Initial experience with the AbioCor Implantable Replacement Heart System

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Objective: We sought to evaluate the safety and efficacy of the first available totally implantable replacement heart (AbioCor Implantable Replacement Heart System) in the treatment of severe, irreversible biventricular heart failure in human patients.

Methods: Seven male adult patients with severe, irreversible biventricular failure ($>70\%$ thirty-day predicted mortality) who were not candidates for transplantation met all institutional review board study criteria and had placement of the AbioCor Implantable Replacement Heart. All were in cardiogenic shock despite maximal medical therapy, including inotropes and intra-aortic balloon pumps. Mean age was 66.7 ± 10.4 years (range, 51-79 years). Four of 7 patients had prior operations. Six had ischemic and one had idiopathic cardiomyopathy. All had 3-dimensional computer-simulated implantation of the thoracic unit that predicted adequate fit. At the time of the operation, the internal transcatheter energy transfer coil, battery, and controller were placed. Biventriclectomy was then performed, and the thoracic unit was placed in an orthotopic position and attached to the atrial cuffs and outflow conduits with quick-connects. The flow was adjusted to 4 to 8 L/min. Central venous and left atrial pressures were maintained at 5 to 15 mm Hg. The device is powered through transcatheter energy transfer. An atrial flow-balancing chamber is used to adjust left/right balance. The balance chamber and transcatheter energy transfer eliminate the need for percutaneous lines.

Results: There was one intraoperative death caused by coagulopathic bleeding and one early death caused by an aprotinin reaction. There have been multiple morbidities primarily related to preexisting illness severity: 5 patients had prolonged intubation, 2 had hepatic failure (resolved in 1), 4 had renal failure (resolved in 3), and 1 each had recurrent gastrointestinal bleeding, acute cholecystitis requiring laparotomy, respiratory failure that resolved after 3 days of extracorporeal membrane oxygenation, and malignant hyperthermia (resolved). There were 3 late deaths: one caused by multiple systems organ failure (postoperative day 56), one caused by a cerebrovascular accident (postoperative day 142), and one caused by retroperitoneal bleeding and resultant multiple systems organ failure (postoperative

day 151). This latter patient was not able to tolerate anticoagulation (no anticoagulation or antiplatelet therapy alone for 80% of the first 60 days) and had a transient ischemic attack on postoperative day 61 and a cerebrovascular accident on postoperative day 130. At autopsy, blood pumps were clean. The 2 patients who had large cerebrovascular accidents had thrombus on the atrial cage struts. These struts have been removed for future implants. There has been no significant hemolysis or device-related infections. The balance chamber has allowed for left/right balance in all patients (left atrial pressure within 5 mm Hg of right atrial pressure). Three patients have taken multiple (>50) trips out of the hospital, and 2 have been discharged from the hospital. Total days on support with the AbioCor are 759.

Conclusion: The initial clinical experience suggests that the AbioCor might be effective therapy in patients with advanced biventricular failure. There have been no significant device malfunctions. Two of these patients have been discharged from the hospital.

The prevalence of heart failure continues to increase, and current estimates are that heart failure affects nearly 5 million people in the United States and 15 million people worldwide.¹ Despite improvements in medical management, 5-year survival remains less than 50% for all patients with heart failure.^{1,2} A recent population-based study demonstrated that survival after the first hospital admission for heart failure was worse than survival for all common malignancies except lung cancer.³ A significant portion of patients with end-stage heart failure could benefit from some type of cardiac replacement therapy. Currently, heart transplantation is the only approved method for replacing the failing heart. However, there is a severe shortage of donor organs, with only 2198 heart transplantations being performed in the United States in the year 2000.⁴ Furthermore, in 3 of the last 4 years, there has been a decrease in the number of heart transplantations performed in the United States.

The AbioCor Implantable Replacement Heart (IRH) system has been under development for more than 2 decades.⁵⁻⁹ This system is the first implantable artificial heart system approved for clinical trials that does not require percutaneous lines. From inception, the device has been designed as destination therapy. A major focus of the device design, in addition to allowing for prolonged life, has been to allow for an acceptable quality of life. Initial animal experience and development was performed by ABIOMED (Danvers, Mass) and the team at the Texas Heart Institute, with funding from the National Heart, Lung, and Blood Institute. Subsequent preclinical implantations were also performed at the University of Louisville under Good Laboratory Practice guidelines. Successful preclinical implantations and reliability studies resulted in US Food and Drug Adminis-

tration approval for a multicenter trial. We report the early human experience with the AbioCor IRH System as destination therapy.

