperative period.

Inclusion criteria for implantation for the United States centers were according to the CardioWest investigational protocol accepted by the FDA: (1) patient listed for heart transplantation and in imminent danger of dying within 48 hours or becoming ineligible for transplant; (2) cardiac index $< 2.01/min/m^2$ with either systolic blood pressure < 90 mmHg or central venous pressure > 18 mmHg and/or at least 2 inotropes: dopamine > 10 mcg/kg/min, dobutamine > 10 mcg/kg/min, epinephrine > 0.02 mcg/kg/min, isoproterenol > 0.02 mcg/kg/min, or amrinone > 10 mcg/kg/min; or 1 inotrope and a balloon pump; (3) pulmonary vascular resistance < 8 Wood units (640 dynes-sec/cm2); (4) absence of active systemic infection; (5) absence of renal or hepatic failure; (6) cytotoxic anti-

body level < 10%; (7) absence of support devices other than the intra-aortic balloon pump. In addition body surface area (BSA) in general > 1.7 m2.[12]

One of the first studies regarding CardioWest TAH was to determine the feasibility of using the TAH as a bridge to transplant. A total of 24 patients met criteria to receive the CardioWest TAH as a BTT (group A). Group A was retrospectively matched with 18 patients (group B) who met the same implantation criteria but did not received the TAH because either the patient refused or the TAH was not available.[13]

All patients in groups A and B had to meet the inclusion criteria. This includes candidacy for heart transplantation, the use of maximal inotropic support with evidence of biventricular failure. In addition there had to be no evidence of systemic infections and/or irreversible end organ damage.

All the patients who received the TAH (group A) had been evaluated and accepted for heart transplantation prior to implant. Group A consisted of 23 males and 1 female with an average age of 46 ± 11 years. The average number of days from admission to implant of the TAH was 11 days. The average number of days on the TAH was 50 ± 42 days. The control group (B) consisted of 15 males and 3 females with an average age of 47 ± 9.3 years. Group B was hospitalized for an average of 42 ± 35 days to the time of transplant or death. Renal and hepatic function parameters were determined and compared in both groups. There were not statistically significant difference in the two groups.

Group A and B were compared in regards to survival and number of complications that each group experienced. In group A, 17 (70.8%) patients required an IABP. A total of 23 patients survived the bridge and reached transplantation. One patient died while on the TAH as a result of mediatinitis. This patient had had a previous coronary artery bypass grafting the week preceding the TAH implantation. A gram negative rod was cultured at the time of the implantation that was the bacteria that caused the mediastinitis. One of the transplanted patients died within 15 days of the transplant as a result of the advance graft atherosclerosis. Therefore a total of 22 patients survived and were alive for more than a year with an average of 31 ± 11 months. This resulted in a success rate of 91.7%. Group A experienced 142 complications or adverse events. None of these adverse events resulted in a direct patient death. The average adverse events per patient was 11 ± 4.

Group B consisted of 18 patients of which 14 (77.8%) required IABP. Eight patients reached transplantation and 10 patients died while waiting. Of the transplanted patients, one died within 3 days and another one at 6 months. The survival rate for the seven patients who were discharged home was 38.9%. This was statistically significant when compared to group A ($p < 0.0003$). The total number of hospital days for group A was 77 ± 52 days, for group B was 42 ± 25 days.

The survival or success rates has been calculated for the current mechanical circulatory support system that are available as a bridge to heart transplantation. The CardioWest TAH appears to have the best survival rate when the patients are selected following a strict selection criteria. The survival rate for those patients who were waiting in the hospital and were not bridged to heart transplantation can serve as the base to compare all devices available.

The outcome of the first 100 patients who had placement of the CardioWest TAH as a BTT was closely studied. The population consisted of 90 males, 10 females. Mean age was 45 years (16-64), mean BSA 1.94 m^2 (1.52-2.37), preimplantation mean cardiac index was 1.81 l/min/m2. The etiologies of the cardiomyopathies were: idiopathic 36, ischemic 35, graft failure 6, valvular 5, viral 5, postcardiotomy 5, and other 13. The average number of days on the TAH was 39 days: A total of 67 patients reached transplantation and 61 were discharged home. Thirty-eight patients died: 32 during the BTT and 6 after implantation. The most common cause of death was multiple organ failure. There were a total of 424 complications (events) in 87 patients, none in 13. The most common complications as percentage of the total events were: infection 43%, renal dysfunction 42%, hepatic dysfunction 38%, bleeding 28%, reoperation 27%, neurologic dysfunction 25%, and respiratory failure 23%.[14]

The complications related to infections was examined in detail in the first 27 who underwent placement of the TAH in this country. The population consisted of 25 males, 2 females, mean age 46.5 ± 10.3 years, body surface area 2.01 ± 0.17 m2° duration of implant 52 ± 42 days. Initial diagnosis included: ischemic cardiomyopathy 10, idiopathic 10, viral 4, valvular 2, and graft failure 1. Infection complications were defined as systemic

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(evidence of leukocytosis and/or fever) or local. The population experienced of 64 infections, range 0-9/patients: 45 systemic and 19 local, 3 patients did not experienced any infection. Twenty-five patients reached transplantation and were discharged home for a survival rate of 92.6%. Two patients died during the bridge: one due to mechanical failure and one due to infection (mediastinitis). Therefore, death due to infections occurred in 3.7%.[15] Previous reports of the total artificial heart experience in the late 1980s described death rates as high as 40%.[16]

Although infection complications are common in the patients who are bridged to heart transplantation with the TAH, mortality from infections is 10 times less than previously reported. This may be the result of a better strategy for bridging to transplant that includes patient selection, mobilization, early central line removal, and waiting until all possible infections are resolved before proceeding to transplant.

At the present time there are several types of devices that are utilized world wide with the intention of bridging patients to heart transplantation. The CardioWest TAH is the only device of its kind that totally replaces the failing heart. When all the devices available are compared (Thoratec, TCI Heartmate, Novacor LVAS, and CardioWest TAH) as to how an effective bridge to transplantation they are, the results are very similar.[17] However, it is important to consider that not all devices can be used in all patients. The device selected should be tailored to the patient's needs.

It is essential that the device can fit in the patient to allow for proper functioning. The current guidelines to place the CardioWest TAH in a patient and expect adequate hemodynamics include: BSA > 1.7 m2, the distance between then posterior aspect of the sternum to the anterior aspect of the vertebral column at the level of T-10 should be at least 10 cm. In addition, a cardiothoracic ratio > 0.5 on a chest radiograph, and a left ventricular end diastolic diameter > 70 mm on echocardiogram. When a fit complication occurs it usually manifest itself as inflow partial occlusion. It occurs when the device partially occludes the inflow of blood into the device at the level of the inferior vena cava right atrial junction or at the level of the pulmonary veins. A complete description of the implantation technique is found elsewhere.[18]

THE NEXT GENERATION OF TOTAL ARTIFICIAL HEARTS

AbioCor Heart

The AbioCor (Abiomed, Inc., Danvers, MA, USA) system is an electrohydaulic TAH. This device is totally implanted and can generate outputs up to 10 L/min. It utilizes transcutaneous energy transmission system (TETS) that provides the power across the skin. Therefore, no drivelines penetrate the skin. The thoracic units consists of an energy converter and two blood pumps that totally replace the human heart. This system allows the TAH to alternate between right and left ventricular systole. The thoracic unit also includes an internal battery and a secondary coil. The internal lining of the pump and the four trileaflet valves that provide unidirectional flow are constructed of polyetherurethane. The stroke volume of each ventricle is approximately 60 cc (Fig. 4). The system is now undergoing animal studies and is expected clinical trails sometime between 2001 and 2003.

Penn State Heart

The Penn State TAH is an electromechanical system that also utilizes the TETS system and is

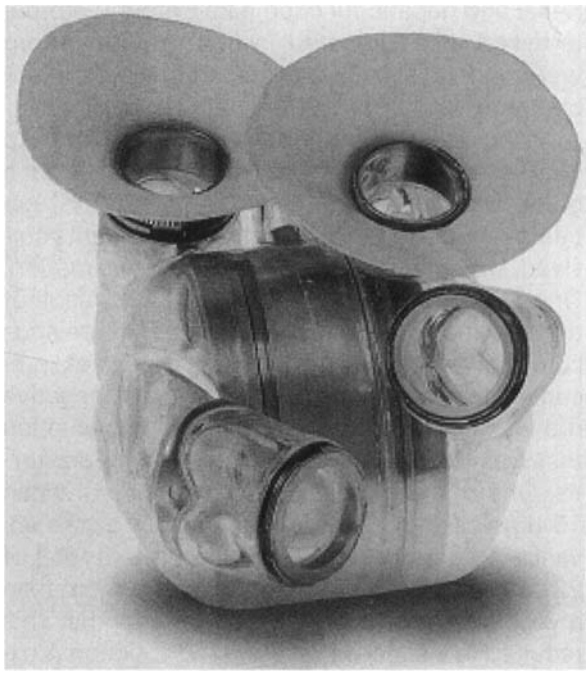

Figure 4. *AbioCor TAH.*

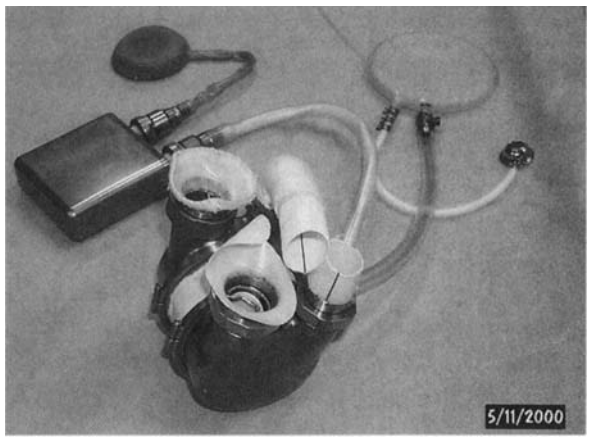

Figure 5. *Penn State TAH.*

implanted in the orthotopic position. The pumps are constructed of a polyurethane polymer with 4 Delrin monostrut valves that maintain unidirectional flow. The stroke volume of each ventricle is approximately 64 cc and the unit can provide an output of about 81/min (Fig. 5). It also is expected to start clinical trials sometime between 2001 and 2003.

The advances that were made in the twentieth century have served to develop devices that could assist the circulation. This new century will probably bring devices that are not even imaginable at this time.

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Appendix 3

Total Artificial Heart Bridge to Transplantation: A 9-Year Experience With 62 Patients

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Background: The SynCardia CardioWest total artificial heart (CardioWest TAH) is a biventricular, orthotopic, pneumatic, pulsatile blood pump driven by an external console. For each ventricle, the length of the blood-flow path is shorter and the inflow and outflow valves are larger than in any other bridge-to-transplant device, resulting in greater blood flow at smaller pre-load. Such a device should be optimal for bridging transplant candidates who have biventricular failure and for whom all other therapies have failed.

Methods: From January 1, 1993, to April 1, 2002, we prospectively studied 62 consecutive CardioWest TAH implant recipients to document safety and efficacy in bridge to transplantation. We used multisystem monitoring and multidrug therapy for anti-coagulation in 58 patients starting September 1, 1994.

Results: Before implantation, patients were critically ill with biventricular heart failure. Mortality in this group from the time of implantation until transplantation was 23%. Causes of death during device support included multi-organ failure (6), sepsis (3), and valve entrapment (2). Forty-eight patients underwent transplantation (77%). Forty-two survived to hospital discharge (68% of the total, 88% of those undergoing transplantation). Adverse events included bleeding (20%), device malfunction (5%), fit complications (3%), mediastinal infections (5%), visceral embolus (1.6%), and stroke during support (1.6%). The linearized stroke rate was 0.068 events per patient-year.

Conclusions: Sixty-eight percent of critically ill transplant candidates for whom medical therapy failed were bridged to transplantation with the CardioWest TAH and survived long-term. Most deaths that occurred during device support were related to pre-implant problems. Infection and stroke were rare events. Therefore, we recommend the CardioWest TAH as the biventricular bridge-to-transplant device of choice.

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The SynCardia CardioWest total artificial heart (CardioWest TAH) is unique among bridge-to-transplant devices because it replaces all 4 valves and both ventricles of the native heart. Orthotopic positioning eliminates concerns about problems resulting from the native heart, such as right heart failure, arrhythmias, problems with native and prosthetic heart valves, clots within the native ventricles, ventricular septal defects, rejection and infarction, and stone heart. Abdominal wall pocket problems seen with left ventricular assist device (LVAD) use, such as pocket infection, wound dehiscence, and gastric compression, also are avoided.

Since the first mechanical cardiac replacements, more than 500 patients have undergone TAH implantation.[1] Four-hundred and fifty of these devices have similar designs (Jarvik-70 and Symbion TAH) accounting for 52 of the 57 patient-years of world experience with TAHs. In 1991, the device was renamed CardioWest TAH. Since 2001, this TAH has been manufactured and supported by SynCardia Systems (Tucson, AZ). From 1991 until now, 260 CardioWest TAHs have been used in bridge to transplantation for a total duration of 35 patient-years and 60% of the world TAH experience.

Several reports have summarized international,[1–3] national,[4] and institutional[5] experiences, as well as technical aspects of the CardioWest TAH and of device implantation.[6–8] The percentage of patients who survive to transplantation (70%–93%) and who are discharged to home after transplantation (65%–89%) compare favorably with percentages reported for LVADs

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and extracorporeal biventricular assist devices (BVADs, 67%–78% undergoing transplantation and 56%–67% discharged).[9]

In a study comparing CardioWest TAH, Novacor left ventricular assist system (LVAS), and Thoratec BVADs in a population of patients who were clinically unstable, inotrope dependent, and failed to wean and who were bridged to transplantation, important differences were documented.[10] Respective results for CardioWest, Novacor, and Thoratec patients included survival, 75%, 56%, and 38%; stroke, 8%, 32%, and 12%, and death from infection, 2%, 13%, and 4%. Authors concluded that the LVAD was best used in more stable patients who had no right heart or end-organ failure. They thought that BVADs and TAHs were more efficacious in sicker patients, especially those with right heart failure. Because of a flow limit of approximately 5 to 6 liter/min and an extracorporeal position, Thoratec BVADs were recommended for small patients (body surface area 1.7 m^2). Because of greater flow capacity (6–9 liter/min), the CardioWest TAH was recommended for larger patients (1.7 m^2) who met orthotopic fit criteria for implantation.

Physical characteristics explain differences in maximal flows delivered by the various devices. The inflow and outflow pathway lengths and diameters are major determinants of flow. The inflow cannulas of the Thoratec are 10 to 12 mm in diameter and are considerably longer (30–40 cm) than are those of the HeartMate (19 mm diameter, 6 cm pathway) and the Novacor (22 mm diameter, 6–9 cm pathway). Thus, a maximal flow of 5 to 6 liter/min is standard for Thoratec. Novacor and HeartMate have a greater flow potential of 6 to 7 liter/min in the absence of right heart failure. The CardioWest TAH has a 27-mm inflow valve with an inflow pathway of approximately 4 mm, making it the most favorable for high flows (7 to 9 liter/min). These and other physical differences among devices explain differing effects in inflammation, coagulation, immunity, and in other physiologic systems as well as in end-organ recovery. Ultimately, careful examination of experiences, comparing different devices and reports that document results with a single device, will determine the relative utility of each of these devices.

Since our last institutional review of results with the CardioWest TAH from 1993 to 1997 in 24 patients,[5] as of April 2002, we have added 38 more patients. This experience with 62 implantations continues to support our confidence in this device for the rescue of mortally ill patients with heart failure.

METHODS

Table 1 lists inclusion and exclusion criteria, which have been previously published.[5] As part of the investigational device exemption (IDE) agreement, all patients included in this study had to be screened and found to be non-candidates for LVAD therapy before consideration for TAH implantation.

Table 1. Inclusion and Exclusion Criteria

Category	Criterion for Inclusion
Age	18
Body surface area	1.7, 2.5 m^2
Heart transplant candidacy	Accepted or acceptable
Central venous pressure	18 mm Hg
Systolic blood pressure	90 mm Hg
Cardiac Index	liter/min/m^2
Or high-dose inotropic support 2 drugs	Example: 10 g/kg/min dobutamine and dopamine
Or intra-aortic balloon pump (IABP)	IABP
Or cardiopulmonary bypass (CPB)	Failure to wean from CPB
Or extracorporeal membrane oxygenation (ECMO) support	ECMO

Category	Criterion for exclusion
Infection	Evidence of active infection
End-organ failure	Irreversible renal or hepatic failure
Panel-reactive antibody	10%
Transplant selection criteria	Any recognized contraindication

We rigorously and prospectively documented adverse events based on previously published[5] definitions, briefly described in Table 2.

Prophylactic antibiotic therapy with vancomycin was administered before surgery and until chest tubes were removed. Other antibiotic therapy was administered only for culture-positive infections.

Anti-coagulation and coagulation monitoring varied in the first 4 patients, but were consistent after September 1994 in 58 consecutive patients and have been described previously in detail.[1,6] Multidrug treatment with heparin, warfarin, aspirin, dipyridamole, and pentoxifylline is modulated according to several monitoring tests (Table 3). Thromboelastography, using recalcified whole blood, is used to titrate heparin and later Coumadin doses to normocoagulability. The aspirin dose is adjusted by following platelet aggregation studies and bleeding times. We seek to maintain platelet responsiveness to collagen with simultaneously decreased responsiveness to arachidonic acid, adenosine diphosphate, and epinephrine. We titrate the bleeding time to 1.5 to 2 times the upper limit of normal, corresponding to 15 to 22 minutes in our center. We use large doses of dipyridamole (from 100–300 mg every 6 hours) to stabilize platelets and follow the same tests as for aspirin. Pentoxifylline is used empirically for its inhibition of cellular adhesion molecules at a dose of 400 mg every 8 hours.[11]

Table 2. Definitions of Adverse Events

Adverse event	Brief definition
Bleeding	Any repeat surgery for bleeding (implant or transplant), any surgery requiring 8 units of blood, chest tube drainage of 200 cc/hour at 4 hours after surgery (implant or transplant), any transfusion of 3 units of blood at 48 hours after implant or transplant
Device malfunction	Any malfunction of the implantable device or of the console
Fit complication	Inadequate device function or pathologic compression of any intrathoracic structures because of inadequate space for the device
Hemodynamic insufficiency	Cardiac index 2 liter/min/m^2 or systolic pressure of 90 mm Hg for 4 hours
Hemolysis	2 levels of 30 mg/dl 24 hours apart and 72 hours after CPB or blood transfusion
Hepatic dysfunction	Total bilirubin 5.0 mg/dl, count a second event only when total bilirubin has fallen below 5.0 for 7 days
Infection	Any positive culture or clinical signs of sepsis with negative culture (in this article, serious infections are defined as those causing death, contributing to death, or delaying transplantation)
Neurologic event	Any new episode of neurologic dysfunction such as TIA, stroke, or seizure. Categories: thromboembolic, hemorrhagic, ischemic, metabolic, and medication induced
Peripheral thromboembolism	Any non-cerebral thromboembolic event resulting in motor, sensory, or ischemic impairment
Renal dysfunction	Serum creatinine 5.0 mg/dl or any post-implant hemodialysis
Repeat surgery	Any surgical procedure after implantation
Respiratory dysfunction	Post-operative intubation for 10 days, or any re-intubation for respiratory dysfunction

CPB, cardiopulmonary bypass; TIA, transient ischemic attack.

RESULTS

From January 1, 1993, until April 14, 2002, a total of 62 patients underwent implantation of CardioWest TAHs. Table 4 shows pre-implantation characteristics. In some cases, the most recent pre-implantation data (such as left ventricular ejection fraction, cardiac index, etc.) available from the patient's chart was listed even though later, at the time of implantation, in all patients, either inotropic support was failing or patients were receiving device support, such as with cardiopulmonary bypass. In other cases, such as with the 3 patients who failed to wean from cardiopulmonary bypass and who had no measurable cardiac index, numbers were unavailable. Thus, mean values rather than ranges, which are subject to such observational problems, are more useful descriptors of this population.

Mean implant times included aortic cross-clamp time of 105 26 minutes (range, 60–206 minutes) and cardiopulmonary bypass time of 124 42 minutes (range, 66–291 minutes). At the time of surgery, blood component use averaged 2 3 units of packed red cells, 6 5 units of fresh frozen plasma, and 1 1 units of platelets. During the first 5 peri-operative days, blood component use was 2 3 units of packed red cells, 2 3 units of fresh frozen plasma, and 1 1 units of platelets. No patients died during implantation.

After implantation, patients were extubated within 4 4 days (range, 0–15), had chest tubes removed within 6 5 days (range, 2–31), and were discharged from the intensive care unit within 12 9 days (range, 4–38). All patients remained in the hospital and walked once or twice per day. They also exercised between 1 and 5 times per week using Wellness Center machines, including treadmills and stationary bicycles. In a small group, peak oxygen consumption was in the 12 to 14 ml/kg/min range.

Table 3. Anti-coagulation and Monitoring

Drug/starting dose	Use	Monitoring goal
Heparin (intravenous) 500 U/hour	Start when chest tube drainage 30 ml/hour for 4 hours; stop when warfarin goal is met	Maintain TEG coagulation index in normocoagulable range
Warfarin (oral) 2.5–5 mg/day	Start at Day 7–14 when hepatic and renal function have returned to normal	Maintain TEG coagulation index in normocoagulable range
Aspirin (oral) 81 mg/day	Start at Day 1–3 depending on platelet count of 75,000 and chest tube drainage of 30 ml/hour for 4 hours	Therapeutic platelet aggregation study and bleeding time 15 min, 23 min
Dipyridamole (oral) 75 mg every 6 hours	Start per NG tube on return to intensive care	Dose increased as platelet count increases also TEG angle and maximal amplitude increases indicate increase in dose
Pentoxifylline (oral) 400 mg every 8 hours	Start per NG tube on return to intensive care	Dose is decreased if patient experiences nausea or vomiting

NG, nasogastric; TEG, thromboelastogram.

Table 4. Pre-implantation Characteristics of 62 CardioWest TAH Recipients

Characteristic	Numeric descriptor generally as mean SD (range)
Gender	51 men, 11 women
Age	50 11 years (18–67)
Body surface area	2.04 0.18 m^2 (1.68–2.80)
Weight	86 13 kg (57–112)
Left ventricular ejection fraction	20% 8% (5–50%)
Cardiac index	1.87 0.48 liter/min/m^2 (0.9–3.0)
Central venous pressure	20 7 mm Hg (4–41)
Pulmonary vascular resistance	213 114 dynes sec cm ^{5} (61–582)
Mean arterial pressure	68 10 mm Hg (46–92)
Serum creatinine	1.7 0.7 mg/dl (0.4–5.2)
Serum total bilirubin	2.0 1.2 mg/dl (0.4–4.7)
Previous cardiac surgery	1 surgery, 32% (20 patients) Multiple surgeries, 13% (8 patients)
Receiving cardiopulmonary bypass (failure to wean)	3 patients
Receiving extracorporeal membrane oxygenation	5 patients
Pre-implant cardiac arrest as cause for implantation	17 patients
Pre-implant ventilator support	19 patients
Pre-implant intra-aortic balloon pump	11 patients
Pre-implant impaired state of consciousness	13 patients

TAH, total artificial heart.

Hemodynamics returned to near normal immediately after TAH implantation. The console settings included left and right ventricular pressures of 190 and 70 mm Hg, respectively. Heart rate averaged 125 beats/min. Vacuum and percent-systole settings were 9 mm Hg and 53%, respectively. Central venous pressure decreased from a pre-implant mean of 20 mm Hg to a post-implant mean of 12 to 14 mm Hg and remained in that range for the duration of support. Cardiac indices increased from a pre-implant level of 1.87 liter/min/m^2 to a post-implant range of 2.7 to 3.3 liter/min/m^2. Perfusion pressure (mean systemic pressure minus mean central venous pressure) increased from 48 mm Hg before implantation to 68 mm Hg after implantation.

Laboratory markers of end-organ function returned to normal in 2 to 4 weeks. Serum creatinine decreased from a pre-implant concentration of 1.7 mg/dl to the normal range (1.2 mg/dl) after 25 days. Blood urea nitrogen concentration decreased from 35 mg/dl before implantation to 20 mg/dl in 45 days. Total bilirubin concentration decreased from 2 mg/dl to 1.2 mg/dl within 20 days.

Table 5. Deaths During Device Support

Patient	Implant days	Cause of death on TAH support
8	21	Multi-organ failure
26	124	Device failure (diaphragm rupture)
65	3	Multi-organ failure
66	14	Device failure (entrapment of tricuspid valve by central venous catheter)
72	9	Multi-organ failure, sepsis
74	1	Hemorrhage, pulmonary edema
83	7	Intracranial bleed
92	318	Multi-organ failure, sepsis
99	2	Sepsis
100	8	Multi-organ failure
107	1	Pulmonary edema
108	40	Multi-organ failure, pneumonia
120	27	Celiac artery obstruction
121	26	Multi-organ failure, bacterial pneumonia

TAH, total artificial heart.

After implantation, hematologic values reflected adequate anti-coagulation, mild hemolysis, and high normal platelet counts. Using the anti-coagulation regimen outlined in Table 3, the coagulation index by thromboelastography remained in the normocoagulable range, the bleeding time remained at approximately 20 minutes, and platelet aggregation was suppressed, except for the response to collagen. International normalized ratios ranged from 2.4 to 3.0. Platelet counts increased from a pre-implant mean of 200,000/ l to a range of 3 to 400,000/ l. White blood cell counts decreased to normal within 20 days. Plasma-free hemoglobin values ranged from 6 to 10 mg/dl, and hematocrit was between 24% and 26%.

Mean time on CardioWest TAH support was 92 91 days (range, 1–413 days). Total days and years of support were 5,604 and 15.5, respectively.

Forty-eight patients (77%) survived to transplantation, and 42 (68% of the total, 88% of those undergoing transplantation) survived to discharge from the hospital after transplantation. Fourteen patients died during device support (23%). Multi-organ failure caused 7 of the 14 deaths. Table 5 shows other causes.

Almost all deaths during device support occurred during the first 30 days after implantation and were attributed to causes relating to the poor condition of the patients before implantation.

After transplantation, 6 patients died (9.8%). They died of graft failure,[2] multi-organ failure,[2] sepsis,[1] and diffuse intravascular coagulopathy[1] (Table 6).

