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The SynCardia CardioWest™ Total Artificial Heart

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INTRODUCTION

Congestive heart failure (CHF) is commonly regarded as the "final common pathway" of cardiovascular decline resulting from all forms of heart disease. Despite advances in the prevention and treatment of many forms of cardiovascular disease, CHF continues to exist as a major and, unfortunately, growing form of morbidity and mortality in the United States and around the world. As myocardial function declines and systemic compensatory systems are activated to support blood pressure and organ perfusion, patients progress through increasingly severe stages of CHF, each with increasing morbidity and mortality.

The past decade has seen significant advances in our understanding of the pathophysiology and pharmacologic approach to the treatment of CHF. These developments have lead to a "shift to the right" of the mortality curve for CHF, with patients living longer with improved quality of life. Unfortunately once patients reach the steep or rapidly declining phase of the mortality curve, i.e. being classified as AHA/ACC Class D and NYHA Class IV CHF, their decline continues in an accelerating fashion. Patients with Class IV CHF face a greater than 75% two-year mortality risk. At that point in their natural history, medical therapy is of limited value.

It is exactly for this group of maximally medically managed patients with persistent and worsening CHF that the field of mechanical circulatory support has emerged (Fig. 1). Over the years, devices have been developed with progressively increasing hemodynamic support capabilities. However, when complete bi-ventricular failure occurs, replacement of total heart pump function is needed. It is for this situation that the Total Artificial Heart has been developed.

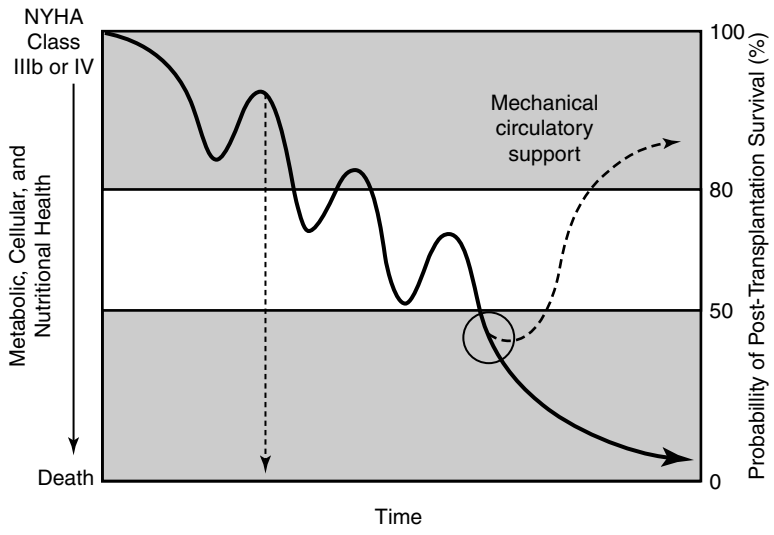

Figure 1 Natural history of New York Heart Association class III/IV chronic heart failure.

In this chapter the background, technical, and clinical experience with the SynCardia CardioWest™ Total Artificial Heart (TAH), the first and only TAH to be approved by the U.S. Food and Drug Administration, is reviewed. Specifically we discuss: (1) the rationale for the TAH, (2) the history of artificial heart technology, (3) technical and operational details of the CardioWest TAH, (4) indications for use of the TAH, (5) clinical experience with the CardioWest TAH, and (6) future applications of the TAH.

RATIONALE FOR THE TOTAL ARTIFICIAL HEART

The artificial heart arose from the unmet clinical need for a device or system capable of completely restoring systemic and pulmonary blood circulation and organ perfusion pressure in patients with failed circulatory systems due to irreversible biventricular dysfunction. Early in the history of TAH development the vision was for the creation of such a device as a long-term permanent cardiac replacement. While this was a laudable initial goal, it proved to be too big a technical, clinical, and social leap in the early days of TAH development (1). With the eventual parallel take-off of heart transplantation, as a result of the advent of effective anti-rejection pharmacology, a new unforeseen rationale for the TAH arose. The growth of transplantation, with inadequate instant donor heart availability created the need for a "bridge," rather than permanent device, capable of sustaining the life of a patient until a donor heart might be procured. Today with advances in TAH development both of these visions, i.e., short term "bridge" and long term "destination therapy," are back in the minds of the medical and technical community and are being actively addressed.

Additional rationale exist for the TAH. These may be categorized as being medical/technical, humanitarian, and economic. On the medical level, the TAH obviates many limitations, which are associated with ventricular assist device (VAD)-mediated cardiac support. Leaving the ventricles intact in the end-stage CHF patient often turns out to be a major liability for the patient. With time it has been demonstrated that the major cause of cardiac failure of patients supported with LVADs is eventual right heart failure.

In this scenario, placement of a second VAD as an RVAD carries a high morbidity and mortality with dramatically reduced bridge-to-transplant success. The TAH provides a complete cardiac solution for this scenario. Further, the minimally contracting myocardium often is a nidus for endoventricular thrombus formation. Placement of VADs in this situation has lead to significant embolization and stroke. Removing the ventricles with orthotopic placement of a TAH significantly reduces this embolic risk. Cardiac arrhythmias, frequent in the end-stage heart, undermine ventricular contractile performance and further reduce VAD function. Cardiac removal and replacement with the TAH overcomes this limitation. The presence of a prosthetic valve in a heart supported by a VAD increases the risk of thrombosis and embolization from the valve. This too is obviated through TAH use. Presence of ventricular septal defects and other structural derangements, which further compromise cardiac output in ventricles supported with VADs, are overcome with the use of a TAH. Finally, use of a device, which occupies the same anatomic location, without the need for violating other body cavities or further crowding the thoracic cavity, has motivated the development of an effective cardiac replacement device.

On the humanitarian level, the clear rationale for the TAH is that it may save lives. The majority of patients that have been recipients of such a device to date have been young to middle-aged patients in the prime of life. While their lives have unfortunately been compromised by devastating cardiovascular disease, they frequently are otherwise fairly healthy. Complete organ replacement in these patients, either with eventual cardiac transplantation or through continued destination therapy support, has the potential to afford them the chance for life with quality. Further, the TAH allows these patients the opportunity to recover from the devastating systemic effects of low circulatory output. Hence the rationale exists to salvage and recover the patient, reducing edema and congestion and increasing vital organ perfusion through the TAH.