Methods

Device Description

The AbioCor IRH System is the first artificial heart system that does not require percutaneous lines or percutaneous access. This system consists of both external and internal components. The 4 internal components are the AbioCor thoracic unit, the battery, the controller, and the transcutaneous energy transfer (TET) coil (Figure 1). The AbioCor thoracic unit is placed in the chest in an orthotopic position after excision of the native ventricles. The thoracic unit consists of an energy converter and 2 pumping chambers that function as the left and right ventricles. The energy converter is situated between the ventricles and contains a high-efficiency miniature centrifugal pump driven by a brushless direct current motor. The motor speed of this pump can vary to account for the different resistances of the systemic and pulmonary vascular systems and systolic ejection durations. This centrifugal pump operates unidirectionally to pressurize a low-viscosity hydraulic fluid. A 2-position switching valve is used to alternate the direction of hydraulic flow between the left and right pumping chambers. This results in alternate left and right systole. The rate of the switching valve determines the beat rate of the device and can be varied between 75 and 150 beats/min, resulting in a range of flows from 4 to 8 L/min. There is a one-to-one correspondence between blood and hydraulic fluid displacement. The displacement of hydraulic fluid to one side results in the creation of a negative pressure in the opposite ventricle. Thus the device is considered an active fill device. An atrial balance chamber is present and allows for decreased right-sided stroke volume to maintain right and left fluid balance.^{8,9} Essentially, a portion of hydraulic fluid is shunted into the balance chamber rather than to the right hydraulic pumping chamber. The amount of fluid that is shunted into the balance chamber can be adjusted manually or automatically on the basis of

Figure 1. Internal components of the AbioCor IRH include the thoracic unit, controller, battery, and TET coil.

the relative left and right filling pressures. The pump motor impeller and the switching valve are the major moving parts of the energy converter. All blood-contacting surfaces of the AbioCor thoracic unit, including the trileaflet valves (24-mm internal diameter), are made of polyetherurethane (Angioflex), resulting in a smooth, continuous, blood-contacting surface from the inflow cuffs to the outflow grafts.

The internal battery is lithium ion based and is able to power the thoracic unit for brief (up to 20 minutes) 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 by means of radiofrequency telemetry. These radiofrequency transmissions from the internal controller to the external console convey information, including continuous real-time telemetry of hydraulic pressure waveforms, system operating parameters, battery status, component temperature, and alarm information. This information is stored for later retrieval and analysis. The internal TET coil receives high-frequency power that is transmitted across the skin from the external TET coil. The internal TET system electronics convert this oscillating current to a direct current that is used to power the thoracic unit and to recharge the internal battery. Dacron velour (E.I. duPont de Nemours) atrial cuffs are sutured to the native left and right annuli and attached to the thoracic unit by means of snap-lock connectors. In the first 6 recipients, the atrial cuffs incorporated 2 curved intersecting plastic struts that were developed during animal trials to prevent collapse of the small bovine native atria that can lead to inflow obstruction to the thoracic unit (Figure 2). The outflow grafts are 32-mm, coated, woven Dacron grafts with 8-mm side ports that are used for deairing.

Figure 2. Atrial cuff with struts. Future implants will be performed with atrial cuffs that do not have these struts.

The 4 external components consist of an external TET coil, batteries, a TET module, and a bedside console (Figure 3). The external TET coil transfers energy across the skin to the internal TET coil and is secured over the internal TET coil with an adhesive dressing.¹⁰ The external TET coil can be connected to either the bedside console or a portable TET module. The bedside console is used during implantation, recovery, and when the patient is in his or her primary residence. The bedside console provides clinicians with a graphic user interface for control and

Figure 3. External components displaying the portable TET module and external batteries attached to a Velcro belt.

monitoring of the implanted system through radiofrequency communication. The console can be configured to operate in different modes for implantation, recovery, and home monitoring. The console can be remotely monitored when connected to a telephone jack through a laptop computer. A rechargeable battery in the console allows it to be disconnected from AC power for brief periods without discharging the patient's internal battery. When the patient is ambulatory, the external TET coil is connected to the portable TET module. The TET module delivers energy to the TET coil from external batteries and contains basic alarm systems that are activated if there is misalignment of the TET coil, low external battery voltage, or a general alarm indicating a potential problem with the system that is determined by reestablishing radiofrequency communication with the bedside console. 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 either be carried in a vest or a handbag or attached to a Velcro belt.

Clinical Trial Design

US Food and Drug Administration approval for initiation of a multicenter clinical trial was granted in January 2001. The original centers were Hahnemann University, Massachusetts General Hospital/Brigham and Women's Hospital, the Texas Heart Institute, the University of California Los Angeles, and the University of Louisville. The University of Arizona Medical Center has recently been added as an investigational center. The AbioCor IRH is intended for use as destination therapy. Therefore patients selected for this clinical trial were not candidates for other types of therapy, including heart transplantation. All patients who are considered as candidates have a 30-day predicted mortality of greater than 70% on the basis of the AbioScore prognostic model or acute myocardial infarction shock scores.¹¹ The AbioScore mortality prediction model was developed on the basis of previous prognostic models, with selection of parameters that had the highest prognostic value for mortality in patients with end-stage heart failure. Initial retro-

spective studies were followed by prospective studies that verified that this was an accurate prediction model. These variables are shown in Table 1. The AbioScore model is used to exclude patients who have a greater than 30% one-month survival.¹²