Adverse Events

Adverse events, as defined in Table 2 are summarized in alphabetical order.

Table 6. Deaths After Transplantation

Patient	Days after transplantation	Cause of death after transplantation
70	1	Graft failure
74	17	Sepsis
83	0	Graft failure
95	2	Diffuse intravascular coagulopathy
116	2	Multi-organ failure, sepsis
123	0	Multi-organ failure, sepsis

Bleeding. Seven patients required 8 units of blood at the time of TAH implantation. Three patients required 3 units of blood in a 24-hour period 48 hours after implantation. Twelve patients returned for a total of 13 repeat surgeries because of bleeding (19.6%). Bleeding was a contributing cause of death in 1 additional patient (Patient 74). Thus, bleeding that required return to surgery or that caused death occurred in 13 patients (21%), Table 7. Bleeding that caused or contributed to death occurred in 3 patients (5%).

Device malfunction. Device malfunction criteria were met for 27 events in 14 patients (23%). In 3 of these patients, death resulted (5%). One patient had a tear in 1 layer of the left ventricular diaphragm several weeks before his death, at post-operative Day 123. The cause of this tear was not determined. It is the only diaphragm tear ever noted in 48 patient-years with this TAH model. The other 2 patients, who accounted for 11 of the 27 device malfunction episodes, had central venous lines that entrapped the tricuspid valve of the CardioWest right ventricle causing pump shutdowns. All 11 other patients had very transient events that were for the most part related to driveline kinking. None of those events had serious clinical consequences.

Fit complication. Six events occurred in 6 patients. Two were associated with death (3%). The first event occurred in a 25-year-old woman who had undergone multiple surgeries for congenital heart disease, including 2 Fontan surgeries. Because of her small size (1.77 m^2), the device was repositioned intra-operatively by tethering it to the 6th rib. The primary cause of death in this patient was bleeding. The second event occurred in a 51-year-old man with ischemic cardiomyopathy who had cardiac arrest before the median sternotomy at the time of implantation. After implantation, he experienced severe pulmonary edema, and his chest could not be closed. Support was withdrawn at the implant day. The other 4 patients underwent repeat surgeries to reposition their devices. Their body surfaces areas were 1.9, 1.8, 1.9, and 2.1 m^2. In none of those 4 did the fit complication influence outcome.

Table 7. Repeat Surgery for Bleeding

Patient number	Post-operative day	Previous history	Findings	Contributed to death or delayed transplantation
74	1	25 yo F, previous BT shunt, Fontan, Fontan revision, severe liver dysfunction, 12-hour implant surgery	Tamponade, massive diffuse hemorrhage	Yes, died on POD 1
120	25	54 yo M, laparotomy on POD 8 for ischemic bowel. Required prolonged heparin anti-coagulation	Cardiac tamponade at POD 25; then developed renal failure and died on POD 28	Yes
1	6	47 yo F, elevated liver function tests, anti-coagulated with heparin	Right atrial tamponade	No
23	7	57 yo M, CABG 6 years previously, receiving heparin	Tamponade	No
92	7	18 yo F, post-partum cardiomyopathy, receiving heparin	Tamponade	No
93	1	56 yo M, CABG, AVR, and mitral repair 6 years previously	Tamponade	No
106	5	60 yo M, idiopathic cardiomyopathy	Tamponade	No
104	0	52 yo M, viral cardiomyopathy	Tamponade from bleeding artery anterior mediastinum	No
114	5	28 yo M with dilated cardiomyopathy and liver dysfunction	Tamponade	No
118	7	44 yo M idiopathic cardiomyopathy	Tamponade, returned twice to operating room before bleeding was controlled	No
113	1	64 yo M, idiopathic cardiomyopathy with uncontrolled bleeding	Tamponade	No
121	1	67 yo M, CABG 3 years previously	Tamponade	No

AVR, aortic valve replacement; BT, Blalock-Taussig; CABG, coronary artery bypass graft; POD, post-operative day; yo, year-old.

Hemodynamic insufficiency. The cardiac index was 2 liter/min/m^2 or the systolic pressure was 90 mm Hg for 4 hours a total of 18 times in 13 patients; 11 of these events occurred in the initial 2 post-implant weeks. Four of these patients underwent transplantation, and the other 9 died. Among those who died, decreased output and hypotension were associated with, but not the cause of, death in 4 patients. For the other 5 who died, the definition for hemodynamic insufficiency was met but was not associated with death.

Hemolysis. Five hemolytic events were identified in 4 patients at post-implant Days 3, 6, 49, 205, and 306. All but 1 resolved within a few days. In that case, the patient underwent transplantation within 3 weeks of the onset of hemolysis. A cause was identified in only 1 case, which was increased dp/dt of the left-sided pump, reversed by changing the console.

Hepatic dysfunction. Twenty-three patients had 24 events. Ninety-six percent of the 24 events occurred within the first 4 post-implant days. These events were interpreted as being secondary to pre-implantation illnesses. No deaths from hepatic failure occurred. Average bilirubin concentrations returned to normal within 45 days.

Infections. One hundred and twenty-six infections were recorded in 48 patients. Of these, 16 infections, occurring in 13 patients (21%), were called serious because they caused or contributed to death or delayed transplantation. During the first post-implant week, 8 infections were associated with death, including 5 bacterial pneumonias, 2 cases of sepsis, and 1 mediastinitis secondary to recent coronary artery bypass graft surgery. Seven patients had delayed infections: 1 gastrostomy tube infection, 2 bacterial pneumonias, 3 serious driveline infections (1 associated with mediastinitis and death, and the other 2 occurred in the same patient who had sub-clinical mediastinitis at surgery and who survived long term). Three cases of mediastinitis occurred, 2 associated with death and 1 that was discovered at transplantation in a patient who has survived to the present time (4 years). Another occurred in a patient who had late *Candida parapsilosis* sepsis and was treated until the time of his successful transplantation. He is now well 2 years after transplantation.

Neurologic events. During support, 1 patient had a stroke with neurologic residual (linearized rate of 0.068 events/patient-year, incidence of 1.6%). The patient had a dense hemiparesis that did not resolve but did not prevent transplantation. Two strokes occurred at the time of device implantation with symptoms noted immediately after surgery (3.2%). In one, the patient had transient expressive aphasia; in the other, the patient had left-hand weakness that completely resolved. Six transient ischemic attacks (9.8%) occurred. Other neurologic events included 5 seizures, 2 cases of anoxic brain damage from central venous catheter entrapment of the tricuspid valve, 3 cases of transient decrease in level of consciousness, and 1 intracerebral hemorrhage related to pre-implant cardiac arrest and resuscitation followed by extracorporeal membrane oxygenation and implantation.

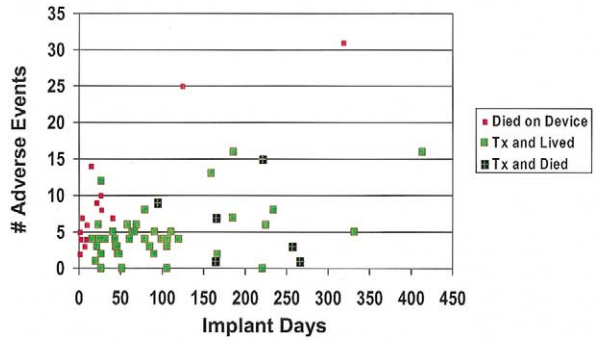

Figure 1. Associations among the number of adverse events per patient, duration of total artificial heart support, and individual patient outcomes (died during device support, underwent transplantation [Tx] and lived, and underwent Tx and died).

Peripheral thromboembolism. Two patients had emboli to abdominal viscera. One who had a celiac artery obstruction died. Five patients had 7 transient visual disturbances suggestive of retinal platelet emboli.

Renal dysfunction. Twelve events occurred in 12 patients who had post-implant creatinine concentrations 5 mg/dl or who required dialysis or continuous hemofiltration. All but 1 of these events occurred within the first 8 post-implant days. In 5 patients, renal dysfunction resolved. In 7 patients, renal failure was associated with death.

Repeat surgeries. Mediastinal repeat surgeries were performed in 13 patients (21%) for 15 episodes of bleeding or atrial tamponade and for 1 suspected fit problem. All but 1 of the repeat surgeries occurred during the first 2 post-implant weeks.

Respiratory dysfunction. Re-intubation was necessary in 16 patients. In 7 of these, respiratory failure was a contributing factor but not a primary cause of death. For the other patients, the events resolved and did not influence outcome.

Figure 1 shows the associations among numbers of adverse events for each patient, duration of support, survival during device support, and survival after trans-

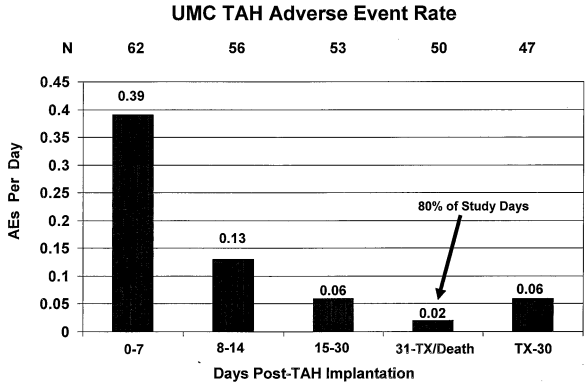

Figure 2. Adverse events (AEs) vs days after implantation and after transplantation (*n* number of patients at risk during the designated time period).TAH, total artificial heart; TX, transplantation; UMC, University Medical Center.

plantation until discharge. Almost all deaths during implant support occurred within 1 month. Almost all of those who died after transplantation had durations of support of 150 days. Thus, it seems that the times of greatest risk are immediately after implantation and after transplantation. In the later group, 83% had been supported for at least 150 days. Figure 1 also documents the total number of adverse events for each patient. Most patients had 3 to 6 adverse events whether or not they survived. Figure 2 plots total adverse events per day vs time after implantation. There were 0.4 adverse events per patient-day during the first post-implant week. The incidence decreased to 0.02 events per patient-day from Day 31 until explantation and then increased to 0.06 events per patient-day from the time of transplantation to 30 days after transplantation.

DISCUSSION

In this study, the patients selected for bridge to transplantation with the SynCardia CardioWest TAH were critically ill. All were either bound for the intensive care unit, decompensating with high-dose inotropic support, or worse. They were judged to be dying with almost no chance of survival to transplantation. In this study, inclusion criteria (Table 1) and pre-implantation characteristics (Table 4) document that these patients were well beyond New York Heart Association Class IV status. All patients were ruled out for LVAD support before TAH implantation. Preliminary control data from the CardioWest IDE National study support the idea that candidates for CardioWest TAH bridge to transplantation have no chance to survive unless they are fortunate enough to undergo transplantation within a few weeks. All controls from that study were either dead (70%) or had undergone transplantation (30%) by the end of 6 weeks from meeting study entrance criteria. In contrast, 80% of CardioWest-supported patients in that study were alive with device support for 40 weeks from implantation and approximately 80% underwent transplantation.

After implantation, increased cardiac indices of 2.7 to 3.3 liter/min/m^2 with central venous pressures in the range of 12 to 14 mm Hg were maintained. The observed cardiac outputs are greater than those seen in our institution with Thoratec, Novacor, HeartMate, and Lion Heart devices. After implantation, early extubation, ambulation, and discharge from intensive care unit were documented. All surviving patients participated in daily exercise programs. Renal dysfunction was rare (12 cases of which 5 resolved), and similar to hepatic dysfunction, it was observed early after implantation and returned to normal organ function in approximately 1 month.

In our patients, after a mean support time of 92 days, 77% of patients underwent transplantation, and 88% of those (68% of the total) survived. After implantation of the CardioWest TAH, most deaths occurred in the first 3 weeks and were related to pre-implantation conditions. One stroke occurred during device support (linearized stroke rate of 0.068 events per patient-year) and 3 cases of mediastinitis occurred: 1 early and associated with pre-implantation coronary bypass and repeat surgeries, 1 late and contributing to death at the time of transplantation, and 1 found incidentally at transplantation in a long-term survivor. Repeat surgery for bleeding was necessary in 19.6% of patients, and bleeding contributed to death in 3 patients.

In our comparative study of CardioWest, Novacor, and Thoratec in bridge to transplantation,[10] we documented survivals to transplantation in 75% of CardioWest recipients, in 56% of Novacor recipients, and in 38% of Thoratec recipients. All these patients were from our program and were chosen for device support using similar criteria. Therefore, we have come to rely on the CardioWest as a dependable device of choice for rescuing very sick patients.

Compared with the recent data for the HeartMate multicenter study,[12] survival to transplantation was 10% better and long-term survival was 11% better with the CardioWest TAH. In the HeartMate study, 48% of patients either bled to death or underwent repeat surgery for bleeding. In our study, 5% of patients had bleeding as a contributing cause of death and 19.6% underwent repeat surgery for bleeding. Thus, the incidence of bleeding is twice that with the HeartMate. Device malfunction is another category in which a significant difference is seen. With HeartMate, 435 device-malfunction events occurred in 280 patients (1.6 per patient) or 1.2 events per 100 patient-days. In our study, 27 events occurred, or 0.4 events per patient, and in fact, only 14 patients had documented events (23%). Three of the

patients accounted for 50% of those events; therefore, true device malfunction was rare. In the HeartMate study, 12% of patients had thromboembolic neurologic events; in our study, combining all strokes (including those associated with implantation or transplantation) and all transient ischemic attacks, 14.6% of patients had events, an incidence similar to that of the HeartMate, the device claimed to have the lowest thromboembolic rate. Further, in this experience, only 1 event resulting in permanent neurologic deficit occurred during device support. Therefore, the linearized rate for such events is 0.068 strokes per patient-year of device support, a rate approaching that expected with mechanical mitral or aortic valves.

Compared with the AbioCor TAH (Danvers, MA), a destination therapy device proclaimed as state of the art, the SynCardia CardioWest TAH has great advantages. It is 50% the size in the orthotopic position (CardioWest, 400 ml; AbioCor, 800 ml). It weighs 7 times less than AbioCor (CardioWest, 160 g; AbioCor, 1,090 g). Both of these factors are extremely important in fitting the device into the patient. For the CardioWest TAH, an adequate fit is critical to preventing compression of the inferior vena cava and of the left pulmonary veins. Therefore, fit criteria including a body surface area of 1.7 m^2 and a large heart (left ventricular end-diastolic diameter of 70 mm) have been published repeatedly. The CardioWest TAH has 2 ventricles that are implanted sequentially and can be moved with respect to each other, making a variety of positions possible and facilitating implantation. This is not the case with the larger, single-body AbioCor. Adequate fitting of the AbioCor has yet to be demonstrated, and compression of the left lower lobe is expected in all but the largest patients with the largest hearts. CardioWest TAH has a greater stroke volume and output (CardioWest, 70 ml stroke volume and output range of 7–9 liter/min; AbioCor, 35–60 ml stroke volume and output range of 4–8 liter/min). The CardioWest TAH is capable of functioning without negative pressure, and even when negative pressure is used to increase the rate of ventricular filling, it is trivial. The AbioCor heart generates up to 40 mm Hg at the atrial level, creating a new intrathoracic pathophysiology known as "atrial suck down," indicating atrial collapse into the atrioventricular valve. Finally, routine long-term survival with the CardioWest TAH has been documented in this bridge-to-transplantation study. Unfortunately, at this early stage, we have yet to see routine long-term survival with the AbioCor.

The SynCardia CardioWest TAH is the device of choice for bridge to transplantation in patients who are critically ill, deteriorating, inotrope dependent, and have biventricular failure. It is a simple pneumatic device that is easily implanted in correctly selected patients. It replaces all 4 valves and both ventricles of the native heart. It allows for early extubation and discharge from intensive care, return of end-organ function, and has notably fewer incidences of bleeding, infection, and thromboembolism. The existence for 20 years of a portable driver compatible with the CardioWest TAH makes it a likely destination therapy. Three patients in Germany are currently living at home with portable drivers running CardioWest TAHs. The current CardioWest TAH, emanating from the original destination therapy trials starting in 1982,[13] is a valuable tool for cardiac transplantation programs now and seems to hold the greatest promise for permanent TAH therapy for end-stage heart disease in the future.

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Appendix 4

CardioWest Total Artificial Heart: Bad Oeynhausen Experience

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Background. **The use of ventricular assist devices (VAD) has become a widely accepted therapeutic option. However, there are still limitations to the patient collective eligible for VAD placement, who might therefore benefit from the implantation of a total artificial heart. We present the first German single-center experience with the CardioWest total artificial heart (TAH) (SynCardia Systems, Tucson, AZ) in 42 patients.**

Methods. **Between February 2001 and December 2003, 42 patients (37 men, 5 women, mean age 51 13 years) received a TAH our Center. Their body surface area ranged between 1.5 and 2.4 (mean, 1.9 0.19) m^2. All patients were in persistent cardiogenic shock in spite of maximum inotropic support and had numerous preoperative risk factors (intraaortic balloon pumping, mechanical ventilation, acute renal failure, previous cardiac surgery, recent cardiopulmonary resuscitation).**

Results. **Duration of support was 1 to 291 days. Eleven patients (26%) underwent successful transplantation; 9 of them could be discharged home. Twenty-two patients died under support, 21 of them from multiple organ failure and 1 patient from a technical problem. Nine patients are still on the device, 4 of them at home after the original CardioWest console was replaced by the Berlin Heart EXCOR driver (Berlin Heart, Berlin, Germany). Exceptional results were achieved in patients with cardiogenic shock after cardiac surgery or after acute myocardial infarction.**

Conclusions. **Against the background of the extremely poor preoperative situation of our patients, the overall survival rate of 48% can be considered as favorable. A prospective, randomized study is planned to find out whether patients with idiopathic dilated or ischemic cardiomyopathy are more likely to benefit from a biventricular assist device or a total artificial heart.**

(Ann Thorac Surg 2005;80:548–52)

The problems resulting from an increasing number of people suffering from congestive heart failure are well known. Although a variety of therapeutic options are available, end-stage heart failure in a significant number of these patients still requires heart transplantation, a procedure widely accepted but facing an enormous shortage in donor organs. In the last two decades, numerous ventricular assist devices (VAD) have been developed and in the meantime are in routine clinical use in many centers worldwide as a bridge to, and even an alternative to, transplantation. However, there are still some limitations to the patient collective eligible for VAD placement. These patients might benefit from the implantation of a total artificial heart (TAH).

In the past decades, several attempts were made to manufacture a TAH, the use of which in its early days, however, was associated with high rates of infection and thromboembolism. A modified version of the Jarvik-7 total artificial heart (CardioWest Total Artificial Heart [SynCardia Systems, Tucson, AZ]) [1] has, meanwhile, been implanted in about 300 patients worldwide. In the following we present the first German experience with the CardioWest TAH implanted in 42 patients in our Center.

The CardioWest TAH is a biventricular orthotopic pneumatic pulsatile pump with two separate artificial ventricles that take the place of the native ventricles. Wire-reinforced air conduits covered with Dacron in the transabdominal wall pathway connect to longer drivelines and to an external console. This console is mobile by virtue of batteries and compressed air tanks, allowing the patient freedom to move about the hospital or other care facilities.

The two artificial ventricles, although differing in the spacing and angulations of the inflow and outflow valves and the entry sites for the conduits for the left and right sides, are basically the same in construction. Each has a rigid spherical outer "housing" that supports a seamless blood-contacting diaphragm, two intermediate diaphragms, and an air diaphragm, all made of segmented polyurethane, and separated by thin coatings of graphite. The inflow (27 mm) and outflow (25 mm) Medtronic-Hall valves (Medtronic Inc, Minneapolis, MN) are mounted on the housing. The diaphragm excursion is essentially

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Table 1. Outcome After CardioWest (SynCardia) Implantation With Regard to Etiology of Heart Failure

	Implants	Tx-ed	Ongoing	Death
Dilated cardiomyopathy	10	1	2	7
Ischemic cardiomyopathy	10	2	2	6
Postcardiotomy heart failure	5	3	1	1
Fulminant myocarditis	4	1	1	2
Acute myocardial infarction	10	4	3	3
Primary graft failure-rejection	2			2
Pulmonary hypertension	1			1
Total	42	11	9	22

Tx-ed transplanted.

from one wall of the housing to the other, allowing the ventricle to fully fill and fully eject nearly 70 mL per beat.

A flexible polyurethane-lined inflow connector is sewn to the atrial cuff of the recipient heart, and then snapped on to the inflow valve mount of the artificial ventricle. On the outflow side, the Dacron outflow connectors are snapped on to the outflow valve mounts of the artificial ventricle after the distal connector anastomoses have been completed.

The external console consists of two pneumatic drivers, one primary and one back-up, transport batteries, air tanks, and an alarm and computer monitoring system. The CardioWest TAH was granted CE approval in Germany in 2000.

Patients and Methods

Selection Criteria

Since the CardioWest TAH became available at our Center in February 2001, our previously published [2] selection criteria for patients scheduled for biventricular support have been modified. Patients with severe cardiogenic shock resulting in extensive multiple organ failure and a body surface area of more than 1.5 m^2 are now more likely to receive the CardioWest TAH. This also applies to patients after massive myocardial infarction in whom a left ventricular or biventricular device cannot be implanted for technical or surgical reasons. Furthermore, patients with postcardiotomy heart failure, who have been supported with other ventricular assist devices for a reasonable period of time and do not show any signs of myocardial recovery, receive the CardioWest after having been evaluated and approved for heart transplantation. In addition, implantation of the CardioWest is indicated in patients with intracardiac shunts or left ventricular thrombi, which make them ineligible for VAD implantation, and in selected cases with primary graft failure or rejection.

Patients

Between February 2001 and December 2003, 42 patients (37 men, 5 women, aged 15 74 years; mean age, 51 13 years) out of a total of 118 patients undergoing mechanical circulatory support (18 of them with Thoratec [Thoratec Laboratories Corp, Pleasanton, CA] biventricular support) received a CardioWest TAH at our Center. Their height ranged from 151 to 192 (mean, 176 11) cm, their weight from 46 to 113 (mean, 79 13) kg. Body surface area was 1.5 to 2.4 (mean, 1.9 0.19) m^2. Left ventricular enddiastolic diameters ranged from 38 to 90 (mean, 67 14) mm, left ventricular endsystolic diameters from 31 to 82 (mean, 60 14) mm. The patient cohort, with regard to etiology of heart failure, is described in Table 1. All patients were in persistent cardiogenic shock in spite of maximum inotropic support. Twenty-eight patients (67%) had been under intraaortic balloon pumping, 31 patients (74%) were under mechanical ventilation, 22 patients (52%) had undergone continuous venovenous hemofiltration because of acute renal failure, 21 patients (50%) had previous cardiac surgery, and 19 patients (45%) had undergone cardiopulmonary resuscitation within the 24 hours prior to CardioWest implantation. Fifteen patients (35%) had been on mechanical circulatory support before for a mean duration of 48 hours (femorofemoral cardiopulmonary bypass, n 11; Thoratec, n 2; Abiomed (ABIOMED, Inc, Danvers, MA), n 1; centrifugal pump, n 1). Thirteen of these patients had received a device for short-term support under resuscitation conditions, but required long-term assistance later. One patient with giant cell myocarditis had initially been on femorofemoral cardiopulmonary bypass for 5 days. Since he showed no recovery, he was switched to Thoratec biventricular support with biatrial cannulation because of the short history of heart disease and the young age of the patient. Unfortunately, after another 7 days of support, a thrombus was detected in the left ventricle leading to CardioWest implantation. In the other patient supported with the Thoratec system after acute myocardial infarction, thrombus formation in the left ventricle was also ob-

Table 2. Preimplant Hemodynamic and Laboratory Data

	Range	Mean/Median
Cardiac index (L/min/m^2)	1.2–3.4	2.0 0.7
Central venous pressure (mm Hg)	8–25	13 5
Mean pulmonary artery pressure (mm Hg)	18–55	32 9
Pulmonary capillary wedge pressure (mm Hg)	12–32	22 6
Pulmonary vascular resistance (dyn · sec · m^5)	107–534	298 120
Systemic vascular resistance (dyn · sec · m^5)	545–1,905	1065 458
White blood count (g/dL)	6.5–29.5	13.4 5.2
Platelets (1,000)	24–326	137 85
Blood urea nitrogen (mg/dL)	24–133	65 29
Creatinine (mg/dL)	0.4–11	2.1 1.9
Bilirubin (mg/dL)	0.4–8.8	2.5 2.5
Lactate dehydrogenase (U/L)	274–21,000	median, 607
Alanin aminotransferase (U/L)	12–20,000	median, 94
Brain natriuretic peptide (pg/mL)	40–2,713	median, 458

Table 3. Complications Under Support

Complication	Incidence
Bleeding	9 (21%)
Reexploration	8 (19%)
Thromboembolic	0.04 events/patient month
Transient ischemic attacks	2 (5%)
Cerebrovascular disorders	1 (2.3%)
Cerebral bleeding	1 (2.3%)
Acute renal failure[a]	3/20 (15%)
Liver failure	11 (26%)
System-related infection	
Driveline	3 (7%)
Mediastinitis	2 (5%)
Abdominal operations	4 (9%)
Hemolysis	3 (7%)
Pneumonia	5 (12%)

[a] In 20 patients without preoperative renal failure.

served after 7 days of support, which made a system change necessary. Preoperative hemodynamic and laboratory data are summarized in Table 2.

Since October 2003, a modified version of the Berlin Heart EXCOR driver (Berlin Heart, Berlin, Germany) [3] has been available for clinical trial at our Center and has replaced the bulky console in our last seven patients receiving the CardioWest device.

Anticoagulation Protocol

During the first 24 hours postoperatively, the patients receive no anticoagulation. On postoperative day (POD) 1, heparin administration is started if blood loss is less than 50 mL/h over 3 consecutive hours (partial thromboplastin time [PTT] target: 50 seconds). A thromboelastographic (TEG) analysis is performed to identify patients with hypercoagulability (maximal amplitude 68 mm), who additionally receive 1 mg/kg acetylsalicylic acid (ASA). On POD 2, heparin dosage is increased to adjust PTT to 60–70 seconds. Repeat TEG is performed to evaluate the effect of ASA administration, which might be adjusted to achieve the recommended platelet inhibition level of 70%. This medication is continued until two weeks postoperatively. If ASA turns out to be ineffective, it is replaced by clopidogrel, the effect of which is also verified by TEG to achieve a degree of inhibition of greater than 40%. Two weeks after surgery, heparin is replaced by warfarin (Coumadin), and ASA, or clopidogrel medication is continued.