Additional rationale for the TAH exists from an economic perspective. In the bridge scenario, allowing patients to recover prior to transplantation has the possibility of reducing the cost of hospitalization through reduced ICU stay and lower acute care levels for patients. Further, in the future, in the United States and presently in Europe, the possibility of recovery and waiting at home prior to transplantation is a reality with a TAH. This has the potential of saving the cost of 60 to 270 days of hospitalization, the duration post-acute recovery that patients wait on average, in the United States and Europe, respectively, for a transplant.

In the "destination therapy" scenario, even greater cost savings are possible. Presently CHF represents the leading cause of hospitalization in the United States and carries a price tag exceeding $27 billion (2). As patients worsen and progress to more advanced stages of CHF, their frequency of hospitalization and the length of stay and associated costs increase. As such, the TAH has the potential of radically improving the quality of life of patients with end-stage CHF, reducing their frequency and extent of hospitalization and their overall cost of care.

HISTORICAL OVERVIEW OF ARTIFICIAL HEART TECHNOLOGY

The artificial heart has had a greater than forty-year development history (Table 1). Initial efforts at creating a complete cardiac replacement artificial organ began as one of several scientific initiatives advocated during the Kennedy administration in the 1960s. In 1964, the National Institutes of Health launched an artificial heart program, fostering the development of partial and full cardiac replacement devices. Parallel efforts began in Texas and in Cleveland on circulatory replacement systems. Reflecting back on the early beginnings of this field differing visions and perceptions of the TAH are recalled.

Table 1 Total Artifical Heart (TAH) Timeline

1964	U.S. Government National Heart Initiative to produce a TAH
1969	Cooley at the Texas Heart Institute performs first human artificial heart implant to bridge a patient for 64 hr until a donor heart is transplanted
1981	Kolff, DeVries, and Jarvik at the University of Utah receive FDA approval to implant a TAH into a human for permanent application
1982	Dr. Barney Clark receives the Jarvik-7 device, lives 112 days
1983	Symbion acquires rights to manufacture Jarvik-7
1985	Copeland at UMC[a] implants the Phoenix TAH, opening the door for the FDA to approve the TAH as a bridge-to-transplant, rather than a permanent implant. He later performs the first successful bridge to transplant with a TAH using the Jarvik-7
1986	The smaller Jarvik-7-70 TAH is first implanted, expanding the use of the TAH into most adults (including women)
1990	The FDA withdraws the study of the Symbion Jarvik TAHs because of quality issues
1991	Symbion transfers all the TAH assets to CardioWest™/UMC
1992	CardioWest receives FDA approval to begin a new study with a modified Jarvik-7-70 design—The Multi-Center PMA Trial
1993	First CardioWest TAH is implanted in a women at UMC. She was successfully transplanted after 186 days
1999	CardioWest receives CE mark approval for clinical use of the TAH in Europe
2001	SynCardia Systems Inc. (Tucson, AZ) was founded to obtain FDA approval and commercialize the TAH
2004	SynCardia CardioWest™ TAH becomes the first TAH to receive FDA approval for use as a bridge-to-transplant in patients with irreversible bi-ventricular failure

[a]UMC, University Medical Center, Tucson, Arizona.
Abbreviations: FDA, food and drug administration; PMA, pre-market approval.

An initial clear memory is that of the dramatic first attempts by Dr. Denton Cooley to save dying patients who could not be weaned from the heart–lung machine after routine cardiac procedures in 1969 with the Liotta TAH (3) and then in 1981 with the Akutsu TAH (4). Next we remember, primarily from extensive media coverage, the use of the Jarvik-7 TAH as a permanent cardiac replacement by DeVries and his team in four patients in Salt Lake City and Louisville (5). The initial attempt at destination therapy led to the first long-term survival (112 days in Dr. Barney Clark) of humans on any type of mechanical circulatory device. Unfortunately, public expectations far exceeded the realities of that era. This was reminiscent of the era when heart transplantation had been banned in nearly every hospital in the world after a shaky but well-publicized start. In reality the goal of complete cardiac replacement was too extensive for the level of scientific, clinical, and social maturation of the era.

In 1985, the authors utilized a TAH for a different indication, that of "bridge to tranplantation," rather than permanent cardiac replacement. The team utilized an unapproved Phoenix TAH as a bridge device, in a desperate situation of a patient who had rejected his heart transplant. After failing at this and preparing for the next experience, the team was fortunate to have the first successful bridge to transplant with a TAH (Jarvik-7) in August 1985 (6).

The Jarvik-7 TAH was designed and tested preclinically in animals by Drs. Kolff, Olsen, Jarvik as well as others from the 1950s through the 1970s (7). The device was specifically designed and durability tested to permanently replace the heart. Dr. William DeVries and his team in the United States implanted four and Dr. Bjarne Semb in Stockholm implanted one Jarvik-7 TAH, with 100-mL ventricles, in the early 1980s. All five implants were in chronically ill patients. Early postoperative complications included

hemorrhage and renal failure. There was one death from hemorrhage occurring 10 days post-implantation. The other four patients died of sepsis, living as long as 620 days (mean survival of 291 days). Two of DeVries' patients suffered thrombo-embolic strokes (8). Dr. Semb's patient was photographed on numerous occasions walking around Stockholm supported by a portable briefcase-sized pneumatic driver. In summary, given the complete absence of long-term human experience with such devices at that time, the results seemed extraordinarily good. Yet, in many ways, the medical profession was not prepared for this technology. Most of the preclinical experience was in healthy growing calves that were resistant to infection, had little if any evidence of stroke, and, unfortunately, had to be euthanized within a few months of implantation as they "outgrew" the device. The major complications of mechanical circulatory devices in humans—bleeding, thromboembolism with stroke, and infection—had not been major problems in calves. Consequently, expectations were high, and the media was disappointed with the early clinical results in man.