Potential candidates must be adult patients with biventricular failure who are receiving maximal medical therapy and who are dependent on inotropes or unable to tolerate inotropes because of severe arrhythmias. Patients are excluded from the study if they are candidates for other conventional therapies, including heart transplantation, or if they have a predicted survival of greater than 30% at 30 days. Other exclusion criteria include end-organ dysfunction that is believed by the clinicians to not be reversible, active infection, severe peripheral vascular disease, blood dyscrasia, and recent stroke or transient ischemic attack caused by atherosclerotic disease. A complete psychosocial evaluation is performed on all potential recipients similar to that performed with patients being considered for transplantation. Patients meeting the appropriate criteria undergo computed tomographic scanning of the chest, followed by a virtual fit evaluation. A 3-dimensional computerized image of the AbioCor thoracic unit is superimposed on the image of the patient's mediastinal and chest wall structures derived from the computed tomographic scan. This computer simulation demonstrates the position and fit of the thoracic unit in a potential recipient's chest. This virtual model allows one to determine whether the AbioCor thoracic unit can be positioned in the chest without impinging on vital structures, such as the left pulmonary veins and the left lower lobe bronchus. The surgical implant team must have a high degree of certainty that the AbioCor thoracic unit will fit in the chest before proceeding with operative implantation. During this extensive evaluation, the patient and his or her family receives intensive education on the device, including the results of reliability studies, preclinical trials, and previous human implantations.

The institutional review board at each of the institutions approved the clinical protocol. For every patient who enters or

considers entering the AbioCor clinical trial, an independent patient advocate is made available to them and their families to assist in the understanding of the potential risks and benefits of entering the clinical trial.¹³ The patient advocate is able to help the patient and his or her family to interpret the contents of the informed consent document. After the implantation procedure, the patient advocate continues to be available to the patient and family for assistance in making other important medical decisions. Each patient advocate has a background in clinical medicine and functions completely independently of both the sponsoring company and the medical teams.

The primary end point of this trial is to determine the effect of the AbioCor on all causes of mortality in patients with severe heart failure and predicted life expectancy of less than 30 days despite optimized medical management. Secondary end points include determination of adverse events, device malfunctions, or complications related to the presence of the device and quality of life.

Operative Approach

At operation, an infraclavicular incision is made, and a pocket is created anterior to the pectoral muscle fascia for placement of the internal TET coil. A median sternotomy incision is then made. The internal TET coil is placed in its pocket, with the cable being passed to the lower part of the sternotomy incision. The incision over the TET coil is then closed in layers. The TET coil is placed before heparinization to decrease the likelihood of a pocket wound hematoma. A sternal retractor is placed, and a pericardial cradle is created. Dissection for the internal battery and controller is made in either the preperitoneal space or deep to the rectus abdominus muscle (ie, anterior to the posterior rectus sheath). Caval tapes are placed, and heparin is given. Cannulation of the aorta or femoral artery is performed depending on the length of aorta available because many of these patients will have had previous cardiac surgeries. A superior vena caval cannula is placed, and a femoral venous cannula is placed and guided up into position just below the junction of the inferior vena cava and the right atrium. Cardiopulmonary bypass is initiated, the caval tapes are snared down, and the aorta is crossclamped. Lidocaine is injected into the ascending aorta to induce diastolic arrest of the heart. The right and left ventricles are excised just below the atrioventricular groove, leaving a small amount of ventricular muscle. The mitral and tricuspid annuli are preserved, and the valves are excised. The left atrial appendage is ligated, and the coronary sinus and patent foramen ovale (if present) are oversewn. The left atrial cuff of the device is trimmed to appropriate diameter and sewn to the native left atrium at the level of the annulus by using 2 layers of running 4-0 Prolene sutures 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 then performed in similar fashion, followed by leak testing. 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 aorta and pulmonary artery. These outflow grafts are then sewn end to end to the great vessels with running 4-0 Prolene sutures. The aortic outflow graft is positioned anterior to the pulmonary artery graft. The AbioCor thoracic unit is then brought up to the operative field, and appropriate

TABLE 1. Simplified AbioScore composite variables

A potential candidate must have at least 6 of the criteria listed in A or at least 4 of the criteria listed in B or C. These factors are combined with the patient's age to determine 30-day survival.