Antibiotic Protocol

Our antibiotic prophylaxis is the same as with other assist devices and consists of a short-term prophylactic administration of cephalosporin (Cefazolin) (3 2 g daily) in all patients until all drains are removed. Further infections are treated according to the antimicrobial sensitivity test. In patients who had been on antibiotic treatment prior to implantation, their regime is replaced by vancomycin, and tazobactam plus piperacillin for at least 4 weeks. Antimycotic prophylaxis was not performed routinely.

Results

The implantation procedure was uneventful in all patients without any intraoperative fatality. Eight patients (most of them after acute myocardial infarction) had fit problems and chest closure was only possible on PODs 2–5. Three of these patients had a body surface area less than 1.7 m^2. However, fit problems were not observed in three other patients with a body surface area less than 1.7 m^2. A bleeding complication defined as blood loss greater than 1,500 cc $\cdot$ m^2 $\cdot$ 24 hours occurred in 9 patients (21%) with 8 of them needing reexploration. This bleeding complication was not surgery-related but was due to the fact that 35% of our patients had been on mechanical circulatory support before with subsequent coagulation disorders. Liver failure as defined by bilirubin greater than 10 mg/dL and transaminase three times as high as the normal value was found in 11 patients (26%) needing molecular adsorbent recirculating system therapy. Renal failure requiring renal replacement therapy occurred in 3 of 20 patients, who had no renal failure preoperatively. Four patients underwent abdominal surgery on the device for mesenteric ischemia. Hemolysis as defined by plasma-free hemoglobin of greater than 50 mg for more than 12 hours was found in 3 patients (Table 3). These patients usually had systemic hypertension thus needing higher driving pressures. Hemolysis could be resolved by reducing the driving pressure in combination with antihypertensive agents.

There were two system-related technical problems. One patient was observed to have a significantly higher right than left pump output with increasing signs of pulmonary congestion and weight gain after 6 months of support. Transthoracic and transesophageal echocardiography did not provide an explanation for this development. He was given diuretics, which improved his pulmonary congestion but the high right pump output remained. Fortunately, a suitable donor organ made immediate cardiac transplantation possible. When investigating the pump, a diaphragm layer on the blood side within the pump turned out to have ruptured with subsequent thrombus formation in the intermediate room. The patient is now doing well at home after cardiac transplantation. In another patient, who died after 5 days of support, the central venous catheter wedge had accidentally been advanced into the tricuspid valve leading to valve dysfunction with consecutive circulatory collapse.

Duration of support was 1 to 291 (mean, 86 89; median, 51) days. Altogether, 11 of 42 patients (26%) underwent successful cardiac transplantation with 10 being discharged home. One patient died from an infection one week post heart transplantation (HTx). Another patient, who had been discharged from hospital, died 6 months after the procedure from acute rejection. Survival in those 9 patients being discharged is 2 to 25 months. Twenty-two patients (52%) died under support, 13 of them from multiple organ failure after 1 to 68 days of support, ie, the preexisting organ dysfunction could not be resolved, 3 patients from mesenteric ischemia (72 to

167 days), 2 patients each from sepsis and multiple organ failure (26 and 87 days), and from cerebral bleeding (52 and 56 days), and one patient each from multiple organ and respiratory failure (37 days) and from a technical problem after 5 days. Mean duration of support among survivors to cardiac transplantation was significantly lower (174 87 days) than in nonsurvivors (43 52 days). Nine patients are still on the device, 5 of them within the hospital, whereas 4 patients could be discharged home for a mean duration of 42 days while on the device after the original CardioWest console was replaced by the EXCOR Berlin Heart driver. Of those 15 patients who previously had been supported by a different assist device, 6 patients underwent cardiac transplantation, 5 of them were discharged from hospital. The patient with giant cell myocarditis supported with three different devices is doing well at home. Table 1 details the results with regard to etiology of heart failure.

Comment

Although a variety of devices for mechanical circulatory support have become available, patients with intracardiac thrombi or shunts, structural damage to the heart, or congenital heart defects are not eligible for the implantation of these assist devices but need a total artificial heart in case of endstage heart failure. This paper describes the application of the CardioWest TAH in one of the sickest patient cohort receiving mechanical circulatory support ever reported as shown by their preimplant hemodynamic and laboratory data. In our recent report on patients bridged to cardiac transplantation with the Thoratec VAD system, preoperative ventilation was shown to be an independent risk factor of death [4]. In the present CardioWest collective, 74% of patients had been on mechanical ventilation preoperatively.

In his recently published paper on 81 patients receiving the CardioWest TAH, Copeland and colleagues [5] reported on a survival to transplantation of 79%, which is markedly higher than that of our collective. However, neither collective is comparable in terms of preoperative risk factors. The Copeland group excluded patients from TAH implantation with a previous vascular assist device or dialysis 7 days before. In contrast, 35% of our patients had been on mechanical circulatory support before and 52% had undergone dialysis for renal failure. Furthermore, the incidence of intraaortic balloon pumping (36% in the Copeland collective vs 67% in our collective), mechanical ventilation (42% vs 74%), previous cardiac surgery (38% vs 50%), and previous cardiopulmonary resuscitation (37% vs 45%) was significantly higher in our group.

In view of the extremely poor preoperative status of the patients presented, the overall survival rate of 48% among these patients can be considered as a favorable result. The main cause of death in our experience was a preimplant multiple organ failure, which turned out to be irreversible after CardioWest implantation. However, an exceptional outcome was found in patients with acute myocardial infarction (AMI) and with postcardiotomy heart failure. Duration of support among survivors with AMI etiology was 185 60 days compared to 39 54 days among nonsurvivors, which is comparable to the support times in the total collective. Patients with these etiologies became acutely sick and their organs did not suffer from long standing low output syndrome compared to patients with a chronic disease like idiopathic dilated or ischemic cardiomyopathy (79% fatalities). Furthermore, severe cardiogenic shock after AMI is usually associated with a high release of cytokines [6]. We assume that the removal of the heart might limit the production of cytokines, which are made responsible for end-organ failure. This hypothesis is the subject of further investigation at our Center.

The body surface area (BSA) always is a main issue when implanting a total artificial heart. In our cohort, 6 patients had a BSA of less than 1.7 m^2, which resulted in a fit problem in 3 patients only with two survivors (one with a fit problem). However, the fit problems were more likely to be associated with the etiology of the disease (AMI, postcardiotomy cardiogenic shock) than with BSA. Nevertheless, the number of this subgroup is too small to make any meaningful conclusions.

Regarding the clinical status at the time of HTx, TAH patients are accepted for HTx as soon as they have no organ dysfunction. In general, they do not have a higher priority in organ allocation than other patients, except for technical problems, uncontrolled infection, or repeated transient ischemic attacks.

Despite a less sophisticated anticoagulation protocol as described by LePrince and colleagues [7] and Copeland and colleagues [8], and considering the more activated platelet function in TAH patients compared to those supported with other ventricular assist devices, the incidence of thromboembolic complications in our very sick cohort was only 0.04 thromboembolic events per patient month, which proves the low thrombogeneity of the system. Similarly, infectious complications were observed less frequently when compared with other systems for mechanical circulatory support [2, 9]. The incidence of liver failure is comparable to that observed among patients supported with the Thoratec biventricular device [2], although the TAH collective had higher preoperative risk factors. However, bilirubin values 6 and 14 days after implantation were higher among Thoratec patients and had generally normalized after 30 days of support. The bilirubin values obtained 14 days postimplantation differed significantly between survivors (1.7 6 mg/dL) and nonsurvivors (5.2 10 mg/dL) (p 0.01).

In our institution, patients who suffer from fulminant myocarditis and are in need of mechanical circulatory support usually receive a ventricular assist device as a bridge to recovery. However, four patients of our cohort had suffered fulminant myocarditis; in three of them a giant cell myocarditis was present, which makes a recovery very unlikely. The other patient had been supported with a different device due to severe cardiogenic shock and was switched to the CardioWest because of thrombus formation in the left atrium. This patient, however, died from multiple organ failure.

Our experience strongly recommends the further evaluation of the total artificial heart concept in the management of patients with cardiogenic shock after acute myocardial infarction and postcardiotomy heart failure. As far as other patients (eg, with idiopathic dilated or ischemic cardiomyopathy) are concerned, a prospective, randomized study is highly recommended to find out whether they are more likely to benefit from a total artificial heart or from biventricular support.

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Appendix 5

Patients With a Body Surface Area Less Than 1.7 m^2 Have a Good Outcome With the CardioWest Total Artificial Heart

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Background: A body surface area (BSA) of 1.7 m^2 was considered as the lower limit to implant a CardioWest Total Artificial Heart (TAH). We reviewed our experience with the TAH in patients with a BSA of less than 1.7 m^2.

Methods: From April 1986 to May 2003, among 149 patients implanted with a TAH in our institution, 30 had a BSA of less than 1.7 m^2 (Group I). Results were compared with the remaining 119 patients (Group II).

Results: One patient in Group I experienced a fitting problem and was left with the chest open. Otherwise, in this group, the Day 1 cardiac index averaged 3.6 0.6 liter/min/m^2, which was significantly higher than the 2.8 0.36 liter/min/m^2 observed in Group II. Post-implantation central venous pressure and mean arterial pressure were similar in both groups: 14.7 3.8 mm Hg vs 14.5 4 mm Hg and 87 23 mm Hg vs 88 19 mm Hg, respectively. In Group I, survival on the device dramatically increased from 9% before 1992, to 36% between 1992 and 1997 and finally reached 75% after then. In the meantime, for the same time periods, global survival to hospital discharge increased from 9% to 36% and reached 50% after 1997. In Group II, global survival to hospital discharge was 25.5% before 1992, 34.6% between 1993 and 1997, and reached 52% thereafter.

Conclusion: The CardioWest TAH can be used in patients with a BSA between 1.5 m^2 and 1.7 m^2 with few fitting problems. In this group of patients, results are similar to those obtained in patients with a BSA greater than 1.8 m^2. J Heart Lung Transplant 2005;24:1501–5. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

The CardioWest Total Artificial Heart (TAH) (SynCardia Systems, Tucson, AZ) is a very efficacious device to bridge to transplantation patients with severe biventricular failure.[1,2] However, the TAH is implanted orthotopically into the chest; therefore, the pericardial cavity has to be big enough to avoid vein compression leading to impairment of the filling of the device once the chest is closed. A body surface area (BSA) of 1.7 m^2 was considered as the lower limit to implant a CardioWest TAH and in an early experience, we reported that a small BSA was a risk factor of death in patients supported with a TAH.[3] Since that report, many small patients have benefited from TAH support in our institution, and recent results have dramatically improved.

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METHODS AND PATIENTS

From April 1986 to May 2003, 149 patients were bridged to transplantation with a Jarvik-7 (CardioWest) TAH. Among them, 30 patients had a BSA of less than 1.7 m^2 (Group I) and are the subjects of this report. There were 20 men and 10 women, with a mean age of 34 18 years (11–55). Results were compared with the other 119 patients with a BSA greater than 1.7 m^2 (Group II). The Group II patients were 108 men and 11 women with a mean age of 40 12 years. For the entire cohort, 11 patients were younger than 25 years old, and the etiology of advanced heart failure was mostly dilated cardiomyopathy (n 111; 74.5%), either idiopathic (n 72) or ischemic (n 39). In Group I, 9 patients (30%) had the following various indications: acute cardiac graft rejection (3), congenital (2), post-cardiotomy (2), hypertrophic (1) and post-partum cardiomyopathies (1). Seven patients, including transplantation patients, had undergone previous cardiac surgery. In Group II, 29 patients (24%) had miscellaneous indications.

All patients had terminal biventricular failure despite high-dose intravenous inotropic support. Pre-operative data are summarized in Table 1. Patients in Group I had a significantly lower body mass index (BMI) than in Group II. In the early experience, many patients were

Table 1. Hemodynamic Data in Group I and II Before and After Implantation

	Group I		Group II	
	Before implantation	After implantation	Before implantation	After implantation
CVP (mm Hg)	21 8	14.7 3.8	16.5 11	14.5 4
WP (mm Hg)	31 7	NA	26.6 8	NA
MAP (mm Hg)	69 10	86.9 23	70 8	88 18
CI (Liter/min/m^2)	1.83 0.62	3.48 0.5	1.9 0.4	2.7 0.6
BMI (kg/m^2)	20.2 2.1	—	23.4 4.2	—

CVP, central venous pressure; WP, capillary wedge pressure; MAP, mean arterial pressure; CI, cardiac index; BMI, body mass index.

referred in an immediate life-threatening condition. They thus received an implant within less than 12 hours after arrival. More recently, patients were transferred earlier, and when possible, we tried to optimize inotropic support by using a Swan-Ganz catheter and echocardiography. The reason for using the TAH in these patients instead of a pneumatic paracorporeal device was the severity of the biventricular failure and the onset of multiorgan failure in most of them.

The BSA was not taken into account as long as the patient had at least a moderately dilated heart. Surgical technique was similar in Groups I and II.[4] However, before closing the chest in small patients, it was sometimes useful to open the left pleural space to tilt the TAH to the left and avoid anteroposterior compression (Figure 1). The ejection tubes were cut long enough (6 to 6.5 cm) to allow this maneuver. This technique was particularly useful in patients with BSA between 1.5 and 1.6 cm^2 (n 10).

A dedicated physician (Dr. Szefner) managed anticoagulation as previously described.[5] Briefly, coagulation was evaluated through a battery of tests with emphasis on whole blood thromboelastography. Patients were rapidly extubated, and aggressive rehabilitation, as well as early feeding, was one of the cornerstones of their management.

In the first few years of the experience, patients received a transplant as soon as a compatible cardiac graft was available. Indeed, more cardiac grafts were available and the short-term safety of the device was unknown. However, cardiac transplantation early after TAH implantation did not provide enough time for the patient to recover end-organ function and was associated with a high post-transplantation mortality. For this reason, TAH recipients were excluded from the cardiac transplantation waiting list until they recovered normal organ function, normal nutritional state, and a good autonomy.

Statistics

Data are expressed as the mean standard deviation. Continuous data were compared with a Student's t-test and the difference was considered as significant when p 0.05.

RESULTS

The ratio of small patients remained quite constant throughout the experience, representing 17% (n 11), 31.4% (n 11), and 19% (n 8) of the indication during the periods of 1986 to 1991, 1992 to 1997, and 1998 to 2003. In Group I, we observed a trend toward a decreasing mean BSA, from 1.6 0.1 m^2 before 1991 to 1.57 0.1 m^2 after 1997; whereas in Group II, it tended to increase from 1.84 0.1 m^2 to 1.92 0.16 m^2 (p 0.05).

Implantation Data

Mean implantation time in Group I was 124 30 minutes, similar to Group II. At Day 1, right and left pneumatic ventricle outputs were 5.74 0.8 liter/min and 5.5 0.8 liter/min, representing a mean cardiac index of 3.6 0.6 liter/min/m^2. In Group II, mean right and left pneumatic ventricle outputs were of 5.5 0.8 liter/min and 5.4 0.7 liter/min, which was similar to Group I. However, since Group II patients had a

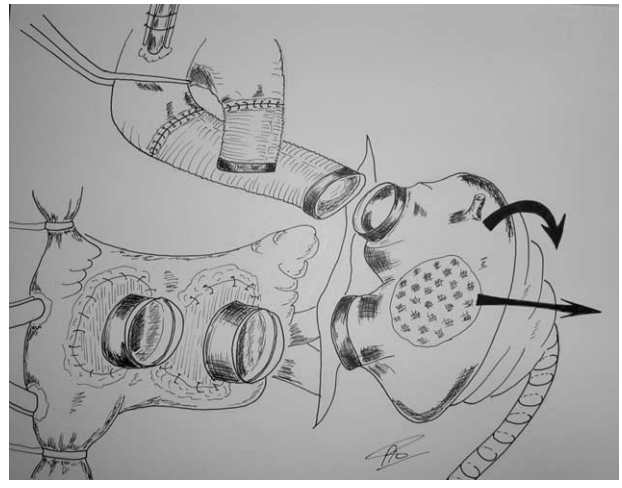

Figure 1. Schematic drawing shows that the left ventricle is pushed to the left and rotated to allow a tilting global movement of the total artificial heart.

larger BSA, the cardiac index was significantly lower than in Group I, with an average of 2.8 0.36 liter/min/m^2.

The mean central venous pressure was 14.7 3.8 mm Hg in Group I and 14.5 4 mm Hg in Group II, and mean arterial pressure was 87 23 mm Hg in Group I and 88 19 mm Hg in Group II. Patient 74 (year 1994) in Group I experienced a fitting problem and was left with an open chest, because any attempt to close it led to TAH output impairment. Indication for TAH implantation in this patient was acute cardiac graft rejection.

Duration of support in Group I was 16 18 days, and those who survived until transplantation had a mean support duration of 20 16 days (2–4). This duration tended to be longer for Group II patients, who survived on the device (40 45 days) but the difference was not significant. Due to organ donor shortage, a change in support duration occurred after 1997. Before 1997, duration of support for transplanted patients was 10 12 days in Group I and 19 23 days in Group II. After 1997, support duration for transplanted patients was 40 50 days in Group I and 66 51 days in Group II.

Complications

None of the Group I patients had a cerebrovascular accident. In Group II, 3 patients (2.6%) had a transient ischemic attack, and 1 patient (0.87%) had a stroke. This patient, who was on oral anti-coagulation therapy, vomited over a 48-hour period but was not switched to intravenous medication. No device dysfunction occurred except for 1 patient in Group II during our early experience. Continuous venovenous hemodialysis was required in 15 patients (44%) in Group I and in 29 patients (24%) in Group II. Eight patients in Group I underwent reoperation for bleeding and 2 experienced atrial tamponade. In both groups, the rate of irreversible hepatic failure was comparable (36% Group I vs 30% Group II). The rate of pulmonary infection associated with clinical sepsis was 5% in Group I and 9% in Group II.

Survival

Survival dramatically improved in Group I throughout the 3 periods. The percentage of patients who survived on the device increased from 9% before 1992 to 36% between 1992 and 1997 and reached 75% after 1997. On-device causes of death were multiorgan failure (64%), infection (21%), and bleeding (15%). In the meantime, global survival to hospital discharge increased from 9% to 36% and reached 50% after 1997. Thus, for patients who received a transplant, respective survival in the 3 periods was 100% (1/1), 100% (1/1), and 66% (4/6). Survival on the device in Group II was 47% (1986–1991), 46% (1992–1997), and 69% (1998–2003). Global survival to hospital discharge was 25.5% (1986–1992), 34.6% (1993–1997), and 52% (1998–2003).

For patients who received a transplant, respective survival in the 3 periods was 54%, 75%, and 75.8%. In this group, if patients with miscellaneous indication for whom results are known to be worse are excluded, global survival was 30%, 42.8%, and 60%, respectively. Survival in the sub-group of patients with s BSA of less than 1.6 m^2 was worse (Table 2). None of the deaths were related to a fitting problem, however.

DISCUSSION

Despite availability of other paracorporeal or implantable pumps, the CardioWest TAH remains our device of choice because of its exceptional hemodynamic performance to bridge to transplantation patients with severe biventricular failure.[6] During the same period of the study, 399 patients were implanted with a mechanical circulatory support device: 149 CardioWest TAH (SynCardia Systems), 91 pneumatic paracorporeal, 128 centrifugal pumps, 28 Novacor (WorldHeart, Ottawa, Canada), and 3 LionHeart (Arrow International, Reading, PA). Throughout this experience, the choice depended on device availability. Actually, our criteria for device selection are:

- If there is a possibility of recovery (i.e., acute myocarditis, post-acute myocardial infarction cardiogenic shock) patients are implanted with a Thoratec pneumatic device (Thoratec, Pleasanton, CA).[7]
- Patients with chronic isolated left ventricular dysfunction are bridged to transplantation with a Novacor device or, more recently, implanted with a LionHeart as destination therapy. This selection explains the low rate of patients with ischemic cardiomyopathy in this series.
- The sickest patients with biventricular failure are bridged to transplantation with the CardioWest TAH.

Table 2. Data for Patients With a BSA Less Than 1.6 m^2 (n 10)

Age	26 13
Gender (female/male)	6/4
BSA	1.5 0.07 (1.37–1.58)
BMI	19.6 2.2
Post-implantation	
Cardiac Index	3.6 0.5
CVP	14 4
MAP	83 15
Survival on device	4 (40%)
Discharged	3 (30%)

BSA, body surface area; BMI, body mass index; CVP, central venous pressure; MAP, mean arterial pressure.

In our experience, BSA is rarely used in the algorithm for device selection and TAH is selected as long as the patient is in biventricular failure with severe end-organ function impairment and has a dilated heart on the chest X-ray. This in accordance with a case reported by Hendry et al[8] of a 15-year-old successfully bridged to transplantation with the CardioWest TAH. When the impact of heart failure on end-organ function is less severe and the patients have a small BSA, we have recently preferred to use the biventricular paracorporeal Thoratec so that the patients could be discharged home. Our experience contrasts with that reported by Copeland et al.[2,9] Indeed, in the United States (US), the CardioWest was used under the US Food and Drug Administration clinical protocol that stipulated a BSA of less than 1.7 m^2 was an exclusion criteria.

The Jarvik-7 was initially designed with 70-ml and 100-ml ejection volumes. In our series, the Jarvik-7 100 ml was implanted in 21 Group I patients with a mean BSA of 1.86 0.13 m^2 vs 1.79 0.1 m^2 in patients implanted during the same period with a Jarvik-7 70 ml. The only difference we noted was higher residual volume with the 100-ml device. Because both sizes of ventricles were shown to have comparable performance, it was decided in 1992 to only use the smaller type of CardioWest.

From our preliminary experience with 37 cases (1986–1988), we reported in 1991 that small BSA was an independent risk factor of death on TAH. A BSA of less than 1.73 m^2 was given a score of 3 and a BSA between 1.73 m^2 and 1.82 m^2 a score of 1.[3] Indeed, in this report, all on-device patients with a BSA of less than 1.72 m^2 died, while 43% of the others survived. Of interest is that only 1 small patient had a fitting problem, and potential impairment of device output in small patients was not mentioned. In the present study, we still report only 1 fitting complication in a small patient. However, device output averaged 5.4 liter/min in Group I and was similar to the output observed in Group II patients. Moreover, since the BSA was lower in Group I, the cardiac index was significantly higher than in Group II (3.5 0.5 vs 2.8 0.36 liter/min/m^2). This result shows that artificial ventricle filling was not at all impaired by small size.

It is clear that the CardioWest TAH is not fully implantable, and fitting it into the chest remains an important challenge for a totally implantable TAH. Many authors reported different imaging tools to study the anatomic relationship between the pericardial cavity, veins and arteries, and surrounding tissues. Park et al[10] even described a custom-designed TAH that used rapid prototyping to improve the directional mismatch of the inflow and outflow conduits. In the AbioCor (Abiomed, Danvers, MA) study, a 3-dimensional computerized image of the thoracic unit was superimposed on the patient's computed tomographic scan-derived chest images to determine if the AbioCor thoracic unit could be positioned into the patient's chest.[11] It is noteworthy that in this study, all patients were quite big, with a BSA from 1.83 to 2.17 m^2. As reported by Dowling et al,[11] it is technically possible to create a diaphragm patch to facilitate the TAH placement.

In our experience with the CardioWest TAH, having 2 independent ventricles was very important for ventricle placement. Indeed, in small patients, the anteroposterior diameter may be too short. Thus, by leaving enough length for the ejection tubes, it was possible to flip the right artificial ventricle to the left, over the left one, to avoid mechanical compression related to the sternal closure.

Despite that TAH was able to assure good output in small patients, the early experience showed a very poor on-device survival of 9%. During the same period, survival was 62% in Group II. With increasing experience, survival improved in Group I and became similar to that observed in Group II for the most recent period (80% on-device survival in Group I vs 73% in Group II). We could not find a modification in patient selection to explain this result. The ratio of patients between Groups I and II was similar in the early and most recent experience, and the mean BSA tended to be even lower in recent years in Group I. Moreover, miscellaneous indications that are known to induce a worse prognosis[12] had the same repartition in Groups I and II throughout the entire experience. We can only hypothesized that even if hemodynamic data as well as preoperative biologic data were similar between groups, the impact on end-organ function was worse in Group I patients, as the major cause of death was multiorgan failure. This hypothesis can also explain why twice as many of the Group II patients required continuous venovenous hemodialysis.

The rate of cerebrovascular accident remained low in both groups, with no cerebrovascular accident reported for Group I patients. As we reported earlier,[12] we can assume that this low rate of cerebrovascular accident can be related to 3 factors. First, the orthotopic implantation of the TAH avoids cannulae and interaction with the native heart. Second, we have a physician dedicated to the coagulation management of under-device patients. Third, we used the so-called "La Pitié protocole" that attempts to reach the equilibrium between the 3 systems involved in coagulation: platelets, pro-coagulant system, and fibrinolytic system.[5] On the other hand, reoperation for bleeding was about 25% in both groups, which is the rate reported for many devices.

Even though it is difficult to compare both groups regarding the survival rate after transplantation because of the small number of patients in Group I, it seemed to

be similar in both groups. It is interesting to note that despite a dramatic increase of duration of support after 1997, with a mean on-device time of 40 days in Group I, and 66 days in Group II, survival after transplantation did not change in Group I and even improved in Group II. Indeed, after 2 to 3 months on the CardioWest TAH, cardiac transplantation can be technically challenging because of strong adhesions, retraction of the atria and great vessels, and inflammatory thickening of the pericardium. To avoid these interactions between the tissues and the TAH surface, we wrap polytetrafluoroethylene patches around the ventricles. We, as others, previously described that this technique facilitates reoperation and inhibits the inflammatory reaction of the pericardium.[13,14]

CONCLUSION

The CardioWest TAH can be used in patients with a BSA between 1.5 and 1.7 m^2, providing similar results as in bigger patients as long as the patients have dilated cardiomyopathy. During the most recent experience in these very sick patients, on-device survival was 70% to 75%, and half of the patients were successfully discharged.