Two major changes were made in the Jarvik-7 based upon that experience (9): Medtronic-Hall valves were substituted for Bjork-Shiley and the rate of pressure rise (dp/dt) by the pneumatic driver was lowered to about 4500 mmHg/sec. The authors began to understand many of the major problems of the total artificial heart in the bridge-to-transplant scenario. After their first implant in August 1985, 37 other centers implanted a total of 198 Jarvik-7 TAHs between 1985 and 1992. Seventy percent of these implants were done between 1986 and 1988. More than 75% of them occurred in eight centers. The remaining centers accounted for less than five cases per center. Thirty-nine of the hearts were the 100-mL size (the last one implanted in 1992) and 159 were with the smaller 70-mL ventricles that are currently used. The last registry of this experience (10) reported that 143 implant patients (72% of those implanted) were transplanted and that 89 (59% of transplants and 43% of the total) were discharged. More than 60% of these patients had the device for less than 2 wk. The rush to transplantation might explain why only 59% of those transplanted were discharged. The average patient age was 42 and the average duration of implantation was 24 days (range 1–603), resulting in 13 patient-years of experience. The cause of patients dying while on device support was: multiple organ failure (17 patients), sepsis (16), neurologic (6), and respiratory (6). Complications included infection (37%), hemorrhage (26%), renal failure (20%), stroke (5%), and transient ischemic attack (4%). A variety of experiences and impressions from this early period have been previously summarized. Among the most compelling publications from that era was a 60-case series from La Pitie Hospital in Paris in which no neurologic adverse events were reported. They used a multicomponent coagulation monitoring and anticoagulant therapy protocol developed by Szefner and colleagues (11).

In 1991, the Jarvik-7 (then called Symbion) study was halted by the FDA. At that point, the technology was licensed to a new start-up company known as CardioWest and the heart was renamed the CardioWest C-70 TAH. A new FDA study was started in 1993. Changes were made in manufacturing and the previous skin button was replaced with Dacron velour attached directly to the air conduits. Only one size (70 mL) was continued in production. In 2001 SynCardia, a company organized to complete the ongoing U.S. clinical trial, proceeded with regulatory submission to the FDA and initiated device commercialization, and renaming the device the SynCardia CardioWest™ TAH. As of June 2005, 612 TAHs of all types had been implanted worldwide. Ninety percent (554 of 612) have been of the CardioWest–type design, accounting for 77 patient-years, or about 91% of the worldwide TAH experience. There have been more than 350 actual CardioWest implants to date, accounting for over 60 patient-years or more than 70% of the worldwide TAH experience.

Presently the only other TAH under clinical investigation is the AbioCor® fully implantable TAH, an electrohydraulic pump that has been implanted in fourteen patients as of June 2005. The size and pumping characteristics are very different from the CardioWest™ TAH. Clinical experience with the AbioCor has thus far been limited and results, including survival and adverse events, have not been published. In May 2005 the US FDA Advisory Panel rejected Abiomed's request for a humanitarian device exemption to market the AbioCor.

TECHNICAL AND OPERATIONAL DETAILS OF THE CARDIOWEST™ TAH

The SynCardia CardioWest™ TAH is a biventricular orthotopic pneumatic pulsatile pump with two separate artificial ventricles that take the place of the native ventricles (Fig. 2A). 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, separated by thin coatings of graphite (Fig. 2B). The inflow (27-mm) and outflow (25-mm) Medtronic-Hall valves are mounted on the housing. The diaphragm excursion is essentially from one wall of the housing to the

(A)

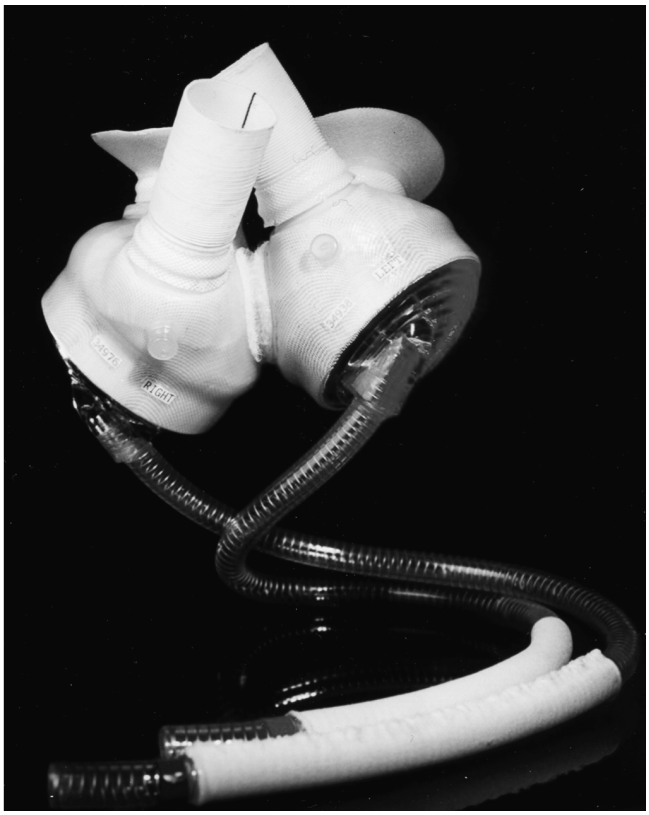

Figure 2 (**A**) SynCardia CardioWest™ Total Artificial Heart. (**B**) Total Artificial Heart ventricle. *Abbreviation*: SPUS, segmented polyurethane solution. (*Continued*)

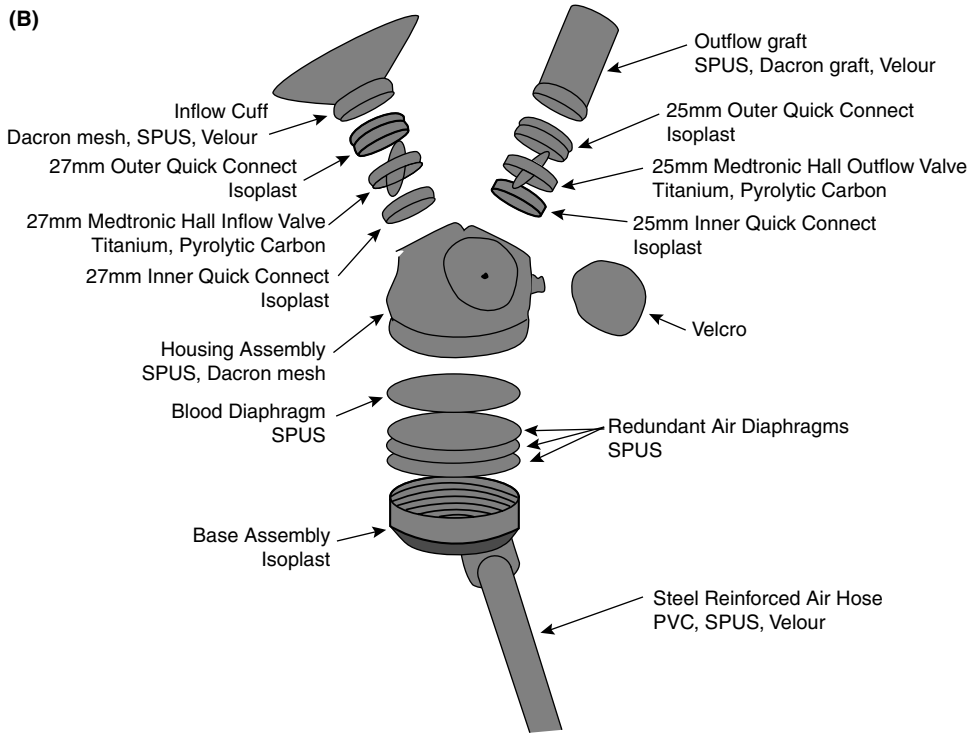

Figure 2 (*Continued from previous page*)