- A. 1) More than one continuous intravenous inotrope
- 2) An intra-aortic balloon pump or other form of mechanical support
- 3) Mean arterial pressure <58 mm Hg
- 4) LVEF <16%
- 5) CVP between 10 and 18 mm Hg or prothrombin time between 17 and 25 seconds
- 6) Abnormal lactate level
- 7) Serum sodium level <133 mEq/L
- 8) Urine output <30 mL/h
- 9) Serum creatine level >3.0 mg/dL
- 10) Acute renal failure
- B. 1) Patient meets UNOS criteria for status 1A
- 2) Body mass index <20 kg/m²
- 3) Arterial pH <7.30
- 4) WBC > 17,000
- 5) Requires support on mechanical ventilator
- 6) Glasgow Coma Scale score <12
- C. 1) Previous heart surgery
- 2) Ischemic heart disease or chronic rejection after heart transplant
- 3) Exercise maximal oxygen consumption of <14 mL · kg⁻¹ · min⁻¹ or 6-min walk <200 m
- 4) QRS duration >110 ms or presence of permanent pacemaker or AICD
- 5) Left ventricular end-diastolic diameter index >4.0 cm/m² or severe mitral regurgitation
- 6) NYHA Class IV >80% of the time for past 6 mo
- 7) Norepinephrine level >900 ng/L or TNF-α >50 ng/L
- 8) AST >310 U/L or CK >2000 U/L

LVEF, Left ventricular ejection fraction; *CVP*, central venous pressure; *UNOS*, United Network for Organ Sharing; *WBC*, white blood cell count; *AICD*, automatic implantable cardioverter defibrillator; *NYHA*, New York Heart Association; *TNF*, tumor necrosis factor; *AST*, aspartate aminotransferase; *CK*, creatine kinase.

electrical connections are made. The thoracic unit is placed in the pericardial space and attached to the left atrial cuff and outflow grafts with snap-lock connectors. Saline is injected into the right ventricle of the thoracic unit to expedite deairing, and the right atrial cuff is connected to the device. The caval tapes are released, and the device is completely deaired by allowing blood and air to be ejected through the side ports arising from the outflow grafts. Once the right side of the heart has been deaired, the side port of the pulmonary artery outflow graft is occluded. The left side of the heart is then deaired through the side port that arises from the aortic outflow graft. The device flow is incrementally increased up to 4 to 5 L/min with the crossclamp on, and all the blood is ejected through the side port originating from the left outflow graft and returned to the cardiopulmonary bypass circuit. Once the device is adequately deaired, the crossclamp is removed, the left side port is occluded, and the patient is weaned from cardiopulmonary bypass onto full device support. The left and right filling pressures are monitored and used to determine the beat rate and to adjust the

balance chamber. Protamine is administered after demonstrating adequate hemodynamics. The sternal edges are approximated. Transesophageal echocardiography is used to determine whether sternal closure impairs flow in the left pulmonary veins. Increased pulmonary vein flow velocity dictates the need to reposition the thoracic unit caudad, anterior, or both. This is readily accomplished by placing sutures through the eyelets on the thoracic unit and around the left lower ribs. Irrigation with topical antibiotics is performed, followed by standard wound closure. Prophylactic intravenous antibiotics are given per each center's protocol. The anesthetic management for these patients has been previously described.¹⁴

Anticoagulation Management

Anticoagulation has been achieved with antiplatelet therapy and heparin, followed by warfarin. Routine monitoring has been with assessment of platelet aggregation, partial thromboplastin time, and the international normalized ratio. The goal of therapy is to maintain an international normalized ratio of between 2.5 and 3.5. Some centers have also used daily thromboelastograms and with this approach have attempted to maintain a normal coagulation index.

Results

Seven patients have been implanted with the AbioCor IRH System. All were male, with an age range of 51 to 79 years. Six of the 7 patients had ischemic and 1 had idiopathic cardiomyopathy. Four patients had previous bypass surgery, with one patient having had 3 prior bypass operations. All patients were inotropic dependent. Five patients had preexisting renal dysfunction, and 3 had preexisting liver dysfunction. Three patients were not considered transplant candidates because of age (≥ 70 years), 4 were excluded because of increased pulmonary vascular resistance, and 2 patients had significant renal dysfunction. The AbioScore predicted a 30-day mortality of greater than 89% in 6 patients and 75% in 1 patient. Body surface area ranged from 1.83 to 2.17 m². Cardiopulmonary bypass times ranged from 125 to 240 minutes.

The first recipient was a 59-year-old man with ischemic cardiomyopathy. He was not a transplant candidate because of increased transpulmonary gradient and chronic renal dysfunction. The operative procedure was uneventful. He was explored for bleeding early after the operation, and on postoperative day 6, a partial dehiscence of the abdominal wall fascia developed that required exploration and closure. This patient was not able to tolerate anticoagulation with heparin or warfarin because of recalcitrant gastrointestinal bleeding. This patient did tolerate antiplatelet therapy, and therefore the initial anticoagulation was with dipyridamole and aspirin. As a result of the gastric bleeding, the aspirin was stopped, and the patient was started on clopidogrel. Thromboelastograms were performed daily and demonstrated that the patient was consistently hypercoagulable on this limited anticoagulation regimen. Multiple attempts were made to restart warfarin, and by the third postoperative

month, this was achieved without further gastric bleeding. During the first 60 days after the operation, the patient was only receiving antiplatelet therapy 80% of the time. He had steady improvement in his level of activity and was able to take more than 20 trips out of the hospital. He had a transient ischemic attack on postoperative day 61 and a large cerebrovascular accident on postoperative day 130. The patient had a large retroperitoneal hemorrhage after his anticoagulation was increased after his stroke. This resulted in multiple system organ failure and death on postoperative day 151.