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Appendix 6

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Chapter 6
Total Artificial Hearts

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Syncardia Cardiowest total artificial heart: overview and developmental perspective

The major advantage of the total artificial heart (TAH) over isolated left ventricular assist devices is the provision of biventricular support. Patients who have massive myocardial damage, such as postinfarction ventricular septal defect, intractable arrhythmias, and mechanical valves or native valvular diseases, who are not candidates for ventricular assist devices are candidates for TAH implantation, because the device is implanted in the orthotopic position. For patients who have advanced cardiogenic shock, such as after massive myocardial infarction or failing left ventricular assist device, the CardioWest TAH (Syncardia Systems, Tucson, Arizona) has provided rescue.

Because the device is implanted orthotopically, it is not used for bridge to recovery. The most obvious disadvantage of the CardioWest TAH is that the console is currently cumbersome and large, although mobile. Patients with this console must remain hospitalized. Finally, the device must fit within the chest without compression of the pulmonary veins or the inferior vena cava, which limits the use of this device to patients with body surface area of $>1.7\ m^2$.

A general discussion of the developmental history of the TAH is found in Chapter 1. The CardioWest TAH emanated from a federal initiative in the early 1960s to develop a TAH. Initial research with the basic technology platform of the current TAH was conducted by Drs. Kolff, Olsen, and

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Jarvik, with a designed aimed at being a permanent cardiac replacement. In the early 1980s, Dr. DeVries and his team in the United States implanted the Jarvik-7 TAH with 100-ml ventricles in four chronically ill patients. In Stockholm, Dr. Bjarne Semb implanted the same device in one patient. One patient died on postoperative day 10 from hemorrhage. The remaining four patients had a mean survival of 291 days, with the longest survival of 620 days. Two of Dr. DeVries' patients suffered thromboembolic strokes. All four patients eventually succumbed to sepsis [1].

Bridge to transplantation using a TAH was first successful in 1985. The patient was a 25-year-old man who had viral cardiomyopathy and a left ventricular ejection fraction of 10%. The Jarvik-7 TAH was implanted when he continued to deteriorate with systolic blood pressure of 60 mm Hg, recurrent ventricular tachycardia, and development of delirium despite maximal medical therapy. Implantation of the Jarvik-7 resulted in immediate improvement of his hemodynamics. This patient was supported for 9 days on the Jarvik-7 TAH and underwent successful transplant. After recovery he returned to work full time [2].

Device description

The SynCardia CardioWest C-70 TAH is a biventricular pneumatic pulsatile pump that replaces the native ventricles and all four valves in the orthotopic position (Fig. 1). Each of the artificial ventricles has a rigid spherical outer housing that supports a seamless blood contacting diaphragm, two intermediate diaphragms, and an air diaphragm. The four diaphragms are made of segmented polyurethane, separated from each other by thin layers of graphite. The 27-mm inflow and 25-mm outflow Medtronic

Fig. 1. SynCardia CardioWest TAH.

Hall valves are mounted on the housing at their respective areas (Fig. 2). The total length of blood flow pathway for each ventricle is 21 cm. The full movement of the diaphragm from one wall of the housing to the other generates 70 mL of volume per beat. The atrial quick connect is a polyurethane lined inflow connector that is sewn to the atrial cuff of the recipient. The entire unit snaps onto the inflow valve mount of the artificial ventricle. The quick connectors of the Dacron outflow conduits are snapped onto the outflow valve mounts of the TAH ventricles after the completion of the anastomoses to the great vessels.

The portion of the driveline that passes through the abdominal wall is covered with Dacron to encourage healing to the surrounding tissue. The external console is connected to the wire reinforced drivelines via 6-foot long tubing. The external console consists of one primary and one secondary pneumatic driver, air tanks, transport batteries, an alarm, and a computer monitoring system (Fig. 3).

The primary driver is set to eject blood fully from the ventricle with each beat. On the right side, the ejection pressure is set 30 mm Hg higher than the pulmonary artery pressure. The left ventricular pressure is set at 60 mm Hg above the systemic arterial pressure to achieve full ejection. The extent of ventricular filling is set by adjustment of the beat rate and percentage systole to allow filling of 50 to 60 mL per beat. This adjustment allows a 10- to 20-mL cushion on the air side of the diaphragm to accommodate for increased venous return, as in the case of exercise or volume loading. The intraventricular pressure at the onset of diastole is set at −10 to −15 mm Hg. The central venous pressure of the patient is maintained at 8 to 15 mm Hg. The combination of these factors allows the CardioWest C-70 TAH to generate a cardiac output of approximately 7 to 8 L/min, maintain the mean arterial pressure between 70 and 90 mm Hg, and maintain a perfusion pressure of 55 to 80 mm Hg. This extent of perfusion generally results in consistent return of normal end-organ functions. In addition to

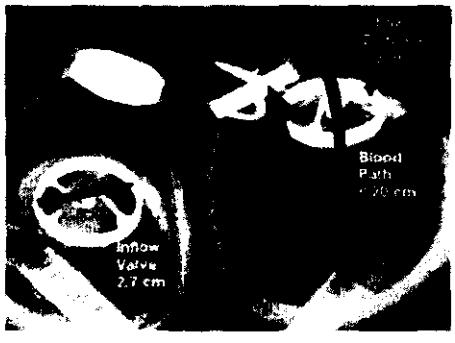

Fig. 2. Inflow and outflow Medtronic Hall valves mounted on the TAH artificial ventricles.

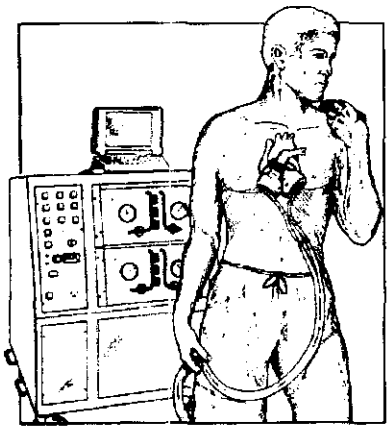

Fig. 3. CardioWest TAH connected to the external console through the drivelines.

maximizing flow and perfusion pressure, it also allows for washing of the blood device contact surfaces, which minimizes risk of thromboembolism.

Design modifications

Currently, the console is large but mobile with batteries and compressed air tanks. Patients are able to ambulate and perform cardiac rehabilitation. Newly designed mobile and fully portable pneumatic drivers and consoles recently were developed and used clinically. To date more than 25 of these new drive systems have been used in Germany and France. These systems have afforded complete ambulation and discharge of patients from the hospital (Fig. 4).

Device implantation and operative considerations

Before systemic heparinization, the arterial outflow conduits are preclotted three times with patient blood. Each of the arterial conduits is exposed to approximately 30 mL of unheparinized blood each time. It is important to expose the grafts completely to the unheparinized blood during this maneuver by stretching them completely while filled with blood. After the third time, the grafts are stretched out and left to dry for approximately 5 minutes, after which time the preclotting process is repeated. After the final preclotting, the grafts are again stretched and left to dry. If a patient was heparinized before reaching the decision of implanting the TAH, the arterial conduits are preclotted with the patient's heparinized blood, protamine, and thrombin.

Immediately after pretreatment of the arterial outflow conduits, the Dacron-covered drivelines are tunneled through and under the left costal margin. The left-sided ventricular driveline is positioned approximately

Fig. 4. A "wearable" driver and console.

2 inches below the costal margin and the midclavicular line. The skin incision is first made approximately 5 cm below the costal margin. A long clamp is used to make the initial tunnel through the subcutaneous tissue, rectus fascia, and rectus muscle and into the chest cavity under direct visualization. This procedure is followed by passing a 1-inch Penrose drain through the tunnel. Progressively larger Hegar dilators are passed through within the Penrose drain to dilate the tunnel. Finally, a driveline is placed within the Penrose drain and pulled through the tunnel. A second small skin incision is made approximately 4 to 5 cm medial to the left ventricular driveline exit site, and an identical tunneling technique is used. Both ventricles are covered within a surgical towel and placed on the left chest until implantation.

The patient is heparinized and placed on total cardiopulmonary bypass. The pleural cavities are not opened. Dissection between the aorta and the pulmonary artery is limited to the proximal portion. The heart is fibrillated after the initiation of total cardiopulmonary bypass. The recipient heart is excised on the ventricular side of the atrioventricular (AV) groove. The incision is extended anteriorly across the right ventricular outflow tract just proximal to the pulmonary valve (Fig. 5). The incision is carried posteriorly across the interventricular septum, and it remains on the ventricular side of the AV groove and leaves a small rim of ventricular muscle. The mitral and the tricuspid valve leaflets are excised to within 2 mm of their respective annuli. The chordae are trimmed. The great vessels are transected just above the sinotubular junctions (Fig. 6). The ostium of the coronary sinus at the right atrium is oversewn to prevent the backflow of blood to the AV groove.

Next, three 15 × 20 cm sheets of expanded polytetrafluoroethylene (ePTFE) are placed within the native pericardium as neo-pericardium.

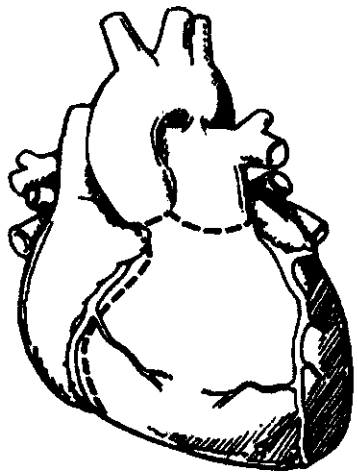

Fig. 5. Ventriculectomy beginning 1 cm below the AV groove and just proximal to the pulmonic and aortic valve.

The first sheet of ePTFE is sutured to the pericardial reflection and as posteriorly as possible at the level of the superior vena cava (SVC), inferior vena cava (IVC), and pulmonary veins on the right side. The second sheet is sutured anteriorly to the left pulmonary veins on the left side. On the diaphragm, the third sheet is placed to cover the entire diaphragmatic refection. The three ePTFE sheets are compressed out of the surgical field and later folded over the CardioWest artificial ventricles anteriorly after completion of the implantation.

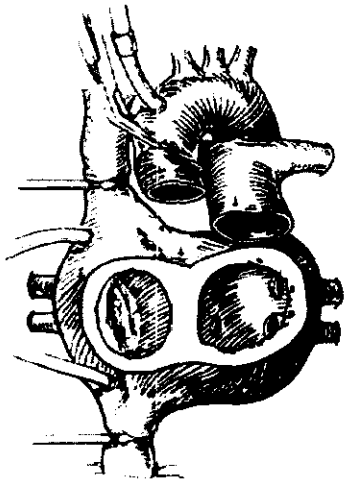

Fig. 6. Ventricular rim with AV valves and chordae excised. The great vessels are transected just above the sinotubular junction.

The outer rims of the left and right atrial cuffs, which consist of approximately 1 cm of ventricular muscle and fat in the AV groove, are buttressed circumferentially with 1-cm wide strips of Teflon felt. The purpose of this is to strengthen the anastomoses between the atrial cuffs and the quick connects and to ensure hemostasis and tamponade any possible bleeding in the AV groove. Large bites with 3-0 polypropylenes sutures are taken to accomplish this task. Next, the atrial quick connects are trimmed to 6 mm from the connectors. They are turned inside out. The left atrial cuff anastomosis to the quick connect is performed using 3-0 polypropylene with MH needles. The suture line includes the Teflon felt strip strengthened free ventricular wall and the interventricular septum. Care is taken to prevent any scallop formation of the quick connect flange. Extra stitches should be placed in any scallops that remain. The right atrial cuff to quick connect anastomosis is performed in a similar fashion. After completion of both anastomoses, the quick connects are everted back to normal configuration. Biologic glue is applied to the suture lines.

The anastomoses of the great vessels begin with the pulmonary artery. The entire length of the pulmonary artery is preserved just distal to the pulmonic valve. The right artificial ventricle that was previously covered and placed on the lateral aspect of the incision is lowered temporarily into the mediastinum to measure the length of the right ventricular outflow conduit, which is usually 6 cm distal to the quick connector. A preclotted arterial outflow conduit is cut to appropriate length. The left ventricular arterial conduit is cut similarly. The length of the left ventricular arterial conduit is usually fairly short at approximately 3 cm. The anastomoses between the arterial conduits and the great vessels are then completed using 4-0 polypropylene in an end-to-end fashion.

After completion of all anastomoses, all suture lines are tested for hemostasis. The quick connect to left atrial cuff anastomoses are tested by inserting the plastic tester. The surgeon places a hand posteriorly and compresses the left and right pulmonary veins. Saline solution is injected via the three-way stopcock into the left atrium (Fig. 7). Any observed leakage is repaired at that time. Testing integrity of the right atrial anastomosis is made simpler because the SVC and IVC are obstructed by the caval tapes. Hemostasis is assessed simply by injection of the saline solution under pressure. The aortic and pulmonic anastomoses are also tested in a similar fashion.

Next, the left artificial ventricle is lowered into the pericardium. The left ventricular outflow should be as close as possible to the native aorta to eliminate conduit angulation. The orientation of the ventricle and the outflow mount is fixed at the time of the atrial connection. To make the connection, the left atrial inflow quick connect is grasped by two large Mayo clamps. The inflow valve mount is inserted into the atrial quick connect by pulling the Mayo clamps and pushing the device in. The left ventricular arterial conduit is fitted onto the outflow valve mount. Care is taken to fill the left artificial ventricle and the left ventricular arterial conduit with saline

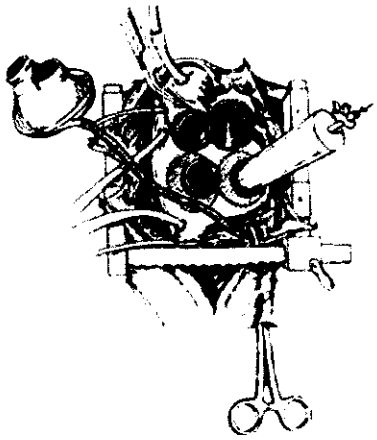

Fig. 7. Testing left atrial cuff for hemostasis after placement of atrial quick connector.

solution as much as possible before completing the attachment. The right atrial inflow quick connect and the right arterial conduit are attached to the right artificial ventricle similarly. The right side is filled by partially releasing the IVC tape, which completes the device implantation (Fig. 8).

The patient is placed in steep Trendelenburg position. The aortic cross clamp is removed with the ascending aorta vented. With the CardioWest TAH pumping at 40 beats per minute, the lungs are vigorously ventilated manually and the ventricles are gently agitated and de-aired under transesophageal echocardiographic guidance. Once the left ventricle is completely de-aired, the TAH pumping rate is increased and cardiopulmonary bypass discontinued while maintaining a central venous pressure of 12 to 15 mm Hg. The cardiac output from the CardioWest TAH is usually approximately

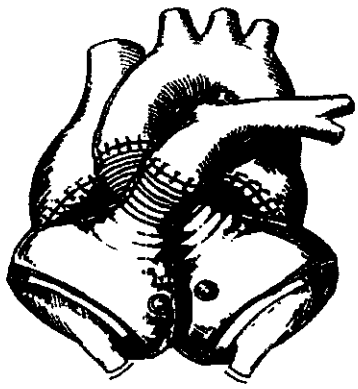

Fig. 8. Complete implantation of the CardioWest TAH in the orthotopic position.

7 to 8 L/min at that point. Protamine is administered. Hemostasis must be obtained meticulously to avoid platelet transfusion (and possible sensitization). The previously secure ePTFE neopericardium is closed over the TAH anteriorly. A rectangular piece of ePTFE is passed around the proximal aorta and secured. The chest is closed in a routine manner, while paying particular attention to the device output, transesophageal echocardiographic monitoring of IVC, and left pulmonary venous flows.

Anticoagulation

At the University of Arizona, a multidrug and multisystem monitoring approach has been used since September 1994. The multisystem monitoring includes thromboelastography, hemoglobin and hematocrit, platelet count, fibrinogen, activated partial thromboplastin time, prothrombin time, international normalized ratio, basic metabolic panel, and liver function tests. These tests are obtained daily for the initial 2 to 4 weeks. Thereafter, they do not exceed twice weekly. The multidrug therapy consists of intravenous unfractionated heparin, which is later converted to warfarin, an antiplatelet agent, aspirin, a platelet-stabilizing agent, dipyridamole, and an anti-inflammatory agent, pentoxifylline (Fig. 9).

Unfractionated heparin therapy is initiated at a dose of 2 to 5 U/kg/h once permanent surgical hemostasis is confirmed. Thromboelastography using recalcified whole blood is used to titrate the unfractionated heparin to normocoagulability. Warfarin therapy is started when a patient demonstrates normalization of renal and hepatic function along with improvement of nutritional status. The therapeutic goal of warfarin is normocoagulability of thromboelastography with heparinase added to the recalcified whole blood. During this time, unfractionated heparin is gradually titrated downward and finally discontinued once a patient achieves 2 consecutive days of normocoagulability on thromboelastography with heparinase.

Antiplatelet aggregation therapy with an antiplatelet agent, aspirin, at 40 to 80 mg/d is instituted once a patient is sufficiently hemostatic and the platelet count is $>50{,}000/\mu L$. Aspirin therapy is monitored by platelet aggregation studies, bleeding time, and platelet count. One of the therapeutic goals is suppression of ADP-, epinephrine-, and arachidonic acid-induced platelet aggregation to 50% to 75% below the lower limit of preserved proaggregatory response to collagen in platelet aggregation studies. Bleeding time is usually obtained twice a week in addition to platelet aggregation studies. The objective is to maintain the bleeding time at 1.5 to 2 times the upper limit of normal but not exceed 23 minutes. Clinically, any evidence of gastrointestinal bleeding is closely scrutinized, because severe gastritis and gastric ulceration are well-known complications of chronic aspirin therapy.

A platelet-stabilizing agent, dipyridamole, is used to increase platelet resistance to activation by the blood-TAH surface and any postimplantation inflammatory response. Immediately upon a patient's return to the intensive

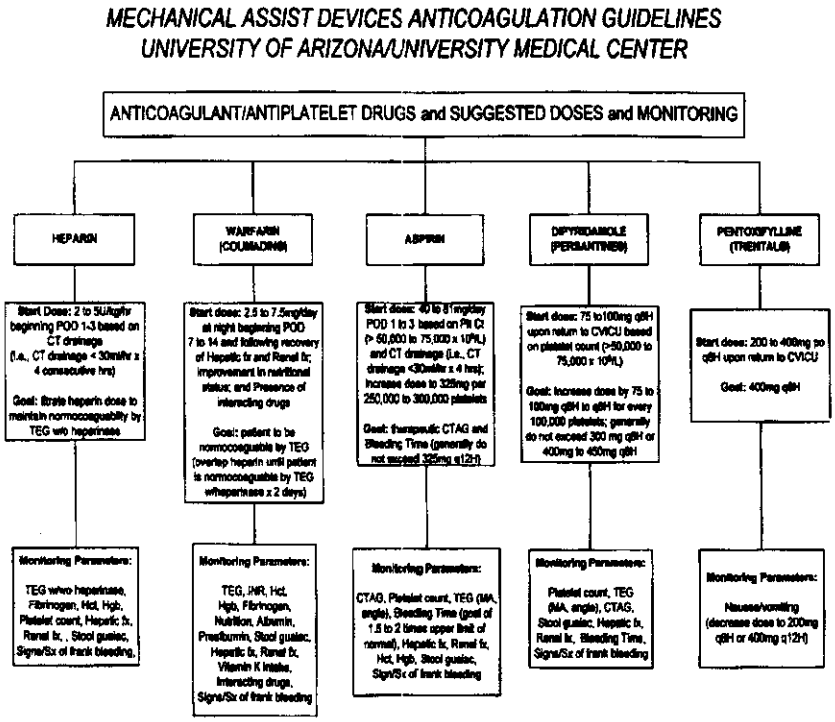

Fig. 9. Multidrug therapy monitored by multisystem laboratories used at the University of Arizona in management of patients who have mechanical devices.

care unit, dipyridamole is prescribed at 75 to 100 mg every 6 to 8 hours. The dosage is increased by 75 to 100 mg every 6 to 8 hours per 100,000/μL increase in the platelet count, with care not to exceed 300 mg every 6 hours or 400 mg every 8 hours. Dipyridamole dosage is modified depending on the vasodilatory effects and headaches that result from the medication.

Along with dipyridamole, pentoxifylline is also given immediately in the postoperative period. Pentoxifylline is recognized to possess significant anti-inflammatory properties along with the capability to stabilize red blood cells and lower fibrinogen levels. The initial dose of pentoxifylline is 200 to 400 mg every 8 hours, which is increased gradually to 400 mg every 8 hours as tolerated. The most cumbersome adverse effect of pentoxifylline is nausea, which usually can be managed by administering the medication with food. If significant nausea persists, however, reducing the dose to 200 mg every 8 hours or 400 mg every 12 hours often alleviates symptoms.

Using the anticoagulation approach, the linearized stroke rate observed was 0.068 strokes/patient year. This result compared favorably with results for patients implanted with the HeartMate left ventricular assist devices as reported in the REMATCH trial [3], patients with valvular replacements on warfarin [4], and patients with atrial fibrillation treated with warfarin [5].

Special management issues: patient selection

Bridge to transplantation with the CardioWest C-70 TAH is reserved for the sickest patients who are failing despite maximal medical therapy. These patients are almost always on multiple high-dose inotropic agents. It is not uncommon for these patients to require intra-aortic balloon pumps or mechanical ventilation to assist in hemodynamic stabilization. A cardiac index of <2 L/min/m^2 by pulmonary artery catheter is usual. Evidence of end-organ hypoperfusion is documented by renal and hepatic dysfunction. Patients are often oliguric and lethargic or confused.

The volume of displacement of the CardioWest C-70 TAH is 750 mL. The two separate ventricles are relatively easy to implant and can be positioned in various arrangements relative to each other and structures within the thoracic cavity. Even so, compression of the left pulmonary veins and inferior vena cava is of consideration when fitting the device in small patients. The CardioWest TAH is suitable for patients with large hearts with left ventricular end diastolic diameter of ≥ 70 mm by echocardiogram, cardiothoracic ratio of >0.5, or a CT scan volume of >1500 mL. Other helpful measures in fitting the CardioWest TAH into patients are body surface area (BSA) of >1.7 m^2 and the anteroposterior diameter from posterior border of the sternum to the anterior border of the vertebral body at T10 on CT scan of ≥ 10 cm (Box 1).

Clinical experience

After the successful initial experience of the Jarvik-7 TAH as bridge to transplantation, 198 Jarvik-7 TAHs were implanted in patients in 38 centers between 1985 and 1992. Of the 198 patients who received the implants, 143 (72%) were transplanted and 89 (59% of patients transplanted and 43% of total patients) were discharged. The average duration on the TAH was 24 days (range, 1–603 days). Most of the patients ($>60\%$) were on the device for less than 2 weeks [6].

In 1991, the Jarvik-7 TAH technology was licensed to a new entity, CardioWest. A new US Food and Drug Administration (FDA) clinical trial for use of this device as bridge to transplantation was initiated in 1993. In 2001, the CardioWest TAH technology was transferred to a new corporate entity, SynCardia Systems, Inc (Tucson, Arizona). The primary mission of SynCardia was to complete the ongoing clinical trial and submit the study for US FDA approval. In October 2004, the US FDA granted approval of the SynCardia premarket approval, which allowed general commercial distribution of the CardioWest TAH as the first approved TAH in the world for use as a bridge to transplantation. As of 2005, 610 TAHs of all types have been implanted worldwide, 90% of which have been CardioWest TAH basic design. Since 1991, more than 350 CardioWest TAHs have been implanted worldwide as a bridge to transplantation, with the total implant time of more than 60 patient years.

Box 1. Patient selection criteria

Inclusion criteria

Candidate for cardiac transplantation
Imminent danger of dying or becoming ineligible for transplantation within 48 hours
New York Heart Association class IV
Hemodynamic insufficiency as documented by
a) Cardiac index ≤2 L/min/m^2 with systolic arterial pressure of ≤90 mm Hg or central venous pressure of ≥18 mm Hg
b) Requirement of at least two of the following:
- dopamine ≥0 μg/kg of body weight/min
- dobutamine ≥10 μg/kg/min
- epinephrine ≥2 μg/kg/min
- other cardioactive drugs at maximal doses
- use of intra-aortic balloon pump
- use of cardiopulmonary bypass or extracorporeal membrane oxygenator

BSA ≥1.7 m^2 or an anteroposterior distance of ≥10 cm from the anterior border of vertebral body to the inner table of sternum at T10 by CT scan

Exclusion criteria

Any ventricular assist devices
Pulmonary vascular resistance ≥640 dyn/sec/cm^{-5} or >8 wood units
Dialysis in previous 7 days
Serum creatinine of ≥5 mg/dL or 440 μmol/L
Liver cirrhosis with total bilirubin of ≥5 mg/dL or 29 μmol/L
Cytotoxic antibody ≥10%

In the pivotal US multicenter investigational device exemption (IDE) trial submitted to the US FDA, 95 patients in five centers received implants with the CardioWest TAH between January 1993 and September 2002 [7]. Seventy-nine percent of the patients who received the CardioWest TAH survived to transplantation. Of those patients, the 1-year survival rate was 86% and the 5-year survival rate was 64%. These statistics compare favorably with contemporary united network of organ sharing-listed patients, who had survival rates of 84.7% and 69.8% for 1 year and 5 years, respectively.

The average age of patients with the CardioWest TAH bridged to transplantation was 51 years. The average body surface area was 2 m^2, and the average weight was 85 kg. Men constituted 86% of the patients and women constituted 14%. These patients all were in the most advanced stages of heart failure (end-stage New York Heart Association class IV). The cardiac

parameters for these patients were left ventricular ejection fraction <20%, cardiac index <1.9 L/min/m^2, and central venous pressure >20 mm Hg. Forty-two percent of these patients required mechanical ventilation before implantation for stabilization. All patients were on maximum inotropic support; 36% required placement of intra-aortic balloon pump for additional hemodynamic stabilization. Twenty percent of patients were on heart-lung machines and could not be weaned. Other indices of end organ hypoperfusion were mean arterial pressure <68 mm Hg, serum creatinine >1.7 mg/dL, total bilirubin >2 mg/dL, and serum aspartate aminotransferase >189.9 IU/L.

The adverse events experienced by patients on CardioWest were typical of those with mechanical support. Infection was the most common adverse event experienced. There was a total of 125 infections during the implantation period: 5 were mediastinitis and 17 involved drivelines. In 7 patients, infection contributed to death. Respiratory infection was the cause of death in 1 patient. None of the 17 patients with driveline infections developed ascending mediastinitis.