other, allowing the ventricle to fully fill and fully eject nearly 70 mL per beat. A flexible polyurethane lined inflow connector called a "quick connect" 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 ventricles after the distal connector anastomoses have been completed.

Wire-reinforced air conduits covered with Dacron in the transabdominal wall pathway connect to longer drivelines and to an external console (Fig. 3). This console is mobile by virtue of batteries and compressed air tanks, allowing the patient freedom to move about the hospital or other care facility. With the current configuration, patients are able to ambulate within the confines of the medical center (e.g., going to the cafeteria, or outdoors). Further, they perform most cardiac rehabilitation exercises, a necessary step toward their full recovery.

Portable pneumatic driver/consoles that provide pneumatic power have been developed and tested and will soon be available (Fig. 4A and B). These will provide increased mobility and, most importantly, discharge from the hospital. A "wearable" disposable driver/console is being developed and will be the third generation of drive power for the CardioWest™, further improving the quality of life of implanted patients.

The external console consists of two pneumatic drivers, one primary and one backup, transport batteries, air tanks, and an alarm and computer monitoring system. Beat rate, % systole (% of cardiac cycle occupied by systole), and left and right driving pressure are manually controlled. Once set, it is rare for these parameters to need resetting. Cardiac

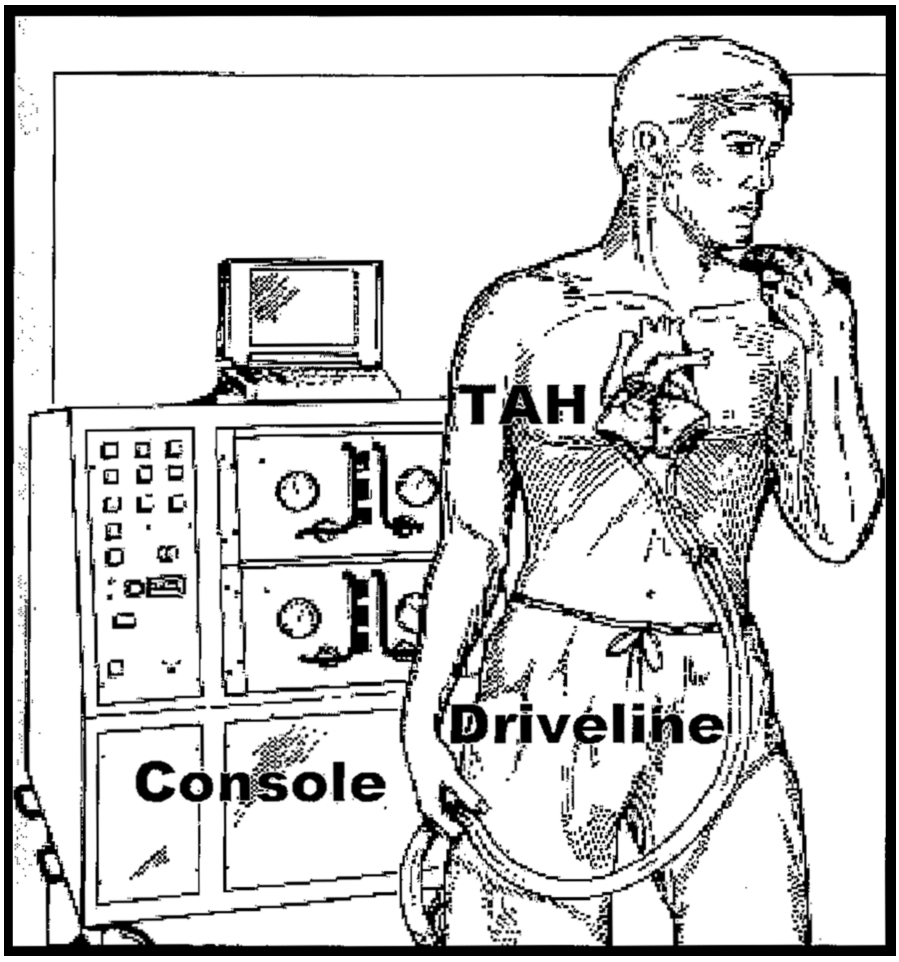

Figure 3 SynCardia CardioWest™ Total Artificial Heart (TAH) System. Note three components: TAH, existing pneumatic driveline, and driver console.

(A)

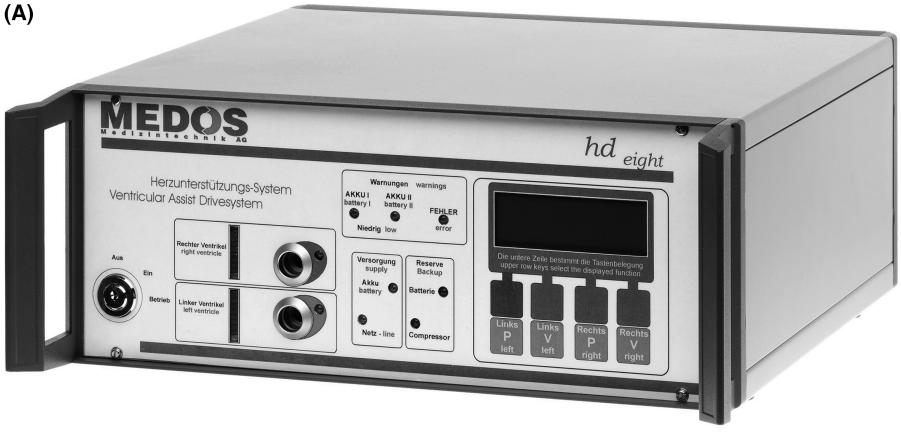

Figure 4 (**A**) SynCardia MEDOS HD8™ Mobile Driver. (**B**) Berlin Heart EXCOR™ Portable Driver. *(Continued)*

(B)

Figure 4 (*Continued from previous page*)

output based on volume of airflow out of the drivelines as well as trend plots of left-sided and right-sided cardiac output are continuously displayed as is drive pressure for each artificial ventricle. Separate ventricular fill volumes are also continuously displayed.