The second recipient was a 70-year-old man with ischemic cardiomyopathy. He was not a transplant candidate because of age and renal dysfunction. The operative procedure was uneventful, and he had an uncomplicated initial postoperative course. He was extubated early after the operation but had to be reintubated for recurrent aspirations, which were documented on video swallowing studies. Because of recurrent aspiration, the patient underwent tracheostomy on postoperative day 40. This patient had 2 episodes of high fever without evidence of infection. The first episode was related to vancomycin and resolved when this drug was discontinued. The second febrile episode resulted in a temperature of 107.1°F, with rapid onset of anuric renal failure and markedly increased liver function test results. A diagnosis of malignant neuroleptic syndrome was made, and the patient was started on dantrolene, with normalization of his temperature within 7 hours. After this febrile episode, the patient required a brief period of hemodialysis, followed by complete recovery of renal function. The patient continued to show progressive improvement and was eventually discharged from the hospital on postoperative day 182 and discharged to home on postoperative day 209.

The third recipient was a 68-year-old man with ischemic cardiomyopathy. He was not a transplant candidate because of pulmonary hypertension with a high transpulmonary gradient. The implantation of the AbioCor IRH was uneventful. His early postoperative course was remarkable for the presence of transient liver dysfunction and acute cholecystitis, for which he required a cholecystectomy. At the time of laparotomy, the patient also had a tracheostomy. The patient also had significant renal dysfunction after the cholecystectomy that required a period of hemodialysis. The patient did have complete resolution of his hepatic and renal function and marked improvement in his functional status. This recipient had a small cerebrovascular accident on postoperative day 97, followed by a large cerebrovascular accident on postoperative day 129. Because of the lack of neurologic recovery, support was withdrawn on postoperative day 142.

The fourth recipient was a 74-year-old man with ischemic cardiomyopathy. He was not a transplant candidate because of age. The recipient had multiple previous cardiac

operations. The implantation was remarkable for the presence of severe adhesions and early coagulopathy. The patient did require an early reoperation for bleeding around the internal battery and from a femoral arterial line. The patient's postoperative course was remarkable for the development of progressive renal dysfunction, which required dialysis, and progressive hepatic dysfunction with marked hyperbilirubinemia. Because of the lack of end-organ recovery, support was withdrawn on postoperative day 56. The patient had no thromboembolic events.

The fifth recipient was a 51-year-old man with idiopathic cardiomyopathy. He was not a transplant candidate because of pulmonary hypertension with a high transpulmonary gradient. He had respiratory failure early after the operation that did not respond to conventional measures and necessitated the initiation of temporary venovenous extracorporeal membrane oxygenation support. Echocardiography at the time of the operation and in the postoperative period demonstrated normal flows in the pulmonary veins. There was rapid clearing of the chest radiograph and improvement in lung function that allowed for removal from extracorporeal membrane oxygenation on the third postoperative day. The cause of the respiratory failure is not known. The patient also had renal dysfunction that required hemodialysis from the second to the eighth postoperative day. This patient did have complete recovery of end-organ function and was discharged from the hospital on postoperative day 70. He was readmitted 20 days later with pneumonia and is currently hospitalized.

The sixth recipient was a 79-year-old man with ischemic cardiomyopathy who was not a transplant candidate because of age. He underwent an uncomplicated implantation with restoration of normal hemodynamics. The patient had a profound coagulopathy, which could not be corrected despite aggressive measures. Because of excessive bleeding, the patient became hypovolemic and entrained air into the right side of the device. Cardiopulmonary bypass was reinstituted, the device was deaired, and the patient was again weaned from cardiopulmonary bypass. The coagulopathy could not be corrected, and the patient died early after the operation.

The seventh recipient was a 61-year-old man with ischemic cardiomyopathy who was not a transplant candidate because of pulmonary hypertension and renal dysfunction. He underwent an uncomplicated implantation of the device with restoration of normal hemodynamics. He had profound coagulopathy and was treated aggressively with cryoprecipitate, fresh frozen plasma, and platelets. He had also received full-dose aprotinin therapy. Approximately 3 hours after the operation was completed, the patient had an acute decrease in the output of the device. Echocardiography demonstrated thrombus in the native right atrium. The patient's chest was reopened and explored with the findings of

thrombus in the native right atrium and pulmonary artery. Despite all attempts at resuscitation, the patient died in the operating room. Autopsy confirmed extensive thrombosis of the pulmonary vasculature and no evidence of deep venous thrombosis. The device was found to be free of thrombus. The autopsy findings were believed to be consistent with an aprotinin reaction.¹⁵⁻¹⁷

Actual survival at 30 days after the operation was 71%, and that at 60 days was 43%. Predicted survival at 30 days with continued medical therapy alone was 13%.