Bleeding was defined as patients requiring repeat exploration (23 events), requirement for more than 3 U of packed red blood cells within a 24-hour period in the first 48 postoperative hours (18 events), requirement of more than 8 U of packed red blood cells during the implantation (13 events), and abdominal bleeding that required surgery [1]. There was a total of 102 bleeding events. Two patients died from bleeding, 1 at the time of implantation and 1 during transplantation.

Neurologic events are the most devastating complications of mechanical circulatory support devices. Twenty-six neurologic events occurred during the period of TAH support. The events included 11 cerebrovascular accidents, 4 transient ischemic attacks, 5 cases of anoxic encephalopathy, 1 case of metabolic encephalopathy, 4 seizures, and 1 case of syncope. Six of the patients who had cerebrovascular accidents had no residua 48 hours after the events, 4 had minor residual deficits, and only 1 patient had a fixed hemiplegia, which caused delay in transplantation. The overall linearized stroke rate was calculated at 0.05 events per month.

Only one incident of serious device malfunction occurred with the CardioWest TAH, in which a perforation was found in one of the four layers of the left ventricular diaphragm. This malfunction contributed to death of the patient on day 124 after implantation. No other device malfunction occurred with more than 12,000 patient-days of use. In three patients, migration of central venous catheters resulted in trapping of the mechanical tricuspid valve of the TAH [7].

The CardioWest TAH and its precursor designs have been implanted in more than 600 patients since 1982. Currently, its primary use is for bridge to transplantation in patents who have irreversible biventricular failure and are in imminent risk of dying. Results with this device have improved with time. Patient survival using the TAH as a bridge has been at the 80% level, which

are results better than achieved with any current ventricular assist device (VAD) or Bi-VAD system. With the advent of practical, effective portable drivers, use of this TAH beyond bridge to transplantation in the domain of destination therapy is on the horizon.

Abiocor total replacement heart: overview and developmental perspective

With the lesson learned from the clinical trials of the Jarvik-7 heart, the National Heart, Lung and Blood Institute initiated funding designed to stimulate development of a TAH with the potential of improving quality of life by allowing for patient discharge and improved ability to perform the activities of daily living. Initially, six centers were funded, with this number being decreased to two centers. The Penn State total electric artificial heart was developed in conjunction with the 3M Company, and the AbioCor implantable replacement heart was developed by ABIOMED in conjunction with the Texas Heart Institute. After extensive preclinical evaluation at the Texas Heart Institute and the University of Louisville, approval for a multicenter trial of the use of the AbioCor implantable replacement heart was granted by the US FDA in early 2001. The first human implant occurred on July 2, 2001, which marked the first time that a totally implantable system had been used in humans to provide complete support of the circulation.

Device description

The AbioCor device is the first replacement heart system that does not require percutaneous lines or the need for percutaneous access [8]. This device consists of external and internal components. The four internal components are the thoracic unit, battery, controller, and transcutaneous energy transfer (TET) coil (Fig. 10). The AbioCor thoracic unit (Fig. 11) contains the left and right ventricles and is placed in the chest in an orthotopic position after excision of the native ventricles. The thoracic unit also contains an energy converter that is situated between the ventricles. The energy converter contains a high-efficiency miniature centrifugal pump that rotates in one direction to pressurize the low viscosity hydraulic fluid. Hydraulic flow is alternately moved between the left and right ventricles, which results in alternate left and right systole. The beat rate of the device can vary between 75 and 150 BPM, which results in a flow up to 8 L/min. A balance chamber is present and allows for adjustment of right-sided stroke volume to maintain right and left balance [1]. Essentially, a portion of hydraulic fluid is shunted into the balance chamber rather than to the right hydraulic pumping chamber, which decreases the volume ejected by the right heart to compensate for bronchial blood flow. All blood-contacting surfaces of the AbioCor thoracic unit, including the trileaflet valves (24-mm internal diameter), are polyetherurethane, which results in a smooth, continuous blood-contacting surface from the inflow cuffs to the outflow grafts [2].

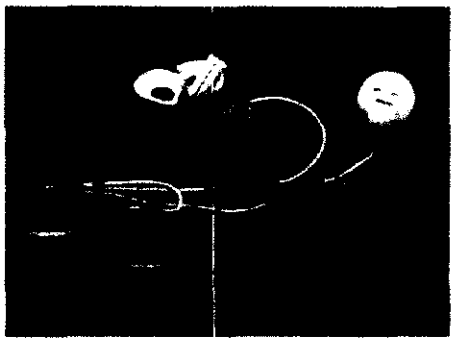

Fig. 10. The four internal components of the AbioCor replacement heart: the AbioCor thoracic unit, the internal TEL coil, the internal battery, and the internal controller.

The internal battery is lithium ion based and is able to power the thoracic unit for brief periods of time. The internal controller drives the energy converter in the thoracic unit, monitors the implanted components, and transmits device performance data to a bedside console via radiofrequency telemetry. These radiofrequency transmissions convey information such as continuous real time telemetry of hydraulic pressure waveforms, system operating parameters, battery status, component temperature, and alarm information. The internal TET coil receives high-frequency power that is transmitted across the skin from the external TET coil. The internal system electronics converts this oscillating current to a direct current that is used to power the thoracic unit and recharge the internal battery [2].

The four external components consist of an external TET coil, batteries, a TET module, and a bedside console. The external TET coil transfers energy across the skin to the internal TET coil. The external TET coil can be connected to either the bedside console or a portable unit. When a patient

Fig. 11. AbioCor thoracic unit.

is ambulatory, the external TET coil is connected to the portable unit (ie, TET module), which contains external batteries and basic alarm systems. The bedside console is used during implantation and recovery and when a patient is in his or her primary residence. The bedside console provides a display screen for control and monitoring of the implanted system via radiofrequency communication. The console can be monitored remotely when connected to a telephone jack via a laptop computer. The external batteries are lithium ion based and are able to provide up to 1 hour of support per pound of battery. The external batteries can be carried in a vest or a handbag or attached to a belt.

Design modifications

Recent changes in software have been implemented to make the device more responsive to the physiologic needs of patients. Previously, patients were maintained on a fixed beat rate, which resulted in postural hypotension. The new software changes allow the device to respond to changes in venous return to the heart.

A second-generation AbioCor device has been in development for years, including two successful preclinical implants. The AbioCor II device is a hybrid of the AbioCor device described previously and the Penn State total artificial heart. The key advantages of the AbioCor II are significant decrease in size and improved geometry. Another advantage is that the device shows lack of active filling, which would preclude the need for struts on the atrial cuffs. The device also has physiologic control modes that are likely to result in improved patient outcomes. The smaller design of the device means that it is likely to fit in most male patients and perhaps up to 50% of female patients.

Device implantation and operative considerations

A standard median sternotomy incision is made with a slight caudad extension. Dissection is performed through this incision to allow placement of the internal TET coil anterior to the pectoral muscle fascia. The TET coil is placed before heparinization to decrease the likelihood of a pocket wound hematoma. Median sternotomy is performed and a pericardial cradle is created. Dissection for the placement of the internal battery and controller is performed in either the preperitoneal space or deep to the rectus abdominus muscle. Standard aortic and bicaval cannulation is performed. Alternatively, cannulation of the superior vena cava and femoral vein can be performed. Cardiopulmonary bypass is initiated and the aorta is cross-clamped. The right and left ventricles are excised just below the AV groove to allow for anastomosis of the atrial cuffs at the level of the annuli. The mitral and tricuspid valve leaflets are excised (Fig. 12). The left atrial appendage is ligated, and the coronary sinus and patent foramen ovale (if present) are oversewn. The left cuff of the device is trimmed to appropriate diameter

Fig. 12. Cardiopulmonary bypass is initiated. The native ventricles are excised, as are mitral and tricuspid leaflets.

and sewn to the native left atrium at the level of the annulus using two layers of running 4-0 prolene reinforced with felt strips. Leak testing is performed after the creation of each anastomosis to decrease the likelihood of suture line bleeding or air entrainment after placement of the device. Anastomosis of the right atrial cuff to the native right atrium is performed in similar fashion followed by leak testing (Fig. 13).

A cast model of the AbioCor thoracic unit is positioned in the chest to determine the appropriate length and orientation of the outflow grafts to the

Fig. 13. The atrial cuffs are anastomosed to the native atria. The atrial anastomoses are then checked for leaks.

aorta and pulmonary artery. These outflow grafts are sewn end-to-end to the great vessels with running 4-0 prolene suture. The aortic outflow graft is positioned anterior to the pulmonary artery graft. The AbioCor thoracic unit is brought up to the operative field, and appropriate electrical connections are made (Fig. 14). The thoracic unit is placed in the pericardial space and attached to the left atrial cuff and outflow grafts via snap-lock connectors. The right ventricle of the thoracic unit is filled with saline, and the right atrial cuff is connected to the device. The caval tapes are released and the device is completely de-aired by allowing blood and air to be ejected through the side ports that arise from the outflow grafts. Once the right side of the heart has been de-aired, the side port of the pulmonary artery outflow graft is occluded. The left side of the heart is then de-aired through the side port on the aortic outflow graft. The device flow is increased up to 4 to 5 L/min with the cross-clamp on, and all the blood is ejected through the side port of the left outflow graft and returned to the cardiopulmonary bypass circuit. Once the device is adequately de-aired, the cross-clamp is removed, the left side port is occluded, and the patient is weaned from cardiopulmonary bypass onto full device support (Fig. 15). The left and right filling pressures are monitored and used to determine the beat rate and adjust the balance chamber. Protamine is administered after demonstrating adequate hemodynamics.

The sternal edges are approximated and transesophageal echocardiography is performed to determine any impaired flow in the left pulmonary veins. Increased pulmonary vein flow velocity dictates the need to reposition the thoracic unit caudad or anteriorly, which is readily accomplished by placing sutures through the eyelets on the thoracic unit and around the left lower ribs. Alternatively, a diaphragm patch can be created that allows the device to sit in a more caudad position [9]. Proper hemostasis is assured.

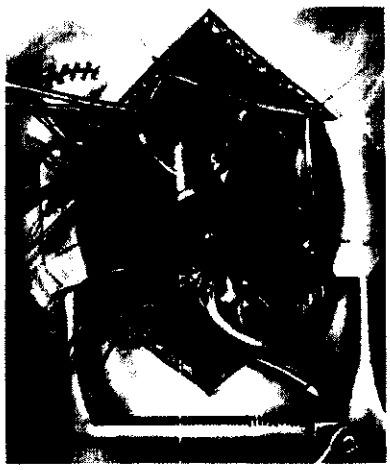

Fig. 14. The AbioCor thoracic unit is brought up to the operative field.

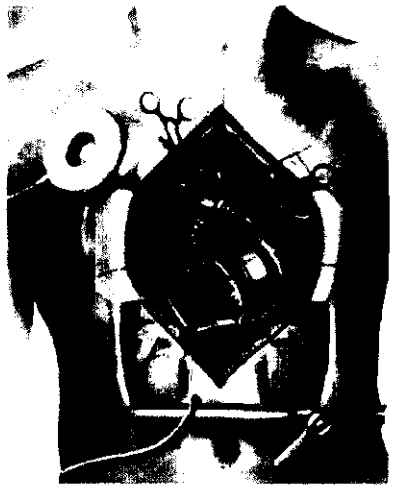

Fig. 15. The AbioCor TAH in its final position after complete de-airing and occlusion of the side ports of the outflow grafts.

followed by standard wound closure. A skilled anesthesia team that is familiar with the function of the device is essential [2].

Special management issues: patient selection

The clinical trial with the AbioCor implantable replacement heart is designed as a destination therapy trial. It excludes patients who are candidates for other types of operative therapies, including heart transplantation. As centers expand their criteria for acceptance into their transplant programs, this alone has limited significantly the number of potential candidates for destination therapy trials. Because of the nature of this clinical trial, it was deemed appropriate to select patients with a high predicted mortality. A model (AbioScore) to predict 30-day survival in patients who have end-stage heart failure was developed. It includes laboratory and clinical parameters, such as age, serum sodium, serum creatinine, need for inotropes or intra-aortic balloon pump, body mass index, left ventricular end diastolic diameter, peak exercise oxygen consumption, presence of severe mitral regurgitation, and New York Heart Association class [2,6].

Patients considered as potential candidates for implantation of the AbioCor implantable replacement heart must have a 30-day predicted mortality rate of more than 70% based on this prognostic model or based on acute myocardial infarction shock scores. Patients are excluded from the clinical trial if they have significant end-organ dysfunction that is not deemed to be reversible, active infection, severe peripheral vascular disease, blood dyscrasia, or recent stroke or transient ischemic attacks caused by atherosclerotic disease. All potential recipients undergo a complete psychosocial

evaluation similar to that performed for potential transplant recipients. Great emphasis has been placed on selection of patients and their families who have a clear understanding of the clinical trial and are able to endure a potentially long postoperative convalescence. Patients who meet all the appropriate criteria undergo CT of the chest, which is followed by AbioFit evaluation, a three-dimensional computerized image of the AbioCor thoracic unit superimposed on the imagery of the patient's mediastinal and chest wall structures. This computer simulation allows viewing of the position of the AbioCor in the potential recipient's chest from every possible angle. This "virtual surgery" predicts the ability to position the AbioCor thoracic unit in the chest without impinging on vital structures, such as the left pulmonary veins and left lower lobe bronchus. Patients are excluded from the trial if evaluation suggests that the thoracic unit will not fit in their chest.

Clinical experience

After decades of development, the AbioCor total replacement heart was introduced in clinical trial in July 2001. Fourteen patients have been enrolled in the clinical trial at four centers. All patients were men who ranged in age from 51 to 79 years. Most patients had multiple reasons that they were not considered as transplant candidates, with the most common reasons being irreversible pulmonary hypertension, age, and renal dysfunction. Two interoperative deaths occurred. Duration of support in patients who survived implant ranged from 53 to 512 days. Five of the 14 deaths in this cohort of patients were related to thromboembolic events.

The initial series of implants was remarkable for significant strokes in three of the first five recipients. These patients were found on autopsy to have thrombus on the struts that were attached to the atrial cuffs. These struts were placed to prevent inflow occlusion of the device by the mobile lateral walls of left or right atrium. The blood pumps and the valves were clean. Because of these autopsy findings, the atrial struts were removed from the atrial cuffs. Three patients received the device with the redesigned atrial cuffs without the presence of the atrial struts. Because of persistent concerns about inflow occlusion without the atrial struts, the atrial cuffs were redesigned to include atrial struts that do not make contact with atrial tissue. This new design was achieved by decreasing the profile of the atrial struts and making the cuffs more conical. Increased emphasis was placed on refinements of anticoagulation protocols, with an increased emphasis on thromboelastography and antiplatelet therapy.

Two patients were discharged from the hospital, with one patient being discharged home for 11 months. Patient and family acceptance has been high, primarily because of the quiet nature of the device, the absence of percutaneous lines, and the need for minimal user input. There have been no episodes of hemolysis or device-related infection and no issues related to software. No problems with electrical interference or other problems related

to electrical safety of the device have been reported. TET has been effective for the duration of support. Recently, the sponsor applied to the US FDA for a humanitarian device exemption, which was reviewed by a US FDA panel. The panel recommended that the device not receive approval for a human device exemption. The company is continuing to work with the US FDA and the investigators to attempt to address the concerns raised by the panel. The device currently can be implanted under a US FDA-approved IDE.

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Appendix 7

Successful Bridge to Transplantation in a Patient With Becker Muscular Dystrophy–Associated Cardiomyopathy

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A 28-year-old male patient diagnosed with Becker muscular dystrophy (BMD)-associated cardiomyopathy was successfully bridged to transplantation with the Cardiowest total artificial heart. Dramatic improvement of muscular functional status occurred following transplantation. J Heart Lung Transplant 2002;21:822–824.

We report a case of successful bridge to transplantation in a young patient diagnosed with Becker muscular dystrophy (BMD)-associated cardiomyopathy.

CASE REPORT

A 28-year-old male patient was initially referred to our pre-transplantation evaluation clinic in January 1999. BMD-associated cardiomyopathy had been diagnosed in 1993. At that time, reduced activity was limited essentially to a lower limb proximal myopathy. He remained stable until the end of 1998 when he had several episodes of congestive heart failure despite optimal medical treatment with acetylcholinesterase (ACE) inhibitors, diuretics and low-dose beta-blockers. Isotopic left and right ejection fractions were 10% and 14%, respectively. In the mean time, peripheral muscular function changed and he progressively lost autonomy and became bed-ridden. At that time, total creatine kinase (tCK) enzyme plasma level was between 576 and 1,589 U/liter (normal range 25 to 195 U/liter).

The patient was registered on the heart transplantation waiting list in February 1999. Two months later, he experienced a new episode of acute heart failure and required increased doses of inotropic medications. Under milrinone 9 g/kg per minute, the patient showed worsening signs of biventricular failure with pulmonary edema and oliguria. Systolic arterial pressure was between 85 and 90 mm Hg with a heart rate at 110 beats/minute. Plasma sodium and blood urea nitrogen (BUN) were 131 and 16 mmol/liter, respectively, and liver function was still normal. A decision was made to implant a Cardiowest total artificial heart (TAH). The immediate post-implantation course was uneventful with no major bleeding and extubation at Day 2. The patient experienced 2 transient ischemic attacks (TIAs) at Days 70 and 79. Muscular rehabilitation under circulatory support was a major concern and despite intensive work the patient remained confined to the bed and chair while he was on circulatory support. Serum tCK developed a narrow peak in the immediate post-operative period. His enzyme level remained in the normal range throughout the entire period of circulatory support except for two short increases. The first increase, which was moderate, occurred approximately 3 weeks after TAH implantation and was related to a re-operation for pericardial effusion. The second peak was noted at 2 months and followed a TIA associated with convulsions. It is of interest to note that tCK level could be related only to peripheral muscle since the heart was removed.

The patient was transplanted after 88 days of circulatory support. During the post-transplantation course the patient required dopamine, dobutamine and nitric oxide medications for 1 week. No compli-

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cations occurred except for mild renal insufficiency. The patient was on triple immunosuppressive therapy that included cyclosporine, azathioprine and steroids. The first year post-transplantation time period was uneventful except for a Grade IA rejection episode. Interestingly, his muscle status progressively improved and, at 18 months post-transplantation, his autonomy returned to the same level as in 1998. After the transplantation, serum tCK had a short post-operative peak, remained within the normal range for 1.5 months and then increased progressively, reaching a higher limit of normal value after 2 months. At 1 year, serum tCK was more than 10-fold the normal value. However, troponin I peaked at Day 2 after transplantation and remained low during the first year post-transplantation.

DISCUSSION

Becker muscular dystrophy (BMD) is an X-linked muscle dystrophy, benign allelic variant of Duchenne muscular dystrophy (DMD) affecting 1 of every 30,000 male births. BMD is due to partial loss of a dystrophin, an intracytoplasmic protein closely associated with actin and sarcolemmal dystrophin-associated proteins. Dystrophin gene mutations (most being deletions) are non–frame shifting, which explains the relative expression of the protein within muscle (in contrast to DMD due to frameshift mutations causing a complete loss of dystrophin). The age of onset is between 5 and 15 years, and mean age at loss of ambulation is approximately 40 years. Dilated cardiomyopathy is very frequent, but is unrelated to the severity of the myopathy.[1] Severe cardiac involvement may occur in patients with mild weakness. In a few cases, X-linked dilated cardiomyopathy is the only manifestation of the disease; however, there is no treatment presently available.

There have been few reports of heart transplantation for BMD-associated cardiomyopathy.[2,3] Rees et al reported 6 patients with muscular dystrophy who underwent cardiac transplantation.[2] Their post-operative course was uneventful and weaning from mechanical ventilation was possible within 36 hours in all patients but 1. Post-operative rehabilitation was more difficult than in other transplanted patients. However, after a mean follow-up of 40 months, all patients except 1 were alive and well and physically rehabilitated, with no recurrence of the underlying graft disease. This series and similar results reported by others[3,4] encouraged us to register our patient on a heart transplant waiting list, because he was a young male and muscular function deterioration was only mild before aggravation due to heart failure.

This is, to our knowledge, the first report of a BMD patient bridged to transplantation with a TAH. The Cardiowest TAH is a 70-cm^3 pneumatic Jarvik 7 artificial heart. After excision of the native ventricles, both pneumatic ventricles are connected to left and right atrioventricular native rings for inflow and to the pulmonary artery and aorta for outflow. Artificial ventricles are connected to a pneumatic console through trans-cutaneous drivelines. Since the first implantation of the Jarvik 7 in 1986, it has been shown that the TAH is a safe and efficient bridge to transplantation in patients with very severe biventricular failure.[5] In our department, the longest duration of support has been 602 days and the thromboembolic rate has been very low in the international experience[5] (0.48 event per patient-year) as well as in our own experience (cerebro vascular accident [CVA] 0%,[6] TIA 1.6%). The major limitation of the device is the large console, which limits patient autonomy and does not allow discharge home.

In the case reported herein, during the period of circulatory support, the patient did not require special management in comparison to other TAH patients, except for intensive rehabilitation. However, even after almost 3 months of adequate hemodynamic support, the patient could not significantly improve his muscular function status. Different reasons can be suggested for this absence of muscular function recovery under TAH. The patient had been confined to bed for several weeks before implantation and could not sit without help. At that time, he had dramatically and rapidly aggravated muscular function, first because of low output syndrome and second because he had no muscular activity. Under TAH, he was totally dependent on rehabilitation technicians. Drivelines, which are well tolerated by most other patients, dramatically limited his motion. Finally, because muscular function deterioration is deeper in patients with muscular dystrophy, recovery is more progressive and takes more time than in other patients with terminal cardiac failure. Even after transplantation, it took 8 to 12 months for the patient to recover and he failed to show signs of recovery during the first 2 months. One could hypothesize that immunosuppression therapy facilitated muscular recovery. However, the only therapeutic protocol used in myopathy is treatment with steroids—and only in Duchenne myopathy and not in BMD.[7] Furthermore, steroids only delay the

progression of the weakness seen in Duchenne myopathy and do not reverse functional deterioration. This is why we postulate that muscular functional improvement in our patient was, at least in part, related to hemodynamic improvement.

In BMD, tCK serum level is always elevated, reaching 2- to 10-fold the normal value, but has no prognostic significance. This enzyme serum level is correlated with muscular activity and tends to decrease when the disease worsens, due to the decrease in muscular activity. The low level of serum tCK in our patient during the circulatory support period reflects the low level of muscular activity during this period. Moreover, we observed a rise in tCK after an episode of convulsions, which is a well-known trigger for tCK increase due to paroxystic muscular activity. After cardiac transplantation we observed the same pattern as that reported by Fiocchi et al[8]: After a short post-operative peak, serum tCK remained low for about 2 months as long as the patient undertook almost no self-initiated movement. Then, tCK increased as the patient increased muscular activity. As reported by Fiocchi et al, the pattern of serum tCK was not related to the cardiac allograft because troponin I remained low after the post-operative period.

This case report illustrates that patients with BMD-associated cardiomyopathy can be successfully bridged to transplantation with mechanical circulatory support. Worsening of muscular functional status related to cardiac failure can be reversed after transplantation although muscular recovery is slow and requires intensive and prolonged rehabilitation work.

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portant implications involving a novel therapeutic treatment.

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CASE REPORTS

Successful Management of Empyema in a Patient With a Total Artificial Heart

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A description of successful management of a patient who developed an empyema as a postoperative complication following the insertion of a CardioWest total artificial heart (TAH) as a bridge to cardiac transplantation is presented. By using traditional methods of management, the patient recovered and went on to transplant.

(Ann Thorac Surg 2003;76:610–1)

With the increasing number of patients needing cardiac transplantation for end-stage heart disease, and the number of donors remaining constant, the use of mechanical circulatory support has evolved as a new standard for bridge to transplant (BTT). The main complications of these devices include infection and thromboembolic events. We report a case of a patient who was treated for empyema while on the total artificial heart (TAH). He recovered, received an orthotopic heart transplant, and was discharged home without significant sequelae.

A 52 year-old male admitted with congestive heart failure (CHF) secondary to ischemic cardiomyopathy was referred for transplantation after failing medical management. He required the placement of an automatic implantable cardioverter device for malignant ventricular arrhythmias. An echo revealed a left ventricular ejection fraction (LVEF) 10% to 20%. He was stabilized, evaluated, and accepted for heart transplantation. During the next few months he had multiple admissions for CHF. Right heart catheterization revealed: CVP (central venous pressure) 18 mm Hg; PCW (pulmonary capillary wedge pressure) 29 mm Hg; CI 1.9 L/min per m^2; and systemic blood pressure 82/52 (mean 65 mm Hg), while on dopamine at 2.5 mcg/kg per min, dobutamine at 10 mcg/kg per min, and milrinone at 0.6 mcg/kg per min. Despite this aggressive support the patient continued to deteriorate and CardioWest TAH (CardioWest Technologies, Tucson, AZ) was implanted as BTT.

The operation was performed via a median sternotomy utilizing cardiopulmonary bypass. The pleural spaces were not entered during the implantation, and the device was protected with fashioned PTFE (polytetrafluoroethylene) membranes. Mechanical ventilation was discontinued on postoperative day 1 (POD 1). He was reintubated 2 days later for respiratory failure as a result of right lower lobe pneumonia. Initial sputum cultures identified the organism *Klebsiella pneumoniae.* Antibiotics were continued according to susceptibilities. Anticoagulation consisting of heparin initially then followed by warfarin, persantine, and aspirin was initiated. He was extubated 2 weeks following surgery, and was recovering slowly. Over the next 2 weeks he developed a right pleural effusion. A computed tomographic (CT) guided 12-French pigtail catheter was placed on POD 34 with evacuation of 1200 cc of serous fluid that revealed 2 PMNs but no organisms. Pleural fluid recultured 5-days later revealed mixed anaerobic flora. Chest CT scan demonstrated a thickened fluid collection with a rind consistent with empyema (Fig 1). On POD 43 he underwent a right thoracotomy with decortication; INR at this time was 2.4, with a bleeding time of 19.5 minutes. He developed a right hemothorax 4-days later requiring a second exploration and evacuation of the hemothorax. He recovered and was relisted as UNOS (United Network for Organ Sharing) status 1A for heart transplantation on POD 75. He underwent orthotopic heart transplantation on POD 159. He recovered without complications and was discharged home after 11 days.

The CardioWest TAH is currently used as a BTT and is under an investigation device exemption from the Food and Drug Administration.