The primary driver is set to fully eject blood (Fig. 5) from each artificial ventricle with each beat. This is achieved by setting the ejection pressures for the right ventricle 30 mmHg higher than the pulmonary artery pressure and the systemic drive pressure 60 mmHg higher than the systemic pressure. The driver, however, is not set to allow the artificial ventricle to fully fill. Filling of 50 to 60 mL per beat by initial adjustment of the beat rate and % systole is optimal. Thus, within the 70-mL artificial ventricle on the air-side of the diaphragm is a "cushion" of 10 to 20 mL (Fig. 6). In the event of increased venous return, as in the cases of exercise or volume loading, some of this air is displaced and cardiac output automatically increases as occurs with the Starling mechanism in a normal heart. Using this protocol coupled with a negative intraventricular pressure at the onset of diastole of 10 to 15 mmHg and a central venous pressure of 8 to 15 mmHg, the cardiac output generated by the CardioWest™ TAH is generally 7 to 8 L/min. Mean arterial pressures are usually in the 70 to 90 mmHg range, resulting in a perfusion pressure of 55 to 80. Delivery of this magnitude of pressure and flow has resulted in consistent return of renal, hepatic, and other end-organ function to normal even in the sickest of patients. Needless to say, there is no concern about right heart failure, pulmonary hypertension, valve issues, or arrhythmias as with LVADs. Further, the flow limitation, always seen with extra corporeal BVADS (Thoratec provides a maximum flow of 5 to 6 L/min), and seen in cases of RV failure with LVADs, is not present with the CardioWest. In a study of CardioWest, Novacor (World Heart Corporation, Ottawa, Ontario, Canada), and Thoratec (Thoratec Corporation, Pleasanton, California, U.S.A.) in very sick deteriorating patients (12) we found that during the first 24 hr post-implant a cardiac index of 2.5 L/min/M^2 correlated positively with survival in all groups. For many American patients with BSAs of >2 M^2 an output of at least 5 to 6 L/min early after implant would be the minimally acceptable value. Our approach at all times with the CardioWest™ TAH has been to maximize cardiac output not only for improved pressure and flow to end organs, but also as

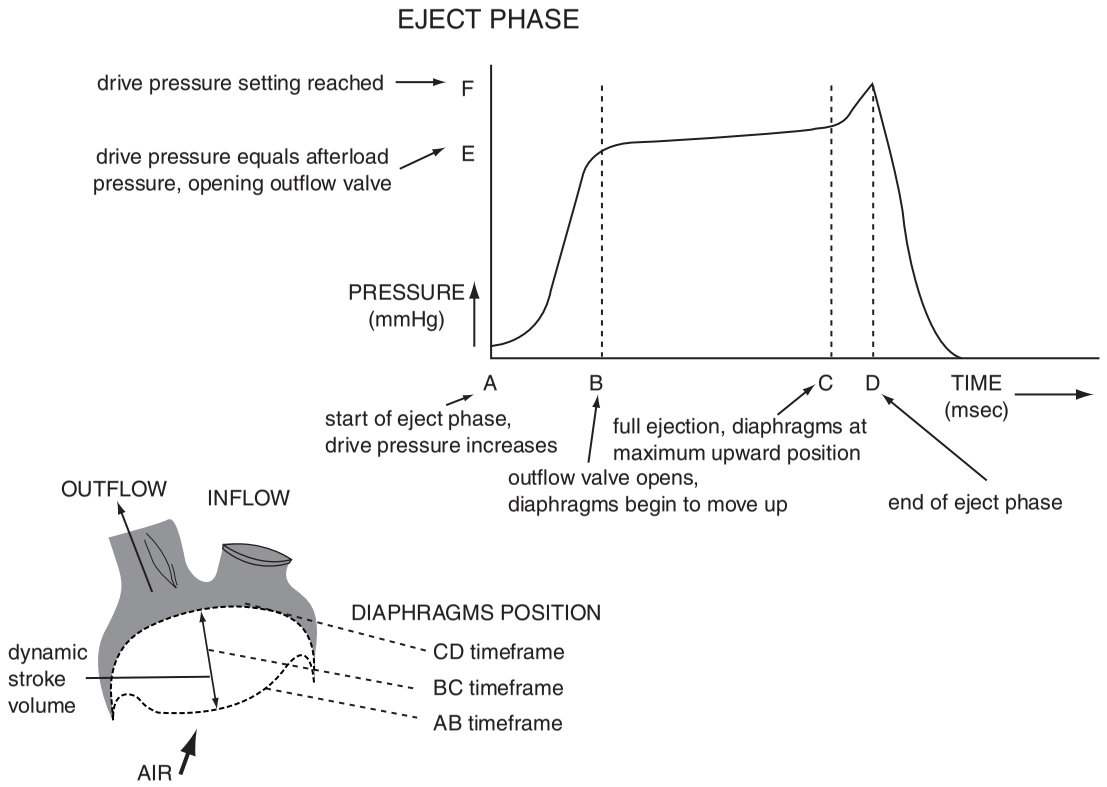

Figure 5 TAH pressure waveform.