All the AbioCor systems operated or continue to operate satisfactorily. The system implanted in the fifth recipient experienced 3 and 2 skipped beats on 2 separate occasions on postoperative days 42 and 43, respectively. This was due to delayed motion of the switching valve of unknown cause. The system continues to function on postoperative day 181 without any further episodes. All implanted components have been well tolerated. The balance chamber has allowed for left-to-right balance in all patients. There have been no patients with significant hemolysis related to the device. There have been no device-related infections.

Four patients improved to the point that they were ambulatory after the operation. Three patients took multiple out-of-hospital excursions. Two patients were discharged from the hospital to a transitional care setting, with one of those patients discharged to home on postoperative day 209. Total days on support with the AbioCor system have been 754. The 2 patients currently on support are at postoperative days 234 and 181. The postoperative course for all patients is summarized in Table 2.

Autopsies were performed on 3 patients. All 3 patients had thrombus adjacent to the lateral atrial cuff struts that were in contact with atrial tissue. The medial atrial struts, which were adjacent to the atrial septum, were clean of thrombus. The blood pumps did not contain thrombus. There was no evidence of infection or significant tissue injury related to the internal components. The patient who died from multiple system organ failure demonstrated pre-existing liver fibrosis caused by chronic passive congestion. This patient had no evidence of kidney or brain infarcts at autopsy.

Discussion

The prevalence of heart failure is high and continues to increase. Current estimates are that heart failure affects nearly 5 million people in the United States alone, with projections that disease prevalence will double in the next 5 years.^{1,2} The aging of the population and advances in preventive medicine and in the management of hypertension, acute myocardial infarction, and diabetes have improved mortality rates from these disorders and contributed to the increased incidence of heart failure.¹⁸ The World Health Organization reports a similar prevalence of heart failure in

TABLE 2. Brief summary of clinical course of initial patients

Patient no.	Implant date	Postoperative course	Autopsy	Status
1	7/2/01	Early reoperation for bleeding. Unable to tolerate anticoagulation because of GI bleeding. Tracheostomy for pulmonary toilet. Slow recovery. Able to take over 20 out-of-hospital trips. TIA POD 61. CVA POD 130. Psoas muscle bleed with resultant MSOF and death POD 151.	Thrombus on atrial struts. Blood pumps clean.	Deceased
2	9/13/01	Initial uncomplicated recovery. Tracheostomy for recurrent aspiration. Malignant neuroleptic syndrome led to acute renal failure. Complete recovery with dantrolene and temporary dialysis. Slow recovery.	NA	Alive and well; discharged to home
3	9/26/01	Early reoperation for tamponade. Laparotomy for acute cholecystitis. Tracheostomy for prolonged ventilatory support. Liver failure and renal failure that required dialysis. Both resolved. Slow recovery. Small CVA POD 97. Large CVA POD 128. Support withdrawn at family's request POD 142.	Thrombus on atrial struts. Blood pumps clean.	Deceased
4	10/17/01	Early reoperation for bleeding around internal battery and from femoral arterial line. Progressive renal dysfunction requiring dialysis. Progressive hepatic dysfunction with marked hyperbilirubinemia. Because of lack of end-organ recovery, support withdrawn POD 56. No T-E events.	Thrombus on atrial struts. Blood pumps clean. Pre-existing liver fibrosis.	Deceased
5	11/5/01	Early respiratory failure of unknown cause. Required veno-venous ECMO support $\times$ 3 days. Tracheostomy for prolonged ventilatory support. Evacuation of hematoma battery pocket and TET coil pocket. TIA POD 56. Slow recovery with hospital discharged POD 70. Readmission for pneumonia POD 90.	NA	Alive; hospitalized for pneumonia
6	11/26/01	Intraoperative death caused by bleeding	NA	Deceased
7	4/9/02	Early postoperative death caused by pulmonary embolus or aprotinin reaction	Thrombus in native right atrium, pulmonary arteries: Blood pumps clean.	Deceased

GI, Gastrointestinal; TIA, transient ischemic attack; POD, postoperative day; CVA, cerebrovascular accident; MSOF, multiple systems organ failure; NA, not applicable; T-E, thromboembolism; TET, transcatheter energy transfer.

less affluent countries caused by valve disease and premature coronary artery disease.¹⁹ The economic effect of this disease is quite significant. The annual expenditure on heart failure management in the United States approached \$38 billion in 1991. Recent estimates for the total cost of heart failure management in 1999 is well over \$50 billion.^{18,20}

The high mortality associated with heart failure is well established.³ Recent data from the REMATCH trial demonstrated that inotrope-dependent patients with advanced heart failure who are not transplant candidates have a 75% 1-year mortality.²¹

The Institute of Medicine has estimated that 60,000 persons could benefit from cardiac replacement therapy. Currently, heart transplantation is the only approved method to replace the failing heart. However, the epidemiologic

effect of heart transplantation is quite limited because of the small number of donor organs. Despite multiple efforts to increase the number of suitable donors, there has been a decrease in donor hearts in 3 of the last 4 years. Long-term survival after transplantation has been limited primarily by the development of allograft coronary artery disease, which contributes to the 4% annual mortality in allograft recipients.⁴ Recent advances in the field of xenotransplantation have led to renewed interest in this field. However, large immunologic hurdles remain, and the demonstration of infection of multiple human cell lines by pig endogenous retrovirus has raised concerns over transspecies disease transmission.^{22,23}