It is a pneumatically driven device consisting of two polyurethane prosthetic ventricles that are placed in an orthotopic position via a median sternotomy. Blood and air are separated by a four-layer diaphragm that retracts

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in diastole and is displaced forward by compressed air during systole, propelling blood at flows of 6 to 8 L/min. Each ventricle has an inflow and outflow mechanical valves that direct blood between the respective atria and great vessels [1]. Once implanted, the ventricular drivelines exit the patient through the skin under the left costal margin and are connected to a driving console.

Empyema is a pleural space infection that can have a variety of etiologies. Most common are pneumonia, thoracic surgery, or trauma. Mortality ranges from 1% to 19% in most patients, however it can be as high a 40% in those that are immunocompromised [2]. The formation of an empyema occurs in three phases: exudative, fibrinopurulent, and organizing phase. The treatment is determined by the phase of the infection and the clinical status of the patient.

Infections following the placement of ventricular assist devices are well established as one of the most common complications [3]. A recent study of infections with the TAH reported 27 patients who had a total of 64 infections: 45 systemic and 19 local. Respiratory tract infection was the most common [4]. Mortality in this population was only 3.7%. Much is written concerning the infections and complications with these artificial devices, but only one offers management advice for noncardiac surgical issues [5]. In this patient, the large empyema posed a significant risk to his life and potentially the function of the TAH. Identifying an empyema early in its course allows for conservative measures such as tube thoracostomy or CT guided drainage, both of which were attempted in the patient. It is when these modalities are not successful that more invasive techniques must be used. With the patient having a TAH, a conservative plan was the original premise for our treatment. With the eventual organization of the empyema fluid and worsening clinical condition, a thoracotomy with decortication was necessary. Had it been sooner in the evolution of his empyema, VATS would have been a good option. A right anterior thoracotomy was performed in this patient with adequate drainage and decortication of the entrapped lung was performed. He did well intraoperatively and postoperatively, going on to transplantation without significant sequelae. This report demonstrates that despite having a mechanical circulatory support device, patients can and should be treated in a conventional manner for this potentially devastating infectious complication.

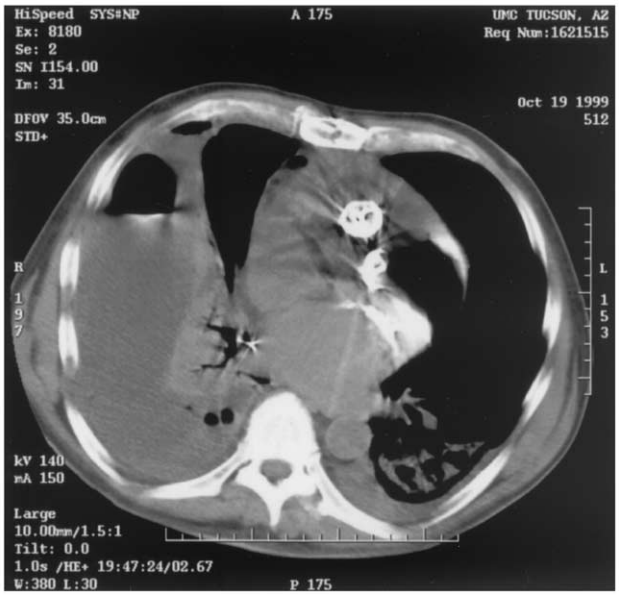

Fig 1. Computerized chest tomogram revealing a right-sided empyema and the CardioWest total artificial heart.

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CASE REPORTS

A Strategy of Hypothermic Circulatory Arrest for Difficult Heart Transplant Postventricular Assist Device

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Donor heart and ventricular assist device excision can be extremely difficult at the time of heart transplant. We present a strategy of hypothermic circulatory arrest established with ventricular assist device cannulas for difficult heart transplants. The device inlet or outlet cannulas already in place, or both, are used to complement the safe cannulation sites available. This approach permits controlled excision of the recipient heart and device, easy access to convert to standard ascending aorta and bicaval cannulation, and minimizes the donor graft anoxia time. Two case reports are presented.

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pathogenic properties of *S. milleri* and GGS. In 89 cases of IE that were due either to *S. milleri* (30) or GGS (59), patients infected with GGS were younger and had more underlying diseases with fewer cardiomyopathies [5]. Additionally, patients with endocarditis from GGS had a more aggressive presentation and evolution of their disease.

There are more than 90 species of scorpions in the United States and approximately 1500 species worldwide. They usually hide under rocks and debris, including shoes. Ninety percent of scorpion stings, however, are isolated to the hands. Most of the lesions resolve with local therapy. In older, or immunocompromised patients, secondary bacterial cellulitis can develop at the sting site. Common skin flora, such as streptococci, are the usual offending microorganisms. If the cellulitis goes untreated, or is insufficiently treated, a bacteremia can result.

IE is more likely to occur in patients with native valve disease or with mechanical valve prostheses. Many cases of IE from streptococci can be cleared with a course of intravenous antibiotics. However, infection with more aggressive organisms, such as *S. milleri* and GGS, may mandate early surgical intervention consisting of valve replacement and débridement. If treatment is delayed, an annular abscess may result that may dramatically increase the mortality from this disease. The mortality rate for patients diagnosed with IE resulting from infection with either *S. milleri* or GGS ranges between 14% to 27% [7].

We chose to perform an aortic root replacement with a homograft in the first patient because the IE resulted in an extensive annular abscess in the setting of a prior aortic valve prosthesis [8]. In the second patient, urgent operative intervention was necessary because of progressive electrocardiogram changes that suggested a rapidly progressing annular abscess affecting the conduction system. An appropriate homograft could not be acquired, and we chose to simply replace the valve and débride and patch the annular abscess. Pathologic analysis of the excised valvular tissue was unremarkable in both patients.

It is possible, but unlikely, that the scorpion was a vector for the streptococcal cellulitis and associated IE. Unfortunately, the species of scorpion was not identified in either case, and knowing the species of the offending scorpions might help with assessing the potential severity of the sting and any associated illnesses. It is not known if scorpions are capable of transmitting bacteria through their stings. More likely, the scorpion sting initiated a series of events that led to IE in patients who were at increased risk of developing infection.

S. milleri is a normal inhabitant of the oropharynx and gastrointestinal tracts in humans, and is less frequently the cause of skin or soft tissue infections. The unusual situation of two patients developing IE with organisms that are not commonly associated with soft tissue infections might suggest that scorpions may be able to transmit bacterial infections. Additional studies are needed to better answer this question. We are unaware of previous reported cases of IE resulting from a scorpion sting, but our experience suggests that treating physicians should be aware of serious infectious sequelae when determining the care plan for patients with scorpion stings.

Local sting wounds should be carefully evaluated and treated with antibiotics capable of covering a broad spectrum of streptococci species. Both elderly and immunocompromised patients should be treated aggressively and followed closely. In addition, patients with known valvular disease, or who have previously undergone valve replacement, may benefit from extended antibiotic coverage. Any signs of continued or recurrent infection should prompt early evaluation for IE by transthoracic or transesophageal echocardiography. If signs of IE are present, particularly if virulent organisms are implicated, aggressive surgical therapy may be required.

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CardioWest Total Artificial Heart in a Moribund Adolescent With Left Ventricular Thrombi

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Bridge to transplant is a well-known strategy to enable patients with congestive heart failure to live until trans-

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plant. A 15-year-old boy with Beckers' muscular dystrophy and cardiomyopathy was accepted for heart transplantation. He suffered a cardiac arrest and was placed on extracorporeal membrane oxygenator. A paracorporeal biventricular assist device and a total artificial heart were considered for bridge to transplant. A CardioWest total artificial heart was chosen because of the patient's size. Multiple left ventricular thrombi were identified at the time of the ventriculectomy. The patient did well with the total artificial heart was transplanted and discharged home. The unknown presence of significant left ventricular thrombi raises the question of outcome with a paracorporeal ventricular assist device.

(Ann Thorac Surg 2005;80:1490–2)

Use of assist devices to bridge patients to transplant is an indispensable tool in the world of end-stage heart failure. Each patient that is evaluated for transplant should also be evaluated for their potential need for a device as a bridge to transplant. The choice of device used to bridge patients to transplant can be highly variable and should be tailored to the patient.

A 15-year-old boy with Becker's muscular dystrophy and subsequent severe cardiomyopathy is presented. He was admitted to our institution for transplant evaluation after 3 to 4 weeks of worsening congestive heart failure. Chronic anticoagulation for his congestive heart failure had not been started by the referring physician as symptoms had presented in a relative short period of time. He required dobutamine to maintain adequate tissue perfusion. Aggressive diuresis was also instituted. Echocardiography demonstrated left ventricular and left atrial dilatation, severely depressed left ventricular function with an ejection fraction of 13% to 17%, moderate tricuspid valve and mitral valve insufficiency, no effusions, and no evidence of ventricular thrombus. Left ventricular end diastolic dimension was 82 mm. He was evaluated and accepted for heart transplantation.

The patient's condition continued to deteriorate with progressive shortness of breath and decrease urine output despite increasing inotropic support. The decision was made to place a pulmonary artery catheter in the cardiac catheterization laboratory. Before beginning the procedure, the patient suffered a witnessed cardiac arrest. Compressions and advanced cardiac life support protocol were instituted. Cardiac function could not be recovered, so the patient was placed on venoarterial extracorporeal membrane oxygenator by femoral cannulation.

The patient was hemodynamically stabilized on extracorporeal membrane oxygenator. He was allowed to awaken from sedation while on extracorporeal membrane oxygenator to evaluate neurologic function before making the decision to implant a device with the intention of bridge to transplant. Time from arrest to compressions was approximately 3 minutes, and time to cardiopulmonary support was approximately 22 minutes. The patient was found to be neurologically intact, and he was taken immediately to the operating room.

Dr Copeland discloses that he has a financial relationship with CardioWest, and Dr Smith discloses that he has a financial relationship with Syncardia.

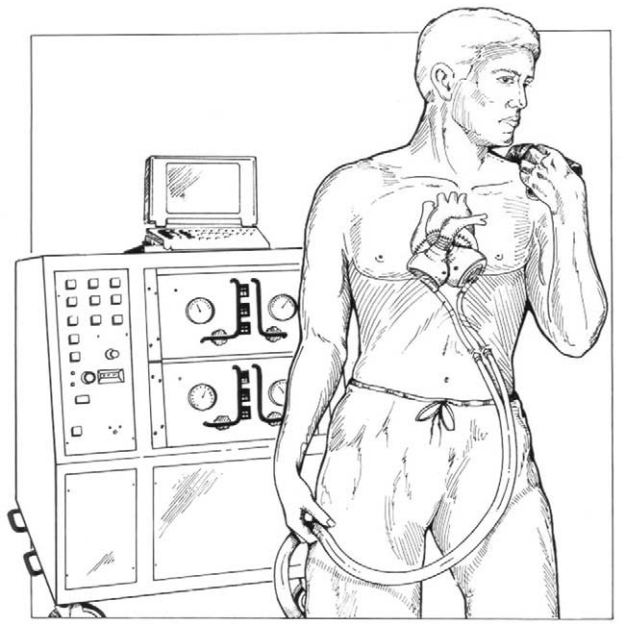

Fig 1. Schematic drawing of the CardioWest total artificial heart.

In the operating room a discussion was undertaken to determine the best device for this patient. Transesophageal echocardiogram in the operating room revealed hypocontractile ventricles and no thrombus. The devices considered were a biventricular paracorporeal system with biventricular cannulation or a total artificial heart. Factors that were considered included the patient size (weight, 90.5 kg, body surface area 2.15 m^2), profound biventricular failure, and no evidence of thrombus on prior echocardiogram. Because of his size and severity of his condition, the decision was made to use the CardioWest [1] total artificial heart (TAH; SynCardia Systems Inc, Tucson, AZ) as a bridge to transplant. One of the benefits of this device with this specific case is that it does not have inflow conduits as other devices. Figure 1 shows a schematic of the TAH in place and how the prosthetic ventricles connect directly to the atria and the great vessels. Furthermore, this device provides the highest output of any device currently available.

After opening the sternum, a biventriculectomy was performed 1 cm distal to the atrioventricular groove. A significant number of moderate size thrombi that were unexpected were identified in the left ventricular cavity (Fig 2). The CardioWest TAH was then implanted without incident, providing flows of 7 to 8 L per minute. Time from initiation of extracorporeal membrane oxygenator to initiation of TAH support was 6.5 hours. The patient was extubated the next day. He was re-listed for heart transplantation United Network for Organ Sharing status

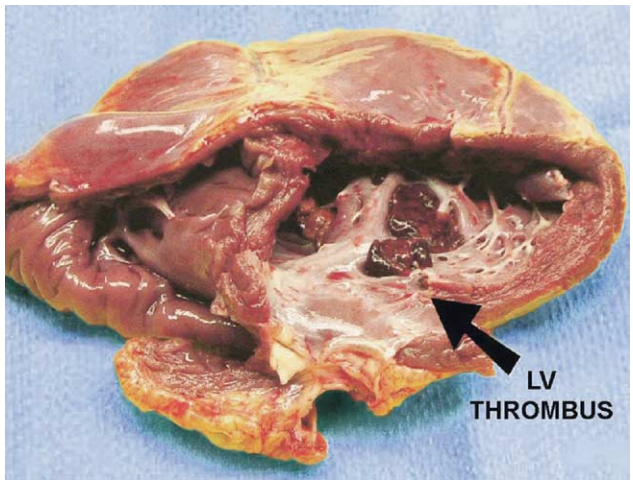

Fig 2. Picture of ventricles showing presence of thrombus.

1A on postoperative day 17. He was transplanted on postoperative day 63 when a suitable donor became available. He was discharged home 2 weeks later. He had no complications while on the CardioWest TAH or after heart transplantation.

Comment

Becker's muscular dystrophy is a X-linked recessive inheritance disorder that manifests with progressive muscle wasting of the legs and pelvis, which is also associated with a loss of muscle mass. This occurs in approximately 3 to 6 in 100,000 male births, and in some cases it affects the myocardium resulting in a cardiomyopathy with biventricular failure.

The literature has shown the effectiveness of both ventricular assist devices and also TAHs as bridges for end-stage heart failure. Left ventricular assist devices, which were first implanted in 1986, are now used in many institutions routinely with 75% to 91% of patients surviving to discharge and 74% surviving to transplant [2, 3]. These devices have inherent risk factors including infection, thromboembolism, cerebrovascular accident, and hemorrhage [4, 5]. The CardioWest TAH also carries the same risks. However it is an effective device for patients in need of high flows for adequate tissue perfusion.

This case illustrates the presence of left ventricular thrombus despite cardiac imaging with current technology. More importantly, it makes the observer wonder what would have been the outcome if a different device was used (eg, for example a device that would have required cannulation of the left ventricular apex). An operator who implants a device that requires left atrial or ventricular cannulation would probably have missed the presence of the left ventricular thrombus. Embolic adverse events are well documented for all types of devices, especially neurologic events. These thromboembolic adverse events are usually attributed to: (1) low flow states or areas of flow stagnation within the device, (2) thrombogenic surfaces, (3) hypercoagulable states, (4) ineffective anticoagulation therapy, or (5) thrombus within the ventricular cavity. The later one is difficult to quantify with current technology. However, a thromboembolic event in this patient may not have been because of any of the first four reasons mentioned and just because of pre-existing thrombus that went undetected.

Cerebrovascular event rates are different for currently used devices. Incidence of such events have been reported to be 39% for the Novacor left ventricular assist device (World Heart; Novacor, Oakland, CA), 16% for the Thoratec HeartMate (Thoratec Corporation, Pleasanton, CA), and 24% for the Thoratec ventricular assist device (Thoratec Corporation) [6, 7]. The incidence for the CardioWest TAH has been reported to be 8% [8]. A possible explanation for this lower incidence as compared with other devices is that the CardioWest TAH eliminates the remaining hypocontractile, thrombogenic left ventricle.

The use of a left ventricular assist device could be considered, however the patient had almost no right ventricular function in the preoperative transesophageal echocardiogram shortly after the cardiac arrest. Furthermore, the use of a cardioplegic arrest with removal of the left ventricular apex with examination for thrombus before insertion of a potential left ventricular cannula may be misleading as no complete assurance can be obtain that all the thrombus has been removed.

This case demonstrates the successful outcome in a terminal patient who required placement of a TAH as a bridge to transplant. The bridge to transplant literature regarding the use in the pediatric population is increasing. Although this patient is placed in the pediatric group by age, he is an adult by size. It appears the outcome in this specific case could have been different with a different device. However, there are many devices available for bridge to transplant and the choice of an appropriate device needs to be individualized to the patient's needs to maximize the likelihood of a successful outcome.

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ABIOMED
Recovering hearts. Saving lives.

August 30, 2007

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Re: Public Comments in Response to the National Coverage Analysis (NCA) for Artificial Hearts (NCD 20.9 and NCD 260.9)

Dear Dr. Phurrough:

ABIOMED, Inc. welcomes the opportunity to provide public comments on the re-consideration of the above-captioned National Coverage Determinations (NCDs) for artificial hearts and related devices and make specific recommendations for coverage for the AbioCor® Implantable Replacement Heart (AbioCor®) as destination therapy in Medicare beneficiaries.

Recommendations

1. **ABIOMED recommends that CMS provide coverage for the AbioCor® Implantable Replacement Heart (AbioCor®) when used as Bi-Ventricular Destination Therapy (BiV-DT) for Medicare beneficiaries who are in advanced, bi-ventricular heart failure and who are ineligible for heart transplantation. We believe coverage can be supported as reasonable and necessary under Soc. Sec. Act. § 1862(a)(1)(A), but would support CMS providing coverage under Section 1862 (a)(1)(E) as Coverage with Evidence Development/Coverage with Study Participation.**

2. **ABIOMED recommends that CMS eliminate the term "artificial heart" from its National Coverage Determinations Manual and policy headings in §20.9 and §260.9 as the term is outdated and does not clearly reflect the advancements in mechanical support for cardiac and circulatory function that have evolved since the former Health Care Financing Administration first issued policy in 1986.**

3. **ABIOMED recommends that CMS consider the nomenclature and categorization for mechanical assistance for circulatory support (MACS) described herein and consider future coverage decisions based upon evidence supporting the device's indication for use in one of three existing covered areas: a) temporary support for recovery; b) temporary support as a bridge-to-transplant; or c) permanent support as destination therapy.**

Background

ABIOMED is a publicly traded company that develops, manufactures and markets medical products designed to assist, recover or replace the pumping function of failing hearts, including the AbioCor® Implantable Replacement Heart, the world's first completely self-contained, internal replacement heart. ABIOMED developed the AbioCor® over a span of 25 years in collaboration with many medical and scientific professionals, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and heart-failure patients and their families.

The AbioCor® system consists of an internal thoracic unit, an internal rechargeable battery, an internal miniaturized electronics package and an external battery pack, handheld alarm monitor and computer console. The AbioCor is the only mechanical assist device for cardiac and circulatory support that is designed to support both ventricles of the heart for patients ineligible for heart transplantation in need of destination therapy. The goal of the device is to completely restore failing cardio-circulatory function.

The AbioCor® was designated as a Humanitarian Use Device by the FDA's Office of Orphan Product Development in September 2003. In September 2006, the FDA approved the AbioCor® under a Humanitarian Device Exemption (HDE). The device—

"[I]s indicated for use in severe biventricular end stage heart disease patients who are not cardiac transplant candidates and who

- *are less than 75 years old*
- *require multiple inotropic support*
- *are not treatable by [Left Ventricular Assist Device] destination therapy, and*
- *are not weanable from biventricular support if on such support."*

(H040006 approved September 5, 2006 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm> [accessed May 3, 2007].)

This indication limits the availability and use of AbioCor® to patients with end-stage cardiac failure who are at imminent risk of death and for whom other treatment options are not available. Although HDEs are approved for use in up to 4,000 patients annually, it is estimated there are only 1,000 patients who could realistically benefit from the AbioCor® annually given the size of the intended use population and the stringent requirements for centers to perform this procedure.

The CMS tracking sheet for artificial hearts expressly states that it will ". . . review other indications for which artificial hearts are approved for use by the FDA. CMS is aware of one other artificial heart currently on the market, through an humanitarian device exemption. Therefore, CMS initiates this national coverage analysis for the artificial heart when used for bridge to heart transplantation and for destination therapy." We understand the statement about one other artificial heart under an HDE to be referring to the AbioCor. Thus, the comments and recommendations herein apply primarily to the AbioCor® as covered item or service when used as destination therapy when used as an HDE.

Discussion of Recommendations

1. ABIOMED recommends that CMS provide coverage for the AbioCor® Implantable Replacement Heart (AbioCor®) for BiVentricular Destination Therapy (BiV-DT) when used in Medicare beneficiaries who are in advanced, bi-ventricular heart failure and who are ineligible for

heart transplantation. ABIOMED supports coverage of the device under Section 1862 (a)(1)(E) or Coverage with Evidence Development (CED)/Coverage with Study Participation.

ABIOMED believes the use of the AbioCor® Implantable Replacement Heart is "reasonable and necessary"and would fit criteria under Section 1862 (a)(1)(A) for the following reasons:

- AbioCor® has been approved by the FDA based upon a finding that the device "does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment." Therefore, in the intended use population, AbioCor is a reasonable treatment option considering available alternatives;

- the two existing NCDs for artificial hearts (§20.9 and §260.9) finding that "artificial hearts" are not reasonable and necessary were issued long before FDA's approval of the AbioCor HDE and were not based on review of any of the evidenceapplicable to the AbioCor;

- CMS has not produced any clinical evidence to support the establishment of the two NCDs, the original decision dates to 1986, and more specifically, CMS has not produced any clinical evidence for a coverage decision applicable to the AbioCor;

- CMS currently covers the use of two single mechanical support devices when used simultaneously for both right and left heart failure (or "biventricular") support; and

- no national coverage pathway for Humanitarian Use Devices (HUDs) commensurate with the level of evidence required for market approval of an HUD is available.

Abiomed's considers the use of the AbioCor® to be reasonable and necessary under Soc. Sec. Act § 1862(a)(1)(A) for the treatment of Medicare beneficiaries with Stage IV end-stage heart failure who have no other viable treatment options, including cardiac transplantation. Without the device, death is imminent in days or weeks. Currently, Medicare covers single-ventricle mechanical support when the left ventricle fails ("single-ventricular" support) in both patients who are transplant eligible ("bridge-to-transplant") as well as those ineligible for transplant ("destination therapy") and covers the use of two single devices used simultaneously. However, CMS does not cover a bi-ventricular device designed to support both ventricles ("bi-ventricular support") regardless of its indication for use. (*See Figure 1)*

Examples of FDA-approved devices	Indication for Use	Mechanical support	Coverage
Abiomed AB5000	Post-Cardiotomy Cardiogenic Shock	Single-ventricle	Yes
Thoratec HeartMate I, NovaCor, IVAD, pVAD	Bridge-to-transplant	Single-ventricle	Yes
Thoratec HeartMate I	Destination Therapy	Single-ventricle	Yes
SynCardia CardioWest	Bridge-to-transplant	Bi-ventricular	No
Abiomed AbioCor	Destination Therapy	Bi-ventricular	No

Figure 1: Current CMS Coverage

Although CMS does not expressly cover devices designed for bi-ventricular support, by coverage of two single ventricular support devices, CMS covers the treatment of patients in bi-

ventricular failure (i.e., both right and left heart failure). According to the INTERMACS ("Interagency Registry of Mechanically Assisted Circulatory Support"), sponsored by CMS, FDA and NIH, since the inception of the registry 47 of the 254 patients (18.5%) who received documented mechanical circulatory support with the potential of hospital discharge were on bi-ventricular support with two devices approved for coverage. [1]

The AbioCor® HDE approval was based upon findings from a 14-patient, 4-center clinical trial conducted between 2001 and 2004 which showed survival benefits averaging 5.2 months (excluding 2 intra-operative deaths), improvement in organ system function, and overall improvement in health-related quality of life, based upon assessment of patients quality of life and family members. The clinical trial was conducted under an IDE. Although a coverage decision from a clinical trial of 14 patients may seem limited in scope this is not inconsistent with the size of clinical studies of orphan drugs involving very small patient populations. For example, alglucosidase alfa (Myozyme®) was recently approved by FDA as an orphan drug for the treatment of Pompe's Disease based upon findings from two clinical trials comprising 39 patients in total. The incidence of Pompe's Disease is estimated to be 1 in 40,000 births. As an FDA-approved orphan drug used according to labeled indications, this drug can be considered reasonable and necessary despite the small study size.

Although ABIOMED believes CMS could support coverage for the AbioCor as reasonable and necessary under Soc. Sec. Act § 1862(a)(1)(A), ABIOMED would support a determination by CMS to provide coverage for the AbioCor® Implantable Replacement Heart (AbioCor®) when it is used in accordance with HDE requirements under a Coverage with Evidence Development (CED)/Coverage with Study Participation (CSP)[2] research study for Medicare beneficiaries who are in advanced, bi-ventricular heart failure and who are ineligible for heart transplantation (under the authority of Soc. Sec. Act Section 1862 (a)(1)(E). The CED pathway provides coverage during the collection of additional data in the context of clinical care that will further assist CMS in determining the impact of covered items and services on the health of Medicare beneficiaries.

The CMS guidance for CED states:

> *". . . for some items or services, CMS may determined that the evidence is very preliminary and not reasonable and necessary for Medicare coverage under Section 1962(a)(1)(A), but, if the following criteria are met, CSP ['coverage with study participation'] might be appropriate:*
>
> *a. The evidence includes assurance of basic safety;*
>
> *b. The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and*
>
> *c. There are significant barriers to conducting clinical trials."*

ABIOMED recommends utilizing the FDA-approved Post-Approval Study (PAS) as the foundation for the AbioCor® CED research study. The PAS provides the level of safety, federal oversight, and patient monitoring customarily captured in the CED process. In its approval order for the AbioCor® device, the FDA describes the PAS as follows:

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[1] INTERMACS Quarterly Report, May 31, 2007; data collection from March 1, 2006 to May 31, 2007.
[2] National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development (http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8; accessed August 13, 2007)

"You have agreed to implement a post-approval study to follow the first twenty-five (25) patients implanted with the Abiomed AbioCor® Implantable Replacement Heart device until death (while on the device) or other outcome (e.g. elective termination by family, device malfunction, etc). A detailed protocol, including but not limited to, patient characteristics at the time of implantation, incidence of adverse events (including definitions) while being supported by the device system, patient outcome(s), standardized anticoagulation protocol, quality of life assessment tools, functional status instruments, neurological function instruments, and the proposed reporting interval (e.g. 6 months) will be submitted to the FDA in the form of an HDE supplement for review and approval within 90 days of the date of this letter. As well, after the first 10 patients have been implanted, CDRH may request panel review of the post-approval study data for their evaluation and recommendation." (FDA approval letter H040006 [September 5, 2006].)