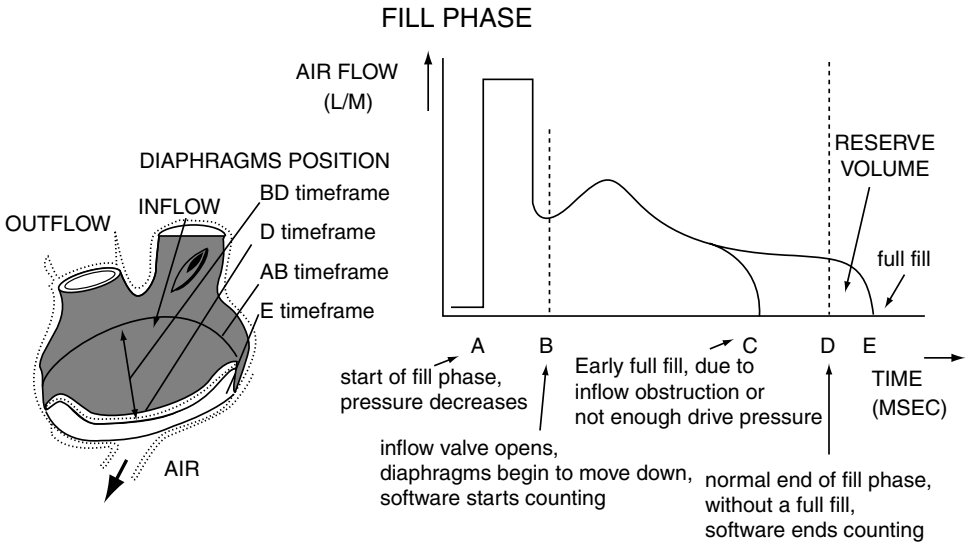

Figure 6 TAH flow waveform.

a strategy to increase "washing" of the device's blood-contacting surface as well, thus reducing the risk of thromboembolism.

INDICATIONS FOR USE OF THE CARDIOWEST™ TAH

The TAH is presently indicated for use in the United States as an in-hospital bridge for patients with end-stage biventricular heart failure awaiting heart transplantation (Table 2). Outside the United States, the TAH has been used for broader indications. In Europe the TAH has been used as a means of bridging patients, though allowing them to be discharged, residing at home while awaiting transplantation. The TAH has also been used outside of the United States as an acute bailout device for patients with irreversible cardiogenic shock associated with acute myocardial infarction. The TAH has further been indicated in cases of post-cardiotomy heart failure, with an inability to wean patients off cardio-plumonary bypass. Recently the TAH has begun initial trial use in Europe for "destination therapy," i.e., as a permanent cardiac replacement device utilizing a new portable mobile driver.

CLINICAL EXPERIENCE WITH THE CARDIOWEST™ TAH

As outlined above, the bulk of the world's TAH experience has occurred with TAH devices built on the technology platform common to the present SynCardia CardioWest™ TAH. The largest recent single center experiences to date have been described in Arizona, Paris, and at Bad Oeyenhausen, Germany.

From 1993–2002 patients, 62 patients (51 men and 11 women) with irreversible bi-ventricular failure underwent implantation with the TAH at Arizona (13). Mean LV ejection fraction and CVP pre-implant were $20 \pm 8\%$ and 20 ± 7 mmHg, respectively. The mean time on TAH support was 92 ± 11 days (range 1–413 d). Seventy-seven percent of

Table 2 Current and Future Applications of the SynCardia CardioWest™ Total Artificial Heart

Applications	Candidate patients
Current (*FDA approved*)	
Bridge-to-transplantation in cardiac transplant-eligible patients at risk of imminent death from bi-ventricular failure (in hospital use)	NYHA Class IV, AHA/ACC Class D CHF—Transplant-eligible with bi-ventricular failure refractory to medical therapy Ischemic, myopathies, intra-op, adult congential heart disease Contraindications to VAD support such as refractory arrhythmias, aortic regurgitation, stenosis or prosthesis, ventricular thrombus or VSD Unresuscitatable cardiac arrest Massive myocardial infarction or direct myocardial injury that affects technical insertion of a VAD through the left ventricle Failure to wean from cardiopulmonary bypass with bi-ventricular injury
Future (*not presently FDA approved*)	
Bridge-to-transplantation in transplant-eligible patients with bi-ventricular failure with anticipated hospital discharge and-out-of hospital use	Same as above
Long-term destination therapy TAH with hospital discharge to the home setting	NYHA Class IV, AHA/ACC Class D CHF—Not transplant-eligible with bi-ventricular failure refractory to medical therapy

Abbreviations: FDA, Food and Drug Administration; NYHA, New York Heart Association; AHA/ACC, American Heart Association/American College of Cardiology; CHF, chronic heart failure; VAD, ventricular assist device; VSD, ventricular septal defect.

patients survived to transplantation, with the TAH. Sixty-eight percent of the total group survived to discharge post-transplantation. Twenty-three percent of patients died during device support. Multi-organ failure caused 50% of these deaths. Adverse events included bleeding (20%), device malfunction (5%), fit complications (3%), mediastinal infections (5%), visceral embolus (1.6%), and stroke (1.6%). The linearized stroke rate was 0.068 events per patient-year.

A similar experience was reported by the group from Paris (14). To date, this group at Hospital La Pitie-Salpetriere has the largest experience with the TAH. Between 1986 and 2001, 127 patients (108 males, mean age 38 ± 13) underwent bridge to transplantation with the TAH. Mean arterial blood pressure and CVP pre-implant were 70 ± 8 mmHg and CVP 27 ± 8 mmHg, respectively. The duration of support increased progressively in the French experience, averaging 2 mo after 1997 with a range from 5–271 days. One patient in their early experience was maintained on the TAH for 602 days, due to pre-implantation pre-formed anti-HLA antibodies. Overall 64% of patients survived to transplantation, with the TAH. Twenty-three percent of patients died during device support. Multi-organ failure caused 67% of these deaths. The clinical thromboembolic event rate they observed was low, with no incidence of CVA and only

2 TIAs. In all, they reported on a total experience of 3606 implant days with only one instance of mechanical dysfunction.

Recently the surgical group at Bad Oeyenhausen reported on their experience as well. Between February 2001 and December 2003, forty-two patients (37 men and 5 women, mean age 51 ± 13 yr) received a TAH. All patients were in persistent cardiogenic shock in spite of maximum inotropic support. Interestingly, ten of the forty-two patients were in cardiogenic shock as a result of massive acute myocardial infarction. Mean duration of support was 86 ± 81 days (range 1 ± 291 d). Eleven of 42 patients (26%) underwent successful cardiac transplantation, with 10 patients being discharged home. Twenty-two patients (52%) died under support, 13 of them from multi-organ failure after 1–68 days of support. They too observed low thromboembolic complication rates, with only one CVA and two TIAs noted.

All of these centers used the TAH for patients with biventricular failure, with adequate thoracic cavity volume to successfully fit the device in the resident space left by excision of the native heart ventricles and valves. Other devices were used for left ventricular dysfunction and biventricular failure in smaller patients who could not fit the TAH.

Overall, all these single center experiences, in medical centers utilizing the TAH for many years or new to the device as of late, demonstrate successful salvage of patients in imminent risk of death utilizing the TAH. Through meticulous attention to anticoagulation, as outlined in these studies, a low thromboembolic event rate was reported.