Clearly there is a need for the development of alternative therapies to replace the failing heart. The AbioCor IRH

System has been in development for decades and has been designed for destination therapy. This system has been designed to be totally implantable without the need for percutaneous lines or percutaneous access. Energy transfer across the skin is readily accomplished with inductive coupling. Placement of the internal TET coil in the infraclavicular fossa has resulted in excellent patient comfort and minimal episodes of misalignment of the internal and external TET coils. An atrial balance chamber that allows for a decrease in right-sided stroke volume has eliminated the need for a compliance chamber and allowed for normal left-to-right balance in all of the recipients. This balance mechanism is one of the significant advances in the design of the device. Manipulation of the device beat rate, motor speeds, and the balance chamber allows for complete control of the circulation from the time the patient is weaned from CPB. The balance chamber has also allowed for rapid manipulation of the left atrial filling pressure, which has been clinically useful when patients have had pulmonary vascular congestion.

One major consideration in all clinical trials is determination of the appropriate patient population. In this trial all patients must be inotrope dependent and have a predicted mortality at 30 days of greater than 70%. Also, patients must not be acceptable candidates for other therapies, including transplantation. As a result, we have selected a very ill cohort of patient, and this has greatly contributed to the postoperative convalescence. One example of this is the fact that all recipients have required tracheostomy for prolonged ventilatory support. This has not been related to the device per se but rather to the preoperative condition of the recipients. Successful completion of this trial might allow for evaluation of this device in patients in a less-debilitated state.

All recipients of the AbioCor artificial heart must have severe biventricular failure. A number of patients were screened for this trial and found to have isolated left ventricular failure and were therefore not considered acceptable candidates. Right ventricular dysfunction was defined by means of standard echocardiographic evaluation and clinical evidence of right-sided heart failure. The number of patients with end-stage heart failure who require biventricular replacement versus left-sided support alone is not known. This trial and other trials with left ventricular assist devices as destination therapy might contribute to an understanding of the need for univentricular versus biventricular support. Clearly there continues to be significant morbidity and mortality related to right ventricular dysfunction, as evidenced by the recent report from Kavarana and associates²⁴ describing a 42.8% mortality in left ventricular assist device recipients who have significant postoperative right ventricular dysfunction. Our clinical impression is that a consistent and normal cardiac output combined with imme-

diate lowering of the right-sided filling pressures that we have seen with the AbioCor IRH has contributed to the reversal of end-organ dysfunction.

Patient selection has also been based on prediction of appropriate fit with the AbioFit virtual fit evaluation. Potential candidates undergo computed tomography of the chest, with the digital files then being entered into the AbioFit software imaging system developed by ABIOMED. This allows for a 3-dimensional reconstruction of the chest, with implantation of the AbioCor thoracic unit in the appropriate orthotopic position. The anatomic relationship of the thoracic unit with surrounding structures can then be viewed from every possible angle. This is a powerful tool that we have become reliant on for selection of patients with appropriate chest dimensions. We have also found the use of transesophageal echocardiography to be invaluable at the time of chest closure to ensure that there is no compression of the left pulmonary veins. Increased pulmonary vein flow velocities were seen in 2 patients at sternal closure, which led to repositioning of the device in a caudad direction with normalization of flow velocities.

There have been multiple morbidities in this patient population, as described above. Three of the 5 patients who survived the early operative period have died, with 2 of these deaths related to stroke. Autopsies in these 2 patients revealed thrombus on the left atrial struts that were in contact with the lateral wall of the left atrium. These struts were placed on the atrial cuffs during the early animal implantations in which fitting of the device had yet to be optimized to avoid collapse of the small bovine atrium by this active fill device. There was no thrombus related to the presence of struts in the animal model. These findings have resulted in the removal of the atrial struts for the next series of clinical implantations. The absence of the atrial struts will hopefully result in an acceptably low level of thromboembolism events without leading to problems with inflow to the device. There was no evidence of infection or significant tissue injury related to the device components.

In summary, the AbioCor system is the first totally implantable replacement heart. Early results from this multicenter trial have demonstrated excellent function of all device components. The system has allowed for excellent patient mobility, with 3 recipients taking out-of-hospital excursions and 2 patients being discharged from the hospital. This multicenter clinical trial is currently ongoing at 6 sites.

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Discussion

Dr Roland Hetzer (Berlin, Germany). I am most grateful for the outstanding privilege to comment on this historical milestone achievement, as presented by Dr Dowling and coscientists.

The totally implantable artificial heart has been a dream of scientists and surgeons since the 1930s and has been realistically sought for the last 50 years. This has become a reality, and Dr Lederman and the ABIOMED Company deserve all our admiration for having pursued and succeeded in this ambitious project. This might be compared with the first journey of man to the moon in 1969. The development will certainly continue, just as the spaceships of today are quite different and much more advanced than the ones then.