This PAS is not intended to serve as the basis for an expansion in the labeling or to support a PMA submission for this device. However, the study is extensive and is intended to collect important information about the use of the device in patients both in the hospital and upon discharge. This data collection required by the FDA mirrors well the data collection requirements required of CED coverage and allows for a dual reporting and monitoring.

A detailed summary of the PAS is included in the Appendix. We shall also be submitting a copy of the full PAS protocol to CMS with a request that CMS consider the full protocol to be proprietary to ABIOMED and not disclosable in response to requests under the Freedom of Information Act.[3]

2. Abiomed recommends that CMS eliminate the term "artificial heart" from its Coverage Manual and policy headings in §20.9 and §260.9 as the term is outdated and misaligned with the advancements in mechanical support for cardiac and circulatory function that have evolved since the policy originated in 1986.

In 1986, the Health Care Financing Administration (HCFA) issued two National Coverage Decisions (NCDs) that applied to "artificial hearts" (*see*, Coverage Manual 20.9 "artificial hearts and related devices" and 260.9 "heart transplants"). Discussions with Medicare's Coverage and Analysis Group in the past have not yielded any documentation or insights as to the data, correspondence, requests or clinical research on which this decision was made. Anecdotal information and historical sources have described HCFA's decision as "preventive" for the purpose of "avoiding confusion" should the Agency issue a coverage decision regarding heart transplantation. The terminology "artificial heart" was used to distinguish mechanical hearts from human hearts and did not, per se, represent a category of devices that was recognized by FDA for market purposes.

The issuance of both NCDs pre-dated the FDA's approval of *any* mechanical circulatory assist device. In 1992, the first mechanical assist device was approved by FDA for circulatory support and Medicare coverage was extended for Medicare beneficiaries who were unable to wean off cardiopulmonary bypass (e.g., post-cardiotomy cardiogenic shock, Coverage Manual §20.9). This was the first coverage decision for mechanical cardiac support. Since 1992, variations of ventricular support devices have been approved by FDA and Medicare has expanded coverage for devices used for "bridge-to-transplant" and "destination" purposes, all of which have been made as revisions to the original coverage decision from 1986. To this day, the term "artificial heart" is not recognized by FDA as a category of medical device for circulatory support or an indication for use and creates an impediment to coverage through its continued colloquial use.

[3] 5 U.S.C. § 552

3. Abiomed recommends that CMS consider the following nomenclature and categorization for mechanical assistance for circulatory support (MACS) and consider future coverage decisions based upon evidence supporting the device's indication for use in one of three existing covered areas: a) temporary support for recovery; b) temporary support as a bridge-to-transplant; or c) permanent support for destination therapy either as LVAD therapy or BiVAD therapy.

MECHNANICAL ASSISTANCE FOR CIRCULATORY SUPPORT (MACS) Coverage Manual §20.9			
TEMPORARY SUPPORT		PERMANENT SUPPORT	
"bridge-to-recovery" indications (BTR) under 20.9(B)(1)	"bridge-to-transplant" indications (BTT) under 20.9(B)(2)	LVAD Destination Therapy (LV-DT) under 20.9(B)(3)	BiVAD Destination Therapy (BiV-DT) under consideration in this NCA

Summary

ABIOMED applauds CMS for its decision to re-consider the national coverage policy on artificial hearts and welcomes this timely opportunity to discuss coverage of the AbioCor® Implantable Replacement Heart as used for destination therapy while additional data is collected. The technology has evolved along a continuum of care and innovation spanning decades. Coverage of the device for Medicare populations facing imminent death from heart failure is timely and necessary. The field of devices for mechanical assist of circulatory support has matured considerably since the original NCD was issued for artificial hearts in 1986. To this end, we also welcome the opportunity to provide comments and recommendations for the elimination of the term "artificial heart" from coverage language and to recommend that CMS utilize the term "mechanical assist for circulatory support" (MACS) and based individual device coverage decisions upon existing coverage indications with the addition of BiVAD destination therapy.

Please contact me at 202-652-2281 (or by e-mail at gmayes@abiomed.com), if you have any questions regarding these comments. We look forward to working with you and your staff to discuss our recommendations and to further refine the research study for CED.

Sincerely yours,

Gwen Mayes

Gwen Mayes, JD, MMSc
Director of Government Relations/Reimbursement

APPENDIX A:
Summary of Post-Approval Study Protocol for AbioCor® Implantable Replacement Heart

- **Study Objective:** A study to determine if the AbioCor® Implantable Replacement Heart when used as Destination Therapy for Medicare beneficiaries is reasonable and necessary. The primary purpose of this study is to demonstrate that patients in cardiac failure at imminent risk of death with no other treatment options can have an extension of life and an improved quality of life if they receive circulatory support with the AbioCor®.

- **Description of the Device:** The AbioCor® system consists of an internal thoracic unit, an internal rechargeable battery, an internal miniaturized electronics package and an external battery pack, handheld alarm monitor and computer console. The thoracic unit weighs approximately two pounds, includes two artificial ventricles with corresponding proprietary artificial valves which provide a seamless blood path, as well as a motor-driven hydraulic pumping system. The implantable electronics package monitors and controls the pumping speed of the heart based on the physiologic need of the patient. The AbioCor® is capable of delivering up to 8 L/min of blood flow over a broad range of physiologic pressures. The device accommodates the difference in outputs required between the left and right ventricles. Implantation is achieved while on cardiopulmonary bypass; the diseased ventricles are excised and cuffs are sewn to the two atrial remants and further connections are made to the aortic and pulmonary vessels.

  The AbioCor® operates on both internal and external lithium batteries. The internally implanted battery is continually recharged from an external power source or from a basic patient-carried external battery pack. This is achieved with an energy transfer device called TET (transcutaneous energy transmission) which comfortably transmits power across the skin, without piercing its surface. External, portable battery packs can be used for many hours and allow the patient to be mobile. The internal battery of the AbioCor® can be used on its own for approximately one half-hour, upon which an external pocket monitor system or console will activate an alarm. There are no protruding wires, tubes, or connection devices that cross the skin barrier. All components are entirely contained within the patient's body or part of the external system.

  The AbioCor is the only mechanical assist device for cardiac and circulatory support that is designed to support both ventricles of the heart for patients ineligible for heart transplantation in need of destination therapy. The goal of the device is to completely restore failing cardio-circulatory function.

- **Overview of Study Design:** The research study is designed to collect clinical and device-related data on patients who are implanted with the AbioCor® Implantable Replacement Heart for Destination Therapy compared to those who are evaluated for the device but are not implanted to determine the net health benefit of patients who receive implants of the AbioCor®. Clinical markers will be collected during the screening, pre-operative, on-support and discharge phases. The research study is designed to follow implanted patients for the remainder of their lives and the status of screened but not implanted patients to the six month post-screening interval.

- **Duration of Study:** 36 months from the effective date of coverage [I would understand this to be the potential duration of the CED/CSP and that the FDA PAS duration is the time to recruit and follow up 25 patients. What is the duration of each patient's enrollment in the study—is it from consent to death?]

- **IRB review:** Same as FDA-PAS. Patient informed consent will be required for enrollment to ensure that patients are properly informed of the risks and potential benefits of the system. Under the requirements of the HDE, each Institutional Review Board (IRB) must approve the use of the AbioCor® Implantable Replacement Heart at their respective center. Hospitals will have in place the staff and procedures that ensure that prospective AbioCor® patients will receive all the information necessary to make a fully informed consent and will have available to them and their families the information necessary to make a full determination of the possible domestic and lifestyle changes associated with the long-term care and monitoring of the implanted device.

- **Patient Advocate:** A patient advocate affiliated with each center will be made available to any candidate for the AbioCor® Implantable Replacement Heart and his or her family. The patient advocate is primarily available to discuss care options such as palliative care and the risks and benefits of device use. Prior to implantation, the patient and his or her family, in consultation with the facility's responsible party, should discuss the circumstance under which the device would be discontinued. Although this decision is not binding, it is advised that patients, their families, and patient advocates discuss these issues in advance.

- **Patient Criteria/Study Population:** Same as FDA-PAS. All candidates will be in NYHA Class IV heart failure as assessed by a heart failure cardiologist. Most, if not all of the patients will be bed-bound at the time of assessment. Patients will undergo a CT or MRI to determine the actual fit of the system components. Covered patients will be those in severe biventricular end stage heart disease patients who are not cardiac transplant candidates and who

    - are less than 75 years old
    - require multiple inotropic support
    - are not treatable by [Left Ventricular Assist Device] destination therapy, and

  Chronic biventricular failure will be based on meeting the following conditions on both sides of the heart: 1) left-sided failure – elevated left atrial pressure (greater than or equal to 18 mmHg), low cardiac index (less than or equal to 2.2 L/min) and low LVEF (less than or equal to 20%), or CT/MRI evidence of distended left atrium (left atrial volume index of greater than or equal to 70 cc/m2); and 2) right-sided failure – elevated right atrial pressure (greater than or equal to 20 mmHg), or evidence of hepatic congestion of cardiac origin with a total bilirubin between 1.5 and 3.5 mg/dL, or CT/MRI evidence of distended right atrium (right atrial volume index greater than or equal to 70 cc/m2).

- **Center Qualifications:** Eligible centers will be 1) CMS-approved heart transplant centers; 2) CMS-approved destination therapy centers; or 3) a facility that has a reasonable expectation of meeting either of the CMS Conditions of Participation for a heart transplant facility or destination therapy center during the 36 months of coverage. Facilities must be a member of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and comply with all data collection and reporting requirements. No more than 10 facilities in the United States will be involved in the research study.

- **Medicare population:** Based upon enrollment in the clinical trial that supported FDA approval, it is anticipated that 80-85% of the patients in the CED research study will be Medicare eligible.

- **Data Collection:** Same as FDA-PAS. Electronic case report forms (eCRFs) will be used to capture study data and will be completed for each enrolled patient. Patient source documents will be the physician's patient records (usually the hospital or physician's chart) maintained by the facility. Patient medical history, implant OR records and financial billing information will be part of the data collection effort. Detailed blood chemistries, vital statistics, clotting assessments, hemotology, infection cultures, fluid balance, and hemodynamic parameters will be collected and reported frequently.

- **Quality of life measures:** Same as FDA-PAS. Measurements include the Kansas City Cardiomyopathy Questionnaire, which will be administered by a hospital worker not directly involved with the patient's care and will be administered on a monthly basis during the patient's hospital stay and at 3-month intervals following discharge. Additionally, the EuroQoL will be administered on a monthly basis while the patient is in the hospital and at 3-month intervals or during scheduled hospital visits following discharge.

- **Neurological Assessments** – Same as FDA-PAS. Assessments will consists of the NIH Stroke Scale (NIHSS) for motor an sensory function, Modified Rankin Scale for overall neurological disability, and a suite of cognitive function tests covering memory, language, visual/spatial perception, processing speed, and abstract/executive function. Examiners will be trained and a central laboratory facility will score the tests.

- **Data Reporting:** Data will be reported by the following entities through the respective requirements: 1) implanting facilities will be a member of and report data to INTERMACS which reports quarterly and annually to member facilities, industry and governmental agencies including FDA, NIH and CMS; 2) ABIOMED will provide data and a summary from the PAS and research study as defined by the CED through a dual reporting mechanism to FDA and CMS simultaneously on an annual basis [Has this been discussed with FDA?]; and 3) ABIOMED will post material information on the FDA post-market website.

- **Website posting/public access:** Early this year, FDA announced that post-market studies would be required to routinely post information for public viewing. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm This requirement applies to HDEs such as the AbioCor. Each listing includes the company's name, the product's name, the approval number and date, and describes the study and compliance with reporting deadlines. The site is similar to that utilized by the National Institutes of Health under www.clinicaltrials.gov required under the Clinical Research Policy. Redundancy will be avoided in reporting and data will be tied to one and/or the other sites for consistency.

- **Rehabilitation:** Same as FDA-PAS. Guidelines for physical activities should follow those prescribed for patients after CABG provided in Exercise Standards (Fletcher, 1995) published by the American Heart Association. Patients will demonstrate short-term rehabilitation during three stages: bed exercises, walking and supervised exercises.

- **Discharge:** Same as FDA-PAS. Facility staff will train patients and caregivers for device maintenance and monitoring at home. Prior to discharge, the patient's home electrical system will be evaluated for compatibility with system support and local emergency personnel will be notified of the patient's arrival and living conditions. At all times, ABIOMED will provide support and call availability for patients and caregivers.

Dear Gentlemen,

In reference to your requests for public comment on the NCA for Artificial Hearts (CAG-0322N), I have attached three peer reviewed articles as medical evidence to support the effectiveness and reasonableness of the CardioWest temporary Total Artificial Heart for use both in hospital and for discharge to home.

Kind regards,

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CardioWest Total Artificial Heart: Bad Oeynhausen Experience

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Background. **The use of ventricular assist devices (VAD) has become a widely accepted therapeutic option. However, there are still limitations to the patient collective eligible for VAD placement, who might therefore benefit from the implantation of a total artificial heart. We present the first German single-center experience with the CardioWest total artificial heart (TAH) (SynCardia Systems, Tucson, AZ) in 42 patients.**

Methods. **Between February 2001 and December 2003, 42 patients (37 men, 5 women, mean age 51 13 years) received a TAH at our Center. Their body surface area ranged between 1.5 and 2.4 (mean, 1.9 0.19) m^2. All patients were in persistent cardiogenic shock in spite of maximum inotropic support and had numerous preoperative risk factors (intraaortic balloon pumping, mechanical ventilation, acute renal failure, previous cardiac surgery, recent cardiopulmonary resuscitation).**

Results. **Duration of support was 1 to 291 days. Eleven patients (26%) underwent successful transplantation; 9 of them could be discharged home. Twenty-two patients died under support, 21 of them from multiple organ failure and 1 patient from a technical problem. Nine patients are still on the device, 4 of them at home after the original CardioWest console was replaced by the Berlin Heart EXCOR driver (Berlin Heart, Berlin, Germany). Exceptional results were achieved in patients with cardiogenic shock after cardiac surgery or after acute myocardial infarction.**

Conclusions. **Against the background of the extremely poor preoperative situation of our patients, the overall survival rate of 48% can be considered as favorable. A prospective, randomized study is planned to find out whether patients with idiopathic dilated or ischemic cardiomyopathy are more likely to benefit from a biventricular assist device or a total artificial heart.**

(Ann Thorac Surg 2005;80:548–52)

The problems resulting from an increasing number of people suffering from congestive heart failure are well known. Although a variety of therapeutic options are available, end-stage heart failure in a significant number of these patients still requires heart transplantation, a procedure widely accepted but facing an enormous shortage in donor organs. In the last two decades, numerous ventricular assist devices (VAD) have been developed and in the meantime are in routine clinical use in many centers worldwide as a bridge to, and even an alternative to, transplantation. However, there are still some limitations to the patient collective eligible for VAD placement. These patients might benefit from the implantation of a total artificial heart (TAH).

In the past decades, several attempts were made to manufacture a TAH, the use of which in its early days, however, was associated with high rates of infection and thromboembolism. A modified version of the Jarvik-7 total artificial heart (CardioWest Total Artificial Heart [SynCardia Systems, Tucson, AZ]) [1] has, meanwhile, been implanted in about 300 patients worldwide. In the following we present the first German experience with the CardioWest TAH implanted in 42 patients in our Center.

The CardioWest TAH is a biventricular orthotopic pneumatic pulsatile pump with two separate artificial ventricles that take the place of the native ventricles. Wire-reinforced air conduits covered with Dacron in the transabdominal wall pathway connect to longer drivelines and to an external console. This console is mobile by virtue of batteries and compressed air tanks, allowing the patient freedom to move about the hospital or other care facilities.

The two artificial ventricles, although differing in the spacing and angulations of the inflow and outflow valves and the entry sites for the conduits for the left and right sides, are basically the same in construction. Each has a rigid spherical outer "housing" that supports a seamless blood-contacting diaphragm, two intermediate diaphragms, and an air diaphragm, all made of segmented polyurethane, and separated by thin coatings of graphite. The inflow (27 mm) and outflow (25 mm) Medtronic-Hall valves (Medtronic Inc, Minneapolis, MN) are mounted on the housing. The diaphragm excursion is essentially

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Table 1. Outcome After CardioWest (SynCardia) Implantation With Regard to Etiology of Heart Failure

	Implants	Tx-ed	Ongoing	Death
Dilated cardiomyopathy	10	1	2	7
Ischemic cardiomyopathy	10	2	2	6
Postcardiotomy heart failure	5	3	1	1
Fulminant myocarditis	4	1	1	2
Acute myocardial infarction	10	4	3	3
Primary graft failure-rejection	2			2
Pulmonary hypertension	1			1
Total	42	11	9	22

Tx-ed transplanted.

from one wall of the housing to the other, allowing the ventricle to fully fill and fully eject nearly 70 mL per beat.

A flexible polyurethane-lined inflow connector is sewn to the atrial cuff of the recipient heart, and then snapped on to the inflow valve mount of the artificial ventricle. On the outflow side, the Dacron outflow connectors are snapped on to the outflow valve mounts of the artificial ventricle after the distal connector anastomoses have been completed.

The external console consists of two pneumatic drivers, one primary and one back-up, transport batteries, air tanks, and an alarm and computer monitoring system. The CardioWest TAH was granted CE approval in Germany in 2000.

Patients and Methods

Selection Criteria

Since the CardioWest TAH became available at our Center in February 2001, our previously published [2] selection criteria for patients scheduled for biventricular support have been modified. Patients with severe cardiogenic shock resulting in extensive multiple organ failure and a body surface area of more than 1.5 m^2 are now more likely to receive the CardioWest TAH. This also applies to patients after massive myocardial infarction in whom a left ventricular or biventricular device cannot be implanted for technical or surgical reasons. Furthermore, patients with postcardiotomy heart failure, who have been supported with other ventricular assist devices for a reasonable period of time and do not show any signs of myocardial recovery, receive the CardioWest after having been evaluated and approved for heart transplantation. In addition, implantation of the CardioWest is indicated in patients with intracardiac shunts or left ventricular thrombi, which make them ineligible for VAD implantation, and in selected cases with primary graft failure or rejection.

Patients

Between February 2001 and December 2003, 42 patients (37 men, 5 women, aged 15 74 years; mean age, 51 13 years) out of a total of 118 patients undergoing mechanical circulatory support (18 of them with Thoratec [Thoratec Laboratories Corp, Pleasanton, CA] biventricular support) received a CardioWest TAH at our Center. Their height ranged from 151 to 192 (mean, 176 11) cm, their weight from 46 to 113 (mean, 79 13) kg. Body surface area was 1.5 to 2.4 (mean, 1.9 0.19) m^2. Left ventricular enddiastolic diameters ranged from 38 to 90 (mean, 67 14) mm, left ventricular endsystolic diameters from 31 to 82 (mean, 60 14) mm. The patient cohort, with regard to etiology of heart failure, is described in Table 1. All patients were in persistent cardiogenic shock in spite of maximum inotropic support. Twenty-eight patients (67%) had been under intraaortic balloon pumping, 31 patients (74%) were under mechanical ventilation, 22 patients (52%) had undergone continuous venovenous hemofiltration because of acute renal failure, 21 patients (50%) had previous cardiac surgery, and 19 patients (45%) had undergone cardiopulmonary resuscitation within the 24 hours prior to CardioWest implantation. Fifteen patients (35%) had been on mechanical circulatory support before for a mean duration of 48 hours (femorofemoral cardiopulmonary bypass, n 11; Thoratec, n 2; Abiomed (ABIOMED, Inc, Danvers, MA), n 1; centrifugal pump, n 1). Thirteen of these patients had received a device for short-term support under resuscitation conditions, but required long-term assistance later. One patient with giant cell myocarditis had initially been on femorofemoral cardiopulmonary bypass for 5 days. Since he showed no recovery, he was switched to Thoratec biventricular support with biatrial cannulation because of the short history of heart disease and the young age of the patient. Unfortunately, after another 7 days of support, a thrombus was detected in the left ventricle leading to CardioWest implantation. In the other patient supported with the Thoratec system after acute myocardial infarction, thrombus formation in the left ventricle was also ob-

Table 2. Preimplant Hemodynamic and Laboratory Data

	Range	Mean/Median
Cardiac index (L/min/m^2)	1.2–3.4	2.0 0.7
Central venous pressure (mm Hg)	8–25	13 5
Mean pulmonary artery pressure (mm Hg)	18–55	32 9
Pulmonary capillary wedge pressure (mm Hg)	12–32	22 6
Pulmonary vascular resistance (dyn · sec · m^5)	107–534	298 120
Systemic vascular resistance (dyn · sec · m^5)	545–1,905	1065 458
White blood count (g/dL)	6.5–29.5	13.4 5.2
Platelets (1,000)	24–326	137 85
Blood urea nitrogen (mg/dL)	24–133	65 29
Creatinine (mg/dL)	0.4–11	2.1 1.9
Bilirubin (mg/dL)	0.4–8.8	2.5 2.5
Lactate dehydrogenase (U/L)	274–21,000	median, 607
Alanin aminotransferase (U/L)	12–20,000	median, 94
Brain natriuretic peptide (pg/mL)	40–2,713	median, 458

Table 3. Complications Under Support

Complication	Incidence
Bleeding	9 (21%)
Reexploration	8 (19%)
Thromboembolic	0.04 events/patient month
Transient ischemic attacks	2 (5%)
Cerebrovascular disorders	1 (2.3%)
Cerebral bleeding	1 (2.3%)
Acute renal failure[a]	3/20 (15%)
Liver failure	11 (26%)
System-related infection	
Driveline	3 (7%)
Mediastinitis	2 (5%)
Abdominal operations	4 (9%)
Hemolysis	3 (7%)
Pneumonia	5 (12%)

[a] In 20 patients without preoperative renal failure.

served after 7 days of support, which made a system change necessary. Preoperative hemodynamic and laboratory data are summarized in Table 2.

Since October 2003, a modified version of the Berlin Heart EXCOR driver (Berlin Heart, Berlin, Germany) [3] has been available for clinical trial at our Center and has replaced the bulky console in our last seven patients receiving the CardioWest device.

Anticoagulation Protocol

During the first 24 hours postoperatively, the patients receive no anticoagulation. On postoperative day (POD) 1, heparin administration is started if blood loss is less than 50 mL/h over 3 consecutive hours (partial thromboplastin time [PTT] target: 50 seconds). A thromboelastographic (TEG) analysis is performed to identify patients with hypercoagulability (maximal amplitude 68 mm), who additionally receive 1 mg/kg acetylsalicylic acid (ASA). On POD 2, heparin dosage is increased to adjust PTT to 60–70 seconds. Repeat TEG is performed to evaluate the effect of ASA administration, which might be adjusted to achieve the recommended platelet inhibition level of 70%. This medication is continued until two weeks postoperatively. If ASA turns out to be ineffective, it is replaced by clopidogrel, the effect of which is also verified by TEG to achieve a degree of inhibition of greater than 40%. Two weeks after surgery, heparin is replaced by warfarin (Coumadin), and ASA, or clopidogrel medication is continued.

Antibiotic Protocol

Our antibiotic prophylaxis is the same as with other assist devices and consists of a short-term prophylactic administration of cephalosporin (Cefazolin) (3 2 g daily) in all patients until all drains are removed. Further infections are treated according to the antimicrobial sensitivity test. In patients who had been on antibiotic treatment prior to implantation, their regime is replaced by vancomycin, and tazobactam plus piperacillin for at least 4 weeks. Antimycotic prophylaxis was not performed routinely.

Results

The implantation procedure was uneventful in all patients without any intraoperative fatality. Eight patients (most of them after acute myocardial infarction) had fit problems and chest closure was only possible on PODs 2–5. Three of these patients had a body surface area less than 1.7 m^2. However, fit problems were not observed in three other patients with a body surface area less than 1.7 m^2. A bleeding complication defined as blood loss greater than 1,500 cc $\cdot$ m^2 $\cdot$ 24 hours occurred in 9 patients (21%) with 8 of them needing reexploration. This bleeding complication was not surgery-related but was due to the fact that 35% of our patients had been on mechanical circulatory support before with subsequent coagulation disorders. Liver failure as defined by bilirubin greater than 10 mg/dL and transaminase three times as high as the normal value was found in 11 patients (26%) needing molecular adsorbent recirculating system therapy. Renal failure requiring renal replacement therapy occurred in 3 of 20 patients, who had no renal failure preoperatively. Four patients underwent abdominal surgery on the device for mesenteric ischemia. Hemolysis as defined by plasma-free hemoglobin of greater than 50 mg for more than 12 hours was found in 3 patients (Table 3). These patients usually had systemic hypertension thus needing higher driving pressures. Hemolysis could be resolved by reducing the driving pressure in combination with antihypertensive agents.

There were two system-related technical problems. One patient was observed to have a significantly higher right than left pump output with increasing signs of pulmonary congestion and weight gain after 6 months of support. Transthoracic and transesophageal echocardiography did not provide an explanation for this development. He was given diuretics, which improved his pulmonary congestion but the high right pump output remained. Fortunately, a suitable donor organ made immediate cardiac transplantation possible. When investigating the pump, a diaphragm layer on the blood side within the pump turned out to have ruptured with subsequent thrombus formation in the intermediate room. The patient is now doing well at home after cardiac transplantation. In another patient, who died after 5 days of support, the central venous catheter wedge had accidentally been advanced into the tricuspid valve leading to valve dysfunction with consecutive circulatory collapse.