The most robust experience reported with the TAH to date was the recently published multi-center PMA trial experience (15). In this trial the hypothesis tested was that use of the TAH in patients with irreversible bi-ventricular failure would saves lives by allowing for effective subsequent transplantation. Inclusion criteria for the study were: patients eligible for transplant, NYHA CHF Class IV, BSA range 1.7–2.5 m^2, and severe hemodynamic insufficiency. From 1993–2002 the TAH was implanted in 95 patients (81 protocol, 15 out-of protocol) with irreversible biventricular failure in imminent danger of death. Major efficacy endpoints included rates of survival to transplantation, overall survival, survival after transplantation and "treatment success," defined as alive, NYHA Class I or II, not on dialysis or a ventilator and ambulating. A control cohort of patients matched with those in the protocol group, without receiving a TAH, was used for contextual comparison.

In this study overall survival to transplantation was achieved in 79% of patients receiving the TAH versus 46% of the controls, $p < 0.001$. Treatment success was achieved in 69% of the implant patients versus 37% of of controls, $p = 0.002$. The mean time from entry into the study to transplantation or death was 79.1 days for the implant group versus 8.5 days among the controls, $p < 0.001$. The overall survival rate at one year was 70% (95% confidence limit, 63 to 77%) in the group receiving an implant as per protocol compared with 31% in the control group, $p < 0.001$ (Fig. 7). Survival at one and five years after heart transplantation was 86% and 64%, respectively, compared with 69% and 34%, respectively in the controls. This data compares favorably with the reported overall UNOS survival data of 84.7% and 69.8%, at one and five years, respectively (16).

In the multi-center trial significant improvement in secondary endpoints was noted as well for the TAH group. Patient's hemodynamic status immediately improved following placement of the TAH, with increased systemic pressure, reduced central vesnous pressure, and increased organ perfusion pressure observed. Cardiac index rose from a baseline pre-implant of 1.9 L/min/m^2 to 3.2 L/min/m^2. Renal and hepatic function and the levels of BUN, creatinine, bilirubin, and transaminases returned to normal within three weeks of implantation. Electrolyte levels, white count, and platelet count also normalized

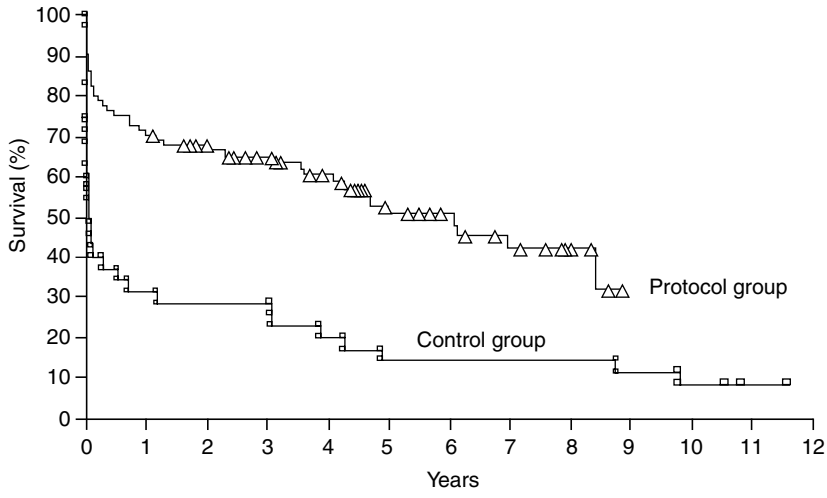

Figure 7 U.S. multi-center trial overall survival curve.

by three to four weeks post-TAH implantation. Quality of life also improved for the TAH group. One week post-implant, 75% of these patients were ambulating. More than 60% of patients were able to walk more than 100 ft. two weeks following implantation.

Seventeen of the eighty-one patients (21%) in the treatment group died before transplantation, compared with nineteen of the thirty-five control patients (54%). Causes of death in the treatment group were: multi-organ failure (in seven patients), procedural or technical complications (4 patients), bleeding (in two), sepsis (in two), CHF (one) and pulmonary edema (one). Causes of death in the control group prior to transplantation were: cardiac arrest (in seven patients), heart failure (seven patients), multi-organ failure (three), acute rejection (one), and pulmonary edema (one).

Detailed records of numerous potential adverse events were taken in this trial. The major adverse events reported, in addition to death, were: bleeding, infection neurologic dysfunction and device malfunction. In the implant group there were 102 bleeding events, fifty-five of which occurred after implantation requiring "takeback" to the operating room for control. All but one of these procedures occurred within the first 21 days of implantation. Only two patients in this series died from bleeding. There were 125 infections recorded in the trial during use of the TAH, fifty being respiratory, 28 GU, 17 involving the driveline, 12 GI, 7 blood borne, six involving indwelling catheters and five mediastinal infections. In sixty eight of the eight one protocol patients (84%) these infections did not delay transplantation or contribute to death. All driveline infections were superficial, with none ascending to the mediastinum. Twenty-six neurologic events were noted in the protocol group, including stroke [11 events in 10 patients (12%)], transient ischemic attacks (4 events), anoxic encephalopathy (5 events), seizure (4 events), and syncope (1 event). Of the strokes observed six of the eleven completely resolved without detectable residua after 48 hr, and four had mild residua with one having persistent hemiplegia. The linearized rate of stroke was 0.05 events per month. One serious device malfunction was observed in the entire experimental cohort, that of a perforation of the pumping membrane. This occurred on day 124 post-implant resulting in a patient death. No other serious device malfunctions have occurred during more than 12,000 patient-days of use of the TAH.

FUTURE APPLICATIONS OF THE CARDIOWEST™ TAH

We are on the verge of a paradigm shift in the field of mechanical circulatory support. It appears clear that as the myriad of devices currently being studied find their nitches, a general rationale is developing for patients with varying degrees of Class IV CHF. In the field of bridge-to-transplant what is becoming clear is that for patients with more mild, typically single, i.e. left ventricular failure, they are well served with LVADs. However as the degree of cardiac failure worsens, with either severe left ventricular failure or the development of bi-ventricular failure, more robust cardiac support and frank replacement systems are needed. It is in this role of complete hemodynamic support where the TAH is emerging as clearly demonstrating its therapeutic superiorty. Of all devices presently available it stands alone in terms of an ability to provide the highest degree of cardiac output of any prosthetic device, up to 9.5 L/min. This type of extensive support is needed to salvage and recover truly end-stage patients. As such the TAH has the potential to emerge as the standard of care for irreversible bi-ventricular failure patients, the indication for which it is presently approved. With time its application to severe single ventricular failure, inadequately supported by a VAD may emerge.