Although 5 of 7 desperately ill patients have died, it should be kept in mind that no other option for survival was seen for them and that survival with a total artificial heart of more than 60 days was considered a success in the study design. This goal has been reached by 4 of the 7 patients.

My comments and questions go to 5 topics.

First, many patients with end-stage heart failure can now be well treated with left ventricular assist devices, with good mobility and quality of life. In fact, among the 650 patients who have received assist devices at my institution, complete cardiac recovery has been observed in more than 40 with myocarditis and cardiomyopathy with subsequent removal of the device, and 25 have been placed on such devices permanently—with the Berlin Heart, the Novacor, the DeBakey MicroMed, and the Arrow Lion Heart—for up to more than 3 years.

There is, however, a proportion of patients who require biventricular support, and I would like to ask Dr Dowling what he thinks the proportion of patients might be who can only be handled with a total artificial heart?

Second, thrombosis, thromboembolism, and anticoagulation complications account for 3 of the 5 deaths. Technical improvements have already been undertaken by the company to diminish this problem. Several of the ventricular assist devices had great benefit from heparin coating of the inner surfaces. My question is, what are the plans for the near future to improve on the thrombogenicity of the AbioCor?

Third, some parts of the AbioCor might be subject to wear and exhaustion. In one of our patients with a Lion Heart, the control system had to be exchanged after 16 months. My question is, what is the estimated lifetime of the various parts of the AbioCor, and how can their need for replacement be anticipated to not endanger the patients?

Fourth, in the various assist devices we have seen different and distinct alterations of vascular regulation, both humoral and neural. What are the reactions of peripheral circulation and their sequelae in the case of a total pulsatile artificial heart?

Finally, long-term substitution of the heart must go along with a high degree of quality of life for the patient. How does the AbioCor comply with this demand? That means noise, perceptible device motion, and anxiety and depression of the patient. Again, I feel highly honored to be selected to comment on this event, and I would like to congratulate Dr Dowling, the responsible surgeons, and the ABIOMED Company on this achievement.

Dr Dowling. Thank you very much for your kind comments. Let me just jump to the questions and try to give a succinct answer.

The first question was one I hear quite often: What percentage of patients will need to be supportive of the total artificial heart? I do not think any of us really know the answer to that question yet. I think this trial and ongoing trials, especially with left ventricular assist devices as destination therapy, will help answer that question. I can tell you that once this device is placed, you have complete control of the circulation. You can adjust the central venous pressure and the left atrial pressure to be whatever you want and the cardiac output to be whatever you want. It seems, from talking to all the investigators, our clinical impression is that this has resulted in a significant decreased incidence of renal dysfunction and hepatic dysfunction and has been very much responsible for getting these patients through the operation and through the immediate postoperative period.

There was a recent article with which I am sure a lot of you are familiar from Columbia by Yoshi Naka that demonstrated that there is still significant morbidity and mortality related to right ventricular dysfunction after left ventricular assist device placement, and in that experienced center, the mortality from significant right ventricular dysfunction was 43%. Therefore hopefully this and other center's trials with other devices will define the need for univentricular versus biventricular support.

The second question is related to the incidence of thromboembolic events. The thing that has already been done, as you mentioned and as was mentioned in the talk, was removal of the atrial struts. I do want to emphasize that the blood pumps were entirely cleaned and at explant looked identical as before implantation. I do not know of any plans in terms of heparin coating of the device. I think hope for the next series of implants is that removal of these

struts will have a favorable effect on the incidence of thromboembolic events.

The estimated lifetime of various parts is not known entirely. The in vitro trials were initiated in April 2000, with a limited number of devices placed then and some devices placed approximately 1 year later. The hydraulic membrane appears to last at least a year, probably longer. The centrifugal pump and the switching valve, which are essentially the only 2 moving parts of the energy convertor, I would guess to have an estimated lifespan in the 3- to 5-year range or longer, but I might be speaking a little bit out of turn because I do not have the hard data on those.

The effects of the peripheral circulation, interestingly, is that the patients have a normal pulse, they have a normal pulmonary artery pressure wave form, and they have normal left and right atrial pressure wave forms. We have not been able to discern any abnormal effects of the artificial heart on the peripheral circulation.

The device is noiseless; you cannot hear the device unless you place a stethoscope or you plant your ear on the chest of one of these recipients. Last Thursday, I forgot to see one of my patients in the office, and I remarked that I am used to being able to hear the patients with left ventricular assist devices when they are here. But the patients with total artificial hearts, you cannot hear their devices at all, even if you are standing right next to them. There is very little motion of the device itself. As you saw from the video clip, there is alternate motion of the hydraulic fluid to the left and right, but the device itself has very little motion. With our limited experience, the patients have not had any excessive anxiety regarding the function of the device. As I mentioned in the talk, it has been very user friendly, and the patients and their families have rapidly adapted to using all the components.