Duration of support was 1 to 291 (mean, 86 89; median, 51) days. Altogether, 11 of 42 patients (26%) underwent successful cardiac transplantation with 10 being discharged home. One patient died from an infection one week post heart transplantation (HTx). Another patient, who had been discharged from hospital, died 6 months after the procedure from acute rejection. Survival in those 9 patients being discharged is 2 to 25 months. Twenty-two patients (52%) died under support, 13 of them from multiple organ failure after 1 to 68 days of support, ie, the preexisting organ dysfunction could not be resolved, 3 patients from mesenteric ischemia (72 to

167 days), 2 patients each from sepsis and multiple organ failure (26 and 87 days), and from cerebral bleeding (52 and 56 days), and one patient each from multiple organ and respiratory failure (37 days) and from a technical problem after 5 days. Mean duration of support among survivors to cardiac transplantation was significantly lower (174 87 days) than in nonsurvivors (43 52 days). Nine patients are still on the device, 5 of them within the hospital, whereas 4 patients could be discharged home for a mean duration of 42 days while on the device after the original CardioWest console was replaced by the EXCOR Berlin Heart driver. Of those 15 patients who previously had been supported by a different assist device, 6 patients underwent cardiac transplantation, 5 of them were discharged from hospital. The patient with giant cell myocarditis supported with three different devices is doing well at home. Table 1 details the results with regard to etiology of heart failure.

Comment

Although a variety of devices for mechanical circulatory support have become available, patients with intracardiac thrombi or shunts, structural damage to the heart, or congenital heart defects are not eligible for the implantation of these assist devices but need a total artificial heart in case of endstage heart failure. This paper describes the application of the CardioWest TAH in one of the sickest patient cohort receiving mechanical circulatory support ever reported as shown by their preimplant hemodynamic and laboratory data. In our recent report on patients bridged to cardiac transplantation with the Thoratec VAD system, preoperative ventilation was shown to be an independent risk factor of death [4]. In the present CardioWest collective, 74% of patients had been on mechanical ventilation preoperatively.

In his recently published paper on 81 patients receiving the CardioWest TAH, Copeland and colleagues [5] reported on a survival to transplantation of 79%, which is markedly higher than that of our collective. However, neither collective is comparable in terms of preoperative risk factors. The Copeland group excluded patients from TAH implantation with a previous vascular assist device or dialysis 7 days before. In contrast, 35% of our patients had been on mechanical circulatory support before and 52% had undergone dialysis for renal failure. Furthermore, the incidence of intraaortic balloon pumping (36% in the Copeland collective vs 67% in our collective), mechanical ventilation (42% vs 74%), previous cardiac surgery (38% vs 50%), and previous cardiopulmonary resuscitation (37% vs 45%) was significantly higher in our group.

In view of the extremely poor preoperative status of the patients presented, the overall survival rate of 48% among these patients can be considered as a favorable result. The main cause of death in our experience was a preimplant multiple organ failure, which turned out to be irreversible after CardioWest implantation. However, an exceptional outcome was found in patients with acute myocardial infarction (AMI) and with postcardiotomy heart failure. Duration of support among survivors with AMI etiology was 185 60 days compared to 39 54 days among nonsurvivors, which is comparable to the support times in the total collective. Patients with these etiologies became acutely sick and their organs did not suffer from long standing low output syndrome compared to patients with a chronic disease like idiopathic dilated or ischemic cardiomyopathy (79% fatalities). Furthermore, severe cardiogenic shock after AMI is usually associated with a high release of cytokines [6]. We assume that the removal of the heart might limit the production of cytokines, which are made responsible for end-organ failure. This hypothesis is the subject of further investigation at our Center.

The body surface area (BSA) always is a main issue when implanting a total artificial heart. In our cohort, 6 patients had a BSA of less than 1.7 m^2, which resulted in a fit problem in 3 patients only with two survivors (one with a fit problem). However, the fit problems were more likely to be associated with the etiology of the disease (AMI, postcardiotomy cardiogenic shock) than with BSA. Nevertheless, the number of this subgroup is too small to make any meaningful conclusions.

Regarding the clinical status at the time of HTx, TAH patients are accepted for HTx as soon as they have no organ dysfunction. In general, they do not have a higher priority in organ allocation than other patients, except for technical problems, uncontrolled infection, or repeated transient ischemic attacks.

Despite a less sophisticated anticoagulation protocol as described by LePrince and colleagues [7] and Copeland and colleagues [8], and considering the more activated platelet function in TAH patients compared to those supported with other ventricular assist devices, the incidence of thromboembolic complications in our very sick cohort was only 0.04 thromboembolic events per patient month, which proves the low thrombogeneity of the system. Similarly, infectious complications were observed less frequently when compared with other systems for mechanical circulatory support [2, 9]. The incidence of liver failure is comparable to that observed among patients supported with the Thoratec biventricular device [2], although the TAH collective had higher preoperative risk factors. However, bilirubin values 6 and 14 days after implantation were higher among Thoratec patients and had generally normalized after 30 days of support. The bilirubin values obtained 14 days postimplantation differed significantly between survivors (1.7 6 mg/dL) and nonsurvivors (5.2 10 mg/dL) (p 0.01).

In our institution, patients who suffer from fulminant myocarditis and are in need of mechanical circulatory support usually receive a ventricular assist device as a bridge to recovery. However, four patients of our cohort had suffered fulminant myocarditis; in three of them a giant cell myocarditis was present, which makes a recovery very unlikely. The other patient had been supported with a different device due to severe cardiogenic shock and was switched to the CardioWest because of thrombus formation in the left atrium. This patient, however, died from multiple organ failure.

Our experience strongly recommends the further evaluation of the total artificial heart concept in the management of patients with cardiogenic shock after acute myocardial infarction and postcardiotomy heart failure. As far as other patients (eg, with idiopathic dilated or ischemic cardiomyopathy) are concerned, a prospective, randomized study is highly recommended to find out whether they are more likely to benefit from a total artificial heart or from biventricular support.

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Implantation of CardioWest Total Artificial Heart for Irreversible Acute Myocardial Infarction Shock

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ABSTRACT

Patients who develop cardiogenic shock after acute myocardial infarction have a very high mortality rate despite early reperfusion therapy. Hemodynamic stabilization can often only be achieved by implanting a mechanical circulatory support system. When, in cases representing expansive myocardial impairment without any chance of recovery, pharmacological therapy and the use of percutaneous assist devices have failed, the implantation of a total artificial heart is indicated. We report our first experiences with this extensive and innovative method of managing irreversible cardiogenic shock patients. The CardioWest total artificial heart was implanted in 5 patients (male; mean age, 50 years). All patients were in irreversible cardiogenic shock despite maximum dosages of catecholamines, an intra-aortic balloon pump and/or a femoro-femoral bypass. In all patients early reperfusion therapy was performed. After implantation of the CardioWest system, all dysfunctional organ systems rapidly recovered in all patients. Four of 5 patients underwent successful heart transplantation after a mean support time of 156 days. One patient died because of enterocolic necroses caused by an embolic event after termination of dicumarol therapy. In summary, our first experiences justify this extensive management in young patients who would otherwise have died within a few hours.

INTRODUCTION

Cardiogenic shock following acute myocardial infarction remains a complication with a very high mortality rate. In larger studies, the incidence in patients receiving inpatient treatment because of acute myocardial infarction is between 5% and 10% [Bengtson 1992; Moosvi 1992; Holmes 1995]. According to autopsy findings, cardiogenic shock occurs when more than 40% of the myocardium has been damaged [Harnarayan 1970; Pafe 1971; Alonso 1973]. The loss of the myocardium can be attributed to either a recent extended myocardial infarction or a combination of recent necrosis and previous infarction scarring [Alonso 1973]. Necrosis is an advancing development, with the size of the myocardial area supplied by the occluded coronary artery determining the emergence of left-ventricular pumping failure. Energy reserves in the myocardium are further depleted by the significantly reduced ejection fraction in such a shock situation, and irreversible cardiogenic shock is the ultimate outcome [Gunnar 1988].

Treatment for cardiogenic shock ranges from drug therapy via interventional or surgical reperfusion measures to the implantation of mechanical circulatory support systems. The conservative, purely pharmacological treatment has an extremely high mortality rate of 80% to 90% [Goldberg 1991; Bengtson 1992]. Thrombolytic therapy in patients with cardiogenic shock is also less than convincing and, according to the data available from controlled studies, has not led to any significant improvement in the survival rate [GISSI 1986; GISSI 1990; Holmes 1995; Berger 1997].

However, the prognosis can be positively and significantly influenced through successful coronary angioplasty [Lee 1991; Moosvi 1992]. If reopening the coronary artery is not successful, however, or if there is a repeat occlusion and the patient remains in cardiogenic shock, then sufficient hemodynamic conditions can only be achieved by implanting a mechanical assist device.

The development of ventricular assist devices (VAD) has advanced considerably over the past 2 decades and the following system types are now available: (1) intra-aortic balloon pump, (2) implantable turbine pump (hemopump), (3) centrifugal pump (femoro-femoral bypass), (4) paracorporeal or partially implantable support system, (5) completely implantable total artificial heart [Körfer 1995].

The first 3 of the abovementioned systems can be implanted percutaneously and therefore by cardiologists in the cardiac catheter laboratory. The most significant of these for interventional cardiologists is the intra-aortic balloon pump, which can be implanted easily and quickly in shock patients, and which affects prognosis positively, especially in combination with successful reperfusion [Mueller 1994].

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Figure 1. The CardioWest total artificial heart–artificial ventricle with Medtronic-Hall prosthetic valves.

If cardiogenic shock persists despite high-dosage drug therapy and the use of percutaneous assist devices, the implantation of an artificial heart system suited to longer-term support is indicated. This type of VAD can assist one ventricle in isolation or both ventricles. Successful weaning from this system and its use as a bridge to heart transplantation have both been reported [Hill 1986; Moritz 1993; Park 2000].

In a few cases, akinesia of the left ventricle remains despite ventricular assistance. Even with appropriate anticoagulation there is a risk of ventricular thrombosis. In other rare cases, sternotomy reveals severe damage of the myocardium. The myocardial tissue is so fragile that it is impossible to implant a paracorporeal or partially implantable system while leaving the heart as it is. With such a VAD recovery is not to be expected. In both cases, the heart should be replaced and the patient bridged to transplantation with a total artificial heart [Copeland 1996].

In this paper, we report our first experience with this complex and innovative treatment strategy for patients with irreversible cardiogenic shock following acute myocardial infarction.

METHODS

The CardioWest Total Artificial Heart

The CardioWest total artificial heart (Syncardia Systems, Tuscon, AZ, USA), implanted in all cases, is a direct successor of the Jarvik 7-70 system. It is a biventricular, pulsatile, and pneumatically driven blood pump that is implanted orthotopically. The ventricles are made of polyurethane; Medtronic-Hall artificial valves (Medtronic, Minneapolis, MN, USA) ensure unidirectional flow (Figure 1). Blood and air are separated by a 4-layer polyurethane septum that retreats during the diastole and advances during the systole via compressed air, driving the blood out of the artificial ventricle. The CardioWest system can guarantee flows of up to 10 L/min, with normal target flows of 6 to 8 L/min. Following implantation of the ventricle, the connecting cable to the drive console is passed out below the left costal arch.

The drive console permits the beat rate, the duration of the systole, and the pressures in the drive lines all to be set individually for each ventricle. The CardioWest system functions on the basis of a complete filling of the ventricles, followed by a complete emptying on each beat. The filling of the ventricles is determined by the atrial pressure on each side; as the atrial pressure increases, the cardiac output and ejection fraction also increase.

Implantation Technique

The implantation technique has been described in detail by Arabia et al [1999]. Here, the most important steps are summarized below.

First the heart-lung machine is connected in the conventional manner. The heart is totally bypassed and then excision begins, using a method that is fundamentally different from that used for transplantation. Both the tricuspid valve annulus and the mitral valve annulus are preserved. Then an incision is made on the ventricular side of the atrioventricular cavity and continued forward across the right-ventricular outflow tract to the proximity of the pulmonary valve. The incision extends backward to the interventricular septum and through the septum, in turn remaining on the ventricular side of the atrioventricular cavity. The incisions are extended from both sides to the pulmonalis bifucation. The large vessels are then prepared slightly above valve level. Following excision of the heart, the right- and left-atrial cuffs are sutured using Teflon felt.

After this, the large vessels are anastomosed, first the pulmonary artery and then the aorta. The conduits are shortened to the appropriate length. Finally, the artificial heart is carefully vented and positioned. An x-ray of the CardioWest total artificial heart after implantation is provided in Figure 2.

Anticoagulation

Circulatory support using the CardioWest total artificial heart initially caused heparinization with activated coagulation time values corresponding to 1.5 times baseline. After removal

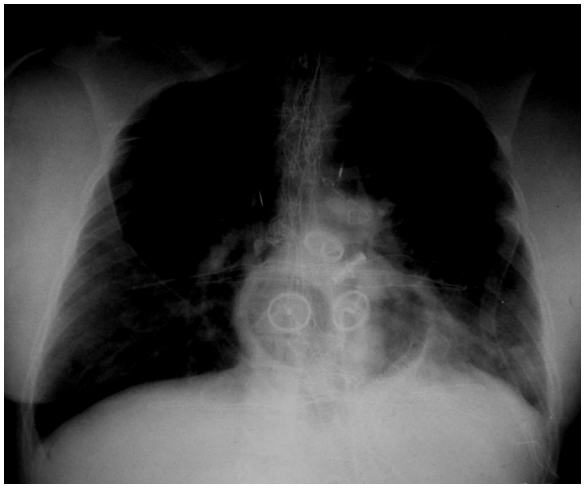

Figure 2. Thoracic x-ray after implantation of a CardioWest total artificial heart.

of the thoracic drainage system, marcumar with target International Normalized Ratio levels of 2.5 to 3.5 was introduced, as well as an additional antiaggregation with 100 mg acetylsalicylic acid.

RESULTS

Case 1

A 39-year-old man with extended myocardial infarction was admitted to an outside hospital. There, coronary angioplasty was performed with stent implantations in the proximity of the left anterior descending artery and the circumflex artery. After 3 days the patient required reanimation. Because of acute occlusion of the left anterior descending artery and the circumflex artery, a repeat percutaneous transluminal coronary angioplasty (PTCA) was performed, with stent implantation and lysis therapy. The cardiac index was 1.6 L/min per m^2.

Still at the other hospital, a Biomedicus femoro-femoral centrifugal pump (Eden Prairie, MN, USA) was implanted to provide hemodynamic stabilization. The patient was then transported to our hospital. Here, surgical myocardial revascularization was performed, with the placement of 2 aorto-coronary venous grafts to the left anterior descending artery and the marginal branch. In conjunction with continued low-output syndrome, the femoro-femoral bypass was retained. After 3 days there was still no indication of myocardial recovery. Severe biventricular dysfunction was observed.

It was decided to implant a biventricular assist device. In the operating theater both the right and left ventricles were akinetic, as well as extensively damaged, with the tissue so fragile as to render the implantation of an assist device to support the existing heart impossible. For this reason, the heart was removed and a CardioWest total artificial heart implanted.

The patient could be extubated on the first postoperative day. After support for 6 days, the previously increased retention levels had returned to the normal range (creatinine from 3 mg/dL to 1.1 mg/dL, urea from 90 mg/dL to 26 mg/dL). The bilirubin level increased on the system to 11.9 mg/dL on the fourth day, after which it continually decreased, entering the normal range after 3 weeks. After a support period of 152 days, the patient was transplanted in a completely mobilized state, free of infection, and with all organ systems recovered.

Case 2

A 44-year-old patient had severe biventricular dysfunction following an extended anterior wall infarction that was first treated with systemic lysis therapy. After 3 days the patient suffered a repeat infarction. A PTCA was performed with stent implantation in the region of the right anterior descending artery. Five days after this, the patient required reanimation. To maintain adequate circulatory conditions, an intra-aortic balloon pump and a femoro-femoral bypass were introduced. Following hemodynamic stabilization, a repeat PTCA of the right anterior descending artery was performed. Since the patient was still in cardiogenic shock and there were no signs of recovery, implantation of a VAD was indicated. Sternotomy and pericardiotomy revealed severe biventricular dysfunction. Both ventricles displayed severe myocardial damage. For this reason, it was decided to implant a CardioWest total artificial heart.

Following the intervention, all the organ systems recovered rapidly. On the third postoperative day the patient could be extubated; during the first 14 days the patient still required intermittent veno-venous hemofiltration. Total bilirubin increased to a maximum 10.4 mg/dL before re-entering the normal range after 14 days. The patient could be successively mobilized and was transplanted after 191 days on support in a good general condition and free of infection.

Case 3

A 59-year-old patient developed severe left-ventricular dysfunction following extended anterior wall infarction in conjunction with severe coronary triple-vessel disease (occlusion of the right anterior descending artery and the right coronary artery, as well as severe stenosis of the circumflex artery). When the patient failed to recover he was transferred to our hospital for implantation of a VAD.

Following placement of an intra-aortic balloon pump, his hemodynamic situation first stabilized but then rapidly deteriorated, so that implantation of a left-VAD (LVAD) was indicated. During surgery, the left ventricle displayed no contractions; the tissue was already clearly fragile. A Thoratec LVAD (Pleasanton, CA, USA) was implanted. Because of the developments described above, the left atrium and the ascending aorta were cannulated rather than the left apex.

Following the intervention, the patient's hemodynamic situation was sufficient, but in the course of the first week increasing right heart failure could be observed, which failed to respond to drug therapy. In addition, the patient was not recovering and developed a thrombus in the left ventricle on the 6th day after device implantation. On the basis of these findings, the implantation of a total artificial heart was indicated.

Following the intervention, veno-venous hemofiltration was carried out as it had been preoperatively and total bilirubin rose to a maximum 5.5 mg/dL. Following extubation, the patient showed a cerebro-organic psychosyndrome that, however, continually improved. Following a 6-week stay in intensive care, the patient could be transferred to a normal ward. Here his general condition improved daily.

After support for 5 months, the patient suffered gastrointestinal hemorrhaging with a significant loss of blood, meaning that conventional dicumarol therapy had to be replaced by intravenous heparinization. A few days later the patient had a transitory ischemic attack. Two days after that the patient complained of severe abdominal pains, and explorative laparotomy revealed necroses caused by an embolic event throughout the intestine. The patient died on the 167th day after implantation of the system.

Case 4

A 73-year-old patient developed cardiogenic shock in conjunction with extended anterior wall infarction. Coronary angiography performed in an outside hospital revealed severe

coronary triple-vessel disease with a 90% stenosis of the main trunk. The patient required reanimation and an intra-aortic balloon pump was implanted in the cardiac catheter laboratory. Following stabilization, the patient was transferred to our hospital.

Here, the creatinine kinase level on admission was already 4.777 U/L, CK-MB was 274 U/L, and cardiac troponin was 346 mg/L. Surgical myocardial revascularization was immediately performed, with venous grafts sequentially to the right anterior descending artery and the diagonal branch, as well as sequentially to the right posterior descending artery and the right posterolateral branch. It proved impossible, however, to wean the patient from the cardiopulmonary bypass, and severe biventricular dysfunction was observed.

After all the conventional measures had been exhausted, it was decided to implant a CardioWest total artificial heart. The patient could be extubated on the third postoperative day. In the first 10 days he required intermittent veno-venous hemofiltration. The total bilirubin level rose to 15.2 mg/dL on the 12th postoperative day and did not re-enter the normal range until 6 weeks after implantation. On the 13th postoperative day, the patient could be transferred to a normal ward. After support for 180 days he was then transplanted in a very good general condition.

Case 5

A 36-year-old patient with extended myocardial infarction and cardiogenic shock underwent coronary angioplasty in an outside hospital, with stent implantation of the right anterior descending artery and the circumflex branch. During this intervention the patient required reanimation. Since he remained hemodynamically unstable even after the intervention, an intra-aortic balloon pump was implanted. The patient was then transferred to our hospital. Here, echocardiography revealed an ejection fraction of 16% and a cardiac index of 1.5 L/min per m^2. Creatinine kinase was 4.524 U/L, CK-MB was 346 h/L, and cardiac troponin was 596 µg/h.

Despite extensive pharmacological therapy and the intra-aortic balloon pump, adequate hemodynamic conditions could not be achieved, so the patient was brought to the operating theater for implantation of a VAD. Here it was discovered that the entire left ventricle was massively infarcted. A CardioWest total artificial heart was implanted.

The patient could be extubated on the third postoperative day. After support for 6 days, both the retention and the bilirubin levels were within the normal range. Lipase increased to 1.200 U/L but no organic correlation could be found using sonography. After 101 days on the system, the patient could be transplanted in a completely mobilized, infection-free condition with all laboratory parameters normal.

DISCUSSION

In the last few decades, the mortality rate for acute myocardial infarction has been significantly lowered through the further development of drug, interventional, and surgical therapies. Despite these therapeutic options, a low percentage of infarction patients (~7%) develop cardiogenic shock [Vogt 1999]. This patient group has an extremely poor prognosis and a hospital mortality rate of 60% to almost 100%. An improvement in survival has been reported through rapid reopening of the infarcted vessel with PTCA or operative myocardial revascularization [Beyersdorf 1990; Allen 1993].

The restoration of adequate blood flow may limit the size of the infarction, prevent infarction extension, or improve the function of the remaining myocardium [Grines 1989], but once the patient is already in cardiogenic shock it is usually too late to save the myocardium within the infarcted area. The patients are often still young—in our study averaging 50 years—and yet have barely any chance of surviving. The only remaining therapeutic option to restore sufficient circulation is the implantation of a mechanical VAD.

Mechanical circulatory support devices are mainly implanted in patients with terminal heart failure as a bridge to

Patient Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	M	M	M	M	M
Age, y	39	44	59	73	36
Weight, kg	77	85	72	80	95
Body surface area, m^2	1.9	2.09	1.88	2.00	2.20
Reanimation	Yes	Yes	No	Yes	Yes
Intra-aortic balloon pump	No	Yes	Yes	Yes	Yes
Femoro-femoral bypass	Yes	Yes	No	No	No
Respiration	Yes	Yes	Yes	Yes	Yes
Ejection fraction, %	18	20	25	20	16
Cardiac index, L/min/m^2	1.6	1.8	1.6	1.7	1.5
Intervention	PTCA + stent LAD/Cx, re-PTCA + stent LAD/Cx + lysis therapy double CABG	PTCA + stent LAD, lysis therapy, re-PTCA LAD	PTCA + stent LAD, initial implantation of a Thoratec LVAD	Quadruple CABG	PTCA + stent LAD/Cx

*PTCA indicates percutaneous transluminal coronary angioplasty; LAD, left anterior descending artery; Cx, circumflex artery; CABG, coronary artery bypass grafting.

heart transplantation [Farrar 1990; Körfer 1995]. Cardiogenic shock following acute myocardial infarction is a more rare indication for the implantation of an assist device [Page 1971; Zumbro 1987; Moritz 1993; Chen 1999; Körfer 1995; Reiss 1995].

Assist devices provide the options of supporting the damaged heart or completely replacing it. Numerous systems are currently available, ranging from the intra-aortic balloon pump via centrifugal and roller pumps and VADs to the total artificial heart. The standard options are to use the system until the patient can be weaned or as a bridge until heart transplantation. The percutaneous systems such as the intra-aortic balloon pump and the centrifugal pump are only suited to short-term support. The prognosis following weaning is poor, however, with survival rates between 0% and 35%, meaning that ultimately the only options with a better prognosis are the use of VADs or replacement of the heart with a total artificial heart [Raithel 1989; Reichmann 1990; Kern 1993; Zeymer 1993; Chen 1999].

Most reports are of isolated left-heart support. Myocardial infarctions primarily restrict left-ventricular output; the implantation of an LVAD thus often appears to be the adequate solution to achieve sufficient circulation. The first system that was used as an LVAD in patients with cardiogenic shock following myocardial infarction was the Thoratec system [Hill 1986]. The patient could successfully be transplanted after being supported on the system for just 2 days.

Chen et al reported their experience with the HeartMate LVAD in conjunction with acute myocardial infarction. Their bridge-to-transplant rate was 64%. Only one patient could be successfully weaned [Chen 1999]. Similarly low weaning rates were also reported by other groups [Park 2000].

With isolated left-heart support 2 significant problems occur [Park 2000]. First, some patients (up to 30%) experience right-heart failure. Second, approximately 30% to 40% of patients develop malignant ventricular arrhythmias [Moritz 1993; Chen 1999; Park 2000]. The implantation of a biventricular support system or a total artificial heart can prevent the abovementioned problems from developing. The biventricular assist device is, however, inferior to the total artificial heart in cases involving irreversible cardiogenic shock. First, the total artificial heart is capable of guaranteeing higher pump flows of up to 10 L/min. Unlike patients with chronic heart failure, patients suffering from acute cardiogenic shock are not use to reduced perfusion of the vital organs; in our experience with both forms of circulatory support, the higher pump flows are crucial to subsequent organ system recovery in these patients. In addition, previously applied toxic doses of catecholamines can be completely discontinued, also preventing secondary organ damage. Second, if the myocardium fails to recover after use of a VAD, there is a risk of ventricular thrombosis. We observed this phenomenon in our third patient, in whom we initially implanted a Thoratec system in the hope that this option would enable him to recover. This, together with right-heart failure, was cause for us to remove his heart and implant a CardioWest system.

One disadvantage of the CardioWest system should not remain unmentioned. The drive console is considerably larger than that of the various VADs available. During the rehabilitation and mobility phases, patients have difficulty moving around without help (Figure 3).

Figure 3. Patients during mobilization on the CardioWest system.

In this paper we have reported our first experiences with the total artificial heart in patients with irreversible cardiogenic shock following myocardial infarction; ie, an extreme form of cardiogenic shock that cannot be treated pharmacologically, interventionally, or with percutaneous assist devices. The marked fragility of the myocardium rendered it impossible to implant a paracorporeal or partially implantable system with the option of weaning on recovery.

The results of this management strategy, which is extensive regarding both financing and personnel, are extremely encouraging. Four of 5 patients who otherwise would certainly have died within the next few hours were successfully transplanted following a mean support period of >5 months. Regretfully one patient died after 167 days on the system because of enterocolic necroses caused by an embolic event, after hemorrhaging had rendered conventional dicumarol therapy impossible.

In all 5 patients, recovery of all dysfunctional organ systems was rapid following implantation of the CardioWest system. All patients could be mobilized on the system and were free of infections throughout the entire support period. Infections in the vicinity of the drive cables, a frequent occurrence with some LVADs, were not observed.

In summary, the implantation of a total artificial heart represents the only life-saving therapeutic option in patients with irreversible cardiogenic shock. In cases where the shock is irreversible, this system is superior to all other assist devices. First experiences in a predominantly young patient cohort produced results that justified the effort involved. In cases of irreversible cardiogenic shock, patients should be given the chance to exhaust the final therapeutic option available to them by ensuring that a center with a mechanical circulatory support program at its disposal is contacted in good time.

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