In addition to bridge applications the TAH has the potential of providing therapeutic benefit to several other groups of patients. One group that would benefit from the TAH is the group of patients with persistent cardiogenic shock following acute myocardial infarction, despite attempted percutaneous or surgical revascularization. This group presently carries a greater than 50% mortality with no viable therapeutic option save for emergency heart transplantation, which is logistically very difficult. Other future applications for the TAH include use for post-cardiotomy cardiogenic shock, rescue of patients failing on VAD devices, patients with cardiogenic shock placed on ECMO and for failed transplants.

In addition to bridge-to-transplantation and other bail-out applications, the CardioWest™ TAH has an even greater long-term potential use—that of serving as a "destination therapy" device. Today CHF is an epidemic that is growing in the United States and world-wide. There are over 100,000 patients per year with NYHA Class IV CHF. As such for these patients their imminent mortality is certain. While many patients have significant co-morbidities or are elderly and many not be considered appropriate candidates for, or for that matter capable of accommodating to, a life-extending technology, there are many patients that would benefit from such a therapy. By conservative estimates upwards of 30,000 patients per year may be candidates for total cardiac replacement with a long-term, i.e., permanent, artificial heart. We must recall that the CardioWest™ TAH was built based on a technology platform aimed for permanent implantation. As mentioned in an earlier section that vision was too big a leap at the outset of clinical use with this device. Now based on over 550 implants and 60 patient-years of experience the time has come to seriously consider utilizing this TAH, with new portable mobile driver technology, as destination therapy for these patients in dire therapeutic need.

CONCLUSION

The CardioWest™ TAH was created and initially tested at the same time as the Thoratec, Novacor, and HeartMate devices. It was designed as a permanent artificial heart and was the first-ever mechanical circulatory device to be used as destination therapy. Several decades have passed since that early experience. Pneumatic technology is still current and being developed, as in existing or new implantable Thoratec VADs the pneumatic

Heart-Mate and the Abiomed BVS 5000 pumps. Portable pneumatic drivers have been available since 1982, and in recent times have allowed discharge to home of substantial numbers of patients, thus reducing the length of hospital stays and making mechanical device support less expensive to society and more tolerable to patients. Within months, portable drivers for the CardioWest™ will be available. The CardioWest™ TAH has had a long and progressive development path. In its present status it has evolved as a successful and robust bridge to transplant device and is the only FDA approved TAH for this indication.

The documented benefits of the CardioWest TAH include the rescue of: critically ill patients with advanced heart failure; patients with biventricular failure, especially those with significant right heart failure, elevated pulmonary vascular resistance, or pulmonary edema; patients with renal or hepatic failure secondary to low cardiac output; patients with massive myocardial damage such as those with post-infarction VSD or irreversible cardiac graft rejection; patients with mechanical valves or native valve disease; and patients with intractable arrhythmias and heart failure. High device outputs with restoration of normal filling pressures result in high perfusion pressures that have led to dramatic recoveries, convalescence, and return to levels of activity compatible with normal life. The average device output with the CardioWest TAH is higher than any other approved or investigational device. The reason for this resides in design simplicity as this device has the shortest and largest inflow pathway.

Stroke, in the authors' own series, is rare with a linearized rate of 0.068 events per patient year using a tailored protocol (17). If the experiences of La Pitie and the University of Arizona are combined, there has been one stroke in 25 patient years (0.04 events/patient year).

Serious infections have been rare. To date there has been only one case of clinical mediastinitis, which contributed to patient death. Drivelines have "healed in" tightly and never caused "ascending" infection. There has not been a case of device endocarditis. Using a broad definition of bleeding, including takeback re-operation for bleeding, bleeding more than 8 units in the first postoperative 24 hr or 5 units over any other 48-hr period, a 25% to 36% incidence has been documented. No cases of fatal exsanguination have resulted. The incidence of bleeding as an adverse event is about 17% lower than the rate reported for the HeartMate VE LVAD, and it is about the same as that reported for Novacor and for Thoratec.

Implantation of this device is not technically difficult. If one follows the guidelines for fitting the device, and takes the recommended advice for implantation, hemostasis is excellent and restoration of immediate cardiac function with high flows is nearly automatic (18). Use of a neopericardium of 0.1 mm EPTFE at the time of implantation (19) assures atraumatic and relatively quick re-entry for transplantation and prevents the normal inflammatory mediastinal reaction that might be desirable in a destination application.

In selected patients the CardioWest™ TAH is the device of choice for bridge to transplantation. When a portable driver becomes available, out-of-hospital management of CardioWest™ TAH patients will be feasible and consideration of this device for long-term applications (e.g., "destination therapy,") will be reasonable. A wearable driver, even smaller than a portable, will improve quality of life and expand the patient population that may be therapeutically served with this system.

In short, the CardioWest™ TAH has come nearly full circle. It was first used as a destination device. It has since been used as a bridge to transplantation in nearly 200 patients as the Jarvik-7/Symbion TAH and, since 1993, in over 350 patients as CardioWest™. The results have improved with time. Thromboembolism and infection

rates have been competitive with currently available devices. Device reliability and durability have been excellent. Survival rates have been very high in a group of perhaps the sickest patients to be supported with any pulsatile device. Pneumatic technology has improved with portability and miniaturization, and there is reason to believe that it will become even better. Application of modern manufacturing techniques to this very simple device raises the possibility of significant manufacturing cost reduction in an era of prohibitive cost for other devices. All of this establishes the CardioWest™ as a valuable device for any program that is seriously interested in end-stage heart disease and a likely device for permanent use in appropriately selected patients.

Increases in CardioWest™ TAH implantations worldwide and expansion of the number of implanting centers will provoke more interest in the uses of this device as well as in its comparison, with other technologies. Portable drivers that are currently used primarily in Germany expand the applicability and practicality of the TAH while reducing the cost by allowing out-of-hospital care. This, in addition to the high pump flows and control of the entire circulation, may have already led to shifts in patient and device selection philosophies. We believe there could well be a paradigm shift underway with regard to TAH use, as the advantages of this technology become apparent in the hands of a greater number of users.

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